EPIDEMIOLOGY OF HEART FAILURE

Epidemiology of heart failure.
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Manuscripts based on studies described in this thesis

Chapter 1

- Mosterd A, Reitsma JB, Ottervanger JP, Deckers JW, Tijssen JGP, Grobbee DE. Epidemiology of heart failure.[In Dutch] Hart Bulletin 1993; 24:245-51.
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Chapter 3

- Mosterd A, Hoes AW, de Bruijne MC, Deckers JW, Linker DT, Hofman A, Grobbee DE. Prevalence of heart failure and (a)symptomatic left ventricular dysfunction in the general population. The Rotterdam Study. Submitted.
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General introduction

"The very essence of cardiovascular practice is the early detection of heart failure"
Sir Thomas Lewis[1]

Cardiovascular mortality rates have declined significantly in most industrialized countries over the past three decades.[2] Nevertheless, cardiovascular disease remains one of the most important causes of morbidity and mortality in Western society, especially as the average age of the population increases.[3,4] Heart failure is rapidly becoming one of the most prevalent cardiovascular disorders and the incidence of heart failure is expected to continue to increase for some time to come.[5,6] Unfortunately, it appears that the declining fatality rate of acute coronary events,[7] resulting in a larger group of persons at increased risk of developing chronic cardiovascular disease, contributes to the rise of heart failure. The paradox of better care is expanded by the observation that treatment of hypertension may actually postpone rather than prevent the onset of heart failure.[8]

The prognosis of heart failure is poor[9] and the economic impact of heart failure on health services is considerable because of the long-term pharmacological treatment and frequent hospitalizations associated with the syndrome. This burden is set to increase further as the prognosis of patients with heart failure is improved by medical and surgical interventions[10-13] and the proportion of the elderly increases in Western society.[4]

A recently developed simulation model predicts a transition from acute to chronic cardiovascular disease, resulting in a dramatic increase in age-adjusted prevalence rates of ischemic heart disease in the Netherlands by 2010, that is largely attributable to heart failure (Figure 1).[5] The lower prevalence in younger age groups is offset by the higher rate in older age groups. The aging of our society will only serve to amplify this trend.

Heart failure is a clinical syndrome that largely defies definition[14]; it develops as a consequence of cardiac disease, and is recognized clinically by a constellation of various signs and symptoms produced by complex circulatory and neurohormonal responses to cardiac dysfunction.[15] The committee that prepared the Dutch heart failure consensus defined heart failure as "cardiac -pumping- dysfunction with accompanying symptoms",[16] whereas objective evidence of cardiac dysfunction has to be present, in addition to symptoms and signs (typically breathlessness, fatigue and ankle swelling), to satisfy the definition of heart failure according to the European Society of Cardiology Task Force on Heart Failure.[17] Packer defined heart failure as "a complex clinical syndrome characterized by abnormalities of left ventricular function and neurohumoral regulation, which are accompanied by effort intolerance, fluid retention and reduced longevity" and likened the different viewpoints from which the syndrome can be regarded to the tale of six blind men and the elephant; only by combining different pieces of information is one able to complete the picture.[18]

Traditionally, heart failure was viewed in terms of hemodynamic consequences and fluid retention resulting from depressed cardiac function. In the 1980's the realization

that neurohormonal activation plays a key role in the onset and progression of heart failure led to use of angiotensin converting enzyme (ACE) inhibitors in heart failure.[19] Treatment with ACE inhibitors resulted in reduction of hospital admissions, morbidity and mortality in patients across the complete clinical spectrum of heart failure, from those with asymptomatic left ventricular dysfunction to patients with end-stage heart failure.[11]

Meanwhile, a new paradigm for heart failure is emerging. Cardiomyopathy of overload and subsequent abnormalities of programmed myocardial cell death (apoptosis) is increasingly viewed as a major contributor to the transition to overt heart failure.[20,21]

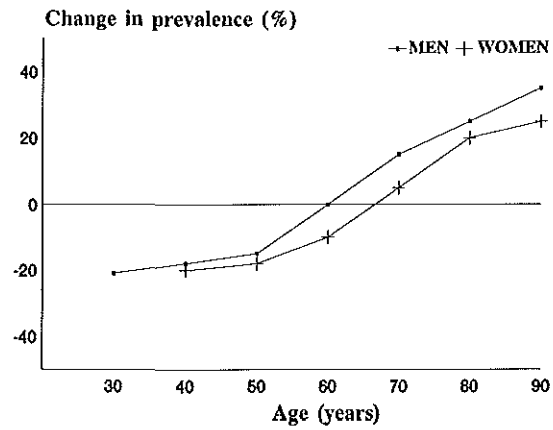

Figure 1. Predicted relative changes in age adjusted ischemic heart disease rates, the Netherlands, 2010 compared to 1985. Rates in 1985 are indicated by the horizontal line at the 0 level. The y-axis indicates the relative change. Adapted from Bonneux et al.[5]

The growing importance of heart failure is reflected in the avalanche of guidelines for the management of heart failure that has been published in recent years.[6,16,17,22-27] Common conclusions are that there is a lack of reliable epidemiological data, a need to develop standardized criteria for the assessment of heart failure and a need for population based research in heart failure. Reliable estimates of prevalence and hospital admissions for heart failure are mandatory to gauge (future) health care expenditures, and information on presymptomatic and early stages of heart failure is a prerequisite in developing preventive strategies. However, epidemiological data on heart failure in general and on early stages of heart failure in particular are surprisingly scarce; apart from the Framingham Heart Study and the "Study of Men Born in 1913", population based data are virtually non existent.[28,29]

This thesis addresses several aspects of heart failure from an epidemiological viewpoint. In chapter 1 an overview is given of currently available information on the epidemiology of heart failure. In chapter 2 currently used and new methods to classify and detect heart failure are evaluated. The epidemiology of heart failure in the Nether-

lands, in terms of prevalence of heart failure and left ventricular systolic dysfunction in the Rotterdam Study,[30] as well as trends in hospital admissions for heart failure from 1980 to 1993, is described in chapter 3. A comprehensive cardiovascular examination (including determination of neurohormones at rest and after peak exercise) was carried out in 160 carefully selected Rotterdam Study participants to gain insight into the early phase of heart failure (chapter 4). Trends in prevalence of electrocardiographic left ventricular hypertrophy - a strong risk factor for development of heart failure - in relation to changes in antihypertensive treatment from 1950 to 1990 were studied in participants of the Framingham Heart Study (chapter 5). Finally, the implications of the studies presented in this thesis are discussed and recommendations for future research are provided.

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1. The epidemiology of heart failure

Introduction

Cardiovascular mortality rates have declined significantly in most industrialized countries over the past three decades.[1] Nevertheless, cardiovascular disease remains one of the most important causes of morbidity and mortality in Western society, especially as the average age of the population increases. Heart failure is rapidly becoming one of the most prevalent cardiovascular disorders and the incidence of heart failure is expected to continue to increase for some time to come.[2-4] Although a great deal is known about the epidemiology of coronary heart disease, much less is known about the epidemiology of heart failure, despite its poor prognosis[5,6] and considerable economic impact on health services because of the long-term pharmacological treatment and frequent hospitalizations associated with the syndrome. This burden is set to increase further as the prognosis of patients with heart failure is improved by medical and surgical interventions,[7-13] the proportion of the elderly increases in Western society,[3] and as the prognosis following myocardial infarction continues to improve with the widespread administration of thrombolytic therapy, the increased use of platelet aggregation inhibitors, ß-blockers, angiotensin converting enzyme inhibitors and revascularization .[14-18]

In this chapter the literature on the epidemiology of heart failure will be reviewed, drawing almost exclusively on data collected in the last 40 years. Prior to this time the classification and understanding of heart failure bears little resemblance to current knowledge and practice. Definition, classification, prevalence, incidence, etiology, risk factors and prognosis of heart failure will be addressed, as well as the costs associated with heart failure. Despite the difficulties in providing a rigorous, yet useable, definition of heart failure and in interpreting the data available on the incidence and prevalence of this condition, enough information is available to allow at least some tentative conclusions to be drawn.

Methods

A search of the Medline Literature Database 1966 - June 1995 was conducted using medical subject headings heart failure (congestive), cardiomyopathy (congestive), epidemiology, diagnosis, prognosis, incidence, prevalence and mortality. The search was extended using lateral references, personal communications with investigators and presentations at recent conferences.

The syndrome

There is no universally agreed upon definition of heart failure.[19] Heart failure is a syndrome which develops as a consequence of cardiac disease, and is recognized clinically by a constellation of various signs and symptoms produced by complex circulatory and neuro-hormonal responses to cardiac dysfunction.[20,21] The syndrome may occur as the end-result of damage caused by a number of disease processes, e.g. coronary artery disease, hypertension, valvular defects, alcohol abuse or viral infection. The presence and severity of heart

failure can be assessed by questionnaires, physical and radiographic examination, and by measures of ventricular performance and exercise capacity. All these methods, however, have major limitations when used independently.[22] It is in the milder degrees of heart failure that most diagnostic difficulties arise, especially in the elderly. Even experienced physicians may disagree on the diagnosis in individual cases if the syndrome is mild.[23] A small number of studies has addressed the sensitivity, specificity and predictive value of symptoms and signs for the presence of heart failure.[24-30] Three were carried out in small, highly selected groups of patients awaiting heart transplant,[24,25,30] and a further three studies took place in larger groups of patients who had been referred for evaluation of ejection fraction (Table 1.1).[26-28] Only one study (in Finland) to date[29] took place in general practice, evaluating patients before they received pharmacological treatment.

Table 1.1. Studies of symptoms and signs for the detection of heart failure.

Study	Study Population	Mean Age	% Men	Gold Standard	Prevalence of Heart Failure
Harlan 1977[26]	1306 patients with coronary artery disease undergoing catheterisation	54	84%	EF* <40%	20%
Mattleman 1983[28]	99 patients referred for evaluation of left ventricular function	57	66%	EF < 50%	44%
Marantz 1988[27]	407 patients referred for evaluation of left ventricular function	64	65%	EF < 40%	50%
Remes 1991[29]	88 patients in whom the general practitioner suspected heart failure	61	42%	Boston criteria[72]	52%

* EF = Ejection Fraction.

From the data available it would appear that shortness of breath has a high sensitivity but low specificity for the presence of heart failure, and that findings on physical examination, conversely, have a high specificity but low sensitivity for the presence of heart failure (Table 1.2). The Dutch Transition project, a study of 22 general practices and covering 40.574 patient years from 1985-1988[31,32] provides figures on the predictive value of shortness of breath and dependent edema on examination for detecting heart failure in general practice. The positive predictive value of shortness of breath, in the presence of coronary artery disease, was 25% for persons aged 65 - 74 years and 44% for persons over 74 years of age. The corresponding figures for edema were 11% and 27%. The Finnish study is unique in studying patients whom general practitioners suspected, on the basis of symptoms and signs, to develop heart failure for the first time.[29] In 34% of such patients heart failure was deemed not present after clinical assessment by a cardiologist and chest radiograph. Obesity, unrecognized myocardial ischemia and chronic obstructive pulmonary disease often led to a false positive diagnosis of heart failure in general practice.

Table 1.2. Sensitivity, specificity, and predictive value of symptoms, signs and chest X-ray findings for heart failure (i.e. ejection fraction < 0.40) in 1306 patients with coronary artery disease undergoing cardiac catheterisation.[26]

	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)
Medical History			
Shortness of breath	66	52	23
Orthopnea	21	81	2
Nocturnal dyspnea	33	76	26
Edema by history	23	80	22
Physical Examination			
Tachycardia (>100/min)	7	99	6
Rales	13	91	27
Edema on examination	10	93	3
Ventricular gallop (S3)	31	95	61
Neck vein distension	10	97	2
Chest X-Ray			
Cardiomegaly	62	67	32

Doppler echocardiography, nuclear studies or cardiac catheterization provide insight into the diastolic and systolic function of the heart but are not able to unequivocally determine the presence or absence of heart failure: abnormal function is not consistently associated with the syndrome of heart failure.[33] The systolic function of the heart is commonly assessed by measuring the ejection fraction of the left ventricle which in undiseased hearts should be greater than 50%. Diastolic dysfunction (prolonged diastolic relaxation or decreased diastolic compliance) prevents the ventricles from being filled adequately at normal filling pressures.[34-37] There is increasing evidence that heart failure can be present in patients with no demonstrable valvular abnormality or systolic dysfunction, but with impaired diastolic function. This condition has been termed "diastolic heart failure" by several authors.[36-38] The distinction between systolic and diastolic heart failure is difficult to make using symptoms, signs and radiographic examination alone.[4,36-46] As noninvasive assessment of diastolic function is fraught with difficulties, it is not surprising that little is known about the epidemiology of diastolic heart failure. Hospital-based series and a report of the first Veterans Administration Cooperative Vasodilator-Heart Failure Trial (V-HeFT I) indicate that heart failure associated with isolated diastolic dysfunction is more frequent as age increases (Table 1.3).[39,47-51] The natural history and treatment of diastolic heart failure may differ from that of systolic ventricular dysfunction.[37,46,50,52,53]

It also has to be noted that ventricular dynamics may vary in one individual over time.[54,55] The effects of exercise or stress on systolic and diastolic function can be marked (especially in patients with coronary heart disease), and many of the indices used in clinical practice are markedly sensitive to changes in the loading of the ventricle, heart rate or drugs[56] and may change with age even in the absence of disease.[57] However, some abnormalities of cardiac function will be demonstrable in all patients with heart failure,[43] if not at rest, at least on stress.

Table 1.3. Prevalence of diastolic dysfunction in persons with heart failure, defined as heart failure in the presence of a normal systolic function.

Study	Description of Study	Mean Age (years)	Definition of normal systolic function	Prevalence of diastolic heart failure
Cohn, 1990[50]*	623 Ve-HFT I participants undergoing baseline radionuclide measurement of left ventricular function	59	Radionuclide EF > .45	13%
Echeverria, 1983[39]	50 consecutive patients with CHF referred to echo lab for evaluation of heart failure	56 ± 13.6	Echocardiographic EF > .50	40%
Dougherty, 1984[47]	188 consecutive patients with CHF undergoing radionuclide evaluation of left ventricular function	63	Radionuclide EF > .45	36%
Soufer, 1985[48]	74 consecutive patients with CHF undergoing radionuclide evaluation of left ventricular function	?	Radionuclide EF > .45	42%
Wong, 1989[49]	54 consecutive patients with CHF older than 70 years undergoing echocardiographic evaluation	80	Echocardiographic EF > .50	63%

* As persons with a normal ejection fraction were excluded from this study, unless radiographic or echocardiographic evidence of left cardiac enlargement was present, the reported prevalence of heart failure with normal systolic function is likely to be an underestimate of the true prevalence.

? No mention in paper.

Exercise testing, though prognostically important in heart failure, is of limited value in the diagnosis even when accompanied by measurement of oxygen consumption and anaerobic threshold.[58] The six minute walk test provides a useful alternative to treadmill exercise testing in the assessment of the severity and prognosis of heart failure.[59-61]

Another frequently used method to determine the severity of heart failure is a functional classification such as the New York Heart Association Classification.[62] Although conceptually simple there is lack of interobserver agreement in classification,[63] and often a patient's own assessment of his or her functional state differs markedly from that of the doctor.

Neurohumoral activation may precede the onset of symptoms and signs in heart failure. Neurohormonal measures are not currently used for the diagnosis of heart failure although the role of such measures (especially of natriuretic peptides) in the detection of left ventricular dysfunction appears to be promising.[64-68]

Because heart failure is a clinical diagnosis there is no single investigation that can be considered as a "gold standard" for confirming the diagnosis. Scoring systems that combine several of the measures discussed above have been developed for use in population-based studies[69-71] and in cardiovascular drug research.[72-74] The various symptoms and signs that may be present in a patient with heart failure are given a score, and if the total score is greater than a predetermined number, the patient is considered to have heart failure (Table 1.4 and appendix). None of the six scores for heart failure encompasses a direct measure of cardiac function, e.g. by means of cardiac catheterization, nuclear ventriculography or Doppler echocardiography. Attempts have been made to validate the Framingham and Boston Scores against such measures as ejection fraction (EF) and left ventricular end-diastolic pressure (LVEDP) at cardiac catheterization.[26,27,72] Individuals with depressed EF are not clearly differentiated from those with a normal EF,[27] with both sensitivity and specificity of the Framingham score to detect an EF $<=$ 40% being 0.63. The corresponding figures for the Boston score were 0.50 and 0.78. Both scores appear moderately useful at identifying individuals with high LVEDP at rest,[26,72] representing, of course, the more severe grades of heart failure.

Doppler echocardiography has revolutionized the assessment of the structure and function of the heart in modern cardiological practice,[40,75-80] but has not been included in a criterion-based approach to date.[81] Few studies have evaluated the use of echocardiography for the detection of heart failure in a non-hospitalized population[79,82]: in a group of 26 men and 44 women (age 45 - 74 years) a combination of several measurements made from M-mode echocardiography (E-point septal separation, fractional shortening and peak lengthening rate) had a positive predictive value of 75% for detecting heart failure as determined by a cardiologist; if abnormalities in these three measurements were not present the probability of heart failure was only 7%.[79] The potential of ultrasound to confirm cardiac abnormality has expanded greatly with the more recent introduction of 2-dimensional, Doppler and color flow imaging methods. The development of Doppler echocardiography has made large scale epidemiological studies realistic, but it is important to recognize the necessity to record and interpret echocardiograms in a standardized and appropriate manner.[83-85]

Table 1.4. Scores for the classification of heart failure (for detailed explanation: see appendix).

	Framingham [69]	Men Born 1913[70]	Gheorghiade[73]	Boston[72]	NHANES[71]	Walma[74]
History						
Paroxysmal nocturnal dyspnea	X	X	X	X		X
Orthopnea	X			X		
Rest dyspnea				X		
Dyspnea on exertion	x		X	X	X	X
Dyspnea (WHO 1-4)[214]		X				
Night cough	x					
Myocardial infarction or angina pectoris[214]		X				
Weight loss	X/x*					
Swollen legs at end of day		X				
Physical examination						
Neck-vein distension	X		X		X	
Increased jugular venous pressure	X†			X		X
Rales	X	X	X	X	X	X
S_3 gallop	X		X	X		X
Hepatojugular reflux	X					X
Hepatomegaly	x			X	X	X
Edema	x		X	X	X	X
Wheezing				X		
Circulation time >=25 sec.	X					
Electrocardiogram						
Tachycardia	x‡		X	X	X	X
Atrial fibrillation		X				
Chest X-ray						
Cardiomegaly	X		X¶	X		
Acute pulmonary edema	X					
Pleural effusion	x		X	X	X	
Interstitial edema			X	X	X	
Pulmonary venous hypertension			X			
Alveolar changes			X	X	X	
Redistribution				X	X	
Pulmonary function						
Vital capacity	x§					

The lack of agreement on the definition and criteria of heart failure, differences in interpretation of symptoms, and the absence of a gold standard for the diagnosis of heart failure result in considerable heterogeneity in the diagnosis of heart failure in clinical trials [86-88] and epidemiological studies. A distinction has to be made between the clinical and the epidemiological approach: in the latter individual misclassification can be accepted provided disease estimates *for the population* remain precise, but in clinical practice every effort is made to correctly diagnose *the individual*. The epidemiological approach is valid to estimate incidence or prevalence, but becomes problematic when describing the patients' clinical characteristics and subsequent clinical course and prognosis. The inclusion of patients who do not have heart failure in this description will introduce a number of biases in relation to etiology, clinical characteristics and investigation results, and the prognosis will appear more benign than is actually the case. For this reason population-based studies of heart failure must employ the same rigorous diagnostic criteria as used in clinical practice if the purpose of such studies is more than to estimate its frequency.

There is a great need for the development of generally agreed criteria for the diagnosis and assessment of heart failure in clinical practice, epidemiological research and clinical trials to enable comparisons to be made between different studies. The Task Force on Heart Failure of the European Society of Cardiology recently published guidelines for the diagnosis of heart failure.[43] To satisfy the Task Force's definition of heart failure both symptoms and objective evidence of cardiac dysfunction have to be present. Reversibility of symptoms on appropriate treatment was considered desirable. Echocardiography was recommended as the most effective tool to demonstrate cardiac dysfunction.

Availability of epidemiological data on heart failure

Epidemiological information on heart failure can be obtained from various sources: general practice surveys, community surveys, national death statistics and hospital morbidity and mortality registrations. Information from these sources can not be readily compared because of differences in ascertainment and classification of heart failure. For studies in general practice the International Classification of Health Problems in Primary Care (ICPPHC) is commonly used.[89] The World Health Organization (WHO) International Classification of Diseases codes and guidelines on their application are usually followed for mortality (death certification) and hospital discharge data,[90] whereas many population-based studies use classification systems that have been specifically designed for those studies.[69-71] Reliability and comparability of mortality and morbidity statistics is limited by variation in data collection and coding and by differences in the approach to diagnosis of cardiovascular diseases within and between countries, and over time.[91]

The MONICA investigators recently reported a lack of evidence to support the diagnosis of coronary heart disease in one in four deaths attributed to coronary heart disease.[92] The reliability of a diagnosis of heart failure in hospital records and hospital discharge forms has been questioned. A study in a district general hospital in England demonstrated that patients who were found to have heart failure by a weekly ward survey frequently had no mention of heart failure in their patient records and vice versa: patients with a diagnosis of heart failure written in the records often did not have heart failure on

examination.[93] A study of autopsies in a Dutch nursing home revealed that often no evidence was found for a diagnosis of heart failure as mentioned on death certificates.[94] A more recent investigation of hospitalizations for heart failure in the Netherlands, however, documented that 80% of cases coded as heart failure fulfilled the Framingham criteria.[95]

Prevalence

The methodology and results of prevalence studies using data collection from medical records supplemented by direct questioning and/or examination of individuals within the general population, drug prescription data analysis, and general practitioner monitoring are summarized in Tables 1.5, 1.6 and 1.7. Prevalence estimates vary widely which reflect the differences in methodology and timing rather than true differences between populations, and the crude prevalence (unadjusted for age) ranges from 3 to 20 individuals per 1000, with a prevalence of 30 to 130 individuals per 1000 for those aged over 65 years.

Analysis of drug prescription data relies upon use of diuretics, with or without abstracting data from the relevant medical records to estimate the prevalence of heart failure.[96,97] This method assumes that all individuals with heart failure have been prescribed a diuretic: this is probably true for those with more than mild degrees of fluid retention, but is likely to miss individuals with mild heart failure, and may therefore underestimate the true prevalence. Overestimation is also possible, as many individuals prescribed a diuretic do not have heart failure. In prevalence studies relying upon data obtained from general practitioners [31,98-102] no attempt has been made to confirm the diagnosis of heart failure. The validity of the diagnosis of heart failure in general practice is known to be relatively poor, [29,77] and this may therefore reduce the value of such studies.

Incidence

Incidence can be determined by two approaches: re-examining individuals within a cohort at intervals to identify those who have developed heart failure; or by a population-based surveillance system in which subjects developing heart failure for the first time are identified.

The Framingham Heart Study and the Study of Men Born in 1913 in Sweden are good examples of the first approach.[2,5,103] The Finnish Study,[104] UK and Dutch general practice studies,[31,100,102] the Rochester study [6] and the United States Two Counties Study [98] are examples of the second approach which has the advantage that incident cases of heart failure presenting to the health care system (either in primary or higher levels of care) are identified prospectively and may therefore be fully characterized at the time of diagnosis rather than retrospectively. Table 1.8 summarizes the results of these studies. The crude incidence (unadjusted for age) in the general population ranges from 1.0 to 5.0 cases per 1000 population per annum, with a steep increase with advancing age: the incidence rate for those aged over 75 years is reported to be as high as 40 cases per 1000 population per annum in some studies.[31,100]

Table 1.5. Population-based studies of congestive heart failure.

Study	Population
United States	
Tecumseh, Michigan 1959-60[215]	Study of a complete community (90% participation rate), 8.641 persons (49% men), heart failure by clinical criteria. 64 cases.
Evans County, Georgia 1960-62[216]	Population of Evans County, 1.840 persons (48% men) 45-75 years, interview and physical examination. Heart failure by clinical criteria. 39 cases.
Vermont/North Carolina, 1962-64[95]	Physician surveillance of own practice in two counties, 22.758 (50% men) and 13.820 (48% men), respectively. 183 and 82 prevalent cases. 19 and 17 incident cases.
NHANES-I, 1971-75[71]*	Sample of non-institutionalized persons throughout the US Estimates based on self report by 14.407 persons (25-74 years, 158 cases) and on clinical examination of a subsample of 6.913 persons (138 cases).
Rochester, Minnesota 1981-82[5]	Review of medical records of Rochester residents <75 years. 46 incidence cases in 1981, 113 prevalent cases on january 1 1982.
Rochester, Minnesota 1986[217]	Stratified random sample of Rochester resident 35 years or older, 2.122 persons (48% men). Heart failure by clinical criteria using questionnaire and review of medical records, 41 prevalent cases.
Framingham, Massachusetts 1948-88[3]	9.405 participants (47% men), biannual examination and interview. 652 incident cases.
CHS, 1989-90[218]†	Cohort of 5.201 persons 65 years and older. Presence of definite heart failure based on interview and information from additional sources (physician / medication use / hospital discharge diagnosis). 104 definite cases, 35 cases of possible heart failure (self report not confirmed by information from additional sources).
Europe	
Sheffield, UK 1950[219]	Prevalence study of a random sample of 476 retired men and women (40% men) living at home.
Göteborg, Sweden 1963-80[103]	855 men (88% of sample) born in 1913. An additional sample was drawn in 1970. Heart failure based on findings from medical interview and examination. 18 prevalent cases at age 50 years, 84 cases at 67 years. Incidence estimated from increase in prevalence with age of sample.
Göteborg, Sweden 1971-77[220]	973 persons (46% men, 70 years) representing 85% of a sample of 70 year olds, examined in 1971/72 and 5 years later. Heart failure by clinical criteria: interview and physical examination of 743 persons attending both examinations (19 and 28 prevalent cases at age 70 and 75 respectively).
Eastern Finland, 1986-88[104]	Surveillance of 11035 persons 45-74 years in rural communities. Examination of persons suspected of heart failure. Heart failure by Framingham and Boston criteria, 51 incident cases.
London, UK 1988[96]	Prevalence study by review of medical records in 3 general practices (30.204 patients); heart failure by clinical criteria in patients who were using diuretics. 117 cases.
Transition project, The Netherlands 1985-88[31]	Surveillance of 22 general practices (40.796 patients, 47.3% men), heart failure classified by general practitioner on clinical criteria.[89] 459 prevalent cases, 245 incident cases.
Nijmegen, The Netherlands 1987-91[109]	Surveillance of 22 general practices (60.691 patient years), heart failure classified by general practitioner on clinical criteria.[89] 701 prevalent and 197 incident cases.
NIVEL, The Netherlands 1987-88[221]	Surveillance of 103 general practices with a total of 335.000 patients during 3 months. Heart failure classified by general practitioner on clinical criteria.
CastelFranco, Italy 1992/94[222,223]	Prevalence study by self report of majority of population in a community combined with verification of prescribed medication. 6529 persons aged 20-64 years (130 cases): 2254 persons aged over 64 years (187 cases).
Denmark, 1994[224]	Prevalence study by questionnaire survey of patients > 40 years in one general practice (n=963). Heart failure based on history of heart disease combined with breathlessness on exertion and use of diuretics, digoxin or angiotensin converting enzyme inhibitors. 25 severe and 37 mild prevalent cases.
Nottinghamshire, UK 1994[97]	Prevalence estimates based on prescription data from one county in UK.
Gen Practice, UK 1991/92[102]	Prevalence and incidence study by general practitioner monitoring of a 1% sample of population of England and Wales registered with 60 volunteer practices throughout the country. 4166 prevalent cases, 1076 incident cases.

* NHANES-I, First National Health and Nutrition Examination.

† CHS, Cardiovascular Health Study, carried out in 4 counties (in North Carolina, Maryland, California and Pennsylvania).

Table 1.6. Prevalence of heart failure, US studies (per 1000 population).

Study	Men	Women	Total
United States			
Tecumseh[215]			
All ages	5.9(3.6-8.2)	8.9 (6.1-11.6)	7,4(5,6-9,2)
Evans County[216]			
45-74 years	24,8(14,6-35,0)	17,8(9,5-26,1)	21.2(14.6-27.8)
Vermont[95]			
All ages	8,6(7,0-10,2)	11,7(9,7-13,7)	10,0(8,8-11,2)
North Carolina[98]			
All ages	8,4(7,7-9,1)	9,0(7,9-10,1)	8,8(7,3-10,3)
NHANES-I[71]			
Self-report			
25-74 years	11	10	11(9.3-12.7)
Clinical score			
25-54 years	8	13	11
55-64 years	45	30	37
65-74 years	49	43	45
25-74 years	19	20	20(17.7-22.3)
Rochester 1981/82[5]			
45-49 years	1	1	
50-54 years	1	2	
55-59 years	7	3	
60-64 years	12	7	
65-69 years	26	11	
70-74 years	28	27	
0-74 years	3,3#	2,1#	2,7#
Rochester 1986[217]			
35-54 years	0	2	1
55-64 years	5	5	5
65-74 years	23	0	12
75+ years	69	80	76
All (35+)	17,6(16,8-18,4)	20,9(20,1-21,7)	19,3 (18,7-19,9)
Framingham*[2]			
50-59 years	8	8	
80-89 years	68	79	
>= 45 years	24	25	
all ages	7.4	7.7	
CHS[218]			
definite			
65-69 years	22	12	
70-74 years	19	15	
75-79 years	32	24	
80-84 years	32	25	
85+ years	29	22	
65+ years	24.4(18.0-30.8)	16.6(12.0-21.2)	20.0(16.2-23.8)
possible			
65+ years	6,2(3,2-9,2)	5,1(2,6-7,6)	5,6(3,6-7,6)

\# Age adjusted to relevant natural population.

* Framingham data pertain to the 1980's.

() 95% confidence interval, calculated as 95% C.I. = (p) ± 1.96 * √((p(1-p))/n). (p = prevalence, n = number of persons in denominator).

Table 1.7. Prevalence of heart failure, European studies (per 1000 population).

Study	Men	Women	Total
Europe			
Sheffield, UK[219]			29.4(14.2-44.6)
Göteborg, Sweden 1963-80[103]			
50 years	21(11.4-30.7)		
67 years	130(104.4-156.4)		
Göteborg, Sweden 1971-77[220]			
70 years	110(77-143)	80(54-106)	93(72-115)
75 years	170(130-210)	110(80-140)	136(112-150)
London, UK[35]			
<65 years			0.6
>64 years			28.0
Total population			3.8(3.2-4.4)
Transition, The Netherlands[31]			
45-64 years	4	3	4
65-74 years	33	29	31
75+ years	93	83	87
all (incl. <45)	10(8.6-11.4)	12(10.6-13.4)	11(10.1-11.9)
Nijmegen, The Netherlands[100]			
45-64 years	8	3	5
65-74 years	49	32	40
75+ years	159	162	161
all (incl. <45)	10.4(9.3-11.5)	12.6(11.4-13.8)	11.6(10.8-12.4)
NIVEL, The Netherlands[221]			
45-64 years	3.0	3.1	3.0
65-74 years	25.6	18.5	21.6
75+ years	69.7	82.9	78.4
all (incl. <45)	4.9	7.8	6.4
CastelFranco, Italy[222]			
<65 years			20(16.6-23.4)
>64 years			83(71.0-95.0)
Denmark[224]			
40-59 years			1.5(0-3.9)
60-69 years			38(26-50)
>69 years			190(165-215)
Nottinghamshire, UK[97]			
30-39 years			0.1
50-59 years			5.5
70-79 years			42
all			13(10-16)
Gen Practice, UK(1991/2)[102]			
25-44 years			0.1
45-64 years			4.2
65-74 years			27.3
75-84 years			74.1
85+ years			140.3
all			8.9

\# Age adjusted to relevant natural population

() 95% confidence interval, calculated as 95% C.I. = (p) ± 1.96 * √((p(1-p))/n).
(p = prevalence, n = number of persons in denominator)

Table 1.8. Incidence of heart failure (per 1000 per annum).

Study	Men	Women	Total
United States			
Vermont[93]			
All ages			5.0(2.8-7.3)
North Carolina[58]			
All ages			3.5(0.9-6.0)
Rochester 1981/82[6]			
45-49 years	1	0	
50-54 years	1	0	
55-59 years	3	1	
60-64 years	6	2	
65-69 years	16	5	
70-74 years	9	10	
0-74 years	1.6(1.0-2.2)#	0.7(0.4-1.0)#	1.1#
Framingham*[2]			
50-59 years	3	2	
80-89 years	27	22	
> = 45 years	7.2	4.7	
all ages	2.3#	1.4#	
Europe			
Göteborg, Sweden[103]			
50-54 years	1.5		
61-67 years	10.2		
Eastern Finland [74]			
(Boston criteria)			
45-54 years	1.9	0	
55-64 years	3.1	1.5	
65-74 years	8.2	2.0	
45-74 years	4.0(2.7-5.3)#	1.0(0.5-1.5)#	
(Framingham crit.)			
45-54 years	2.2	0.2	
55-64 years	3.3	2.2	
65-74 years	7.7	2.9	
45-74 years	4.1(2.8-5.4)#	1.6(0.9-2.3)#	
Transition, The Netherlands[31]			
45-64 years	3.1	2.5	2.8
65-74 years	20.1	16.2	18.0
75+ years	50.3	39.6	43.5
Nijmegen, The Netherlands[100]			
45-64 years	2	2	2
65-74 years	17	11	13
75+ years	45	38	40
all ages	3.1(2.5-3.7)	3.4(2.8-4.0)	3.3(2.9-3.7)
NIVEL, the Netherlands[221]			
45-64 years	1.2	1.2	1.2
65-74 years	14.4	9.2	10.4
75+ years	39.6	42.8	41.6
all ages	2.8	4.0	3.6
General Practice, UK(1991/2)[102]			
45-64 years	1.4	1.0	1.0
65-74 years	9.3	7.4	8.3
75-84 years	22.7	16.2	18.6
85+ years	29.1	32.9	32.0
all ages			2.3

\# Age adjusted to relevant natural population

* Framingham data pertain to the 1980's

() 95% confidence interval, calculated as 95% C.I. = (I ± 1.96 * √n)/(PJ).
(n= number of incident cases, PJ= personyears of observation).

Etiology

Heart failure is the common end-result of many different disease processes that impair cardiac function.[105] Coronary artery disease and hypertension (either singly or together) account for the vast majority of cases of heart failure within the developed world. Valvular heart disease is now much less commonly the underlying etiology of heart failure than previously.[106] Rheumatic valvular heart disease and nutritional cardiac disease are much more common in the developing world[107,108] and consequently the prevalence and incidence of heart failure in younger age groups is greater. In a substantial minority of cases the etiology is unknown, and the term "cardiomyopathy" is applied.[109-112] The relative frequencies of each pathology vary from one series to another: autopsy and hospital-based data tend to be rather selected, and produce a different league table from that based on community studies (Table 1.9).[106,113,114]

Table 1.9. Etiology of heart failure.

	Teerlink et al*[113]	Framingham Heart Study†[106]	
Etiology		Men	Women
Ischemic	50.3%	59%	48%
Non Ischemic	49.7%	41%	52%
Hypertensive	3.8%	70%	78%
Idiopathic	18.2%		
Valvular	4.0%	22%	31%
Other‡	10.3%	7%	7%
No etiology provided	13.3%		

* based on 31 reports on heart failure published from July 1989 to June 1990

† Framingham Heart Study, 32 year follow-up.
Percentages add up to over 100% as hypertension and coronary artery diseas were not regarded as mutually exclusive causes in the Framingham Heart Study

‡ other: viral, ethanol, amyloidosis, postpartum etc.

The Framingham Heart Study reported hypertension as the sole or contributory cause of heart failure in over 70% of cases.[115,116] The importance of hypertension and valvular heart disease as causes of heart failure has declined steadily in the Framingham Cohort since the 1950's, concomitant with an increase in the importance of coronary artery disease and diabetes mellitus.[106,117] There is limited evidence also that deaths from heart failure amongst younger individuals (aged 45-54) have decreased, at least in the United States. It has been suggested that this is due to hypertension detection and treatment programs.[118] Certainly, an overview of trials of pharmacological treatment of hypertension does suggest that effective intervention in individuals with hypertension may reduce the age standardized incidence of heart failure by as much as 50%.[119] Whether such an effect will be observed outwith the context of carefully conducted clinical trials is as yet unknown. Hypertension appears to be more important in the development of heart failure in black than in white persons; an analysis from the SOLVD registry indicated that hypertension was the cause of left ventricular dysfunction in 32% of blacks but only in 4% of whites.[120]

Community based studies other than Framingham have not found hypertension to be such a common underlying cause of heart failure.[82,96,104] Most probably this is related to a temporal trend reducing the importance of hypertension as a cause of heart failure,[106] although different definitions of hypertension and differences between the USA and other developed countries may also play a role. Furthermore, patients with a history of hypertension may be normotensive at the time of presentation with heart failure ("burnt out" hypertensives). Indeed, ischemic heart disease was listed as the primary cause of left ventricular dysfunction in 83% of prevention and 71% of treatment patients in the SOLVD studies, a prior myocardial infarction being present in 80% of prevention and 66% of treatment arm patients.[114] Despite hypertension not being listed as a primary cause of systolic ventricular dysfunction over 36% of prevention arm patients and over 41% of treatment arm patients had a history of hypertension.[121,122] Accordingly, the population attributable risk of hypertension for heart failure is considerable; 59% in women and 39% in men.[123]

Risk factors

Risk factors for the development of heart failure in the general population have been examined in the Framingham Heart Study (Table 1.10) and the Study of Men Born in 1913.[2,103,106] Not surprisingly, factors indicative of the presence of cardiovascular disease greatly increase the risk of occurrence of heart failure. Coronary heart disease confers a fourfold increase of risk. Following myocardial infarction, 14-20% of patients will develop heart failure within 5-6 years.[124,125] Progressive dilatation of the left ventricle within 4 weeks of myocardial infarction greatly increases the chance of heart failure.[81,126,127] Hypertensive cardiovascular disease with electrocardiographic evidence of left ventricular hypertrophy carries an even higher risk of development of heart failure, increasing the risk more than fifteenfold. Echocardiography provides a more sensitive and reliable indicator of increase in left ventricular mass, which has been demonstrated to be associated with higher rates of cardiovascular disease and death.[128] No population-based studies relating echocardiographically assessed left ventricular mass to occurrence of congestive heart failure have been published to date.

There are many other pathophysiological markers associated with an increased risk of heart failure, reflecting the changes associated with increasing cardiac damage: increased heart volume on chest radiograph, T-wave abnormalities on the electrocardiogram, and a reduced peak expiratory flow rate amongst many others.[103,106,129] Diabetes mellitus appears to be a more powerful risk factor in women than men[2] and only part of this increased risk can be attributed to concomitant hypertension, obesity and dyslipidaemia. Diabetes alone may induce important structural and functional changes in the myocardium that increase the risk of heart failure. Body weight is also an independent risk factor for heart failure,[2,103] but interestingly, total cholesterol is not. A high total cholesterol to high density cholesterol ratio is, however, powerfully associated with an increased risk of heart failure presumably due to coronary heart disease. Cigarette smoking increases the risk of heart failure, possibly through the same mechanism, but the relationship becomes weaker with increasing age.[103]

Table 1.10. Age-adjusted relative risks for the development of heart failure (Framingham Heart Study; 36 year follow-up).[106]

	Men		Women	
Age (years)	35-64	65-94	35-64	65-94
Serum cholesterol*	1.2	0.9	0.7	0.8
Hypertension†	4.0	1.9	3.0	1.9
Glucose Intolerance	4.4	2.0	7.7	3.6
LVH (ECG criteria)	15.0	4.9	12.8	5.4

* Serum cholesterol > 6.3 mmol/liter.
† Hypertension: blood pressure > = 160/95 mm Hg or on antihypertensive treatment.

Prognosis

The prognosis of untreated heart failure is unknown. All studies that provide information on survival and prognosis date from the era in which diuretics have been in use. Information on the prognosis of heart failure can be derived from population-based studies, hospital series and the placebo arm of heart failure trials. The latter source however reflects a highly selected group of patients that enter clinical trials and one should keep in mind that the placebo effect has been shown to be considerable in patients with heart failure.[130] Whatever the source of data, heart failure is associated with a marked reduction in life expectancy at any age.

Population-based studies

The Framingham Heart Study reported a mortality rate higher than that found in the trials of therapy in mild to moderate heart failure. Once heart failure had developed only 25% of men and 38% of women were alive at 5 years[5] with a median survival of only 1.66 years in men, and 3.17 years in women. This reflects a mortality rate 6 to 7 times that of the general population of the same age. The incidence of sudden death was 5 times that of the general population.[131] Heart failure in the event of acute myocardial infarction carries an extremely poor prognosis.[132] If death within the first 90 days of development of heart failure is excluded from the data (e.g. deaths from heart failure soon after a myocardial infarction), as is the case in most clinical trials, the median survival in Framingham Heart Study subjects increases to 3.2 years in men, and 5.4 years in women.[5] The poor prognosis of heart failure was confirmed in the study in Rochester, Minnesota, with only 66% alive 1 year after the diagnosis of heart failure.[6] Mortality 5 years following the onset of heart failure was 26% in men having mild to moderate heart failure in the Study of Men Born in 1913.[133] NHANES reported a 10 year mortality of 43% in men and women aged 25 to 74 years with self reported heart failure.[71]

The mortality rate of patients with heart failure may increase with age: the Framingham Study reported a 27% increase in mortality rate per decade of life in men, and a 61% gradient in women.[2] This has not been confirmed in other studies.[134,135] Framingham data also suggests that women may not only develop heart failure less frequently than men, but may also benefit from a lower mortality rate when they do develop heart failure.[2]

The Framingham Heart Study reported approximately 50% of all deaths in those who developed heart failure were "sudden" (death within one hour of the onset of symptoms, the incidence of such a mode of death being 5 times that of the general population.[131] Despite lack of agreement on the definition of sudden death[88] recent trials of pharmacological therapy in heart failure have also reported that approximately half of all deaths are sudden (Table 1.12),[136] the remainder, with few exceptions, being cardiovascular, with the majority being due to progressive pump failure. The precise mechanisms implicated in sudden death in patients with heart failure remain to be elucidated, but anti-arrhythmic therapy (with the possible exception of amiodarone in severe heart failure[137]) has not been shown to prevent such deaths.[138,139] The benefit of ACE inhibitors in recent heart failure trials is largely due to the prevention of death due to progressive pump failure with little or no effect on sudden death.[8] Syncope in persons with advanced heart failure confers a high risk of sudden death.[140]

Hospital-based studies

Hospital series tend to reflect the patient population of specialist referral centers and thus often include only the more severe cases of heart failure.[110] Franciosa reported a mortality rate of 34% at 1 year, 59% at 2 years, and 76% at 3 years in a series of 182 men with chronic heart failure refractory to standard medical therapy at that time.[134] Wilson documented another series of patients with severe heart failure referred for consideration of vasodilator therapy.[135] All of these patients experienced symptoms at rest or on minimal exertion. Mortality was 48% at 1 year and 68% at 2 years. However, Andersson[141] reported a much lower mortality rate (50% at 5 years) in a retrospective study of all patients aged less than 65 years discharged from hospitals in Western Sweden with a coded diagnosis of heart failure. The authors checked all coded patients' hospital records to confirm the diagnosis of heart failure, but would have presumably missed cases of heart failure that were not coded as such on discharge from hospital. Such cases may be expected to be, if anything, less severe than those correctly coded.

A recent hospital-based study from Denmark reported a one year mortality of 21% in 190 patients under age 76 (mean age 64 years) who had heart failure by clinical criteria.[142] Patients with myocardial infarction and malignant disease were excluded. A similar study from Montreal, Canada of 153 consecutive patients presenting to the emergency room with decompensated heart failure reported a one year mortality of 33%.[143] Patients with myocardial infarction or concomitant terminal disease at the time of presentation to the emergency room were excluded from analysis. Mortality in 94 men older than 75 years (mean age at onset of heart failure 82.5 years) was reported to be 28% at one year follow-up, compared to 16% in an age-matched control group.[144]

The prognosis in patients with heart failure and impaired systolic function is worse than that of those with heart failure and normal systolic function (Table 1.11),[50,53,145,146] which in turn is worse than that found in patients with coronary artery disease without congestive heart failure and with a normal ejection fraction.[147]

Table 1.11. Prognosis of patients with heart failure with normal versus impaired systolic function.

	N	Mean follow-up (months)	Total mortality (%)	Average mortality (per 100 patient yrs)*	Abnormal systolic function¶
Cohn, 1990[50]†		28			EF < 0.45
normal function	83		19 (23%)	9.9	(Radionuclide)
impaired function	540		253 (47%)	20.1	
Ghali, 1992[145]		‡			FS < 0.24
normal function	22		8 (36%)		
impaired function	56		36 (64%)		
Aronow, 1990[146]		§			EF < 0.50
normal function	68		38 (56%)		(Echocardiography)
impaired function	9		83 (85%)		

* Average mortality: (total mortality / follow-up) x 12.
¶ EF: ejection fraction, FS: fractional shortening.
† Persons with a normal ejection fraction were excluded from this study, unless radiographic or echocardiographic evidence of left cardiac enlargement was present.
‡ Follow-up ended after 48 months, mean follow-up not mentioned.
§ Mean follow-up not mentioned.

Pharmacological trials

Further data on the prognosis of heart failure is available from the placebo arms of the trials of pharmacological agents in heart failure (Table 1.12).[122,148-150] As these trials were composed of a highly selected group of patients the generalizability of such data is not clear. The first CONSENSUS Study enrolled only patients with severe heart failure (symptoms at rest) and reported a mortality rate of 52% at 1 year in the placebo group.[149] The trial excluded patients with acute pulmonary edema, unstable angina or haemodynamically significant aortic or mitral stenosis, and may therefore underestimate the mortality in a less selected group of patients with such severe heart failure. A later trial included patients with a wider spectrum of severity and reported a correspondingly lower mortality of approximately 15% at 1 year in the placebo group.[122] A Veterans Administration Study reported a similar mortality of 19.5% at 1 year in the placebo arm.[148] The Acute Infarction Ramipril Efficacy (AIRE) Study reported a one year mortality of 14.0% in the placebo arm in patients with symptomatic heart failure in the first few days following myocardial infarction.[150] This study excluded patients with severe symptoms (NYHA Class IV).

Studies in patients with asymptomatic left ventricular dysfunction reported one year mortality rates of 5.8% (SOLVD prevention) and 11.6% (SAVE) in the placebo groups.[121,151] The higher mortality in the SAVE study can be attributed to the fact that all participants had suffered a myocardial infarction 3 to 16 days prior to enrollment.

Table 1.12. Mortality in placebo arms of 4 recent trials in patients with heart failure [122,148-150] and 2 trials in patients with asymptomatic left ventricular dysfunction.[121,151]

Study	n	Mean Follow-Up (months)	Total Mortality (%)	Average Mortality*	Sudden Death (% of total mortality)	Description of patients
Heart failure						
V-HeFT I, 1986[148]	273	28	120 (44.5%)	18,9	45%†	Symptomatic heart failure, EF < 45%
Consensus I, 1987[149]	126	6	68 (54.0%)	108	48.5%‡	NYHA IV, severe symptomatic heart failure
SOLVD treatment, 1991[122]	1284	41	510 (39.7%)	11,6	22.2%§	NYHA II - III, EF < 35%
AIRE, 1993[150]	992	15	222 (22,4%)	17,9	¶	Clinical heart failure following myocardial infarction, NYHA class IV excluded
Asymptomatic LV dysfunction						
SOLVD prevention, 1992[121]	2117	37	334 (15.8%)	5,1	31.4%§	No symptoms of heart failure, EF < 35%
SAVE, 1992[151]	1116	42	275 (24.6%)	7,0	55.8%	No symptoms of heart failure, 3-16 days following myocardial infarction, EF < 40%

* Average mortality (per 100 patient years): (total mortality / follow-up) x 12 months.
† 45% of deaths in treatment and placebo groups combined; not specified for placebo group separately.
‡ Combining sudden cardiac death within 1 hour (20.6%) and within 24 hours of new symptoms (27.9%).
§ Arrhythmia without worsening heart failure.
¶ Sudden death not reported.

Predictors of prognosis

There is conflicting evidence on whether patients with underlying coronary artery disease do better or worse than those with other (or unknown) etiologies of heart failure. Franciosa reported a significantly lower survival in patients with severe heart failure and electrocardiographic or coronary arteriographic evidence of coronary artery disease as compared with idiopathic dilated cardiomyopathy (54% versus 77% at one year, $p<0.01$ by log-rank test of life-table analysis) in a hospital-based series.[134] Similar differences in survival were found in the first Veterans Administration heart failure study.[148] Wilson did not observe a difference in survival between heart failure patients having coronary artery disease or primary cardiomyopathy.[135] This is in contrast to community data from Framingham that suggests that, if anything, men who develop heart failure due to coronary artery disease do better than those with other etiologies of heart failure.[2] Such a discrepancy between studies remains unexplained although many biases may exist in selected hospital series. Differences in establishing the diagnosis of coronary artery disease may also play a role. For example, angiographic evidence of coronary artery disease is not routinely available in population-based studies.

There has been much interest in clinical and investigative features and characteristics predictive of outcome in patients with heart failure.[152] Functional capacity, hemodynamic measures of cardiac function, arrhythmias and neurohumoral parameters have been studied in relation to mortality.[153] Maximal oxygen uptake and duration of exercise test, right and left ventricular ejection fraction, pulmonary capillary wedge pressure, ventricular arrhythmias, levels of catecholamines and atrial peptides have been shown to predict prognosis in patients with heart failure.[59,76,142,146,153-170] In the SOLVD-Registry functional class (New York Heart Association Class),[62] the result of a simple symptom-limited exercise test (the 6 minute walk test) and left ventricular systolic function (as assessed by ejection fraction) were the strongest independent predictors of one year mortality rate and hospitalization rates.[59] Not all series have found that such variables predict survival: functional class appears to be the most consistent - the more severe the functional impairment, the worse the prognosis. Arrhythmias appear to provide little prognostic information regarding the occurrence of sudden death.[138]

Secular trend in prognosis

Information on secular trends can be obtained from The Framingham study because of the long follow-up period and the uniform case definition throughout the length of follow-up. The incidence of heart failure in men 50-59 years of age in the Framingham Heart Study declined from 16 per 1000 per year in the fifties to 6 per 1000 per year in the seventies.[171] No improvement in survival over 4 decades has been noticed,[2] but the effect of the relatively recent introduction of angiotensin converting enzyme inhibitor therapy on survival has not been examined as yet. A recent meta-analysis demonstrated an impressive 23% reduction in mortality in trials of ACE inhibitors in heart failure[8] but the gain in life expectancy is measured in months rather than years. Furthermore, it appears that a substantial proportion of heart failure patients is not receiving optimal treatment.[172,173]

Mortality data

In the United States, the number of deaths ascribed to congestive heart failure as the underlying cause of death rose from 130 000 in 1970 to 267 000 in 1988.[106,118] Part of this increase may be explained by the increasing proportion of the elderly within the population ("the greying effect") but age-adjusted death rates for heart failure (per 100 000) increased from 7.2 to 8.8 for white men, and from 4.6 to 6.3 in white women from 1979 to 1988. For blacks these figures were 11.4 and 13.2 for men and 8.6 and 10.1 for women respectively. After 1988 age standardized rates started to decline; to 7.2 and 5.3 for white men and women in 1990 and 11.0 and 8.2 in blacks respectively.[174] However, as the US standard certificate of death was revised in 1989 this decline may to some extent be artificial. At all ages the death rate from cardiac failure is greater in black than white patients in the United States.[175,176] This may be related to the increased prevalence of hypertension[177,178] and early coronary artery disease in the black population,[179] although poorer access to health care may also play a part.[180,181]

In Canada, despite an increase in absolute number of deaths with a primary diagnosis of heart failure, age-adjusted death rates for heart failure have declined in the period between 1980 and 1990.[182] It was hypothesized that this could be attributed to an improved survival of patients with heart failure. Nevertheless, a true decline in age-adjusted death rates or a spurious decline because of temporal changes in coding practice is conceivable as well.

Mortality data from other countries is limited. In the United Kingdom the death certificate explicitly forbids heart failure to be entered as the primary cause of death, and instead the underlying pathological process is specified, e.g. coronary heart disease. Attempts to estimate mortality figures for deaths from heart failure from death certification in the UK are unlikely to be valid.[183]

Hospital morbidity data

Hospital morbidity data are readily obtainable but relate, however, only to those individuals who have required hospital (usually inpatient) treatment and therefore do not necessarily reflect the incidence or prevalence of the condition within the community. Any change in the number of patients admitted or discharged from hospital over time may relate more to changes in the perceived usefulness of inpatient assessment and treatment, and changes in awareness of the condition, than to any real change in incidence or prevalence. The accuracy of available data may also vary within and between countries and over time.[91]

The number of hospital discharges with heart failure coded as the primary diagnosis in Scotland rose by 60% between 1980 and 1990 to 210 per 100 000 population per annum.[184] A similar increase has also been recorded in Sweden for the years 1970-1986: counting only one admission per year for any individual there was an 80% increase in discharges for heart failure in men, and a 130% increase in women,[133] with an even more marked increase in those aged over 75 years. Data from The Netherlands suggest an increase of the same magnitude.[185] The absolute level of admissions with heart failure is probably of the same order in England: using data from a West London Hospital the estimated admission rate for heart failure in 1988 was 180 per 100 000 population.[186]

In the United States in 1991 congestive heart failure was the primary discharge diagnosis in about 790.000 hospitalizations and constituted the leading "diagnostic related

group" among hospitalized patients aged over 65 years of age,[4] more than double the number observed in 1978, and more than 5 times the number in 1970.[187,188] This reflects a year-on-year age-adjusted increase in hospitalizations from 82 per 100 000 population in 1970 to 281 per 100 000 in 1990. The method of reimbursement for medical expenses throughout that period of time changed with the introduction of "diagnostic related groups" in 1983 and this may have affected the absolute numbers to some degree, but is unlikely to explain such a massive and steady increase. Among black patients in the US rates of hospitalization are even higher than white patients, probably reflecting a greater incidence and prevalence of heart failure in the black population.[187,189,190]

A high readmission rate is characteristic of patients with heart failure.[185,191,192] A survey of 7 hospitals (2 university and 5 general) in the Netherlands in 1991 and 1992 indicated that 16% of patients were readmitted with heart failure within 6 months of their first admission.[185] An increase in the readmission rate has been noted in Scotland: 17.3% of patients with heart failure were admitted twice or more in 1983, increasing to 22.3% in 1990.[184] Given this frequent rehospitalization of patients with heart failure, the number of hospital discharges rather than the number of individual patients discharged may exaggerate the size of the problem. The Swedish study,[133] however, demonstrated an age-adjusted increase in the number of heart failure admissions, even after exclusion of readmissions. The increase particularly concerned persons older than 75 years, as was the case in the Scotland and the Netherlands.[184,185] Multidisciplinary interventions may be useful to reduce the high readmission rate in the elderly.[193]

The hospital case fatality rate for heart failure in the USA in 1990 was 7.5% with heart failure listed as first diagnosis for all ages, and only slightly higher in those aged over 65 years (8.4%), down from 9.3 and 10.5% in 1982.[189] In-hospital mortality in men in the Netherlands declined from 19.8% in 1980 to 15.4% in 1993. For women these figures are 17.4% and 15.1% respectively.[185] Case fatality in Scotland dropped from 22.3% to 16.2% for men and from 23.5% to 19.6% in women in the period 1980 to 1990.[184] Average duration of hospitalization for heart failure in the Netherlands decreased from 21.6 days in 1980 to 15.2 days in 1993.[185] In Scotland the duration decreased from an average of 34 days in 1980 to 20 days in 1990.[184] The striking difference in case fatality rate and average duration of hospitalization for heart failure between the United States and Scotland/The Netherlands may to some extent be attributed to differences in coding practices and patient groups studied. For example, the length of stay for heart failure in Scotland was heavily skewed by the extreme length of stay of patients with heart failure in geriatric wards as opposed to cardiology units,[184] for which the length of stay was similar to that found in the United States and Sweden, 8.0 (1990) and 7.9 (1989) days, respectively.[187,194]

Economic impact of heart failure

Heart failure is the single most frequent cause of hospitalization for people aged 65 years and older[124] and, following hypertension, the leading cardiovascular cause for outpatient physician visits in the United States.[124,195] It is estimated that 3 million persons in the US are afflicted by heart failure (nearly 1.5% of the adult population) and the associated health care cost in 1989 was estimated at more than $8 billion; of which $6.4 billion was spent on hospital care,

$500 million on professional services, $1.7 billion on nursing home care and $200 million on pharmaceuticals.[106] European data on health care costs associated with heart failure are scarce. A conservative estimate was that 1% of the national health care budget in the Netherlands in 1988 (i.e. 436 million Dutch guilders) was spent on heart failure.[196] German data indicate that 6.8 billion DM was spent on heart failure in the Federal Republic of Germany in 1985.[197] In the United Kingdom the economic cost of heart failure to the National Health Service was conservatively estimated at £ 326.4 million, representing 1.1% of the total NHS expenditure.[198] £ 213.8 (65.5%) was spent on hospital admissions for heart failure. Heart failure related costs in Sweden were estimated at 800 million SEK in 1985: 500 million SEK being spent on hospital care and 300 million SEK in primary health care.[194]

The fourfold increase in risk of stroke in individuals with heart failure also adds to the economic burden of heart failure for both individuals and the health service.[106]

ACE inhibitors have been shown to decrease the number of hospital admissions for heart failure. There were 138 fewer patients hospitalized for heart failure in the group treated with an ACE inhibitor (1285 patients) compared with those treated with conventional heart failure therapy (1284 patients) over the 4.5 years of the SOLVD Treatment trial, with 288 fewer episodes of hospitalization overall.[122] As the bulk of heart failure related costs is attributable to hospitalizations the widespread prescription of ACE inhibitors would appear to be highly cost effective.[199-202] The use of digoxin was recently also reported to be cost effective.[203]

Conclusions and directions for future research

Heart failure is an important and growing public health problem: it is the cause of substantial morbidity and mortality, and it consumes a significant proportion of the health care budget in most developed countries. Notwithstanding the lack of a clear definition and differences in methodology of the studies discussed in this paper some general conclusions can be drawn. The incidence and prevalence of heart failure increase markedly with age and the most common etiologies of heart failure (in the developed world) are coronary artery disease and hypertension. Left ventricular hypertrophy is the strongest risk factor for the development of heart failure. The number of hospital admissions due to heart failure has been steadily increasing in developed countries for some time, and this rise is only partially explained by changes in the proportion of elderly within these populations.

There is no evidence to date that the prognosis of heart failure in the community has improved despite advances in therapy over the last 4 decades. However, the effect of the widespread implementation of drugs that, in clinical trials, have shown to prolong life in patients with congestive heart failure may not have become evident on a population level. Still, the case fatality rate for patients hospitalized with heart failure appears to be declining. It is worrisome, nevertheless, that many patients with heart failure do not receive optimal treatment.[172,173]

The observed increase in hospital admissions for heart failure may seem paradoxical in view of the declining cardiovascular mortality rates and improvements in hypertension treatment in most countries in the developed world.[1,204] The declining coronary heart disease mortality rates have been attributed to a declining incidence and a lower case fatality rate of

coronary heart disease, the latter being more important.[171,205] It is conceivable that more individuals are surviving the initial cardiac damage produced by e.g. myocardial infarction, only to develop heart failure at a later date when the heart can no longer compensate for its reduced pumping capacity. Data from the Framingham study tends to confirm this impression: over the last 40 years the average age of onset of heart failure has been steadily increasing.[5] It has also been suggested that the treatment of hypertension merely postpones the onset of heart failure to an older age rather than preventing it.[118] The improved treatment options for patients with heart failure may well explain the declining hospital case fatality rates, at the same time increasing the number of patients at increased risk for readmission.

A recently developed simulation model predicts a transition from acute to chronic cardiovascular diseases in the near future in the Netherlands, resulting in an age-adjusted increase in the number of patients with heart failure.[3] This increase will be markedly accentuated by the aging of the population, resulting in an increase in the number of elderly heart failure patients in whom presentation of symptoms may be atypical[206-209] and readmissions are frequent.[191,192] It is likely that other industrialized countries will go through a similar transition.

Given the results of the SOLVD (prevention) and SAVE studies the importance of detection of persons with asymptomatic left ventricular dysfunction has increased.[121,151] Detection of asymptomatic left ventricular function is feasible using echocardiography,[210] whereas clinical prediction rules and neurohumoral measurements may also have a role in the near future.[66,211-213] Definite criteria are still to be established and the cost-effectiveness of screening asymptomatic subjects is not known.

Although important steps have been made[43,91] much further work is needed to develop and validate diagnostic criteria for heart failure which utilize modern cardiological investigations, and which can be applied in both clinical and epidemiological research. A clinical case definition is necessary in population surveys which aim to characterize individuals correctly in terms of etiology, cardiac anatomy and function, and morbidity and mortality. Future studies of heart failure should be population-based if the aim is to reliably measure the incidence and prognosis of unselected cases of heart failure. Hospital-based series cannot provide this information. Such an approach will permit an evaluation of the comparative importance of the various etiologic factors, the development of more powerful prognostic indices, and sound comparisons between populations, within populations and over time: vital statistics appear too unreliable to allow meaningful comparisons.

The burden of heart failure within our communities can also be monitored by this approach and by systematically following up incident cases given current best treatment any change in the clinical course of this syndrome will be detected. Whilst clinical trials of new treatment should ideally be conducted in the same patient populations inevitably there is case selection and so it is incumbent on those randomizing patients to define, through registers, the populations from which these patients come. It will then be possible to describe what proportion of heart failure patients are likely to benefit from such new treatments in the future. Finally, we need to ensure current scientific evidence on treatment is translated into clinical practice to ensure maximum benefit to the population.

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Appendix. Description of six scores for the classification of heart failure (Also see Table 1.4).

- Framingham Heart Study[69]:

1. Developed for assessment of heart failure in a population-based study.
2. Heart failure present when two major (X) or one major (X) and two minor (x) criteria are fulfilled.

* Weight loss >= 4,5 kg in 5 days in response to treatment. Major criterion if weight loss occurred during therapy for heart failure, otherwise minor.
† Increased jugular venous pressure: > 16 cm of water.
‡ Tachycardia: heart rate >= 120/min.
§ Vital capacity down 1/3 from maximum.

- Study of men born in 1913[70]:

1. Developed for assessment of heart failure in a population-based study.
2. No, latent or manifest heart failure if stage is 0, 1, 2/3 respectively.

No history, no signs and no treatment for CHF	Stage 0
Cardiac score >0	Stage I
Cardiac score >0 and dyspnea or treatment with digitalis or loop diuretic	Stage 2
Cardiac score >0, dyspnea and treatment with digitalis or loop diuretic	Stage 3

Dyspnoea grade according to the WHO-classification[214]

No dyspnoea	0
Do you get short of breath when walking quickly on the level or walking up-hill?	1
Do you get short of breath when walking with someone of your own age on the level?	2
Do you have to stop because of shortness of breath when walking at your own pace on the level?	3
Do you get shortness of breath when washing or dressing?	4

Cardiac score

History of heart disease(@)	1-2*
Angina pectoris	1-2*
Swollen legs at the end of the day	1
Dyspnoe at night	1
Pulmonary rales	1
Atrial fibrillation	1

*1=in the past, 2=during the last year. (@) Angina pectoris or myocardial infarction.
A maximum of 2 points was given for those reporting both a history of heart disease angina.

- Walma[73]:

1. Developed for assessment of heart failure in patients on diuretic therapy in general practice.
2. Heart failure (arbitrarily) considered present if score >= 3.

Paroxysmal nocturnal dyspnea	3
Dyspnea on exertion	2
Increased venous pressure	2
All other items	1

Tachycardia present if heart rate >100/min.

- Boston Score[72]:

1. Developed for assessment of heart failure in 150 general medical outpatients who were on long-term digitalis therapy.
2. No, possible or definite heart failure if score equals 0-4, 5-7, 8-12 points respectively.

History	
Rest dyspnea	4
Orthopnea	4
Paroxysmal nocturnal dyspnea	3
Dyspnea on walking on level	2
Dyspnea on climbing	1
Physical examination	
Heart rate (91-110/min, 1; >110/min, 2)	1/2
Elevated jugular venous pressure (> 6 cm H_2O 2; > 6 cm H_2O, plus hepatomegaly or edema 3)	2/3
Rales (basilar 1; > basilar 2)	1/2
Wheezing	3
S_3 gallop	3
Chest X-ray	
Alveolar pulmonary edema	4
Interstitial pulmonary edema	3
Bilateral pleural effussion	3
Cardiothoracic ratio >= 0,5	3
Upper-zone flow redistribution	2

No more than 4 points allowed from each of the 3 categories.

- NHANES score[71]:

1. Developed for assessment of heart failure in a national health survey.
2. Heart failure present if score >= 3.

History	
Short of breath when hurrying on the level or up slight hill?	1
Short of breath when walking at ordinary pace on the level?	1
Do you stop for breath when walking at own pace?	2
Do you stop for breath after 100 yards on the level?	2
Physical examination	
Heart rate 91-110, 1 point; >110, 2 points	1/2
Rales basal, 1 point; >basal, 2 points	1/2
Neck vein distension	1
Neck vein distension & edema/hepatomegaly	2
Chest X-ray	
Cephalization of pulmonary veins	1
Interstitial edema	2
Alveolar fluid & pleural fluid	3
Interstitial edema & pleural fluid	3

- Gheorghiade[73]:

1. Developed to assess severity of heart failure in patients on digoxin with "documented congestive heart failure based on the presence of clinical or radiographic evidence of heart failure or both".
2. Each item contributes one point. Heart failure (arbitrarily) considered present if score >= 3.
   ¶ Cardiomegaly on chest X-ray if cardio-thoracic ratio >0.5

2.1. Classification of heart failure
An assessment of 6 heart failure scores

Introduction

Heart failure is rapidly becoming one of the most prevalent cardiovascular disorders and a further increase in the incidence of heart failure is expected in the near future.[1-3] Heart failure carries a poor prognosis[4,5] and has a considerable economic impact because of long-term pharmacological treatment and frequent hospitalizations associated with the syndrome. Heart failure has been defined by Packer as "a complex clinical syndrome characterized by abnormalities of left ventricular function and neurohumoral regulation, which are accompanied by effort intolerance, fluid retention and reduced longevity".[6] However, no single definition of heart failure has gained universal acceptance,[7] resulting in considerable diagnostic heterogeneity in heart failure studies.[8-10]

Epidemiological data on heart failure in the population at large are surprisingly scarce.[1] This may, in part, be attributed to the lack of consensus on the definition of heart failure and the absence of a gold standard to determine the presence or absence of heart failure. Presence and severity of heart failure can be assessed with use of questionnaires, physical and radiographic examination, and by measures of ventricular performance and exercise capacity. All these methods, however, have major limitations when used independently.[11] Scoring systems combining several of the abovementioned methods have been developed in epidemiological studies and clinical trials. To our knowledge, a formal comparison of the individual scoring lists to classify heart failure has not been performed.

The aim of the present study was to assess the characteristics of available scores to determine the presence or absence of heart failure in population based studies. Moreover, the performance of these scores was evaluated in a sample of older subjects.

Methods

Computer-based searches in the Medline database combined with lateral references identified six scores to classify heart failure (Table 2.1.1).[12-17] A seventh score,[18] was not included in our study as it is virtually identical to the so called Boston score.[15]

Study population. The scores were applied to 54 participants of the Rotterdam Study. The Rotterdam Study is a population based follow-up study of 7,983 inhabitants aged 55 years or older living in the Rotterdam suburb of Ommoord. The design of the study has been described in detail elsewhere.[19] Baseline measurements were carried out from March 1990 to July 1993 and the overall response rate was 78%. The participants in our study were recruited from the first 308 participants of the Rotterdam Study (113 men and 194 women, mean age at baseline examination 67.0 (SD 7.7) and 67.1 (SD 8.3) years, respectively) who underwent echocardiography and answered all questions included in the heart failure score developed for the "Study of Men Born in 1913".[13] As auscultation of the lungs was not routinely performed in the first phase of the Rotterdam Study, the presence of rales or rhonchi could not be used in constructing the Men Born in 1913 score. The 308 participants were classified according to this score as having no (n=152), latent (n=104) or manifest heart failure (n=52)(Table 2.1.2). From this group 60 persons younger than 75 years were selected and invited to participate in the present study.

Table 2.1.1. Scores for the classification of heart failure (for detailed explanation: see appendix, Chapter 1).

	Framingham[12]	Men Born in 1913[13]	Walma[17]	Boston[15]	NHANES[16]	Gheorgiade[14]	Rotterdam Study
History							
Paroxysmal nocturnal dyspnea	X	X	X	X		X	
Orthopnea	X			X			
Rest dyspnea				X			
Dyspnea on exertion	x		X	X	X	X	
Dyspnea (WHO 1-4)[21]		X					X
Night cough	x						
Myocardial infarction or angina pectoris[21]		X					X
PTCA or CABG ‖							X
Weight loss	X/x*						
Swollen legs at end of day		X					
Physical examination							
Neck-vein distension	X				X	X	
Increased jugular venous pressure	X†		X	X			
Rales	X	X	X	X	X	X	X
S3 gallop	X		X	X		X	
Hepatojugular reflux	X		X				
Hepatomegaly	x		X	X	X		
Edema	x		X	X	X	X	X
Wheezing				X			
Circulation time >=25 sec.	X						
Electrocardiography							
Tachycardia	x‡		X	X	X	X	
Atrial fibrillation		X					X
Left ventricular hypertrophy							X
Myocardial infarction							X
Chest X-ray							
Cardiomegaly	X			X		X¶	
Acute pulmonary edema	X						
Pleural effusion	x			X	X	X	
Interstitial edema				X	X	X	
Pulmonary venous hypertension						X	
Alveolar changes				X	X	X	
Redistribution				X	X		
Pulmonary function							
Vital capacity	x§						

‖ PTCA: percutaneous transluminal angioplasty, CABG: coronary artery bypass surgery.

Table 2.1.2. Prevalence of heart failure in 308 Rotterdam Study participants according to the heart failure score developed for the Study of Men Born in 1913.[13]

		Stage 0 (No Heart Failure)	Stage 1 (Latent Heart Failure)	Stage 2/3 (Definite Heart Failure)
Men	N	54	42	17
	Prevalence in % (95% C.I.)	48 (39 - 57)	37 (28 - 46)	15 (8 - 22)
	Age (years, ± s.e.)	68 ± 1	69 ± 1	72 ± 2
Women	N	98	62	35
	Prevalence in % (95% C.I.)	50 (41 - 59)	32 (23 - 41)	18 (11 - 25)
	Age (years, ± s.e.)	68 ± 1	70 ± 1	70 ± 1

Efforts were made to include persons with chronic obstructive pulmonary disease, a condition frequently accounting for false positive diagnoses of heart failure,[20] and to include sufficient numbers of persons suspected of having heart failure. 24 persons were randomly selected from the group with heart failure stage 0 (no heart failure) according to the Study of Men Born in 1913 score (12 persons from those with dyspnea and 12 persons from those without dyspnea); 12 were randomly selected from the group with heart failure stage 1 (possible heart failure) and finally, 24 persons were invited from the group having definite heart failure (heart failure stage 2 or 3) according to the Men Born in 1913 score (all three persons with heart failure stage 3 were invited as were those with heart failure stage 2 who were using diuretics other than loop diuretics (n=5), and the remaining 16 persons were randomly selected from the group with heart failure stage 2).

In total, 56 (93.3%) persons agreed to participate. Two of them, both with definite heart failure according to the Men Born in 1913 score, were ultimately not able to attend because of symptoms severely limiting their activities of daily life. Examination of the general practitioner's records showed that both persons had congestive heart failure.

During a two hour visit to the research center all participants underwent the following tests in order to allow assessment of the six heart failure scores.

- *History*. A trained interviewer administered a standardized questionnaire, including all history items of the six heart failure scores and questions on relevant non-cardiac medical history (e.g. pulmonary disease, diabetes mellitus, renal and hepatic diseases), smoking habits, alcohol consumption and current medication use. Information on chest pain, dyspnea and intermittent claudication was obtained by means of the WHO questionnaires.[21]
- *Weight, height and blood pressure measurements*. Height and weight were measured with participants wearing light clothes and without shoes. Blood pressure was measured on the right arm with the participant in sitting position using a random zero sphygmomanometer. The average value of two consecutive blood pressure readings was taken as the blood pressure value.
- *Standardized physical examination* was carried out by a cardiologist (JWD) to verify the presence of dyspnea, jugular venous distension, rales and rhonchi, a third or fourth heart sound, cardiac murmurs, hepatomegaly and ankle edema.

- *Peak expiratory flow* was measured using a mini Wright peak flow meter, developed for use in general practice. The highest value of three consecutive measurements was used in the analysis.
- A *standard 12-lead electrocardiogram (ECG)* was recorded using an ESAOTE laptop electrocardiograph (Florence, Italy). All ECG's were digitally stored and analyzed using the MEANS program, a standardized and validated ECG software program.[22] Computer generated diagnoses were verified by a cardiologist (JWD).
- *Frontal and lateral chest X-rays* were made at maximal inspiration in standing position using General Electric MPG-50 X-ray equipment. All chest X-rays were reviewed, using a standardized scoring form, by a radiologist (AS) who was blinded to the clinical information. Thoracic and cardiac diameters were measured to calculate the cardio-thoracic ratio.[21] and the absence or presence of pleural effusion, upper zone flow redistribution, alveolar or interstitial edema and signs of chronic obstructive pulmonary disease were assessed.
- *M-mode echocardiography* was performed with the participant in the partial left decubitus position, using a 2.25 MHz transducer (ATL Ultra Mark 4). 2-Dimensional imaging using parasternal long-axis views was performed to aid M-mode studies. Measurements were made according to the recommendations of the American Society of Echocardiography using a leading edge to leading edge convention.[23] Left ventricular internal dimension (LVIDed), ventricular septum (IVS) and left ventricular posterior wall (LVPW) thickness were measured at end diastole as defined by the onset of the QRS complex. Left ventricular internal dimension at end systole (LVIDes) was determined at the nadir of septal motion. The percentage fractional shortening (FS) was calculated as 100[(LVIDed - LVIDes)/LVIDed].
- *Doppler echocardiography.* From the apical 4-chamber view mitral flow was sampled at the mitral valve leaflet tips using a 2.25 MHz pulsed wave Doppler probe (ATL Ultra Mark 4). After initial recording on videotape, mitral flow contours of 10 beats were traced off-line. Peak early (E, m/s) and late diastolic inflow velocity (A, m/s) were measured to calculate the ratio of early to late diastolic inflow velocity (E/A ratio).

Classification of heart failure. All participants were classified according to the six heart failure scores by one observer (AM), using information obtained by medical history (interviewer), physical examination, electrocardiogram and chest X-ray. For the assessment of the presence of heart failure a cut-off point of $>=3$ was arbitrarily chosen for Gheorgiade's score, as this score was initially developed for the assessment of severity of heart failure in patients on digoxin with (previously) documented heart failure.[14] Likewise, a cut-off point of $>=3$ was arbitrarily chosen for the presence of heart failure according to Walma's score, although a score >4 was used as an indication to resume diuretic therapy in the original paper.[17] The other scores were applied as outlined in Table 2.1.1.[12,13,15,16]

The cardiologist was asked explicitly to classify participants as having no, possible or definite heart failure using all clinical information obtained at the research center (including his own medical history taking and echocardiographic data). In addition, the

cardiologist graded all participants according to New York Heart Association (NYHA) class.[24] The cardiologist was not aware of the results of the six heart failure scores.

Statistical methods. Sensitivity, specificity, and positive and negative predictive value with 95% confidence intervals for the presence of heart failure were determined for the six heart failure scores with the cardiologist's opinion taken as the gold standard.[25] The sensitivity is the proportion of persons with disease according to the gold standard that is correctly identified by the test, whereas specificity is the proportion of persons without disease according to the gold standard, that is correctly identified by the test. The positive predictive value is the proportion scoring positive that has the disease according to the gold standard, while the negative predictive value is the proportion of those with a negative test result, that is without the disease according to the gold standard. Separate analyses were carried out for ***possible*** heart failure (defined as the presence of either possible or definite heart failure according to the cardiologist) and ***definite*** heart failure (defined as the presence of definite heart failure according to the cardiologist). "Receiver operating characteristic" (ROC) curves were constructed to graphically display sensitivity and specificity at different cut-off levels for heart failure scores with a discrete numerical scale.[26,27] Data were analyzed using the STATA statistical package.

Results

The six scores for the classification of heart failure are presented in Table 2.1.1.[12-17] All scores incorporate information from medical history and physical examination. An electrocardiogram, though helpful, is not strictly necessary in the construction of the heart failure scores as tachycardia and atrial fibrillation can be assessed during physical examination. All but two scores,[13,17] require a chest X-ray. The Framingham Heart Study score is the only one to incorporate vital capacity. Three scores were developed for use in large epidemiological studies,[12,13,16] and the other scores were developed for studies on cardiovascular drugs.[14,15,17] Walma's score was specifically designed for use in general practice, a setting in which chest X-rays and electrocardiograms are not routinely available.[17]

The characteristics of the 54 study participants are presented in Table 2.1.3. On clinical grounds the cardiologist judged definite heart failure to be present in five persons and in another 12 persons, heart failure was considered possible. The five participants who were diagnosed with definite heart failure all had known coronary artery disease. Heart failure was relatively mild with only two participants being classified as NYHA III and none as NYHA IV. As expected, NYHA class and cardio-thoracic ratio on chest X-ray were higher and fractional shortening was lower in persons with definite heart failure compared to persons with no or possible heart failure. The low average heart rate in persons with definite heart failure can be ascribed to the use of beta-blockers by two of them at the time of examination. Mean peak flow rate in participants without heart failure was affected by chronic obstructive pulmonary disease.

Table 2.1.3. Characteristics of the participants included in the validation study of six heart failure scores. Means with standard error, or %.

		Cardiologist's diagnosis (gold standard)		
	All	No Heart Failure*	Possible Heart Failure*	Definite Heart Failure*
N	54	37	12	5
Age (yrs)	66.3 ± 0.8	65.1 ± 0.9	67.8 ± 1.4	71.5 ± 2.7
Men (%)	20 (37)	12 (32)	4 (33)	4 (80)
Height (m)	1.66 ± 0.01	1.65 ± 0.01	166.3 ± 0.02	168 ± 0.01
Weight (kg)	73.5 ± 1.7	71.0 ± 2.0	76.0 ± 3.7	86 ± 2.9
Heart rate (/min)	65.4 ± 1.4	63.9 ± 1.6	70.9 ± 3.0	62.8 ± 7.1
Systolic blood pressure (mm Hg)	133.6 ± 2.7	132.9 ± 3.5	134.1 ± 6.0	137.4 ± 5.7
Diastolic blood pressure (mm Hg)	84.5 ± 2.1	84.7 ± 2.3	82.8 ± 5.0	86.6 ± 10.0
Use of antihypertensive medication (%)	14 (26)	10 (27)	3 (25)	1 (20)
Myocardial infarction (%)†	8 (15)	4 (11)	1 (8.3)	3 (60)
Coronary artery disease (%)‡	15 (28)	4 (11)	6 (50)	5 (100)
Fractional shortening (%)§	39.3 ± 1.0 (n=48)	40.1 ± 1.1 (n=33)	37.9 ± 3.0 (n=11)	32.5 ± 3.0 (n=4)
E/A ratio	0.90 ± 0.03	0.91 ± 0.04	0.85 ± 0.06	0.92 ± 0.13
CT ratio chest X-ray	0.48 ± 0.01	0.47 ± 0.01	0.50 ± 0.02	0.53 ± 0.03
Peak flow rate (l/m)	375.0 ± 19.5	371.1 ± 22.9	365 ± 47.7	428 ± 59.4
COPD (%)¶	10 (19)	8 (22)	2 (17)	0
NYHA classification (score)	1.6	1.5	1.8	2.4

* Heart failure as assessed by cardiologist (JWD). Separate analyses were carried out for ***possible*** heart failure (defined as the presence of either possible or definite heart failure according to the cardiologist) and ***definite*** heart failure (defined as the presence of definite heart failure according to the cardiologist).

† Myocardial infarction on electrocardiogram or by history.

‡ History of myocardial infarction or angina pectoris, percutaneous transluminal angioplasty, coronary artery bypass grafting or presence of major electrocardiographic abnormalities (atrial fibrillation, myocardial infarction, left ventricular hypertrophy, severe repolarization abnormalities).

§ Fractional shortening at examination, missing values substituted by values at baseline examination Rotterdam Study (n=12) if available.

¶ Chronic obstructive pulmonary disease was considered to be present if participants were treated by a pulmonologist for COPD, were using bronchodilators / oral corticosteroids or had chest X-ray evidence of COPD.

Table 2.1.4a. Sensitivity, specificity, area under ROC curve (AUC) and predictive values of six heart failure scores for the detection of ***possible*** heart failure. ***Possible*** heart failure defined as the presence of either definite or possible heart failure according to the cardiologist. 95% confidence intervals in parentheses.

	Sensitivity	Specificity	AUC	Positive predictive value	Negative predictive value
Framingham Heart Study	0.71 (0.49 - 0.93)	0.89 (0.79 - 0.99)		0.75 (0.54 - 0.96)	0.87 (0.76 - 0.98)
Boston Score	0.41 (0.17 - 0.65)	0.97 (0.89 - 1.00)	0.77 (0.62 - 0.92)	0.88 (0.64 - 1.00)	0.78 (0.66 - 0.90)
Study of Men Born in 1913	0.76 (0.56 - 0.96)	0.76 (0.62 - 0.90)		0.59 (0.38 - 0.80)	0.88 (0.77 - 0.99)
Gheorgiade	0.47 (0.23 - 0.71)	0.95 (0.88 - 1.00)	0.85 (0.73 - 0.97)	0.80 (0.55 - 1.00)	0.80 (0.68 - 0.92)
NHANES	0.53 (0.29 - 0.77)	0.86 (0.75 - 0.97)	0.80 (0.66 - 0.94)	0.64 (0.39 - 0.89)	0.80 (0.68 - 0.92)
Walma	0.82 (0.64 - 1.00)	0.86 (0.75 - 0.97)	0.87 (0.75 - 0.99)	0.74 (0.54 - 0.94)	0.91 (0.82 - 1.00)

Table 2.1.4b. Sensitivity, specificity, area under ROC curve (AUC) and predictive values of six heart failure scores for the detection of ***definite*** heart failure. ***Definite*** heart failure defined as the presence of definite heart failure according to the cardiologist. 95% confidence intervals in parentheses.

	Sensitivity	Specificity	AUC	Positive predictive value	Negative predictive value
Framingham Heart Study	1	0.78 (0.66 - 0.90)		0.31 (0.08 - 0.54)	1
Boston Score	1	0.94 (0.87 - 1.00)	0.95 (0.82 - 1.00)	0.63 (0.30 - 0.96)	1
Study of Men Born in 1913	0.8 (0.45 - 1.00)	0.63 (0.49 - 0.77)		0.18 (0.02 - 0.34)	0.96 (0.89 - 1.00)
Gheorgiade	1	0.90 (0.82 - 0.98)	0.96 (0.84 - 1.00)	0.50 (0.19 - 0.81)	1
NHANES	1	0.82 (0.71 - 0.93)	0.96 (0.83 - 1.00)	0.36 (0.11 - 0.61)	1
Walma	1	0.71 (0.58 - 0.84)	0.89 (0.70 - 1.00)	0.26 (0.06 - 0.46)	1

Sensitivity, specificity, areas under the ROC-curve and predictive values of the different scores for the detection of heart failure, using the cardiologist's opinion as a gold standard, are presented in Table 2.1.4. All scores had a high sensitivity for the detection of ***definite*** heart failure, the Men Born in 1913 score being the only one that fell short of a sensitivity of 1. Gheorgiade's and the Boston score had a specificity of 0.9 or over to exclude ***definite*** heart failure. The study of Men Born in 1913 and Walma's score had the highest sensitivity for the detection of ***possible*** heart failure (defined as the presence of definite or possible heart failure according to the cardiologist).

The influence of the cut-off levels chosen to define the presence of heart failure on sensitivity and specificity is demonstrated by the ROC curves of the Boston score, Gheorgiade's score, NHANES score and Walma's score for the detection of ***possible*** or ***definite*** heart failure (Figure 2.1.1 and 2). For example a cut-off value of 3, as shown by the asterisk in the ROC curve in Figure 2.1.2 was arbitrarily chosen for the score used in Gheorgiade's digoxin stop study, resulting in values of 1 and 0.90 for sensitivity and specificity to detect ***definite*** heart failure. A higher cut-off value (4) resulted in decreased sensitivity (0.60) and increased specificity (0.96). Lowering the cut-off value to 2 gave a sensitivity of 1 and a specificity of 0.53. The areas under the curve, both for ***possible*** and ***definite*** heart failure, were comparable for the four scores. Positive predictive values of all six scores for the detection of ***possible*** heart failure were higher than those for ***definite*** heart failure, the reverse being the case for the negative predictive value (Table 2.1.4). Gheorgiade's and the Boston score had the highest positive predictive values for both ***possible*** and ***definite*** heart failure.

Discussion

The detection of (early stages of) heart failure is notoriously difficult. In a Finnish study all patients whom their general practitioner suspected of having heart failure were evaluated by a cardiologist before treatment was started.[20] In 46% heart failure was not present. Notably, chronic obstructive pulmonary disease, angina pectoris and obesity (especially in women) were mistaken for heart failure. The need to validate and standardize diagnostic criteria for heart failure has recently been stressed by task forces on heart failure of the National Heart Lung and Blood Institute (USA) and the European Society of Cardiology.[3,28]

In clinical trials, heart failure is usually defined using clinical criteria and NYHA classification,[29,30] or the presence of a low ejection fraction, e.g. less than 35%.[31] Despite its widespread use, the NYHA classification is prone to considerable interobserver variation.[32] Moreover, heart failure can be present in those with an ejection fraction over 40%. This may be caused by impaired diastolic function.[33-35] Conversely, persons with an ejection fraction under 40% may have no symptoms of heart failure at all.[36-38]

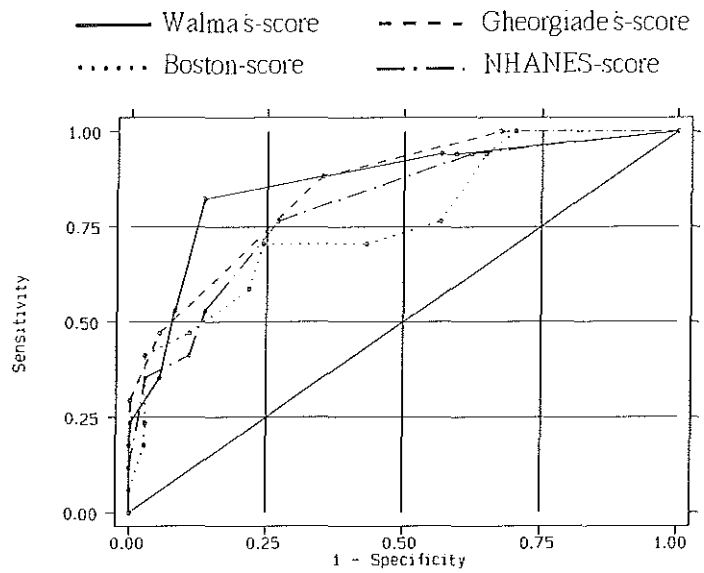

Figure 2.1.1. Receiver operating characteristics of Boston score, Gheorgiade's score, NHANES score and Walma's score for the detection of ***possible*** heart failure. ***Possible*** heart failure defined as the presence of either definite or possible heart failure according to the cardiologist.

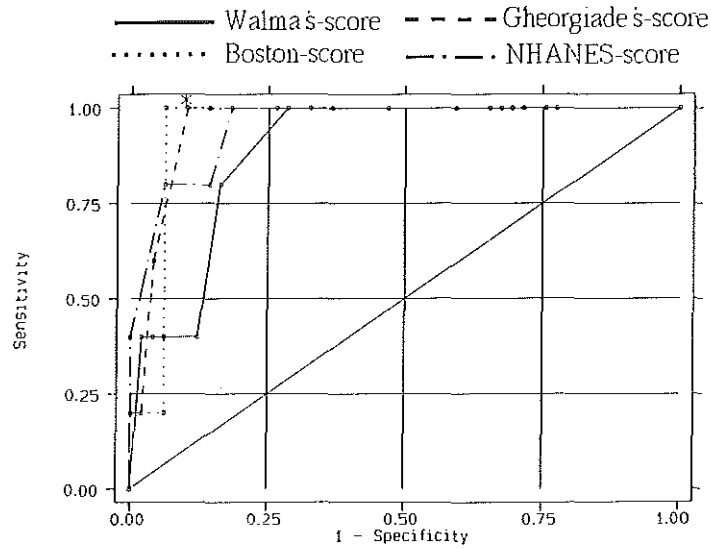

Figure 2.1.2. Receiver operating characteristics of Boston score, Gheorgiade's score, NHANES score and Walma's score for the detection of ***definite*** heart failure. ***Definite*** heart failure defined as the presence of definite heart failure according to the cardiologist.
* indicates cut-off level of 3 (Gheorgiade's score).

We evaluated six scores that have been proposed to determine the presence of heart failure, in a group of 54 carefully selected non-hospitalized subjects. Three scores have been validated to a certain extent.[12,13,15] In a group of 407 patients (mean age 64 years, 66% men), undergoing resting radionuclide ventriculograms, both sensitivity and specificity of the Framingham score to detect an ejection fraction $<= 40\%$ were 0.63.[39] The corresponding figures for the Boston score were 0.50 and 0.78. It has previously been demonstrated that a Boston score greater than 4 points has a 0.90 sensitivity for detecting a pulmonary capillary wedge pressure of 12 mmHg or greater in patients undergoing non-emergency right heart catheterization.[18] The score used by the study of Men Born in 1913 uses dyspnea on exertion as the main classification criterion. By using a scoring test, cardiac causes for dyspnea are separated from pulmonary causes of dyspnea.[13,40] Although the test to discriminate between cardiac and pulmonary causes of dyspnea has been validated, the scoring system for heart failure as such has not, to our knowledge.[41] No formal validation of the other three scores[14,16,17] has been reported.

Our preliminary findings suggest that, except for the score used in the Study of Men Born 1913, all scores have a high sensitivity for the detection of definite heart failure as defined by a cardiologist (Table 2.1.4). The sensitivity for the detection of possible heart failure was considerably lower for all scores, except for the score of Men Born in 1913 and Walma's score. Gheorgiade's and the Boston score showed the highest positive predictive values for both ***possible*** and ***definite*** heart failure.

Sensitivity and specificity of scores to detect heart failure are particularly important in population based studies and screening programs. A high sensitivity at the cost of a higher number of false positives can be justified in studies in which false positives can be detected by means of additional diagnostic procedures (e.g. echocardiography). The Study of Men Born in 1913 score relies heavily on the assessment of dyspnea, resulting in a relatively high percentage of false positives as many persons may have dyspnea without a cardiac cause. This may partly explain the higher prevalence of heart failure reported in Sweden compared to findings in the Framingham Heart Study.[1] Sensitivity and specificity of both the Framingham Heart Study and Boston scores for the detection of heart failure are higher than reported in a previous study.[39] This may in part be attributed to the use of a different gold standard.[39] Instead of ejection fraction $<40\%$, our study was based on a cardiologist's opinion as a gold standard. Thus, participants with clinical evidence of heart failure were classified as having heart failure, regardless of ejection fraction. Furthermore, our 54 participants were selected from the general population, whereas the validation of the Framingham Heart Study and Boston score took place in a hospital based setting.[39]

In day to day clinical practice positive and negative predictive values of a certain test are more important than sensitivity and specificity, as predictive values indicate the probability that the test results, whether positive or negative, provide the correct diagnosis. Because of their high positive predictive value for heart failure the Boston score and Gheorgiade's score appear to be the most useful for planning clinical interventions. The high rate of false positives when using the score of the Study of Men Born in 1913 is reflected in a low positive predictive value.

Some limitations of our study have to be addressed. Firstly, the number of participants was small, resulting in relatively wide confidence intervals of diagnostic properties, in particular for the diagnosis of definite heart failure. Secondly, we did not include criteria (circulation time, vital capacity) in this study that are not routinely used in the clinical diagnosis of heart failure. Thirdly, we used the Study of Men Born in 1913 score for selection of both male and female participants in our study, although the score has been developed for men only. However, no evidence is available to indicate that the score would perform differently in women. Finally, as a result of our sampling procedure the prevalence of heart failure and chronic obstructive pulmonary disease in our study group was higher than that in the general population. Although this will not affect the performance of the heart failure scores relative to each other, absolute values of sensitivity, specificity and predictive values may be different in the general population.

Interestingly, none of the six scores we addressed in this study encompassed a direct measure of cardiac function, e.g. by means of cardiac catheterization, nuclear ventriculography or (Doppler) echocardiography. Doppler echocardiography provides an efficient, noninvasive method of measuring cardiac function and has been recommended for diagnosis and management of heart failure, especially since the distinction between systolic and diastolic heart failure is difficult, when based on symptoms, signs and radiographic examination only.[33,42-44] In the near future there may also be a role for neurohormones in the detection of heart failure.[45,46]

The anticipated increase in number of patients with chronic heart disease, especially heart failure,[2] and the benefit of prompt and early treatment of heart failure[31,37,38,47,48] make it necessary to develop tools to detect heart failure in early stages and to provide reliable estimates of prevalence and incidence of heart failure in the general population using standardized, validated scoring systems. Efforts to fully characterize persons (at increased risk of) developing heart failure in the general population, both in terms of signs and symptoms at initial presentation and neurohumoral profile as well as Doppler echocardiographic characteristics appear warranted to gain more insight into early stages of this syndrome.

Out of the six scores we studied five (Framingham Heart Study, Gheorgiade, Boston, NHANES and Walma's score) are broadly similar in terms of capability to detect ***possible*** or ***definite*** heart failure. All scores have a high sensitivity for the detection of ***definite*** heart failure. Sensitivity for the detection of ***possible*** heart failure appears to be lower for all scores. For use in epidemiological research or in a primary care setting Walma's score is particularly attractive as it does not require a chest X-ray or electrocardiogram.

Given its atypical presentation and the low sensitivity of the scores for ***possible*** heart failure, an objective assessment of cardiac function (e.g. by echocardiography) appears useful in the detection of early stages of heart failure.[28] Widespread application of echocardiographic examination often is not feasible in large scale epidemiological studies. Application of one of the scores to all participants, followed by subsequent

objective measurement of cardiac function (e.g. by Doppler in combination with M-mode or two dimensional echocardiography) in participants scoring high on these lists probably is the most efficient method to assess the presence or absence of heart failure. Expert review of the available information (including follow-up information) on subjects identified as having (possible) heart failure by these methods may further enhance the accuracy of heart failure detection.

Addendum

In addition to the assessment of six previously described scores to classify heart failure, the diagnostic characteristics of the newly developed Rotterdam Study heart failure score were evaluated (Table 2.1.1). This score was used subsequently to estimate the prevalence of heart failure in the population-based Rotterdam Study (Chapter 3.1) and incorporates information from standardized questionnaires, electrocardiography, physical examination and review of specialists' records (for a detailed description, see Chapter 3.1.1).

The presence of shortness of breath at rest or on exertion,[21] ankle edema and pulmonary crepitations is verified. If at least two of these are present in combination with evidence of cardiac disease (angina pectoris,[21] myocardial infarction, documented coronary artery bypass surgery, documented percutaneous transluminal angioplasty, atrial fibrillation or electrocardiographic left ventricular hypertrophy), while shortness of breath could *not* be attributed to chronic obstructive pulmonary disease (as indicated by use of chronic obstructive pulmonary disease medication -ATC code r03-), heart failure was considered present. As such, the Rotterdam Study heart failure score follows the suggestions by the task force on heart failure of the European Society of Cardiology.[28] According to these guidelines objective evidence of cardiac dysfunction has to be present in addition to symptoms (e.g. shortness of breath or fatigue, at rest or during exercise, ankle swelling) to establish the presence of heart failure. Given the size of the study information from medical history and electrocardiography rather than echocardiography was used to establish the presence of cardiac dysfunction.

The sensitivity (0.8, 95% C.I. 0.45 - 1) and specificity (0.98, 95% C.I. 0.94 - 1) as well as the positive (0.8, 95% C.I. 0.45 - 1) and negative predictive value (0.98, 95% C.I. 0.94 - 1) of the Rotterdam Study score in the detection of ***definite*** heart failure compare favorably to the other heart failure scores studied. The accuracy of the assessment of heart failure in the Rotterdam Study is increased further by verification of the indication for cardiovascular medication use with the participant by the examining physician (see chapter 3.1.1).

References

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2.2. The routine 12 lead electrocardiogram in the detection of left ventricular dysfunction

Introduction

Heart failure is rapidly becoming one of the most common cardiovascular disorders and a further increase in its incidence is expected.[1] This may be partly attributed to improved survival related to the widespread use of angiotensin converting enzyme (ACE) inhibitors. The benefit of ACE inhibitors is not restricted to patients with overt heart failure, but extends to persons with mild heart failure and asymptomatic left ventricular (LV) dysfunction. Echocardiography has been recommended as the method of choice to detect LV dysfunction.[2] Although most heart failure patients are detected and treated by general practitioners, routine application of (Doppler) echocardiography in general practice is limited by costs and low accessibility of echocardiographic services. A recent study described the value of the routine 12 lead electrocardiogram for the detection of LV systolic dysfunction.[3] In the absence of major electrocardiographic abnormalities the probability of LV systolic dysfunction was negligible (negative predictive value 98%).

The sensitivity of electrocardiography to detect LV dysfunction was estimated to be as high as 94%. It was concluded that Doppler echocardiographic examination could be withheld in subjects without major electrocardiographic abnormalities, as only 6% (1 - sensitivity) of persons with LV dysfunction would be missed. The study was carried out in a relatively selected group of 534 persons who had been referred to an open access echocardiography service by their general practitioner. Since characteristics of diagnostic procedures differ according to disease severity and patients studied, we set out to confirm the value of the electrocardiogram to detect LV systolic dysfunction in a large population-based sample.

Methods and results

The present study was part of the Rotterdam Study, a prospective follow up investigation in 7,983 persons aged 55 years or older.[4] Baseline measurements included 12 lead electrocardiography and Doppler echocardiography. Electrocardiograms were digitally stored and analyzed using the MEANS program, a validated software program.[5] The electrocardiogram was considered abnormal in the presence of atrial fibrillation or flutter, myocardial infarction, LV hypertrophy, bundle branch block, or left axis deviation. Left ventricular end diastolic and end systolic dimensions were measured from M-mode recordings. Fractional shortening ((LVEDD - LVESD)/LVEDD x 100%) was used as an index of LV systolic function. Impaired LV systolic function was deemed present if fractional shortening was $< 25\%$, comparable to a LV ejection fraction of 42.5%.[6]

In 1,980 participants (mean age 65.6 years (SD 7.5), 45% men) complete electrocardiographic and echocardiographic data were available. Major electrocardiographic abnormalities were present in 441 participants (22.2%) and impaired LV systolic function in 59 participants (3.0%) (Table 2.2.1).

Table 2.2.1. Electrocardiographic findings and LV systolic function in 1921 persons.

	Impaired left ventricular systolic function§	Preserved left ventricular systolic function	Total
Abnormal electrocardiogram	32	409	441
Normal electrocardiogram*	27	1512	1539
Total	59	1921	1980

Sensitivity: 32 / 59 = 54% (41-67%) Positive predictive value: 32 / 441 = 7% (5-10%)
Specificity: 1512 / 1921 = 79% (77-81%) Negative predictive value: 1512 / 1539 = 98% (97-99%)
95% confidence intervals in parentheses.

* Normal electrocardiogram, i.e. absence of major electrocardiographic abnormalities (see text)
§ Impaired LV systolic function defined as fractional shortening less than 25%

Separate analyses were performed for the 522 persons aged 70 years or over (since heart failure is more prevalent at higher age) and for the 865 participants with a high prior probability of heart failure (Tables 2.2.2 and 3, respectively). The latter group was defined as persons who received treatment for hypertension, reported dyspnea on exertion (in the absence of pulmonary medication), prior myocardial infarction, angina pectoris, a history of coronary artery bypass surgery, percutaneous transluminal angioplasty or were found to have ankle edema. The prevalence of LV dysfunction was higher in subjects > 70 years of age (4.2%) and subjects at increased risk of heart failure (4.5%).

Table 2.2.2. Electrocardiographic findings and LV systolic function in persons aged 70 years or older.

	Impaired left ventricular systolic function	Preserved left ventricular systolic function	Total
Abnormal electrocardiogram	14	178	192
Normal electrocardiogram	7	323	330
Total	21	501	522

Sensitivity: 14/21 = 67% (43-85%) Positive predictive value: 14/192 = 7% (4-12%)
Specificity: 323/501 = 64% (60-69%) Negative predictive value: 323/330 = 98% (96-99%)

Table 2.2.3. Electrocardiographic findings and LV systolic function in persons at increased risk of heart failure.

	Impaired left ventricular systolic function	Preserved left ventricular systolic function	Total
Abnormal electrocardiogram	25	220	245
Normal electrocardiogram	14	606	620
Total	39	826	865

Sensitivity: 25/39 = 64% (47-79%) Positive predictive value: 25/245 = 10% (7-15%)
Specificity: 606/826 = 73% (70-76%) Negative predictive value: 606/620 = 98% (96-99%)

Of participants with a normal electrocardiogram, 98% had no evidence of LV systolic dysfunction (negative predictive value). Of all participants with echocardiographically determined LV systolic dysfunction electrocardiographic abnormalities were observed in 54% (sensitivity) in our population-based study. Sensitivity was higher in participants aged 70 years or over and high risk participants (67% and 64%, respectively), whereas the negative predictive value remained unchanged. Positive predictive value was less than or equal to 10% in all groups.

Discussion

In this population-based study we confirmed the high negative predictive value of the electrocardiogram to demonstrate the absence of LV dysfunction.[3] In our study however, withholding echocardiography in the absence of major electrocardiographic abnormalities would lead to 46% (1 - sensitivity) of persons with LV dysfunction remaining unrecognized. This proportion was lower, but nevertheless appreciable, in persons > 70 years of age and persons at increased risk of heart failure (33% and 36%, respectively). The lower sensitivity in our study compared to the recent report by Davie et al is attributable to differences between the study populations. Our results are based on a general population sample, whereas the patients of Davie et al were suspected to have LV dysfunction.[3] The prevalence of LV dysfunction was low in our study, both overall and in the two subgroups studied. This probably reflects the fact that our study comprised relatively healthy persons, in whom ejection fraction is known to change little with increasing age.[7] The low positive predictive value of the electrocardiogram in detecting LV dysfunction relates to the low prevalence of LV dysfunction. Accordingly, the value of the electrocardiogram to uncover LV dysfunction in population based studies appears to be minimal.

Withholding echocardiography in persons without major electrocardiographic abnormalities would therefore result in a considerable underestimation of the prevalence of LV systolic dysfunction in population-based studies. We conclude that, although the electrocardiogram remains useful in the diagnostic process to exclude the presence of LV dysfunction, echocardiography is an essential tool to detect LV dysfunction in population-based studies.

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2.3. Multifrequency bioimpedance analysis of body water in previously unsuspected heart failure

Introduction

Bioelectrical impedance measurement provides a straightforward, simple and inexpensive technique to study body composition.[1] Various studies have demonstrated the use of bioelectrical impedance in the estimation of fat free mass and total body water.[2-4] Furthermore, recent studies have suggested that, by using multifrequency bioimpedance measurements, (changes in) intracellular and extracellular water compartments may be estimated.[5-7] The impedance method is based on the principle that water is the only medium in the body that conducts electricity. The volume of body water is related to the length of the conductor (approximated by height) squared divided by impedance to electrical current. Both intracellular and extracellular water offer resistance to the flow of current. At low frequency (<5 kHz) electrical currents cell membranes act as small capacitators preventing the current from entering the cells. At higher frequencies, however, the membrane resistance is short-circuited and electrical current is conducted through both the intracellular space and extracellular space. This results in a reduction in impedance to flow of current compared with lower frequencies and allows both total body water and extracellular water to be estimated.

Fluid retention is one of the key features of heart failure, a clinical syndrome for which no gold standard or generally accepted definition is available.[8] Heart failure has been defined by Packer as "a complex clinical syndrome characterized by abnormalities of left ventricular function and neurohumoral regulation, which are accompanied by effort intolerance, fluid retention and reduced longevity".[9] Heart failure is rapidly becoming one of the most prevalent cardiovascular disorders and a further increase in the incidence of heart failure is expected.[10,11]

To our knowledge, no studies on multifrequency bioimpedance measurements of extracellular and total body water in heart failure have been published to date. The goal of this study was to assess the use of bioimpedance measurements of extracellular and total body water to detect heart failure in persons drawn from the general population.

Methods

Study population This was a cross-sectional study in a group of 54 participants of the Rotterdam Study, participating in a validation study of six heart failure scores used in epidemiological research.[12] The Rotterdam Study is a population-based follow-up study of 7,983 inhabitants aged 55 years or older living in the Rotterdam suburb of Ommoord. The design of the study has been described in detail elsewhere.[13] Baseline measurements were carried out from March 1990 to July 1993 and the overall response rate was 78%.

The participants for the present study were recruited from the first 308 participants of the Rotterdam Study (113 men and 195 women, mean age at baseline examination 67.0 (SD 7.7) and 67.1 (SD 8.3) years respectively) who answered all questions included in the heart failure score developed for the "Study of Men Born in 1913".[14]

In the selection of 60 persons younger than 75 years who were invited to participate in the present study, efforts were made to include persons with chronic obstructive pulmonary disease, a condition frequently accounting for false positive diagnoses of heart failure,[15] and to include sufficient numbers of persons suspected of having heart failure. 24 persons were randomly selected from the group with heart failure stage 0 (no heart failure) according to the Study of Men Born in 1913 score (12 persons from those with dyspnea and twelve persons from those without dyspnea), twelve were randomly selected from the group with heart failure stage 1 (possible heart failure) and finally 24 persons were invited from the group having definite heart failure (stage 2 and 3) according to the Men Born in 1913 score. In total, 56 (93.3%) persons agreed to participate. Two of them, both with definite heart failure according to the Men Born in 1913 score, were ultimately not able to attend because of symptoms severely limiting their activities of daily life. Inspection of the general practitioners records showed that both persons had diagnosed congestive heart failure.

The study was approved by the Medical Ethics Committee of the University Hospital Rotterdam. All participants gave informed consent.

Measurements All participants were evaluated within a five day time span. During a two hour visit to the research center all participants underwent the following tests.

- *History*. A trained interviewer administered a standardized questionnaire on cardiac and relevant non-cardiac medical history (e.g. pulmonary disease, diabetes mellitus, renal and hepatic diseases) and current medication use. Information on chest pain and dyspnea was obtained by means of the WHO questionnaires.[16]
- *Weight, height, waist-hip ratio and blood pressure measurements.* Height (centimeters) and weight (kilograms) were measured with participants wearing light clothes and without shoes. Body mass index(kg/m^2) was calculated as $weight/(height/100)^2$. Waist and hip circumference were measured to calculate waist-hip ratio as a measure of obesity. Blood pressure was measured on the right arm with the participant in sitting position using a random zero sphygmomanometer. The average value of two consecutive blood pressure readings was taken as the blood pressure value.
- *Standardized physical examination* was carried out by a cardiologist to verify the presence of dyspnea, jugular venous distension, rales and rhonchi, a third or fourth heart sound, cardiac murmurs, hepatomegaly and ankle edema.
- *Bioelectrical impedance analysis.* Using a Humanim, multifrequency impedance analyzer (Dietosystem, Milan, Italy) bioelectrical impedance was measured at multiple frequencies (ranging from 0.3 kHz to 100 kHz) at the left side of the body and electrodes placed as described by Lukaski et al.[17] Participants had been fasting at least 3 hours prior to bioimpedance measurement and measurements were performed after voiding. The amount of extracellular water, total body water and fat free mass was estimated by prediction formula's (see appendix).[18,19]
- *Peak expiratory flow* was measured using a mini Wright peak flow meter. The highest value of three consecutive measurements was used in the analysis.

Table 2.3.1. Characteristics of the participants. Mean values with standard deviation, or %.

		Cardiologist as gold standard	
	All (n = 54)	No Heart Failure* (n = 49)	Definite Heart Failure* (n = 5)
Age (yrs)	66.3 ± 5.8	65.8 ± 5.6	71.5 ± 6.0
Men (%)	20 (37)	16 (33)	4 (80)
Height (m)	1.66 ± 0.7	1.65 ± 0.7	1.68 ± 0.2
Weight (kg)	73.5 ± 12.5	72.2 ± 12.3	86 ± 6.4
Body mass index (kg/m^2)	26.7 ± 3.8	26.3 ± 3.7	30.5 ± 2.4
Waist-hip ratio	0.85 ± 0.09	0.84 ± 0.08	0.92 ± 0.14
Heart rate (/min)	65.4 ± 10.5	65.6 ± 10.0	62.8 ± 15.9
Systolic blood pressure (mm Hg)	133.6 ± 20.4	133.2 ± 21.1	137.4 ± 12.7
Diastolic blood pressure (mm Hg)	84.5 ± 15.4	84.3 ± 14.8	86.6 ± 22.4
Use of antihypertensive medication (%)	14 (26)	13 (27)	1 (20)
Use of diuretics	14 (26)	14 (29)	0
Use of ACE inhibitors	2 (4)	1 (2)	1 (20)
Myocardial infarction (%)†	8 (15)	5 (10)	3 (60)
Coronary artery disease (%)‡	15 (28)	10 (20)	5 (100)
CT ratio chest X-ray	0.48 ± 0.05	0.47 ± 0.05	0.53 ± 0.06
Fractional shortening§	39.3 ± 7.1 (n=48)	39.9 ± 6.9 (n=44)	32.5 ± 6.0 (n=4)
NYHA classification	1.6	1.6	2.4
COPD (%)¶	10 (19)	10 (20)	0
Peak flow rate (l/m)	375 ± 143	369.6 ± 144	428 ± 134

* Participants (n=12) who were considered to have possible heart failure were classified as no heart failure for the purpose of this analysis.
† Myocardial infarction on electrocardiogram or by history.
‡ History of myocardial infarction or angina pectoris, percutaneous transluminal angioplasty, coronary artery bypass grafting or presence of major electrocardiographic abnormalities (atrial fibrillation, myocardial infarction, left ventricular hypertrophy, severe repolarization abnormalities).
§ Fractional shortening at examination, missing values substituted by values at baseline examination Rotterdam Study (n=12) if available.
¶ Chronic obstructive pulmonary disease was considered to be present if participants were treated by a pulmonologist for COPD, were using bronchodilators / oral corticosteroids or had chest X-ray evidence of COPD.

- A *standard 12-lead electrocardiogram (ECG)* was recorded using an ESAOTE laptop electrocardiograph (Florence, Italy). All ECG's were digitally stored and analyzed using the MEANS program, a standardized and validated ECG software program.[20] Computer generated diagnoses were verified by a cardiologist.
- *Frontal and lateral chest X-rays* were made at maximal inspiration in standing position using General Electric MPG-50 X-ray equipment. All chest X-rays were reviewed, using a standardized scoring form, by a radiologist who was blinded to the clinical information. Cardio-thoracic ratio was calculated[16] and the absence or presence of pleural effusion, upper zone flow redistribution, alveolar or interstitial edema and signs of chronic obstructive pulmonary disease was assessed.
- *M-mode echocardiography* was performed with a 2.25 MHz transducer (ATL Ultra Mark 4). 2-Dimensional imaging was performed to aid M-mode studies. Left ventricular internal dimension (LVIDed) at end diastole, as defined by the onset of the QRS complex, and at end systole (LVIDes), as defined by the nadir of septal motion, was measured.[21] The percentage fractional shortening, calculated as 100[(LVIDed - LVIDes)/LVIDed], was used as an index of systolic function.

Classification of heart failure

The cardiologist was asked explicitly to classify participants as having no, possible or definite heart failure using all clinical information obtained at the research center (including his own medical history taking and echocardiographic data). In addition, the cardiologist graded participants according to New York Heart Association (NYHA) class.[22] Classification and grading was done without knowledge of the bioimpedance findings. For the analysis of bioimpedance data persons with definite heart failure were compared to those classified as having either no or possible heart failure.

Statistical methods

Relations of selected variables to extracellular and total body water were studied using linear regression analysis. Age, gender and height adjusted values of extracellular and total body water were calculated using the coefficients obtained in the linear model. Data were analyzed using the STATA statistical package.

Results

The characteristics of the 54 participants are presented in Table 2.3.1. On clinical grounds the cardiologist judged heart failure to be present in five persons and possible in another twelve persons. The five participants who were diagnosed as having definite heart failure had known coronary artery disease, but were not treated for heart failure at the time of the study. One of them was using an angiotensin converting enzyme inhibitor because of hypertension, in combination with digoxin for atrial fibrillation. However, this person was not on diuretics, the treatment of choice (at time of the study) for heart failure in general practice. Heart failure was relatively mild in subjects participating in this study, only two participants were classified as NYHA III and no one as NYHA IV. As expected, NYHA class and cardio-thoracic ratio on chest X-ray were higher and fractional

shortening was lower in persons with definite heart failure compared to persons with no or possible heart failure. The low average heart rate in persons with definite heart failure can be ascribed to the use of beta-blockers by two of them at the time of examination. Mean peak flow rate in the no heart failure group was affected by persons with chronic obstructive pulmonary disease.

Body composition of participants in the no heart failure group appeared to be essentially normal, with total body water constituting 54.0% and 47.7% of body weight in men and women respectively. Mean fat free mass was estimated at 53.0 kg in men and 49.9 kg in women. Mean volume of extracellular and total body water was appreciably higher in persons with definite heart failure (Table 2.3.2). As this difference may be explained by other factors than the presence or absence of heart failure, the relation of extracellular and total body water to selected variables (gender, age, height, waist-hip ratio, coronary artery disease and use of diuretics or ACE-inhibitors) was studied. Gender, height, waist-hip ratio and presence of heart failure were strongly related to both extracellular and total body water. After adjustment for gender and height the association of waist-hip ratio to extracellular and total body water disappeared. Mutually adjusting for height, gender and presence of heart failure, extracellular water was 1.8 liters (95% confidence interval (CI) 1.0 - 2.6) higher in men than in women, and extracellular water was 0.15 liter (95% CI 0.09 - 0.20) higher for each centimeter increase in height. Corresponding figures for total body water were 5.5 (95% CI 2.9 - 8.2) and 0.4 liter (95% CI 0.2 - 0.6).

Following adjustment for gender, height and presence of heart failure neither extracellular nor total body water was related to age, presence of coronary artery disease or use of diuretics or ACE-inhibitors. After adjustment for differences in gender, height and age, the presence of heart failure was still associated with higher extracellular and total body water volumes, 1.2 (95% CI 0.2 - 2.3, p 0.03) and 3.3 (95% CI 0.0 - 6.7, p 0.05) liters, respectively (Table 2.3.2).

Table 2.3.2. Estimates of extracellular and total body water based on multifrequency bioimpedance measurements, in persons with and without heart failure. Values are means ± s.e.

	Cardiologist as gold standard	
	No Heart Failure* (n = 49)	Definite Heart Failure* (n = 5)
Extracellular water (l)	14.6 ± 0.3	17.0 ± 0.7
Total body water (l)	35.1 ± 0.9	41.8 ± 2.2
Adjusted for age, gender and height†:		
Extracellular water (l)	14.7 ± 0.1	15.9 ± 0.6
Total body water (l)	35.4 ± 0.4	38.7 ± 1.8

* Heart failure as assessed by cardiologist. Participants (n=12) who were considered to have possible heart failure were classified as no heart failure for the purpose of this analysis.

† Adjustment using mean values and coeffients from linear regression model, e.g.:
$ECwater_{adj} = ECwater - (\beta_{age}*(age - age_{mean})) - (\beta_{sexe}*(sexe - sex_{mean})) - (\beta_{height}*(height - height_{mean}))$.

Using the coefficients obtained in a multiple linear regression model we calculated age, height and gender adjusted values for extracellular and total body water (Tables 2.3.3 and 4, Figures 2.3.1 and 2) and tentatively explored the potential use of bioimpedance estimates of body water for detection of heart failure. At a cut-off level of 14.9 liters (extracellular water), sensitivity and specificity for heart failure were 0.80 (95% CI 0.45 - 1.00) and 0.63 (95% CI 0.49 - 0.77). A cut-off level of 36.4 liters (total body water) resulted in values of 0.80 (95% CI 0.45 - 1.00) and 0.59 (95% CI 0.45 - 0.73) for sensitivity and specificity, respectively.

Table 2.3.3. Sensitivity (0.8, 95% CI 0.45 - 1.00) and specificity (0.63, 95% CI 0.49 - 0.77) for the detection of heart failure using 14.9 liters extracellular water as cut-off.

Extracellular water (liters)	Heart failure absent	Heart failure present	Total
< 14.9 liters	32	1	33
> = 14.9 liters	17	4	21
Total	49	5	54

Table 2.3.4. Sensitivity (0.8, 95% CI 0.45 - 1.00) and specificity (0.59, 95% CI 0.45 - 0.73) for the detection of heart failure using 36.4 liters total body water as cut-off.

Total body water (liters)	Heart failure absent	Heart failure present	Total
< 36.7 liters	29	1	30
> = 36.7 liters	20	4	24
Total	49	5	54

An additional analysis was carried out to examine the group classified as having possible heart failure by the cardiologist. Mean values of extracellular (14.7 liters, 95% CI 14.2 - 15.1) and total body water (35.4 liters, 95% CI 34.2 - 36.7), adjusted for differences in gender, height and age, in these participants did not differ significantly from values of persons without heart failure (14.7 liters, 95% CI 14.4 - 15.1 and 35.4 liters, 95% CI 34.3 - 36.5).

Discussion

We studied the use of multifrequency bioimpedance measurement of extracellular and total body water in the detection of heart failure in 54 persons drawn from the general population. Following an extensive examination, five participants were found to have heart failure by a cardiologist. None of them was known to have heart failure. Water retention is one of the key features of heart failure, usually demonstrated by evidence of pedal or sacral edema or crepitations on auscultation of the lungs. Edema is a manifestation of an increase in interstitial volume, manifest clinically if more than 1,5 - 3 liters is retained.[23] Accordingly, in our study the presence of heart failure had a somewhat stronger association with an increase in extracellular than total body water.

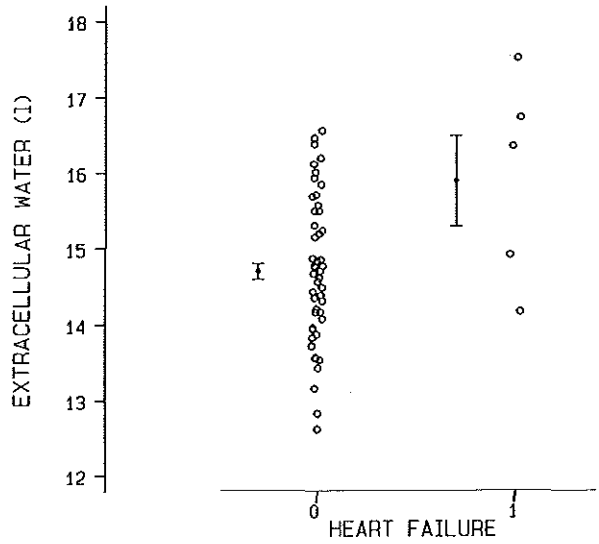

Figure 2.3.1. Extracellular water in persons with (n=5) and without (n=49) heart failure. Values are adjusted for age, gender and height.
Mean value ± 1 standard error is indicated by bars.

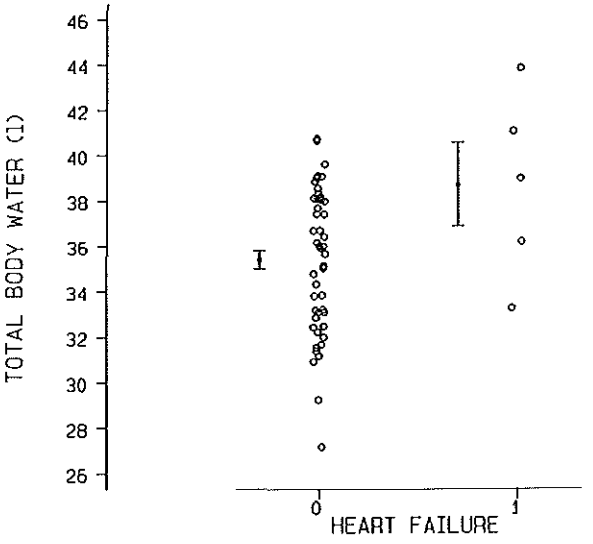

Figure 2.3.2. Total body water in persons with (n=5) and without (n=49) heart failure. Values are adjusted for age, gender and height.
Mean value ± 1 standard error is indicated by bars.

Average weight was 14 kilograms higher in the heart failure group, 48% (6.7 liters) of which could be attributed to total body water. In the absence of heart failure one would expect only 20% of the difference in weight to be caused by water; the remaining 80% by fat, assuming there is no difference in muscle mass. If anything, heart failure patients can be expected to have a lower muscle mass because of the physical deconditioning associated with the syndrome. After adjustment for differences in gender, height and age total body water persistently accounted for more than 20% of the difference in weight between groups.

Gender, height and heart failure were found to be the most important determinants of extracellular and total body water. After adjustment for gender, age and height bioimpedance measurement indicated that extracellular water was 1.2 liters (95% CI 0.2 - 2.3) higher and total body water was 3.3 liters (95% CI 0.0 - 6.7) higher in the heart failure group. While adjustments were made for height, we decided not to adjust for weight, as this would have resulted in non significant differences in extracellular and total body water between groups, attributable to overcorrection because of the strong relation of water to weight.

Recent developments in treatment have increased the value of early detection and treatment of heart failure, in order to postpone or prevent complications and prolong survival.[24] Detection of early stages of heart failure is hampered by the relatively atypical presentation, the complexity of the syndrome and lack of consensus on a definition of heart failure.[15,25] In a Finnish study all patients whom their general practitioner suspected of having heart failure were evaluated by a cardiologist before treatment was started.[15] In 46% heart failure was deemed not present. Notably, chronic obstructive pulmonary disease, angina pectoris and obesity (especially in women) were mistaken for heart failure. The anticipated increase in patients with chronic heart disease, especially heart failure,[11] makes it necessary to develop reliable tools to detect heart failure in early stages. Echocardiography provides an efficient, noninvasive method of measuring cardiac function and has been recommended for diagnosis and management of heart failure.[26] Unfortunately, echocardiographic examination often is not feasible in large scale epidemiological studies and in general practice.

We studied the use of multifrequency bioimpedance measurements, a method providing directly interpretable results and not requiring specially trained observers, in the detection of heart failure. The main limitation of our study relates to the small number of participants, including only five persons deemed to have definite heart failure, resulting in relatively large confidence intervals. Nevertheless, our study indicates that there may be a role for bioimpedance measurements of extracellular and total body water in the detection of heart failure in persons before treatment is initiated. The role of bioimpedance measurements to monitor fluid balance in persons with heart failure once treatment has started also appears to merit attention.

Appendix

Prediction formula's for extracellular water,[18] total body water,[18] and fat free mass[19] using bioimpedance measurements.

extracellular water (liters) = $0.24253*\text{height}^2/\text{imp}_{1000} + 4.1$,

total body water (liters) = $0.51303*\text{height}^2/\text{imp}_{100000} + 6.3$,

fat free mass (kilograms) = $0.340*\text{height}^2/\text{imp}_{50000} + 0.1534*\text{height} + 0.273*\text{weight} - 0.127*\text{age} + 4.56*\text{sex} - 12.44$.

Imp_{1000} is impedance at 1000 Hz, sex is a dummy variable (0 woman, 1 man).

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2.4. Changes in mitral flow with age: a cross-sectional and longitudinal analysis

Introduction

Transmitral flow velocity, as measured by Doppler echocardiography, reflects left ventricular filling dynamics and instantaneous pressure differences between the left atrium and ventricle.[1,2] Although Doppler echocardiography does not provide direct information on intracardiac pressures, the method has been used widely for indirect noninvasive assessment of diastolic function of the heart.[3-5] The contribution of diastolic dysfunction to cardiac diseases, in particular heart failure, is increasingly being recognized.[6,7] Many factors have been shown to influence transmitral flow, including age,[8-18] loading conditions of the heart,[19-22] systolic function,[18,23] heart rate,[15,16,18,24-26] and PR interval.[26,27]

The Framingham Heart Study reported age to be the predominant determinant of Doppler indices of left ventricular diastolic function in a sample of 127 healthy subjects with a mean of age 50 years, reducing early and increasing late diastolic inflow velocities.[15] The age-related decline in peak early velocity E (PVE) concomitant with an increase in peak late -atrial- velocity A (PVA), resulting in a decline in peak velocity E/A ratio (EAR), has been reported in other cross-sectional studies of mitral flow as well.[8-18]

Cross-sectional studies, however, may give a biased estimate of the true change, for example as a result of survivor bias.[28-30] To our knowledge, information on longitudinal changes in mitral flow patterns in individuals drawn from a non hospitalized population has not been published to date. We set out to to obtain cross-sectional estimates of changes in mitral flow patterns with age in a large group and compare them to prospectively obtained longitudinal estimates in a sample of this group.

Methods

Study population. Subjects were recruited from participants of the Rotterdam Study. The Rotterdam Study is a population-based follow-up study on prevalence, incidence and determinants of chronic disabling diseases in 7,983 persons aged 55 years or older living in the Rotterdam suburb of Ommoord. Cardiovascular, neurologic, locomotor and ophthalmologic diseases form the core interest of the Rotterdam Study, the design of which has been described in detail elsewhere.[31] Baseline measurements, including medical history, a brief physical examination, 12-lead electrocardiography and Doppler echocardiography, were carried out from March 1990 to July 1993 and the overall response rate was 78%. The Rotterdam Study was approved by the Medical Ethics Committee of the Erasmus University Medical School. All participants gave informed consent.

A total of 1246 Participants, all younger than 71 years, underwent Doppler echocardiography at their baseline examination in 1992 and 1993. As mitral flow may be altered in the presence of impaired left ventricular systolic function,[32] 312 persons, whose fractional shortening was less than the 25th percentile, were excluded, leaving a group of 933 participants. Baseline information in a random sample of 500 participants of this group was used to obtain cross-sectional estimates of change in mitral flow parameters with age. In addition, another random sample of 50 participants was drawn for a

longitudinal assessment of mitral flow changes with age. At the Rotterdam Study research center those subjects underwent the following tests during a 2 hour follow-up visit, that on average took place 1.1 years after the baseline examination.

- *Medical history and standardized physical examination.* One physician (AM) verified medical history, in particular events that occurred since the baseline examination, and obtained information on cardiac and relevant non-cardiac history and current medication use. A physical examination was carried out and blood pressure was measured using an automated blood pressure device (Dinamap model 8100, Criticon, Florida). The average value of two consecutive blood pressure readings was taken as the blood pressure value. Height and weight were measured with subjects wearing light clothes and without shoes.
- A *standard 12-lead electrocardiogram (ECG)* was recorded using an ESAOTE laptop electrocardiograph (Florence, Italy). All ECG's were digitally stored and analyzed using the MEANS program, a standardized and validated ECG software program.[33] Computer generated diagnoses were verified by a cardiologist.
- *M-mode echocardiography* was performed with the participant in the partial left decubitus position, using a 2.25 MHz transducer (ATL Ultra Mark 4). 2-Dimensional imaging using parasternal long-axis views was performed to aid M-mode studies. Measurements were made according to the recommendations of the American Society of Echocardiography using a leading edge to leading edge convention.[34] Left ventricular internal dimension (LVIDed) was measured at end diastole as defined by the onset of the QRS complex and at end systole (LVIDes) as determined at the nadir of septal motion. The percentage fractional shortening (FS) was calculated as 100[(LVIDed - LVIDes)/LVIDed] and used as an index of systolic function.[35]
- *Doppler echocardiography.* From the apical 4-chamber view mitral flow was sampled at the mitral valve leaflet tips using a 2.25 MHz pulsed wave Doppler probe (ATL Ultra Mark 4). Doppler echocardiography was performed during quiet respiration using a standardized protocol. Baseline recordings of the 50 participants were made by two technicians. The technician who performed all follow-up examinations, had done 16 of the baseline examinations. After initial recording on videotape, mitral flow contours of 5 representative beats, preferrably consecutive, were traced off-line. Peak early diastolic inflow velocity (E, m/s) and peak late diastolic inflow velocity (A, m/s) were measured and averaged using dedicated software, that also provided the ratio of early to late diastolic inflow velocity (E/A ratio). Tracing of both baseline and follow-up mitral flow recordings of the 50 longitudinal study participants was done in random order by one person (BC), who was blinded to clinical information and date of recording. Persons who had suffered a major cardiovascular event (stroke, bypass surgery, myocardial infarction) in the interim (n=1, silent myocardial infarction), with significant valvular abnormalities (n=1, severe aortic regurgitation) and two persons in whom Doppler echocardiographic recordings were inadequate at follow-up were excluded from the analysis.

Electrocardiographic and Doppler echocardiographic procedures at baseline and follow-up visits were identical. Mitral flow recordings of persons other than those included in the longitudinal study were traced by a different observer (JS). Blood pressure

at baseline was the average value of two consecutive measurements by a research nurse, using a random zero mercury sphygmanometer. Cardiovascular medication was defined as the use of diuretics, ß blocking agents, calcium channel blocking agents, ACE inhibitors, nitrates, glycosides, antiarrhythmics, platelet aggregation inhibitors or oral anticoagulants. Furthermore the indication for cardiovascular medication use was verified with participants (e.g. hypertension, angina pectoris etc).

Statistical methods. Data were analyzed using the STATA statistical package. Change in study parameters was calculated by subtracting the baseline value from the follow-up value. Using the baseline data of 500 participants, linear regression analysis was performed to obtain a cross-sectional estimate of change in mitral flow parameters per year increase of age. Those estimates were compared to both cross-sectional (baseline visit) and longitudinal estimates in the 50 participants of the follow-up study. Longitudinal estimates were obtained by dividing change in mitral flow parameters by follow-up time in years. Multivariate linear regression analysis was used to adjust for differences in previously identified determinants of mitral flow (body mass index, heart rate, systolic blood pressure, systolic function and duration of PR interval). The Student's t-test was used to test for differences in changes in mitral flow parameters between the two echo technicians who performed the baseline examination and between participants who were on any cardiovascular medication versus those who were not.

Results

Baseline characteristics of the participants are presented in Table 2.4.1. The longitudinal results of this study are based on a comparison of mitral flow data of 46 subjects obtained at baseline and at follow-up, on average 1.1 years later (95% C.I. 1.0 - 1.2).

Table 2.4.1. Baseline characteristics of study participants.

	Cross-sectional study group* (n = 500)	Longitudinal study group† (n = 46)
Age (years)	61.9 (± 4.0)	61.7 (± 4.0)
Men (%)	47	50
Height (cm)	170 (± 9)	170 (± 8)
Weight (kg)	75 (± 12)	72 (± 9)
Myocardial infarction (%)‡	7	4
Coronary artery disease (%)§	10	7
Use of antihypertensive medication (%)	12	15
Use of cardiovascular medication (%)¶	8	9

Values are group means ± 1 standard deviation or percentages.

* Characteristics of 500 Rotterdam Study participants used to provide cross-sectional estimates of changes in mitral flow with age.

† Characteristics of 46 Rotterdam Study participants who participated in a follow-up study to provide longitudinal estimates of changes in mitral flow with age.

‡ Myocardial infarction on electrocardiogram or by history.

§ History of myocardial infarction, angina pectoris, percutaneous transluminal angioplasty, coronary artery bypass grafting or myocardial infarction on ECG.

¶ Other than for treatment of hypertension

Table 2.4.2 provides mean values of mitral flow parameters in 500 Rotterdam Study participants and demonstrates a progressively lower peak mitral flow E/A ratio with increasing age. For comparison, values in healthy persons aged 60 to 70 years in two previous studies are provided; the population-based Framingham Heart Study and a multicenter study from Italy.[15,17] Peak mitral flow velocity E/A ratio is remarkably similar in the three studies, whereas absolute values for peak early (E) and late (A) mitral flow are higher in our study.

Baseline and follow-up values of three frequently used indices of left ventricular diastolic function are presented in Table 2.4.3. Mean values for body mass index, heart rate, duration of PR interval, blood pressure and systolic function are presented as well. After adjusting for differences in body mass index, heart rate, PR interval duration, systolic function and blood pressure the results remained essentially unchanged, as shown in Table 2.4.3. Adjusted peak early (E) and late (A) mitral flow velocity, as well as adjusted peak velocity E/A ratios of all 46 participants at baseline and follow-up, are graphically presented in Figures 2.4.1 to 3.

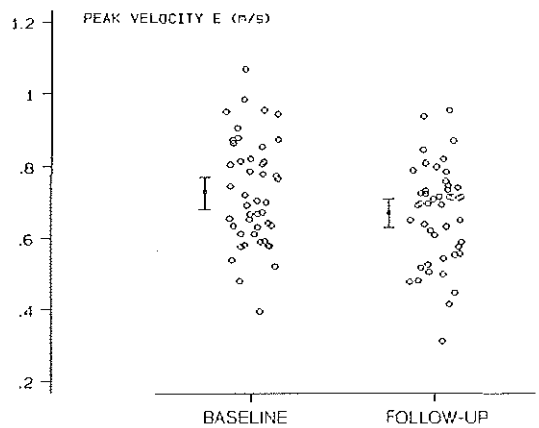

Figure 2.4.1. Peak early mitral flow velocity E (m/s) at baseline and follow-up.
Adjusted for differences in body mass index, heart rate, PR interval duration, systolic blood pressure and systolic function.
Mean values with 95% confidence intervals are indicated by bars.

Table 2.4.2. Mean values (± SD) of mitral flow parameters in 500 Rotterdam Study participants and two previous studies.[15,17]

	Rotterdam Study					Framingham[15]	Italy[17]
	55-59 yr	60-64 yr	65-69 yr	P_{trend}	60-69 yr	60-69 yr	60-69 yr
N	184	197	119		316	22	43
Peak velocity E (m/s)	0.70 ± 0.13	0.69 ± 0.14	0.69 ± 0.14	0.408	0.68 ± 0.12	0.55 ± 0.11	0.60 ± 0.10
Peak velocity A (m/s)	0.63 ± 0.15	0.69 ± 0.13	0.71 ± 0.15	< 0.001	0.71 ± 0.13	0.55 ± 0.10	0.63 ± 0.14
Peak velocity E/A	1.16 ± 0.27	1.03 ± 0.24	1.01 ± 0.26	< 0.001	0.98 ± 0.21	1.03 ± 0.26	1.00 ± 0.20

Table 2.4.3. Mean values of mitral flow parameters and determinants of mitral flow at baseline and follow-up.

	Cross-sectional study group (n = 500)	Longitudinal study group (n = 46)			
	Baseline mean ± s.e.	Baseline mean ± s.e.	Follow-up mean ± s.e.	Change (95% C.I.)	Adjusted change* (95% C.I.)
General characteristics					
Age (yr)	61.9 ± 0.2	61.7 ± 0.6	62.8 ± 0.6	1.11 (1.03, 1.19)	
Body mass index (kg/m^2)	25.7 ± 0.3	25.0 ± 0.3	25.2 ± 0.4	0.18 (-0.21, 0.57)	
Heart rate (/min)	67.0 ± 0.4	65.5 ± 1.2	62.9 ± 1.7	-2.7 (-6.0, 0.6)	
PR interval duration (msec)	165.2 ± 1.5	167.0 ± 3.1	168.6 ± 3.2	1.61 (-0.99, 4.21)	
Systolic blood pressure (mmHg)	138.2 ± 1.0	135.5 ± 3.2	138.3 ± 2.0	2.82 (-2.37, 8.01)	
Diastolic blood pressure (mmHg)	75.9 ± 0.5	74.3 ± 1.6	74.7 ± 1.5	0.45 (-3.40, 4.28)	
Fractional shortening (%)	37.9 ± 0.4	40.7 ± 0.7	42.5 ± 0.9	1.81 (-0.15, 3.76)	
Mitral flow indices					
Peak velocity E (m/s)	0.70 ± 0.01	0.73 ± 0.02	0.67 ± 0.02	-0.06 (-0.09, -0.02)	-0.06 (-0.09, -0.02)
Peak velocity A (m/s)	0.67 ± 0.01	0.67 ± 0.02	0.70 ± 0.02	0.03 (0.00, 0.05)	0.03 (0.00, 0.05)
Peak velocity E/A	1.07 ± 0.01	1.11 ± 0.04	0.98 ± 0.03	-0.13 (-0.20, -0.06)	-0.13 (-0.20, -0.06)

* Change adjusted for differences in body mass index, heart rate, PR interval duration, systolic blood pressure and fractional shortening, using coefficients obtained in a linear regression model that also incorporated age.

e.g., $Evelocity_{adj} = Evelocity_{mean} - (\beta_{bmi}*(BMI - BMI_{mean})) - (\beta_{hr}*(HR - HRm_{mean})) - (\beta_{prd}*(PRD - PRD_{mean})) - (\beta_{sbp}*(SBP - SBP_{mean})) - (\beta_{fs}*(FS - FS_{mean}))$

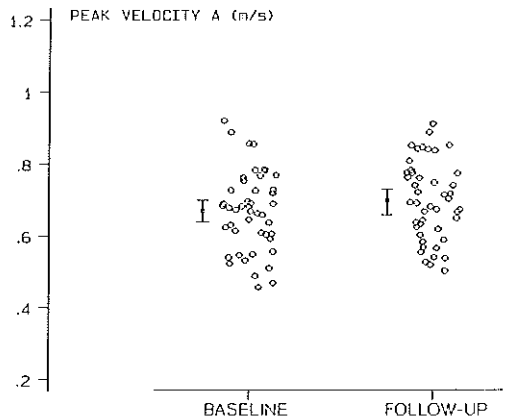

Figure 2.4.2. Peak late mitral flow velocity A (m/s) at baseline and follow-up. Adjusted for differences in body mass index, heart rate, PR interval duration, systolic blood pressure and systolic function.

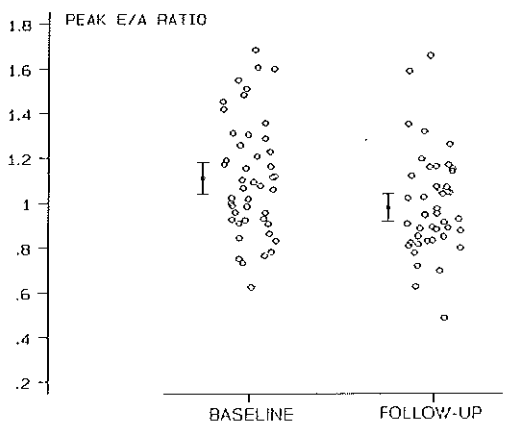

Figure 2.4.3. Ratio of peak early to late mitral flow velocity at baseline and follow-up. Adjusted for differences in body mass index, heart rate, PR interval duration, systolic blood pressure and systolic function.
Mean values with 95% confidence intervals are indicated by bars.

A separate analysis was carried out to verify the possible bias introduced by working with two echo technicians. We did not find a different change in mitral flow parameters according to the echo technician who performed the baseline examination (p=0.32, 0.22, 0.96 for difference between groups in peak velocity E, A, and E/A ratio change, respectively). A similar analysis was done to verify the possible influence of cardiovascular medication use on changes in mitral flow parameters. Cardiovascular medication may influence compliance and/or relaxation of the left ventricle, or at least indicate the presence of a condition influencing relaxation (e.g. hypertension or ischemia). However, no different change in mitral flow was observed when comparing participants who used cardiovascular medication at baseline to those who did not (p=0.33, 0.90, 0.17 for difference between groups in peak velocity E, A, and E/A ratio change, respectively).

Finally, a comparison of cross-sectional to longitudinal estimates of annual changes in mitral flow was made (Table 2.4.4). Longitudinal changes were appreciably larger than would have been inferred from a cross-sectional analysis.

Table 2.4.4. Annual changes in mitral flow indices. Comparison of cross-sectional and longitudinal estimates.

	Cross-sectional population (n = 468)*	Longitudinal study group (n = 46)	
	cross-sectional	cross-sectional†	longitudinal
Peak velocity E (m/s)	-0.001 (-0.004, 0.002)	-0.011 (-0.023, 0.001)	-0.059 (-0.091, -0.027)
Peak velocity A (m/s)	0.007 (0.004, 0.010)	0.005 (-0.005, 0.014)	0.024 (-0.001, 0.050)
Peak velocity E/A	-0.014 (-0.020, -0.009)	-0.029 (-0.048, -0.010)	-0.132 (-0.197, -0.067)

Values are mean annual changes in mitral flow parameters with 95% confidence intervals. Estimates are adjusted for differences in body mass index, heart rate, PR interval duration, systolic blood pressure and fractional shortening.

* Based upon 468 participants for whom complete data were available.

† Cross-sectional estimate of change based on mitral flow indices at baseline examination.

Discussion

Previous studies have descibed age-related changes in diastolic mitral flow pattern, reporting reduced early and increased late inflow velocities with increasing age. However, all these studies were cross-sectional, comparing mitral flow patterns across subjects of different age. In addition to providing cross-sectional estimates in a large group of 500 persons ages 55 - 70 years, we prospectively studied changes in mitral flow associated with aging in a population-based sample of 46 subjects with a mean age of 61.7 years at baseline. During a relatively short follow-up time of slightly over one year, we observed a decrease in early peak velocity E, concomitant with an increased peak atrial velocity A, resulting in a decreased E/A ratio. Adjustment for differences in body mass index, heart rate, PR interval duration, blood pressure and fractional shortening, did not influence the results.

Our prospective study confirms the notion of previous cross-sectional studies that mitral flow patterns change with advancing age. Interestingly, longitudinal estimates of annual changes in mitral flow parameters in this study were much larger than estimated by a cross-sectional analysis.

Several considerations have to be taken into account when comparing changes observed in longitudinal studies to cross-sectional estimates of change obtained in the same population.[28-30] Selection and survivor bias as well as cohort and period effects may lead to different estimates of change. Although by definition none of the 46 longitudinal study participants died or was lost to follow-up, survivor bias may have contributed to the smaller change estimated from the cross-sectional analysis. If, for example, persons with a low E/A ratio have a higher risk of dying prematurely, the E/A ratio in the younger study participants would be lower due to the presence of a group at increased risk of death, who would therefore not contribute to the older, surviving group. A reduced E/A ratio is the most commonly observed abnormal left ventricular filling pattern,[2] that has been noted in patients with hypertension, hypertrophic cardiomyopathy and coronary artery disease.[4,5] These disorders are associated with increased mortality. Consequently, cross-sectional analyses of change in E/A ratio can be expected to underestimate those observed from a longitudinal study.

Given the relatively small (15 years) age range of our study group it is not conceivable that cohort effects played a major role. Period effects are also thought to be negligible in our study. Recordings of our study participants were made by two experienced echo technicians who adhered to a protocol that did not change over the study period.

Change of mitral flow patterns was not influenced by the echo technician performing the baseline recording. The same echo machine was used throughout the study period and the person who traced the mitral flow recordings was blinded to clinical information and date of recording. Finally, sources of error and confounding may be larger in cross-sectional analyses which may affect the estimates of change. By prospectively comparing follow-up to baseline measurements in individuals interindividual variation is eliminated and changes are implicitly controlled for time-dependent confounding factors. This may further enhance the accuracy of longitudinal estimates of change.

In conclusion, our longitudinal findings confirm and expand previous studies that demonstrated age related changes in mitral flow indices, indicating that these changes may actually be greater than previous cross-sectional studies have suggested. This may partly be due to diastolic abnormalities acting as a marker for co-morbid conditions which may cause premature mortality.

The pathophysiology of age-related changes in diastolic function of the heart is complex and incompletely understood.[6,9,36,37] Cellular hyperplasia, cell death, fibrosis, decreased calcium sequestration and increased passive stiffness may underlie changes in left ventricular diastolic function with aging in humans. The combined influence of these mechanisms on active relaxation and passive filling of the left ventricle are difficult to interpret and may only be partially reflected in changes in mitral flow patterns. The importance of age should be appreciated, for example when using Doppler diastolic flow indices in the evaluation and management of diastolic heart failure.

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3.1. Prevalence of heart failure and (a)symptomatic left ventricular dysfunction in the general population. The Rotterdam Study

Introduction

Heart failure, a syndrome which develops as a consequence of cardiac disease, recognized clinically by a constellation of signs and symptoms produced by complex circulatory and neurohormonal responses to cardiac dysfunction,[1,2] is rapidly becoming one of the most common cardiovascular disorders. The incidence of heart failure is expected to continue to increase.[3] Despite the poor prognosis,[4,5] and considerable economic impact on health services because of long-term pharmacological treatment and frequent hospitalizations associated with the syndrome,[6] epidemiological data on heart failure are relatively scarce.[7]

This may be attributed to the atypical symptoms of the early stages of heart failure, the ongoing debate on the definition of heart failure and the lack of a gold standard to assess the presence of heart failure.[8,9] According to the guidelines of the European Society of Cardiology objective evidence of cardiac dysfunction has to be present in addition to symptoms (e.g. shortness of breath or fatigue, at rest or during exercise, ankle swelling) to establish the presence of heart failure.[10] Benefits of ACE inhibition have conclusively been documented in persons with impaired left ventricular systolic function either with or without overt symptoms and signs of heart failure.[11-13] Heart failure in persons with intact left ventricular systolic function, often referred to as diastolic heart failure, is less well characterized in terms of epidemiology and optimal treatment.[14-16]

The translation of benefits of recent clinical trials in heart failure to larger groups of heart failure patients will to a large extent be determined by the feasibility of methods to detect left ventricular dysfunction in unselected and non-hospitalized subjects. Echocardiography has been recommended as an essential tool in the evaluation of persons suspected of heart failure,[10,17] in particular in the assessment of left ventricular systolic function. However, routine application of echocardiography in population-based studies is costly, time consuming and requires considerable expertise.[18] To our knowledge, no papers have been published to date that provide estimates of left ventricular systolic dysfunction in the population at large.

We set out to estimate the prevalence of heart failure in the population-based Rotterdam Study and to relate echocardiographic findings in a sample of participants to symptoms and signs associated with heart failure. Thus, we were able to estimate the prevalence of asymptomatic left ventricular systolic dysfunction in the general population.

Methods

Study population This study forms part of the Rotterdam Study, a population-based cohort study on prevalence, incidence, and determinants of chronic disabling diseases in the elderly.[19] The four main areas of interest of the Rotterdam Study are cardiovascular,

neurologic, ophthalmologic and locomotor diseases. The first cross-sectional survey started in 1990 and was completed in June 1993. All inhabitants of Ommoord, a suburb of Rotterdam, the Netherlands, who were 55 years or older were invited to participate in the study by mail and contacted by phone two weeks later. Names and addresses were drawn from the municipal register, which is reliable, complete, and updated weekly. Of the 10,275 eligible subjects, 7,983 (78%) agreed to participate and signed informed consent. Participants were interviewed at home and subsequently examined at the research centre.

History A trained interviewer administered a standardized questionnaire to obtain information on medical history (e.g. myocardial infarction, coronary artery bypass surgery, percutaneous transluminal angioplasty) and current medication use. The presence of angina pectoris and shortness of breath was assessed by means of the WHO questionnaires.[20] Shortness of breath was defined as WHO grade I or higher dyspnoea, reflecting shortness of breath at rest or on moderate exertion. Drug use was coded according to the Anatomical Therapeutic Chemical (ATC) classification index.[21]

Height, weight and blood pressure measurements Height and weight were measured with participants wearing light clothes and without shoes. Blood pressure was measured on the right arm with the participant in sitting position using a random zero sphygmomanometer. The average value of two consecutive blood pressure readings was taken as the blood pressure value. Body mass index was calculated as weight(kg)/height(m)^2.

Standardized physical examination was carried out by a study physician to verify the presence of ankle edema and pulmonary crepitations or rhonchi. The research physicians were trained to reduce interobserver variability.

A *standard 12-lead electrocardiogram (ECG)* was recorded using an ESAOTE laptop electrocardiograph (ESAOTE Biomedica, Florence, Italy). All electrocardiograms were digitally stored and analysed using the MEANS program, a standardized and validated ECG software program.[22] Myocardial infarction was defined as myocardial infarction on the electrocardiogram. In addition, if participants reported a history of myocardial infarction without electrocardiographic evidence at the time of examination, myocardial infarction was deemed present, provided that evidence of myocardial infarction was found in specialists' records. The electrocardiogram was also used to assess the presence of atrial fibrillation and left ventricular hypertrophy.

Echocardiography was performed with the participant in the partial left decubitus position (Toshiba SSH-60A). 2-Dimensional imaging using parasternal long-axis views was performed to aid M-mode studies. Measurements were made according to the recommendations of the American Society of Echocardiography using a leading edge to leading edge convention. Left ventricular internal dimension (LVIDed) was measured at end diastole, as defined by the onset of the QRS complex and at end systole (LVIDes), as determined at the nadir of septal motion. The percentage fractional shortening (FS) was calculated as 100[(LVIDed - LVIDes)/LVIDed] and used as an index of systolic function. Impaired left ventricular function was deemed to be present if fractional shortening was less than or equal to 25%, corresponding to a left ventricular ejection fraction of 42.5%.[23]

Classification of heart failure A two-step approach was used to assess the prevalence of heart failure. Firstly, the presence of shortness of breath at rest or on exertion,[20] ankle edema and crepitations was determined. If at least two of these were present in combination with evidence of cardiac disease (angina pectoris, myocardial infarction, documented coronary artery bypass surgery, documented percutaneous transluminal angioplasty, atrial fibrillation or electrocardiographic left ventricular hypertrophy), while shortness of breath could *not* be attributed to chronic obstructive pulmonary disease (as indicated by use of chronic obstructive pulmonary disease medication -ATC code r03-), heart failure was considered present. This combination had a sensitivity of 80% and a specificity of 98% to detect the presence of definite heart failure as determined by a cardiologist on clinical grounds in a previous pilot validation study in a sample of 54 carefully selected Rotterdam Study participants.[24]

Secondly, the examining physician used standardized questions to verify the indication of cardiovascular medication with the participant. In case diuretics, glycosides or angiotensin converting enzyme inhibitors were used, a possible indication of heart failure (as opposed to hypertension, arrhythmias etc.) was verified and classified as no, possible or definite. Only participants with a definite indication for heart failure, in whom objective evidence of cardiac disease was found, were included.

Statistical methods Data were analysed using the STATA statistical package. We calculated age- and sex-specific prevalence figures of heart failure and left ventricular systolic dysfunction. As information on indication for cardiovascular medication use and shortness of breath was not obtained in the beginning of the Rotterdam Study, prevalence estimates are based on 5,540 participants (age 68.9 $\pm$ 8.7 years, 2,251 men), in 1,677 of whom (age 66.2 $\pm$ 8.2 years, 779 men) auscultation was performed. The mean age of the group of 5,540 was slightly below the mean age of the complete Rotterdam Study cohort aged 55 to 95 years (age 70.5 $\pm$ 9.5 years, 3,100 men), but auscultation was performed in a younger subset of participants. The prevalence figures are presented in 10 year age groups, separately for men and women, and according to whether or not auscultation was used in the assessment of heart failure. Binomial confidence intervals (95%) were calculated for prevalence estimates. Analysis of covariance was performed to calculate age adjusted prevalences of heart failure according to whether or not auscultation had been performed. To determine whether the difference in age-adjusted prevalence of men and women was statistically significant, we used logistic regression analyses with age and gender as independent and the presence of heart failure as dependent variables.

Results

Prevalence of heart failure. Table 3.1.1a. shows the age- and sex specific percentages of subjects who were classified as having heart failure. The overall prevalence of heart failure in persons aged 55 years or over was 4.2% (95% C.I. 3.3 - 5.1) based on persons for whom complete data were available. The prevalence increased with age, with the exception of the highest age group in men. No relevant differences in overall age adjusted prevalences of heart failure in men and women, neither for those who underwent auscultation ($p=0.26$) nor for those who did not ($p=0.83$), were observed.

Table 3.1.1a. Prevalence (%) of heart failure in the Rotterdam Study (95% confidence intervals in parentheses).

	Men				Women				Total			
	Complete score		No auscultation*		Complete score		No auscultation		Complete score		No auscultation	
Age (yr)	N	Heart Failure	N	Heart failure	N	Heart failure	N	Heart failure	N	Heart failure	N	Heart failure
55-64	420	0.7 (0.1-2.1)	481	0.8 (0.2-2.1)	484	0.6 (0.1-1.8)	741	0.3 (0.0-0.9)	904	0.7 (0.2-1.4)	1222	0.5 (0.2-1.1)
65-74	273	3.7 (1.8-6.6)	615	3.7 (2.4-5.6)	255	1.6 (0.4-3.9)	905	2.8 (1.8-4.1)	528	2.7 (1.5-4.4)	1520	3.2 (2.3-4.2)
75-84	69	14.4 (7.2-25.1)	326	5.5 (3.3-8.6)	116	12.1 (6.7-19.4)	592	6.8 (4.9-9.1)	185	13.0 (8.5-18.7)	918	6.3 (4.8-8.1)
85-94	17	5.9 (0.1-28.7)	50	8.0 (2.2-19.2)	43	14.0 (5.3-27.9)	153	15.7 (10.3-22.4)	60	11.7 (4.8-22.6)	203	13.8 (9.4-19.3)
Total	779	3.1 (2.0-4.5)	1472	3.3 (2.5-4.4)	898	3.0 (2.0-4.3)	2391	3.8 (3.1-4.7)	1677	3.0 (2.3-4.0)	3863	3.6 (3.0-4.2)
Adjusted*		3.9 (2.7-5.2)†		2.9 (2.0-3.8)‡		4.3 (3.1-5.5)†		3.3 (2.6-4.1)‡		4.2 (3.3-5.1)†		3.1 (2.5-3.7)‡
Mean age (s.e.)		65.7 ± 0.3		69.4 ± 0.2		66.6 ± 0.3		70.5 ± 0.2		66.2 ± 0.2		70.1 ± 0.1

* No auscultation performed
† Age adjusted to age distribution of group that did not undergo auscultation
‡ Age adjusted to age distribution of group that underwent auscultation.

Table 3.1.1b. Prevalence of heart failure in the Rotterdam Study, compared to other recent studies.

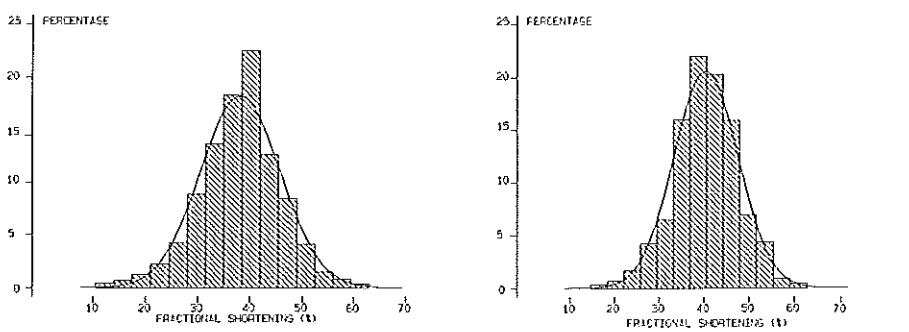
	Rotterdam Study (The Netherlands)			General practice[28] (United Kingdom)	NHANES[27] (U.S.A)			Transition[31] (The Netherlands)			Nijmegen[29] (The Netherlands)		
Age (yr)	Men	Women	All	All	Men	Women	All	Men	Women	All	Men	Women	All
55-64	0.7	0.6	0.7		4.5	3.0	3.7						
65-74	3.7	1.6	2.7	2.7	4.9	4.3	4.5	3.3	2.9	3.1	4.9	3.2	4.0
75-84	14.4	12.1	13.0	7.4									

Systolic function. In 2,823 persons M-mode recordings were made to measure left ventricular systolic function. In 19.7% (n=556) M-mode registrations were deemed inadequate to reliably measure left ventricular dimensions. Persons in whom M-mode registrations were unsuccessful were more likely to be older (OR 1.07, 95% C.I. 1.05-1.09 for each year increase of age), have a higher body mass index (OR 1.06, 95% C.I. 1.03-1.09 for each kg/m^2 increment), and to use medication for chronic obstructive pulmonary disease (ATC code R03, OR 1.9, 95% C.I. 1.2-2.7). Although the rate of successful M-mode recordings was higher in men than in women, this difference did not reach statistical significance (OR 1.12, 95% C.I. 0.93-1.35).

The gender specific distribution of fractional shortening in 2,267 participants (mean age 65.7 ± 7.4 years, 1,028 men) is shown in Figure 3.1.1. The percentage with impaired left venticular systolic function was 5.5 (95% C.I. 4.1-7.0) in men and 2.2 (95% C.I. 1.4-3.2) in women (Table 3.1.2.). The age adjusted prevalence of left ventricular systolic dysfunction was approximately 2.5 times higher in men (OR 2.7, 95% C.I. 1.7 - 4.3). Fractional shortening did not change appreciably with age, but was on average somewhat higher in women than in men (Figure 3.1.2.).

Table 3.1.2. Prevalence of left ventricular systolic dysfunction in 2267 Rotterdam Study participants (95% confidence intervals in parentheses).

Age (yr)	Men		Women		Total	
	N	LV systolic dysfunction	N	LV systolic dysfunction	N	LV systolic dysfunction
55-64	548	3.7 (2.2-5.6)	674	1.2 (0.5-2.3)	1230	2.3 (1.5-3.3)
65-74	368	7.6 (5.1-10.8)	388	3.1 (1.6-5.3)	756	5.3 (3.8-7.1)
75-84	102	6.9 (2.8-13.6)	150	3.3 (1.1-7.6)	252	4.8 (2.5-8.2)
85-94	10	10.0 (2.5-44.4)	19	10.5 (1.3-33.1)	29	10.3 (2.0-27.3)
Total	1028	5.5 (4.1-7.0)	1239	2.2 (1.4-3.2)	2267	3.7 (2.9-4.5)



Men (n = 1028)
Mean age: 65.5 ± 7 years
Mean fractional shortening: 38 ± 8 %

Women (n = 1239)
Mean age: 65.8 ± 8 years
Mean fractional shortening: 40 ± 7 %

Figure 3.1.1. Gender specific distribution of fractional shortening, a measure of left ventricular systolic function, in 2,267 participants of the Rotterdam Study.

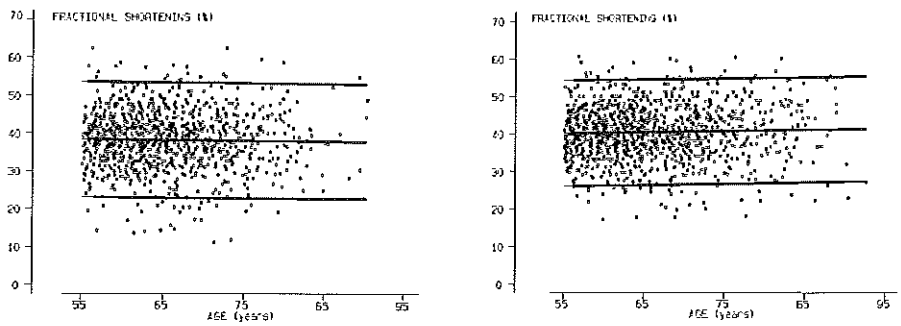


Figure 3.1.2. Gender specific relation of fractional shortening to age in 2,267 Rotterdam Study participants. Regression lines with 95% confidence intervals are indicated (solid lines).

The relation of left ventricular function to symptoms and signs of heart failure was explored in 1,698 participants in whom information on presence of heart failure and M-mode data was available. Of the 35 persons deemed to have heart failure by symptom and signs, only 10 (29%, 95% C.I. 15 - 46%) had M-mode echocardiographic evidence of left ventricular systolic dysfunction (Table 3.1.3.). More importantly, of 60 persons with left ventricular systolic dysfunction only 24 (40%, 95% C.I. 28 - 53%) were found to have at least one of the three cardinal signs of heart failure (shortness of breath, ankle edema or pulmonary crepitations).

Table 3.1.3. Relation of heart failure to left ventricular systolic dysfunction in 1698 Rotterdam Study participants.

	M-mode echocardiography		
Heart failure	Normal left ventricular systolic function	Impaired left ventricular systolic function*	Total
Heart failure absent	1613	50	1663 (98%)
Heart failure present	25	10	35 (2%)
Total	1638 (96%)	60 (4%)	1698

* Impaired left ventricular systolic function: fractional shortening $<= 25\%$.

Discussion

The overall prevalence of heart failure in our population-based study was estimated at 4.2% and the age-adjusted prevalence of heart failure did not differ between men and women. A consistent and rapid increase in the prevalence of heart failure with age was observed. Left ventricular systolic function, measured by fractional shortening, did not decrease appreciably with age. The prevalence of impaired left ventricular systolic function was 3.7%, and about 2.5 times higher (5.5%) in men than in women (2.2%). 60% of persons with left ventricular systolic dysfunction had no shortness of breath, ankle edema or pulmonary crepitations.

The diagnosis of heart failure is fraught with difficulties. Most population-based

studies employ a combination of medical history, physical examination, electrocardiography and chest X-ray to detect heart failure, although some have relied solely on drug prescription data.[7,24] We used a previously validated combination of signs and symptoms, that bears resemblance to the definition of heart failure proposed by the task force on heart failure of the European Society of Cardiology,[10] in addition to verification of indication for cardiovascular medication use. Ideally, each person should undergo a complete comprehensive cardiovascular examination, including echocardiography, and the presence of heart failure should be established by consensus evaluation of available information by a panel of experts. This approach has not been used to date in population-based studies of the prevalence of heart failure. In a study of incident heart failure that is currently carried out in the framework of the Rotterdam Study, however, this strategy is used, as is the case in the Hillingdon Heart failure study.[25] Initially, auscultation of the lungs was not part of the routine Rotterdam Study examination and thus performed only in 1,677 of 5,540 participants for whom otherwise complete information was available. However, given the relatively low proportion of subjects that was found to have crepitations, it is not surprising that age adjusted prevalence estimates in those who underwent auscultation did not differ appreciably from those who did not.

The overall response in our study was good, but nonresponse may have led to an underestimation of the prevalence of heart failure, as it is conceivable that older people and diseased persons were less likely to participate. Due to the size of our study population left ventricular systolic function was estimated by fractional shortening, rather than by 2D echocardiographic determination of ejection fraction. In the absence of major wall motion abnormalities fractional shortening can be assumed to reliably reflect left ventricular systolic function.[23] Several studies on the prevalence of heart failure in the United States and Europe have been reported.[4,7] Most studies were carried out in general practice and only few can be regarded as truly population-based. An increase of heart failure with age is a consistent finding, although the Cardiovascular Health Study found that prevalence of heart failure did not increase further in persons over 85 years.[26] Some studies reported a higher overall prevalence in men,[4,5,26] whereas others found a higher overall prevalence in women.[27-30] Although differences in case finding procedures and diagnostic criteria may hamper comparison between studies, our prevalence estimates are similar to estimates from recent studies in general practice in the Netherlands and UK (Table 3.1.1b.).[28,29,31] Higher prevalence estimates were reported by a recent population-based study in the USA.[27]

The prevalence of left ventricular systolic dysfunction in the present study was lower than the 8% reported in a group of 1,000 participants (ages 26-75 years) of the Glasgow Monica risk factor survey,[32] of whom less than half (42%) had asymptomatic left ventricular systolic dysfunction. In that study, left ventricular dysfunction was defined as left ventricular ejection fraction $< 35\%$, estimated by 2D echocardiography. Our findings may represent a conservative estimate of left ventricular systolic dysfunction as systolic dysfunction may be more frequently observed in participants whose echocardiogram was of inadequate quality and in non-responders. On the other hand, in large population-based studies, one should be aware of the strong influence of regression to the mean.[33] Upon remeasurement, persons with a low fractional shortening will tend to show an upward shift towards the mean fractional shortening, and thus may not be regarded as truly having left ventricular systolic dysfunction.

We did not observe a difference in (age adjusted) prevalence between men and women. Selective non response of elderly men, accounting for the leveling off of prevalence in men older than 85 years, may have led to an underestimation of prevalence in men, whereas selective misclassification of heart failure in women,[34] who are for example more likely to have non cardiac edema, may have inflated prevalence in women. Nevertheless, it is possible that the prevalence difference between women and men is minimal. Age adjusted discharge rates for heart failure in the Netherlands were at times higher in women than in men in the 1980's,[6] and a recent report of the Framingham Heart study indicates that diastolic heart failure, carrying a better prognosis than heart failure with impaired left ventricular systolic function, is more prevalent in women.[35]

In conclusion, heart failure has an appreciable prevalence in the general population, that increases with age and does not differ markedly between men and women. The prevalence of left ventricular systolic dysfunction is in the order of 3.7% and is more frequently observed in men than in women. The majority of persons with left ventricular systolic dysfunction show none of the cardinal symptoms of heart failure and can be regarded as having asymptomatic left ventricular systolic dysfunction. Similarly, about 70% of subjects with clinical heart failure had normal left ventricular systolic function. Diastolic left ventricular dysfunction may play a role in the symptoms and signs of heart failure in these individuals.

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3.2. Increase in hospitalization rates for heart failure in The Netherlands, 1980-1993

Introduction

Heart failure is a complex clinical syndrome representing a common and important health problem.[1] In 1988 the direct medical costs of heart failure in The Netherlands were estimated at 182 million pounds, corresponding to 1% of the total health care budget for that year.[2] The prognosis of a patient with heart failure is poor. In the Framingham heart study 75% of men and 60% of women died within 5 years after the establishment of the diagnosis of heart failure.[3] Despite this importance, reliable estimates of the incidence and prevalence of heart failure in the general population are surprisingly scarce. This may be attributed to the atypical symptoms of the early stages of heart failure, the ongoing debate on the definition of heart failure and the lack of a gold standard to assess the presence of heart failure.[4] Hospital based registries provide some insight into the occurrence of heart failure in the population.

Increases in age adjusted discharge rates for heart failure in the United States, Sweden, and Scotland have been reported in recent years.[5-8] A recently developed model predicts a further increase in the number of heart failure patients in The Netherlands in the coming decades.[9] We describe the trend in hospitalization for heart failure in The Netherlands from 1980 to 1993. Furthermore, we assessed the frequency and timing of readmissions for heart failure during a 2-year period in a subset of 7 hospitals.

Patients and methods

Population figures were obtained from the office of Statistics Netherlands, Voorburg, The Netherlands. The number of hospital discharges for heart failure by 5 years age groups were derived from the National Medical Register of SIG Health Care Information, Utrecht, The Netherlands. From 1986 onwards all hospitals (university and general) in The Netherlands participated in this register. In 1980, the starting year of our analysis, already 95% of all hospitalizations in The Netherlands were recorded. Based on this coverage we used appropriate multiplying factors to estimate the yearly number of hospital discharges in The Netherlands before 1986. All records contain a principal diagnosis coded according to International Classification of Diseases Clinical Modification (9th revision),[10] age and gender of the patient, status at discharge (dead or alive), and length of hospitalization. We used the following codes to identify discharges for heart failure: heart failure (428.x), hypertensive heart disease (402.x), and myocardial degeneration (429.1). Only admissions with a first-listed (principal, main) discharge diagnosis of heart failure were included in this analysis. In-hospital mortality (as a percentage) was calculated by dividing the number of hospitalizations with discharge status dead by the total number of hospitalizations for heart failure.

To calculate the average age at admission we assumed that all persons were admitted at, on average, the midpoint of each 5 year age category. Age adjusted discharge rates were calculated by direct standardisation using the "new" European Standard

Population as a standard.[11] Tests for linear trend were performed with Poisson regression.[12] Furthermore, as the registry does not provide data on individual patients, we conducted a survey to obtain individual records of patients with heart failure to estimate the contribution and timing of readmissions. Seven hospitals (2 university and 5 general) participated on a voluntary basis. This survey spanned a 2-year period from 1991 to 1992 and covered 6.3% of all hospitalizations for heart failure in that period. Time to readmission was analyzed using Kaplan-Meier curves. Separate curves for readmission were constructed in patients with one, two, or three previous hospitalizations, respectively. Endpoints were the dates of readmission whereas for starting points the dates of discharge were used. Patients who died during their stay in the hospital were excluded from the subsequent readmission analysis.

Results

Table 3.2.1 lists the total number of discharges for heart failure, the mean length of stay, and the average age at admission. The total number of hospital discharges for heart failure rose from 7377 in 1980 to 13022 in 1993 for men, and from 7064 to 12944 for women. The contribution of heart failure to the total number of hospital discharges in The Netherlands in 1993 was 1.7%. International Classification of Diseases code 428 (heart failure) was by far the most common (98.8% in 1993) of the codes we combined for this study. The average age at admission increased slightly during the study-period (Table 3.2.1). On average women were 4.5 years older than men. There was a marked and steady increase in the age adjusted discharge rates for both men and women (Figure 3.2.1). From 1980 to 1993 the age adjusted discharge rates for heart failure increased by 48% in men and by 40% in women. Analysis of age specific discharge rates showed that the rise in the number of discharges was more pronounced in the higher age groups (figure 3.2.2 and 3.2.3). The test of trend for all age-groups was significant ($p < 0.05$). In every age group the risk of hospitalization for men was higher than for women.

In 1993 the average length of hospitalization for patients with heart failure was 14.0 days for men and 16.4 days for women. The length of hospital stay declined steadily from 21.6 days in 1980 to 15.2 days in 1993. Slightly longer hospitalization times were observed with increasing age (Table 3.2.2). In all age groups women stayed longer in the hospital than men, on average 1.6 days. During the study period the difference in length of stay between men and women decreased. 15.3% of all patients with a principal discharge diagnosis of heart failure in 1993 died in the hospital. In-hospital mortality was strongly age related. After stratification for age, in-hospital mortality for men was higher than for women in all age groups (figure 3.2.4). During the study period age adjusted in-hospital mortality decreased from 19.9% in 1980 to 15.5% in 1993 in men, and from 17.8% to 14.9% in women.

The survey conducted in 7 hospitals for the years 1991 and 1992 yielded 3090 admissions with a first-listed discharge diagnosis of heart failure in 2440 patients. This corresponds to a 6.3% sample of all hospitalizations for heart failure in The Netherlands in that period.

Table 3.2.1. Number of hospital discharges for heart failure, mean length of stay, and mean age at admission in The Netherlands from 1980 through 1993.

Year	Men			Women		
	no of discharges	mean length of stay (days)	mean age at admission (years)	no of discharges	mean length of stay (days)	mean age at admission (years)
1980	7 377	19.1	71.2	7 064	24.3	75.0
1981	7 626	18.9	71.5	7 382	22.7	75.3
1982	8 504	18.4	71.6	7 868	22.5	75.6
1983	8 917	17.4	71.8	8 445	21.5	75.8
1984	9 143	17.1	72.1	9 113	20.6	76.0
1985	9 927	16.6	72.1	9 501	19.9	76.4
1986	10 471	16.7	72.1	10 143	19.7	76.9
1987	11 085	16.3	71.9	10 348	19.0	76.6
1988	11 472	16.1	72.1	10 849	19.5	76.8
1989	11 698	15.4	72.2	11 308	18.5	76.9
1990	12 420	15.0	72.1	11 548	18.0	76.9
1991	12 522	14.8	72.2	12 015	17.5	76.8
1992	12 432	14.4	72.1	11 936	16.9	76.9
1993	13 022	14.0	72.5	12 944	16.4	77.4

Source: SIG Health Care Information

Table 3.2.2. Length of hospitalization (days) for heart failure in The Netherlands by age and gender in 1980, 1984, 1988, 1993.

Year	Men age group in years			Women age group in years		
	<60	60-80	80+	<60	60-80	80+
1980	17.8	19.1	19.9	20.8	24.2	25.1
1984	15.1	16.9	18.4	16.8	20.3	21.7
1988	15.1	15.9	17.1	16.4	19.2	20.1
1993	13.4	13.8	14.8	14.0	16.0	17.1

Source: SIG Health Care Information

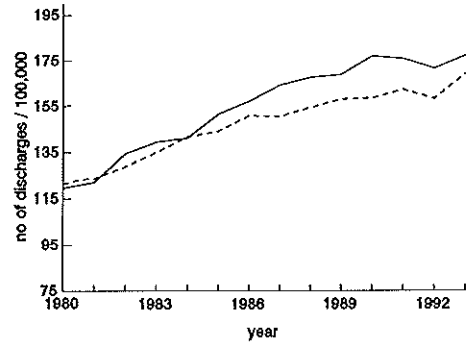

Figure 3.2.1. Age adjusted discharge rates for heart failure for men (solid line) and women (broken line) The Netherlands, 1980-1993. The "new" European Standard Population was used as a standard.

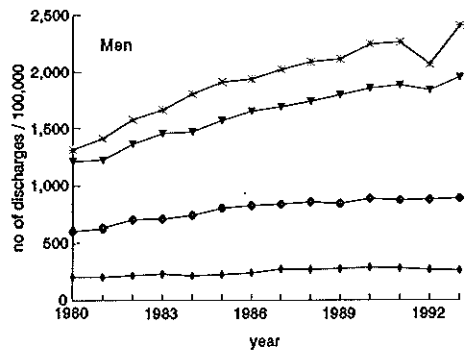

Figure 3.2.2. Age specific heart failure discharge rates for men, The Netherlands, 1980-93. Age groups in years: ♦ =55-64, ● =65-74, ▼=75-84, *=85 and over.

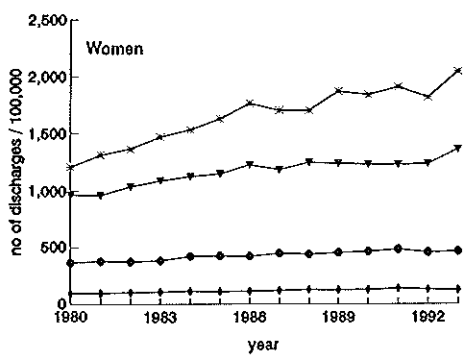

Figure 3.2.3. Age specific heart failure discharge rates for women, The Netherlands, 1980-93. Age groups in years: ♦ =55-64, ● =65-74, ▼=75-84, *=85 and over.

Source: SIG Health Care Information.

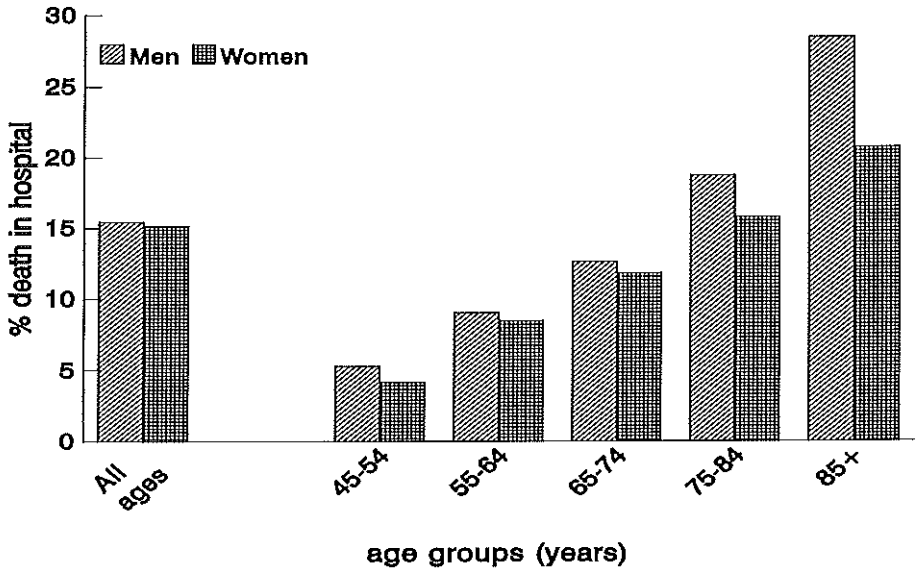

Figure 3.2.4. Age specific in-hospital mortality for heart failure in 1993 in men and women. Source: SIG Health Care Information.

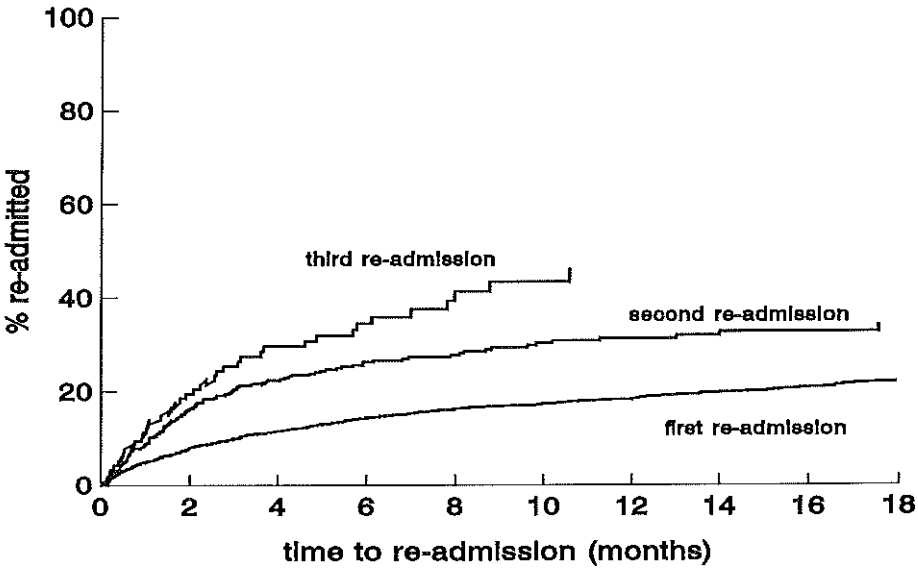

Figure 3.2.5. Separate curves (Kaplan-Meier) of the time to readmission for heart failure in patients with one, two, and three previous hospitalizations for heart failure. Individual data on 2440 patients from a survey in seven hospitals during a 2-year period. Men and women combined.

The inclusion of hospital admissions with a non first-listed discharge diagnosis of heart failure would have increased the number by 86% from 3090 to 5740. Within the 2-year period 18% of the patients was admitted more than once, and 5% more than twice. The percentage of patients readmitted for heart failure within six months after their first discharge was 14% (95% CI 13% to 16%). Of all patients discharged (alive) after their second hospitalization 26% (95% CI 21% to 30%) and of all patients after their third hospitalization 34% (95% CI 25% to 43%) were readmitted within six months (figure 3.2.5).

Discussion

This study shows a pronounced increase in age adjusted discharge rates for heart failure for both men and women in The Netherlands during the last 14 years. Similar increases have been reported in the United States of America, Sweden, and Scotland.[5-8] Compared to Scotland there was a difference in the absolute rate (1990: 212/100,000 in Scotland versus 160/100,000 in The Netherlands), but time trends were very similar. From 1980 to 1990 the crude discharge rate in Scotland increased 63%, compared to 57% in The Netherlands.[8] Explanations for the discrepancy in absolute rate could be differences in the age structure of the two countries, differences in admission policy, differences in the place of heart failure among the list of discharge diagnoses, and a true difference in prevalence of heart failure between the two countries.

We will discuss three possible explanations for the rise in age adjusted discharge rates for heart failure. These are an increase in the incidence of heart failure, the longer survival of heart failure patients, and changes in admission policy and coding practice.

Increase in incidence of heart failure?

Hospital statistics can not be used as a measure of incidence of heart failure per se, although an increase in incidence of heart failure in the general population should eventually be reflected in higher hospitalization rates. For an estimate of the prevalence and incidence of heart failure in the general population other types of studies are needed.

The two main causes of heart failure in the Western World are coronary heart disease and hypertension.[13] Mortality from coronary heart disease in The Netherlands started to decline in the early seventies and continued to do so, like in many other Western countries.[14-16] It is believed that this decline is caused by a decrease in incidence as well as by improved survival of patients with coronary heart disease.[17] Data from the Framingham study suggest that one third of the decline in coronary heart mortality was caused by a decline in incidence and two thirds by a lower case fatality.[18 19] If this scenario is true it will eventually lead to an increase in the number of patients with chronic heart disease, including heart failure.[9] The recent, widespread use of thrombolysis will probably further improve the survival after acute myocardial infarction, but at the same time will increase the number of patients having an impaired cardiac reserve/left ventricular function and therefore at a higher risk of developing heart failure.[17,20]

Similar to the United States there has been a decline in prevalence of hypertension

in The Netherlands during the last decades,[21] making it an unlikely contributor to the suggested increase in incidence of heart failure. However, from 1987 the percentage of people on treatment treated for hypertension has started to decline in The Netherlands,[22] contrary to the United States of America where a steady increase was observed over the past 3 decades.[23] The importance of the control of hypertension in the prevention of heart failure remains uncertain. Yusuf argued that the treatment of hypertension does not prevent heart failure, but merely postpones its onset.[24]

Longer survival of patients with heart failure?
During the last decade several advances have been made in the treatment of heart failure,[25] most recently the introduction of angiotensin-converting enzyme inhibitors. Although a recent meta-analysis demonstrated an impressive 23% reduction in mortality in trials of ACE inhibitors in heart failure, the gain in life expectancy is measured in months rather than years.[26] Furthermore, as the translation of observed benefits in clinical trials to larger groups of heart failure patients takes time,[27] a substantial effect on survival during our study period is doubtful. The Framingham Heart Study for example did not find an improvement in survival following the onset of heart failure in the period 1948-1988.[3] Obviously, this does not exclude the possibility that newer treatment for patients with severe heart failure has resulted in an increase in hospitalizations.

Changes in admission policy and coding practice?
The number of hospital admissions is directly influenced by changes in admission policy and coding practice. Unfortunately, these changes are difficult to measure and to quantify. The growing attention among physicians for heart failure and the progress in the pharmacotherapy of heart failure could have been a reason to admit more patients to the hospital, especially in the elderly. In addition, the more widespread use of echocardiography has made confirmation of heart failure in its earlier stages easier. Given the constraints on the health care budget it is unlikely that milder forms of heart failure are admitted to the hospital more often. Few studies have been done to evaluate the quality of the coding process. A recent survey in The Netherlands indicated that 80% of the patients discharged with ICD code 428 (heart failure) fulfilled the Framingham criteria for heart failure.[28]

Heart failure is characterized by long hospitalization times and frequent readmissions. This adds to the importance of heart failure in terms of costs. Despite a continuous decrease, the average length of stay for heart failure is still appreciably longer than for acute myocardial infarction (15.2 days compared to 11.6 days in 1993).

Within a 2-year period 18% of the patients were admitted more than once. The proportion of patients that returned to the hospital increased with every new admission (figure 3.2.5). Our survey yielded a conservative estimate of the number of readmissions in patients with heart failure. First of all, readmissions to a different hospital could not be detected. Secondly, admissions prior to our fixed time period (1991-1992) were not taken into account. Therefore, admissions marked as a first admission in our survey might in

reality have been a readmission, because of a hospitalization for heart failure prior to our time window.

In conclusion, age adjusted discharge rates for heart failure in The Netherlands increased by 48% for men and by 40% for women in the period 1980 to 1993. Readmissions within a short period of time are a distinguishing feature among heart failure patients. In view of the expected rise in the number of persons above the age of 65 years and the ongoing progress in medical care a further increase in the number of hospitalizations for heart failure is likely. More efforts are needed to prevent and delay the development of heart failure in high risk patients, and more research is needed into the factors influencing the decision to (re)admit patients with heart failure to the hospital.[29]

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4. Neurohormonal activation at rest and after maximal exercise in presymptomatic heart failure.

Introduction

Heart failure is rapidly becoming one of the most prevalent cardiovascular disorders and a further increase in its incidence is expected in the near future.[1,2] Heart failure carries a poor prognosis and has a considerable economic impact, because of long-term pharmacological treatment and frequent hospitalizations associated with the syndrome. The clinical spectrum of heart failure ranges from asymptomatic left ventricular (LV) dysfunction to NYHA class IV patients awaiting cardiac transplantation.[3] Further insight into asymptomatic LV dysfunction is important in order to better understand the transition into overt heart failure and to develop (therapeutic) strategies to postpone or prevent the onset of overt heart failure.

Neurohormonal activation plays an important role in heart failure[4-6]; it appears to precede overt heart failure[7] and it provides prognostic information.[8,9] Furthermore, the outcome of treatment is related to modulation of neurohormonal activation.[10,11] Recently, it has been suggested that neurohormonal parameters may be used as markers for presymptomatic ventricular dysfunction.[12,13]

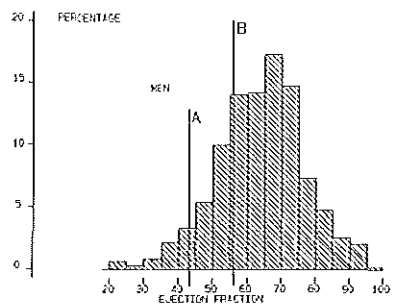
Although animal models have shed light on the processes involved in the early stages of heart failure, studies in humans to date are limited to hospital based populations. The aim of the present study was to assess characteristics of asymptomatic persons in the general population, who are at an increased risk of developing heart failure. Accordingly, we set out to determine if neurohormonal activation occurs in the early stages of heart failure and if the neurohormonal response to exercise is modified in subjects with impaired LV systolic function.

Methods

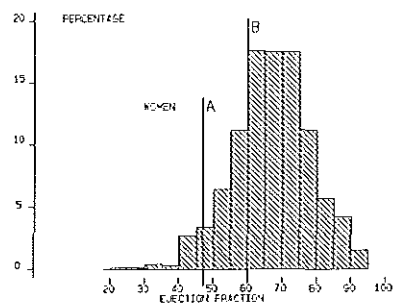
The *study population* consisted of 160 participants of the Rotterdam Study, a population based follow-up study of 7,983 inhabitants aged 55 years or older living in the Rotterdam suburb of Ommoord. The design of the study has been described in detail elsewhere.[14] Briefly, the Rotterdam Study investigates determinants and occurrence of cardiovascular, neurogeriatric, locomotor and opthalmologic diseases. Baseline measurements (including medical history, physical examination, measurement of blood pressure, electrocardiography, carotid ultrasound and Doppler echocardiography) were carried out from March 1990 to July 1993. The overall response rate was 78%.

For the purpose of the present study the 1568 participants were considered, who underwent echocardiography at their baseline examination in 1992 or 1993, and who were younger than 71 years at that time. Seven persons had died at the time of the present study and 293 subjects were excluded because of neurologic disease (n=118), use of medication for chronic obstructive pulmonary disease (n=56) or because systolic function could not be accurately determined from the echocardiogram (n=119).

The distribution of the ejection fraction, estimated as 1.7 x fractional shortening,[15] of the remaining general population sample of 1268 persons is shown in Figure 1. Eighty persons with the lowest ejection fraction ("at risk" group, mean age 62.6 years, s.d. ± 4.0, ejection fraction 41%, s.d. ± 7, at baseline) and 80 persons with a normal ejection fraction, randomly sampled from those with an ejection fraction above the 25th percentile and not on medication for heart failure ("control" group, mean age 61.2 years, s.d. ± 3.7, ejection fraction 70%, s.d. ± 8, at baseline) were invited to participate in the present study.



595 men, age 62.0 yr (s.d. ± 3.9)
ejection fraction 64.0 % (s.d. ± 13.1)



673 women, age 61.7 (s.d. ± 4.1)
ejection fraction 66.9 %, (s.d. ± 11.7).

Figure 4.1. Ejection fraction (estimated as EF = 1.7 x Fractional Shortening) of a general population sample of 1268 persons. Participants for the present study were sampled from the extreme left end (to the left of line a) of the ejection fraction distribution ("at risk" group) and from the area to the right of line b (ejection fraction > 25th percentile) constituting the control group.

During a three hour visit to the research center all participants underwent a comprehensive cardiovascular examination, consisting of:

- *Medical history and standardized physical examination.* One physician (AM) verified medical history, in particular events that occurred since the Rotterdam Study baseline examination, obtained information on cardiac and relevant non-cardiac history (e.g. pulmonary disease, diabetes mellitus, renal and hepatic diseases) and on current medication use. Information on chest pain, dyspnoea and intermittent claudication was obtained by means of the WHO questionnaires.[16] A physical examination was carried out to verify the absence or presence of dyspnoea, jugular venous distension, rales and rhonchi, a third heart sound, cardiac murmurs, hepatomegaly and ankle edema. Height and weight were measured with participants wearing light clothes and without shoes. Blood pressure was measured in the supine position using an automated device (Dinamap model 8100, Criticon, Florida). The average value of three to five consecutive blood pressure readings was taken as the blood pressure value.
- A *standard 12-lead electrocardiogram (ECG)* was recorded using an ESAOTE laptop electrocardiograph (Florence, Italy). All ECG's were digitally stored and analyzed using

the MEANS program, a standardized and validated ECG software program.[17] Computer generated diagnoses were verified by a cardiologist (JWD).

- *Peak expiratory flow, forced vital capacity and first second forced expiratory volume* were measured using a pocket sized flow and spirometer device (electronic diary card spirometer, EDC, Micro Medical, Rochester, U.K.). In a recent validation study this device was tested with a mechanical calibrator.[18] EDC reliably measured peak expiratory flow and first second forced expiratory volume, whereas vital capacity was systematically underestimated by 0.45 liter ($VC_{diary\ card} = 0.45 + 1.00*VC_{mechanical\ calibrator}$, standard error of estimate 0.29 liter). The average value of three highest of five consecutive measurements was used in the analysis. Forced vital capacity adjusted for the 0.45 liter underestimation is presented.

- *Frontal and lateral chest X-rays* were made at maximal inspiration in standing position using General Electric MPG-50 X-ray equipment. Thoracic and cardiac diameters were measured to calculate the cardio-thoracic ratio.[16]

- *Echocardiography* was performed with the participant in the partial left decubitus position, using a 2.25 MHz transducer (ATL Ultra Mark 4). 2-Dimensional imaging using parasternal long-axis views was performed to aid M-mode studies. Measurements were made according to the recommendations of the American Society of Echocardiography using a leading edge to leading edge convention.[19] LV internal dimension (LVIDed), ventricular septum (IVS) and LV posterior wall (LVPW) thickness were measured at end diastole as defined by the onset of the QRS complex. LV internal dimension at end systole (LVIDes) was determined at the nadir of septal motion. The percentage fractional shortening (FS) was calculated as 100[(LVIDed - LVIDes)/LVIDed] and used as an index of systolic function. Ejection fraction (EF) was estimated as EF = 1.7 x FS, using Quinones' prediction formula.[15]

- *Doppler echocardiography*. From the apical 4-chamber view mitral flow was sampled at the mitral valve leaflet tips using a 2.25 MHz pulsed wave Doppler probe (ATL Ultra Mark 4). After initial recording on videotape, mitral flow contours of 5 representative, preferably consecutive, beats were traced off-line. Peak early (E, m/s) and late diastolic inflow velocity (A, m/s) were measured to calculate the ratio of early to late diastolic inflow velocity (E/A ratio), that was used as a crude index of LV diastolic function. Doppler echocardiography was performed during quiet respiration using a standardized protocol by the same echo technician during the whole study period.

- A graded symptom limited *exercise test* with respiratory gas analysis was carried out on an electronic bicycle ergometer (Lode, Groningen, The Netherlands) with incremental steps of 20 watt/min starting at 25 watt. All subjects were able to adequately perform a bicycle ergometer test. Participants breathed through a three-way low resistance valve with a clamp placed on the nose. Expired air was analyzed with a Mijnhardt Oxycon 4 system (Mijnhardt B.V., Bunnnik, The Netherlands), providing information on oxygen consumption, carbon dioxyde production and ventilation at 30 second's intervals. Gas analyses were made by a paramagnetic O_2 and infrared CO_2 analyzer. Heart rate was continuously monitored with 12 lead ECG registration (CardioPerfect, Cardio Control, Rijswijk, The Netherlands). Systemic arterial pressure was recorded at rest and at peak

exercise, manually with a mercury sphygmomanometer, as well as each minute during exercise. A minimum of 3 minutes was allowed before starting each exercise test to ensure that stable resting measurements were made. Participants were encouraged to exercise to exhaustion. Subjective assessment of perceived exertion was obtained at maximal exercise using the modified Borg scale (0 to 10 scale).[20] Criteria for reaching a maximal effort were a maximal respiratory exchange ratio (the ratio of carbon dioxyde production to oxygen consumption at peak exercise) greater than 1, or a maximal heart rate greater than the age-predicted maximal heart rate (according to Astrand's formula: 220 - age)[21] or a peak VO_2 greater than predicted using Wasserman's formula, that takes into account weight, age and gender.[22] We took peak VO_2 consumption, expressed as percentage of predicted peak oxygen consumption as a measure of exercise capacity.

- *Laboratory.* Venous blood was drawn in prechilled tubes after at least 30 minutes of supine rest for plasma neurohormonal variables and biochemical measurements. Directly following peak exercise another blood sample was drawn for neurohormonal measurements. Within 10 minutes of the drawing of the blood, samples were centrifuged at 4°C at 3.000 x g for 10 minutes and plasma was stored at -70°C. All samples were analyzed in a blinded manner without knowledge of the participant's characteristics in a dedicated neurohormone core laboratory at the Department of Internal Medicine I at the University Hospital Dijkzigt in Rotterdam. Plasma norepinephrine[23] and renin[24] were measured as previously described. Commercially available radioimmunoassay kits were used for measurement of aldosterone (Coat-a-Count, Diagnostic Products Corporation, Los Angeles, CA), arginine vasopressin (AVP) (Incstar, Stillwater, MN), atrial natriuretic peptide (ANP) (Nichols Institute, Wijchen, the Netherlands) and N-terminal atrial natriuretic peptide (N-ANP) (Biotop, Oulo, Finland).

Statistical methods

Upon remeasurement at entry for the present study, ejection fraction remained relatively stable in the control group (71%, s.d. $\pm$ 11, versus 70%, s.d. $\pm$ 8, at baseline, $p = 0.18$), but increased in the "at risk" group (63%, s.d. $\pm$ 12, versus 41%, s.d. $\pm$ 7% at baseline, $p < 0.01$). This can be attributed to regression to the mean,[25] as persons in the "at risk" group were sampled from the left end of the ejection fraction distribution (Figure 4.1). To account for the effect of regression to the mean and in order to examine in particular neurohormonal mechanisms in persons whose ejection fraction was persistently low, the "at risk" group was redefined, based on the 33rd percentile of ejection fraction at the follow-up examination, in an "intermediate" (ejection fraction > 33rd percentile, i.e. ejection fraction 59%) and "at risk" group (ejection fraction <= 33rd percentile).

Non parametric tests were used for comparisons of data with a non-normal distribution (Mann-Whitney Two-Sample Statistic for differences in neurohormones between groups and Wilcoxon's signed-rank test for comparison of neurohormones before and after exercise). Linear regression analysis, using log transformed variables if mandatory, was performed to test for trends between groups and to study the relation of neurohormones to LV ejection fraction and left atrial diameter in the total group of 160 participants.

Table 4.1. Characteristics of participants (all classified as NYHA I). "At risk" group reclassified according to the 33rd ejection fraction percentile in intermediate and at risk.

	Control	Intermediate	At risk
		> 33rd percentile	< = 33rd percentile
	n = 80	n = 54	n = 26
Age (yr)	62.4 ± 3.8	63.8 ± 3.9	63.9 ± 4.1
Men (%)	40 (50)	24 (44)	16 (62)
Height (cm)	170 ± 9	168 ± 9	171 ± 8
Weight (kg)	75 ± 12	76 ± 11	76 ± 13
Hemodynamic data			
LV Ejection fraction(%)	71 ± 11	70 ± 7	50 ± 10
Heart rate (beats/min)	67 ± 11	72 ± 12	70 ± 11
Systolic blood pressure (mm Hg)	139 ± 14	141 ± 16	151 ± 30
Diastolic blood pressure (mm Hg)	74 ± 9	75 ± 9	79 ± 17
Mitral flow E/A ratio	0.99 ± 0.02	0.93 ± 0.03	0.98 ± 0.08
Medical history			
Myocardial infarction (%)*	4 (5)	5 (9)	6 (23)
Angina pectoris (%)	5 (6)	7 (13)	3 (12)
PTCA (%)	1 (1)	0	1 (4)
CABG (%)	2 (3)	3 (6)	3 (12)
Ischemic heart disease (%)†	7 (9)	9 (17)	7 (27)
Hypertension (%)‡	17 (21)	13 (24)	12 (46)
Diabetes mellitus (%)	2 (3)	1 (2)	1 (4)
Dyspnoea > grade I WHO[16]	13 (16)	16 (30)	11 (42)
Edema§	5 (6)	8 (15)	6 (23)
Drug therapy			
Diuretics (%)	3 (4)	3 (6)	1 (4)
Digitalis (%)	1 (1)	0	0
ACE inhibitors (%)	1 (1)	3 (6)	6 (23)
ß blockers (%)	11 (14)	5 (9)	4 (15)
Calcium channel blockers (%)	4 (5)	4 (7)	1 (4)
Combined diuretic and ß blocker (%)	2 (3)	1 (2)	2 (8)
Nitrates (%)	3 (4)	3 (6)	1 (4)
Anticoagulants (%)	1 (1)	0	2 (8)
Antiplatelet agents (%)	4 (5)	10 (19)	2 (8)
Lipid lowering drugs (%)	3 (4)	5 (9)	2 (8)
Pulmonary function tests¶			
Forced vital capacity (l)	3.4 ± 0.9	3.2 ± 0.9	3.1 ± 1.0
Peak flow rate (l/sec)	7.2 ± 2.4	6.8 ± 2.4	6.1 ± 2.3
1 sec. forced expiratory volume (l)	2.8 ± 0.6	2.6 ± 0.7	2.4 ± 0.8
CT ratio chest X-ray	0.44 ± 0.04	0.44 ± 0.04	0.46 ± 0.04
Biochemical measurements			
Serum sodium (mmol/liter)	138 ± 3	139 ± 3	139 ± 4
Serum potassium (mmol/liter)	4.1 ± 0.4	4.1 ± 0.3	4.3 ± 0.9
Serum creatinine (mmol/liter)	75 ± 12	73 ± 10	76 ± 17
Serum urea (mmol/liter)	5.9 ± 1.3	5.6 ± 1.1	6.4 ± 1.4

Values are mean values ± SD unless otherwise indicated.

* Myocardial infarction by ECG or history

† Ischemic heart disease defined as: Angina pectoris by Rose questionnaire, previous myocardial infarction/CABG/PTCA or use of anti-anginal medication.

‡ On antihypertensive medication or systolic BP > = 160 mm Hg or diastolic BP > = 90 mm Hg.

§ Edema on physical examination or history of edema developing during the course of the day.

¶ Information on pulmonary function available in 50 controls, 49 intermediate, 26 at risk participants.

Subsequently, multivariate linear regression analysis was used to adjust for age, gender, medication used and level of predicted maximal oxygen consumption reached at peak exercise. All p-values reported are for two-tailed tests, considering values < 0.05 as statistically significant.

Results

Characteristics of participants are provided in Table 4.1. Upon standardized review of all available information by a cardiologist none of the participants was judged to have clinically symptomatic heart failure; all were classified as NYHA class I. Ischemic heart disease and hypertension, the two main causes of heart failure,[2] were more frequent in the "at risk" group, as were dyspnoea and edema. Cardio-thoracic ratio was increased in these subjects and pulmonary function was diminished. The predominant indication for the use of diuretics, ß-blockers and angiotensin converting enzyme (ACE) inhibitors was hypertension in all groups (Table 4.1).

Exercise characteristics are provided in Table 4.2. Although not all reaching statistical significance, trends of diminished peak heart rate, peak systolic blood pressure, maximal load, maximal oxygen consumption and percentage of predicted maximal oxygen consumption reached were apparent. The proportion of subjects that reached the age-predicted heart rate, age-predicted oxygen consumption and a gas exchange ratio greater than 1 at peak exercise was lower in the "at risk" participants. Hence, fewer participants in this group performed a maximal effort, according to the criteria set out in the methods section. Nevertheless, perceived exertion was highest in the "at risk" group.

Table 4.2. Exercise characteristics of participants. "At risk" group classified according to the 33rd ejection fraction percentile.

	Control	Intermediate	At risk	
	n = 80	n = 54	n = 26	P_{trend}
Heart rate, before exercise (beats/minute)	92 ± 2	94 ± 2	90 ± 3	ns
Heart rate, at peak exercise (beats/minute)	151 ± 2	150 ± 3	141 ± 4	0.04
Systolic blood pressure, before exercise (mm Hg)	142 ± 2	143 ± 2	137 ± 4	ns
Systolic blood pressure, at peak exercise (mm Hg)	201 ± 3	206 ± 3	196 ± 4	ns
Maximum load (watt)	143 ± 5	130 ± 7	129 ± 9	0.08
Peak O_2 consumption (ml/kg/min)	25.3 ± 0.8	24.2 ± 1.0	23.7 ± 1.3	ns
Percent of predicted O_2 consumption reached*	107 ± 3	110 ± 4	102 ± 4	ns
Participants reaching maximal effort (%)#	77 (96)	50 (93)	20 (77)	0.004
Borg scale	5.5 ± 0.1	5.7 ± 0.2	6.2 ± 0.2	0.02

Values are means ± s.e., or percentages.

* Predicted peak 0_2 consumption was calculated using Wasserman's formula, that takes into account weight, age and gender.[22]

\# Criteria for reaching a maximal effort were a maximal respiratory exchange ratio (the ratio of carbon dioxyde production to oxygen consumption at peak exercise) greater than 1, a maximal heart rate greater than the age-predicted maximal heart rate (according to Astrand's formula: 220 - age)[21] or a peak VO_2 greater than predicted using Wasserman's formula.[22]

NS Not significant at $p < 0.05$.

Results of neurohormonal measurements at rest and following peak exercise are presented in Table 4.3 and Figure 4.2. Mean values with 95% confidence intervals and overall significance are shown in Table 4.3. ANP was the only hormone that was elevated at rest as well as after exercise in the "at risk" group, ANP_{rest} 60 pmol/l (40-81 pmol/l) and $ANP_{exercise}$ 80 pmol/l (54-107 pmol/l), compared to controls, ANP_{rest} 34 pmol/l (29-38 pmol/l) and $ANP_{exercise}$ 50 pmol/l (44-56 pmol/l) ($p < 0.01$ at rest and $p = 0.02$ peak exercise), as well as compared to the "intermediate" group, ANP_{rest} 35 pmol/l (31-40 pmol/l) and $ANP_{exercise}$ 53 pmol/l (45-61 pmol/l) ($p = 0.01$ at rest and $p = 0.07$ peak exercise). Consequently the trend across groups (control, "intermediate", "at risk") for ANP was highly significant, both at rest ($p < 0.001$) and at peak exercise ($p = 0.002$) (Table 4.3). Renin was highest in the "at risk" group, $renin_{rest}$ 12.2 μunits/l (8.0-16.3 μunits/l) and $renin_{exercise}$ 20.9 μunits/l (12.5-29.4 μunits/l), compared to the control group, $renin_{rest}$ 8.7 μunits/l (7.6-9.8 μunits/l) and $renin_{exercise}$ 15.1 μunits/l (12.8-17.3 μunits/l) ($p = 0.06$ at rest, $p = 0.06$ peak exercise), and less so compared to the "intermediate" group, $renin_{rest}$ 10.2 μunits/l (8.1-12.2 μunits/l) and $renin_{exercise}$ 19.2 μunits/l (14.3-24.1 μunits/l) ($p = 0.33$ at rest, $p = 0.32$ peak exercise). The resulting trends were of borderline significance ($p = 0.02$ at rest, $p = 0.05$ at peak exercise). All neurohormones increased appreciably upon exercise ($p < 0.0001$, Figure 4.2).

The results remained essentially unchanged after categorization of the at risk group by mean ejection fraction (63%), instead of by the 33rd percentile of ejection fraction (59%).

The relationship of LV systolic function as well as left atrial diameter to neurohormones at rest and peak exercise was studied in the aggregate data of the 160 participants. Univariate analyses revealed a weak negative association of resting renin ($p = 0.04$) and N-ANP ($p = 0.04$) to systolic function, that disappeared on adjustment for age and gender (p values 0.16 and 0.05, respectively). Exercise norepinephrine was higher in persons with higher ejection fraction ($p = 0.03$), whereas the strong inverse relation of ANP to LV systolic function was confirmed ($p < 0.001$ at rest and peak exercise). These associations remained similar adjusting for age and gender (p values 0.001, < 0.001 and 0.05, for exercise norepinephrine, resting and exercise ANP) and did not change appreciably upon additional adjustment for the use of medication (diuretics, ß blockers or ACE inhibitors).

Although relatively few participants were using diuretics ($n = 7$, 4.4%), ß blockers ($n = 20$, 12.5%) or ACE inhibitors ($n = 10$, 6.3%), multivariate linear regression analysis demonstrated significant relations between medication use and neurohormones, that generally persisted upon adjustment for age, gender and LV systolic function. The use of diuretics was associated with higher norepinephrine, renin and aldosterone concentrations, but no relation of diuretics to ANP was found. In persons on ß blockers norepinephrine, ANP and N-ANP were higher, but renin was lower and no relation to aldosterone was demonstrated. In those who used ACE inhibitors both renin and (N)-ANP were higher, whereas norepinephrine and aldosterone did not differ from persons not on ACE inhibitors.

Table 4.3. Plasma neurohormones following 30 minutes of supine rest and directly following peak exercise. Values are group mean and 95% confidence intervals.

	Control	Intermediate	At risk	
	n	n > 33rd percentile	n <= 33rd percentile	P_{trend}
Plasma norepinephrine (pg/ml)				
Rest	n=80 328 (298 - 360)	n=54 313 (278 - 348)	n=26 301 (241 - 360)	0.326
Peak exercise	n=77 1517 (1287 - 1747)	n=53 1391 (1138 - 1643)	n=25 1237 (955 - 1520)	0.179
Plasma renin (μunits/ml)				
Rest	n=80 8.7 (7.6 - 9.8)	n=54 10.2 (8.1 - 12.2)	n=25 12.2 (8.0 - 16.3)	0.024
Peak exercise	n=78 15.1 (12.8 - 17.3)	n=53 19.2 (14.3 - 24.1)	n=24 20.9 (12.5 - 29.4)	0.049
Plasma aldosterone (pg/ml)				
Rest	n=80 37 (28 - 46)	n=54 44 (35 - 53)	n=26 37 (26 - 48)	0.730
Peak exercise	n=78 149 (129 - 169)	n=53 157 (136 - 179)	n=25 143 (115 - 171)	0.946
Plasma arginine vasopressin (pg/ml)				
Rest	n=79 0.8 (0.6 - 1.0)	n=54 0.7 (0.5 - 0.8)	n=26 0.9 (0.7 - 1.2)	0.931
Peak exercise	n=78 5.2 (3.3 - 7.1)	n=54 4.7 (2.9 - 6.5)	n=25 3.5 (1.6 - 5.4)	0.331
Atrial natriuretic peptide (pmol/l)				
Rest	n=80 34 (29 - 38)	n=54 35 (31 - 40)	n=26 60 (40 - 81)	< 0.001
Peak exercise	n=79 50 (44 - 56)	n=53 53 (45 - 61)	n=25 80 (54 - 107)	0.002
N-terminal atrial natriuretic peptide (pmol/l)				
Rest	n=80 382 (334 - 429)	n=54 333 (299 - 369)	n=26 488 (334 - 642)	0.197
Peak exercise	n=78 454 (395 - 513)	n=53 389 (349 - 430)	n=25 560 (372 - 747)	0.349

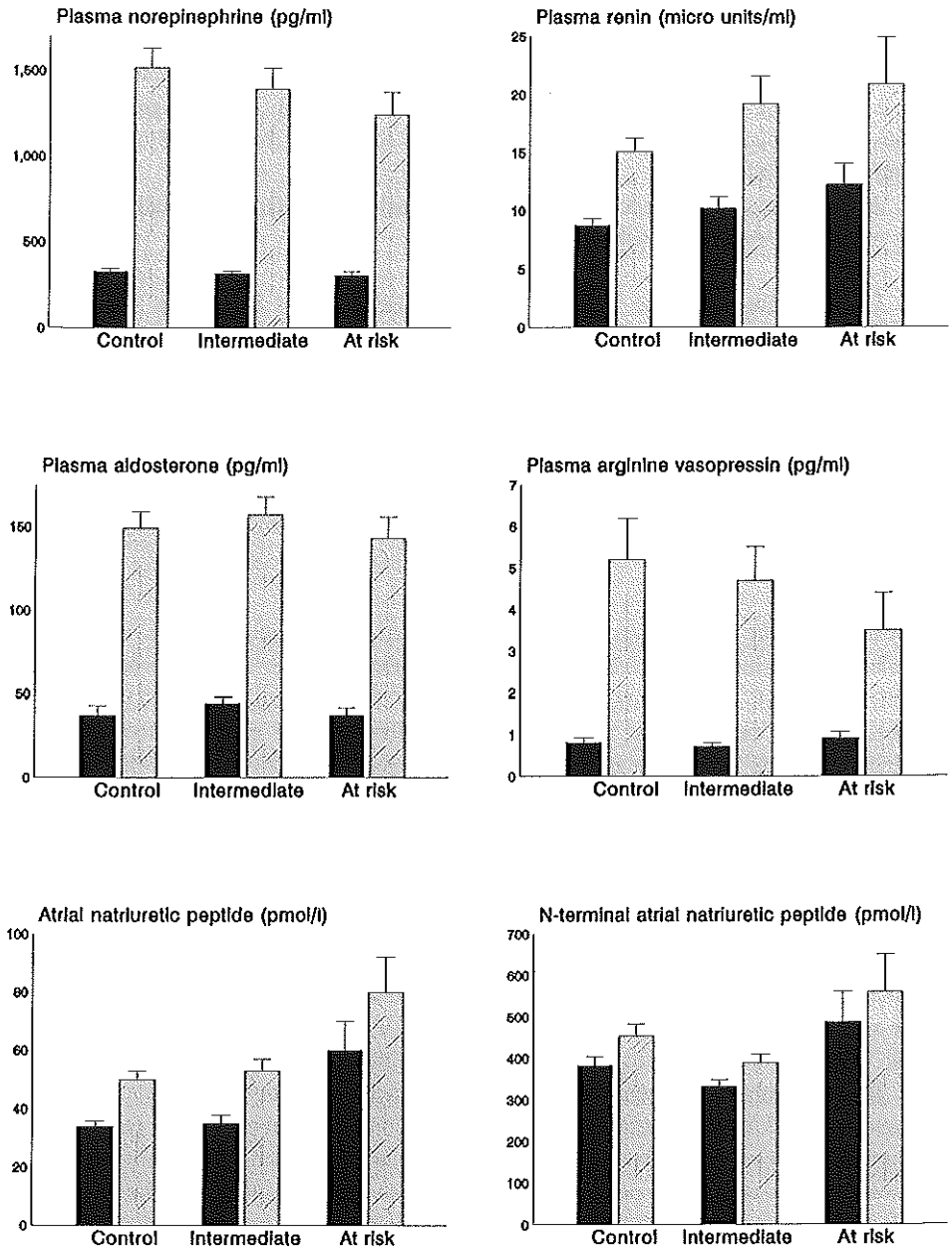


Figure 4.2. Neurohormones values at rest and following peak exercise. Mean values + 1 standard error. Black bars represent rest values, striped bars represent exercise values.

Of the six neurohormones studied, only the atrial natriuretic peptides were found to have a positive association to left atrial diameter, that was highly significant for ANP ($p = 0.01$ at rest and peak exercise, adjusted for age and gender) and less so for N-ANP ($p = 0.05$ at rest and $p = 0.04$ peak exercise, adjusted for age and gender). These relations did not change appreciably upon additional adjustment for the use of diuretics, ß blockers or ACE inhibitors.

All analyses were repeated using log transformed neurohormonal values; the results remained essentially unchanged.

For norepinephrine the increase upon exercise was less in persons with a lower ejection fraction ($p = 0.02$, 14 pg/ml higher increase for each % increase in ejection fraction, 95% C.I. 2 - 26), whereas for the other neurohormones studied increases upon exercise were not related to resting ejection fraction. As it is conceivable that participants who did not reach their predicted maximal oxygen consumption during the exercise test did not attain maximal neurohormonal values, we repeated the analyses adjusting for percentage of maximal predicted oxygen consumption reached. The results remained similar.

Discussion

The results of our study indicate that asymptomatic LV dysfunction is characterized particularly by an increase in ANP, at rest as well after exercise. ANP also had the strongest relation to left atrial diameter. All neurohormones increased significantly following exercise. Despite the fact that they reached a similar level of exercise, the increase in norepinephrine was smaller in persons with lower ejection fraction, suggesting a blunted sympathetic response to exercise in early stages of heart failure.

Methodology

This study is the first to evaluate neurohormonal characteristics at rest and directly following peak exercise in persons with subclinical LV dysfunction, and as such may contribute insight into mechanisms involved in the transition of asymptomatic LV systolic dysfunction to clinically overt heart failure. The advantages of our study relate to the fact that it was a single center, population based study using highly standardized procedures for the selection and subsequent comprehensive cardiovascular evaluation of 160 participants. Equal numbers of men and women were included, whereas previous studies of (asymptomatic) LV dysfunction predominantly comprised men. The percentage of participants on cardiovascular medication was relatively small. Neurohormones were measured at rest and after peak exercise since one of the study hypotheses was that neurohormonal activation would only become apparent upon exercise. Measurement of oxygen consumption during exercise allowed to adjust for percentage of predicted maximal oxygen consumption reached.

Echocardiography was employed to detect persons with impaired LV systolic function. Apart from a higher frequency of ischemic heart disease and hypertension, the "at risk" participants had more symptoms and signs associated with heart failure. In

addition, they had diminished pulmonary function, that could not be attributed to chronic obstructive pulmonary disease, and diminished peak oxygen consumption. This expands findings from previous studies that documented a decrease in pulmonary function in heart failure[26] as well as reduced exercise capacity in persons with asymptomatic LV dysfunction.[27] The control group was well defined, underwent the same examination and was sampled from the same population.

In addition, our study demonstrates that the effect of regression to the mean should be appreciated when using ejection fraction to detect LV systolic dysfunction in population based studies and indicates that repeated echocardiographic measurements are necessary in these studies.

Pathophysiological implications

Heart failure is initiated by an abnormality in cardiac function; subsequently neurohormonal activation and cardiac remodeling accompany the development of chronic heart failure.[5,28,29] Following studies that documented elevated plasma norepinephrine, renin, ANP, aldosterone and AVP in patients with severe heart failure,[4] the SOLVD investigators demonstrated that both vasoconstrictor and vasodilator systems (ANP, AVP, renin and norepinephrine) are activated in early stages of heart failure and that neuroendocrine activation progresses with the development of symptoms.[7,30] Closer inspection of the data, however, revealed a considerable overlap in neurohormones in controls and persons with (a)symptomatic heart failure, indicating that neurohormonal activation may be highly variable within as well as between groups. After exclusion of patients (20%) on diuretics, that are known to activate the renin-angiotensin-aldosterone (RAA) system,[31] plasma renin activity did not differ between controls and patients with a left ventricular ejection fraction of 35% or less, either with or without overt symptoms and signs of heart failure. Thus, sympathetic nervous system activation and release of ANP and AVP appear to precede activation of the RAA system in persons with LV dysfunction. A subsequent report based on 859 patients of the SOLVD registry (mean ejection fraction 30 $\pm$ 9%, 69% of whom had signs of congestive heart failure), indicated that neurohormonal activation is related to severity of LV dysfunction.[30] Of the four neurohormones studied (norepinephrine, renin, AVP and ANP), ANP had the best correlation with LV ejection fraction.

The increase in ANP and, to a smaller extent, N-ANP in our study participants with impaired LV systolic function demonstrates the importance of natriuretic peptides in the pathophysiology of heart failure.[32] ANP has emerged as a predictor of the occurrence of heart failure,[33] a marker of the severity of heart failure[34] and as a strong prognostic indicator in (a)symptomatic LV dysfunction.[9,35] ANP has vasodilator and natriuretic effects that counterbalance vasoconstriction and sodium retention by the kidneys as a result of activation of the sympathetic nervous system, the renin-angiotensin-aldosterone system and AVP in heart failure. The N-terminal part of the atrial natriuretic prohormone appears to reflect the degree of heart failure,[36] and has been implied to be useful in the detection of asymptomatic LV dysfunction.[12,37] The atrial natriuretic peptides are released from secretory granules in the atria upon atrial stretching. The observed relation between

(N)-ANP and left atrial diameter in our study is in accordance with this pathophysiologic mechanism.

Animal models indicate that early heart failure may be characterized by sympathetic activation with peripheral vasoconstriction and increased ANP in the absence of activation of the RAA system.[38,39] The early increase in ANP in our study appears to confirm this pathophysiological mechanism and expands two previous studies,[7,40] that found increased ANP values in early heart failure, to a general population sample. Interestingly, although in the aggregate data of 160 study participants resting N-ANP was higher in those with worse LV systolic function, this relation was not as strong as for ANP. Contrary to ANP, exercise N-ANP was not higher in subjects with impaired LV systolic function. This may reflect the longer half life of N-ANP resulting in more stable plasma concentrations.

As patients with heart failure have increased ANP synthesis in the atria as well as ventricles,[41] modulation of plasma ANP, e.g. by inhibition of ANP degradation, may offer new possibilities for the early treatment of heart failure.[42] From this pathophysiological point of view, the use of diuretics may actually be counterproductive in the early stages of heart failure. Apart from directly stimulating the RAA system, diuretics may also decrease ANP. This leaves the RAA activation unopposed, leading to progression of heart failure. Indeed, the use of diuretics in our study was associated with higher norepinephrine, renin and aldosterone concentrations, whereas no relation to (N)-ANP was found. Both ANP and N-ANP were higher in persons on ACE inhibitors and ß blockers. In the latter group renin was lower, a finding that appears to support the use of ß blockers in heart failure.[43,44]

Neurohormones increase during exercise in patients with heart failure.[45] Francis demonstrated that sympathetic drive in NYHA class III/IV heart failure patients is attenuated, when adjusting for percentage of predicted peak O_2 reached.[46] In NYHA class II/III heart failure patients both a blunted[47] and a comparable response[48] of ANP to exercise has been reported. However, in neither of these two studies adjustments were made for the percentage of predicted peak O_2 consumption reached. Our study expands Francis' findings to NYHA class I persons with impaired LV function, who were also found to have an attenuated sympathetic drive. For the other neurohormones studied, we observed a similar increase with exercise, regardless of ejection fraction, that remained essentially similar after adjustment for percentage of predicted peak O_2 consumption reached.

Summary

In conclusion, early heart failure appears to be characterized particularly by an increase of ANP, at rest as well as following maximal exercise, and a blunted response of the sympathetic system to exercise. The findings suggest that drugs such as ANP degradation inhibitors rather than diuretics may constitute a pathophysiologically sound approach to the treatment of early heart failure. Lastly, repeated echocardiographic measurements are mandatory when screening for LV systolic dysfunction in the general population.

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5. Impact of hypertension treatment on prevalence of high blood pressure and cardiac target organ damage. The Framingham Heart Study 1950 - 1989

Introduction

Hypertension is an important contributor to morbidity and mortality from cardiovascular disease.[1] The proportion of persons with hypertension who are on treatment has risen steadily over the past four decades.[2-6] Consequently, the proportion of persons with high blood pressure has declined in the United States population.[6] Several clinical trials have shown that treatment of hypertension reduces the incidence of cardiovascular disease sequalae.[2,7] Long-term benefits of antihypertensive therapy have been demonstrated for the general population as well.[8,9] However, the contribution of improved treatment of hypertension to the decline in ischemic heart disease mortality rates is difficult to assess for the population at large.[10]

Risk of cardiovascular disease at any level of high blood pressure increases markedly for patients with target organ damage of the heart, kidneys, brain or large arteries.[2] Left ventricular hypertrophy is causally related to high blood pressure and represents evidence of hypertensive target organ damage.[2,11-15] Individuals with electrocardiographic evidence of left ventricular hypertrophy are at increased risk for a variety of cardiovascular disease sequelae, including angina pectoris, myocardial infarction, stroke, congestive heart failure and sudden death.[11,16-21] Treatment of high blood pressure has been shown to prevent the development of left ventricular hypertrophy or reverse it.[11,16,22-26] A recent analysis from the Framingham Heart Study indicated that reversal of electrocardiographic evidence of left ventricular hypertrophy results in a decreased risk for the development of cardiovascular disease.[17]

The Framingham Heart Study has obtained blood pressure measurements, information on the use of antihypertensive medication, and electrocardiograms in a standardized manner since its inception in 1948. The goals of this investigation were to describe temporal trends in high blood pressure and its treatment in a general population sample and to determine if control of high blood pressure has resulted in a concomitant decline in the prevalence of hypertensive target organ damage, as evidenced by electrocardiographic left ventricular hypertrophy.

Methods

Study population and cardiovascular examination

The Framingham Heart Study began in 1948 with the enrollment of 5209 men and women 28 to 62 years of age.[27,28] These participants have been examined every two years since. In 1971 another cohort of 5124 men and women, who were the children, or the spouses of the children of the original participants, was enrolled.[29] The offspring participants have been examined four times since. Because left ventricular hypertrophy was rare in younger participants and since no participants 75 years and older were available for temporal trends analysis in the early years of the study, the analysis has been restricted to persons

aged 45 to 74 years from 1950 to 1989.

Each examination included an extensive cardiovascular history and physical examination, blood pressure determinations, 12-lead electrocardiogram and measurement of other physiologic variables. Morbidity and mortality were continuously monitored by hospital surveillance and by communication with personal physicians and relatives of study participants. All new cardiovascular events were reviewed by a panel of three experienced investigators. Detailed descriptions of sampling methods, examination techniques and procedures, and the criteria for various end points related to cardiovascular disease have been published.[27-30]

Body mass index was calculated as weight(kg)/height(m)^2. Readings of systolic and diastolic blood pressure were taken from the left arm of each subject with a mercury-column sphygmanometer while the subject was sitting. Readings were recorded to the nearest even number. A large cuff was used when required. The beginning of the fifth Korotkoff phase (disappearance) was used to determine diastolic pressure unless the sound persisted to zero, in which case the beginning of the fourth phase was recorded.

Definition and categorization of normal and high blood pressure

Systolic and diastolic blood pressure were based on the average of two separate measurements recorded by the examining physician at each examination. High blood pressure (irrespective of treatment) was defined as systolic blood pressure greater than or equal to 160 mmHg or diastolic blood pressure greater than or equal to 100 mmHg. This corresponds to stage II or higher hypertension according to the criteria established in the fifth report of the Joint National Committee (JNC V) on Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension stages were as follows stage 1, systolic BP 140-159 mmHg or diastolic BP 90-99 mmHg; stage 2, systolic BP 160-179 mmHg or diastolic BP 100-109 mmHg; stage 3, systolic BP 180-209 mmHg or diastolic BP 110-119 mmHg and stage 4, systolic BP $>=$210 mmHg or diastolic BP $>=$120 mmHg.[2]

Electrocardiographic methods and definition of left ventricular hypertrophy

Resting 12-lead electrocardiograms were routinely obtained at each clinic visit. All electrocardiograms obtained from the first to 20th biennial examination of the original cohort and from the first to fourth examination of the Offspring Study participants were used to determine the prevalence of electrocardiographic left ventricular hypertrophy.

These examinations span the time period 1950 to 1989. The initial diagnosis of left ventricular hypertrophy was made by the examining physician at the time of the routine clinic visit on the basis of fulfillment of at least one of the following voltage criteria: R wave $>$ 1.1 mV in aVL; R wave $>=$ 2.5 mV in V5 or V6; S wave $>=$ 2.5 mV in V1 or V2; sum of S in V1 or V2 plus R in V5 or V6 $>=$ 3.5 mV; sum of R in I and S in III $>=$2.5 mV. One reader, blinded to clinical information, measured each of the left ventricular hypertrophy voltage criteria for all electrocardiograms identified as showing left ventricular hypertrophy by the study physician at the time of the clinic examination.

In addition, the amplitudes of the R wave in AVL and the S wave in V3 were measured; their sum was considered as an index of the severity of left ventricular

hypertrophy.[31,32] All electrocardiographic voltages were measured to the nearest 0.1 mV. All subsequent electrocardiograms of subjects diagnosed with left ventricular hypertrophy by the study physician were reviewed as well. All tracings were then analyzed by a second blinded reader (DL), who reviewed voltage criteria and measurements and graded the repolarization features. Repolarization was categorized as normal, mildly abnormal (ST-T flattening, isolated ST depression or T wave inversion) or severely abnormal ("strain" pattern - ST depression in association with inverted or biphasic T waves).

For this investigation electrocardiograms were eligible for inclusion only if a diagnosis of left ventricular hypertrophy was confirmed upon blinded review. In addition, tracings with a sum of R in aVL and S in V3 less than or equal to 1.3 mV, and those with normal repolarization were excluded. A combined voltage of 1.3 mV equals the 25th percentile of a reference group of persons with electrocardiographic left ventricular hypertrophy in a previous study.[17] The 50th and 75th percentile cutpoints in that study were 1.8 mV and 2.3 mV, respectively. Electrocardiograms with complete right or left bundle branch block, Wolff-Parkinson-White syndrome, prior Q-wave myocardial infarction and all tracings obtained in subjects who were receiving digoxin were excluded from analysis.

Statistical methods

Age adjusted mean values of blood pressure and body mass index, antihypertensive medication use, and prevalence of high blood pressure (>= stage 2, irrespective of treatment) as well as electrocardiographic left ventricular hypertrophy were determined for the four decades studied, for men and women separately. Age adjustment was carried out using least squares regression.

The generalized estimating equation method was used to test for trends in use of antihypertensive medication, prevalence of high blood pressure and electrocardiographic left ventricular hypertrophy.[33] This method adjusts for repeated measurements on the same individuals. The model included age and examination year as independent variables. The latter was used to test for temporal trends in prevalence. The generalized estimating equation method was also employed to determine if the prevalence trends persisted in a gender specific multivariate analysis adjusting for age and body mass index.

In a gender specific multivariate logistic model the relation of age, systolic blood pressure, body mass index, treatment with antihypertensive medication, and decade of examination (independent variables) to the presence of electrocardiographic left ventricular hypertrophy (dependent variable) was studied. All statistical tests were two-sided. A result was considered statistically significant if $p < 0.05$.

Results

Study population

Of the 5,209 original subjects (2,336 men, 2,873 women) from the Framingham Heart Study who were enrolled in 1948, 839 men and 990 women developed left ventricular hypertrophy during follow-up to 1990. LVH developed in 125 men and 27 women of the 5124 offspring participants (2,483 men, 2,641 women) whose enrollment started in 1971.

After exclusions, 672 men and 593 women, ages 45 - 75 years, developed left ventricular hypertrophy between 1950 and 1990 (Table 5.1). The ECG analyses are based on a total of 51,756 person-examinations with follow-up.

Table 5.1. Derivation of study population.

	Original Cohort		Offspring		
	Men	Women	Men	Women	Total
Subjects					
Subjects at examination 1	2,336	2,873	2,483	2,641	10,333
Subjects who developed LVH*	839	990	125	27	1981
For ages 45 - 74 years from 1950 - 1990					
Person-examinations contributed	21,099	27,979	3,691	3,756	56,525
Subjects who developed LVH	695	702	81	20	1498
ECG exclusions					
prior Q wave myocardial infarction	25	10	1	0	36
bundle-branch block	19	22	3	1	45
Wolff-Parkinson-White syndrome	0	0	0	0	0
use of digoxin	56	96	0	0	152
Remaining subjects with LVH	595	574	77	19	1265
Eligible sample for ECG analysis					
Person-examinations contributed†	18,311	26,286	3,499	3,660	51,756

* Combined voltage RaVL and SV3 > 1.3 mV and repolarization abnormalities present, in addition to fulfillment of standard voltage criteria (see methods).

† Person-examinations contributed following application of ECG exclusion criteria to all participants.

Hypertension treatment, blood pressure and electrocardiographic left ventricular hypertrophy

Table 5.2 presents age adjusted temporal trends in blood pressure, body mass index, use of antihypertensive medication, prevalence of high blood pressure, and prevalence of left ventricular hypertrophy by calendar decade for men and women separately. Increased use of antihypertensive medication was accompanied by declines in prevalence of stage II or greater high blood pressure and electrocardiographic left ventricular hypertrophy. The prevalence of electrocardiographic left ventricular hypertrophy declined from 4.5% in men in the 1950's to 2.5% in the 1980's. Corresponding figures for women were 3.6% and 1.1%. Trends in prevalence of high blood pressure stages are presented in Table 5.3. Accompanying the general decline in high blood pressure was a greater proportional decline in higher stages of blood pressure.

Table 5.2. Temporal trends in antihypertensive medication use, prevalence of high blood pressure and LVH. Men and women ages 45-74 years, age adjusted values.

Age 45-74 years	Men					Women				
Decade	1950s	1960s	1970s	1980s	Change*	1950s	1960s	1970s	1980s	Change*
Person-examinations	5,695	6,882	4,766	4,467		7,552	9,753	6,828	5,813	
Mean Age (yr.)	54	57	61	59		54	58	62	61	
Mean systolic BP†	137.4	137.3	134.7	133.2	- 1.6 (-2.3)	145.3	139.9	132.6	130.4	- 4.7 (-4.6)
Mean diastolic BP	84.5	83.7	82.5	81.8	- 1.0 (-1.5)	85.7	82.7	79.2	79.2	- 2.5 (-2.5)
BMI (kg/m^2)‡	25.9	26.2	26.6	27.2	0.5	26.3	25.7	25.5	25.8	- 0.03
HTN-Rx use(%)§	2.3	7.3	16.3	24.6	128% (123%)	5.7	13.8	20.6	27.7	70% (78%)
High blood pressure(%)¶	18.5	17.5	14.2	9.2	- 25% (-29%)	28.0	21.2	11.0	7.7	- 42% (- 43%)
ECG-LVH(%)	4.5	3.2	1.8	2.5	- 24% (-23%)	3.6	2.2	0.6	1.1	- 41% (- 41%)

* Mean change per decade, adjusted for age as well as for age and body mass index (in parentheses).
All changes are highly significant ($p < 0.0001$), with exception of BMI in women ($p = 0.77$).
† Blood pressure (mmHg)
‡ Body Mass Index
§ HTN-Rx use: use of antihypertensive medication
¶ SBP >= 160 mmHg or DBP >=100 mmHg, irrespective of antihypertensive medication

Table 5.3. Temporal trends in severity of high blood pressure (irrespective of treatment). Men and women ages 45-74 years, values adjusted for differences in age and body mass index.

Age 45-74 years	Men					Women				
Decade	1950s	1960s	1970s	1980s	Change*	1950s	1960s	1970s	1980s	Change*
Person-examinations	5,695	6,882	4,766	4,467		7,552	9,753	6,828	5,813	
>= stage 2 (%)†	19.1	17.7	14.0	8.1	- 29%	27.2	21.3	11.4	7.7	- 29%
>= stage 3 (%)‡	7.0	5.4	2.7	1.3	- 42%	10.7	7.8	2.4	0.9	- 54%
>= stage 4 (%)§	1.8	0.8	0.3	0	- 63%	2.5	1.4	0.2	0.1	- 68%

* Mean change per decade, adjusted for age and body mass index
† stage 2: SBP >= 160 mmHg or DBP >= 100 mmHg
‡ stage 3: SBP >= 180 mmHg or DBP >= 110 mmHg
§ stage 4: SBP >= 210 mmHg or DBP >= 120 mmHg

Prevalence of electrocardiographic left ventricular hypertrophy and the proportion of persons having more severe degrees of left ventricular hypertrophy (combined voltage > 1.8 mV and > 2.3mV) showed parallel declines (Table 5.4). In men the percentage electrocardiograms demonstrating severe repolarization abnormalities decreased from 1.6% in the 1950's to 0.8% in the 1980's. For women these figures were 1.4% and 0.4%. The combined voltage of the R wave in lead aVL and S wave in lead V3, an index of the severity of left ventricular hypertrophy showed a similar trend (Table 5.4). Among subjects with left ventricular hypertrophy mean combined voltage declined from 23.0 mV in the 1950's to 21.0 mV in the 1980's for men. For women these figures were 23.8 mV and 20.0 mV, respectively.

As expected, the presence of electrocardiographic left ventricular hypertrophy had a strong positive association to age in both men and women (Table 5.5). Multivariate odds ratios of systolic blood pressure, body mass index, antihypertensive medication use and decade of examination for electrocardiographic left ventricular hypertrophy are presented as well. Higher systolic blood pressure levels conferred a higher risk of electrocardiographic left ventricular hypertrophy. A higher body mass index was associated with a higher prevalence of left ventricular hypertrophy in men, but with a lower prevalence in women. Subjects treated with antihypertensive medication were more likely to have left ventricular hypertrophy and left ventricular hypertrophy was less common in the 1960s, 1970s and 1980s, compared to the 1950s.

Table 5.5. Risk factors for ECG LVH. Multivariate odds ratios for the prevalence of electrocardiographic left ventricular hypertrophy.

	Men			Women		
	OR	95% CI	P	OR	95%CI	P
Age(yr)	1.03	1.02 - 1.05	0.0001	1.07	1.06 - 1.09	0.001
Systolic BP(mmHg)	1.04	1.04 - 1.05	0.0001	1.03	1.03 - 1.04	0.001
BMI (kg/m^2)*	1.03	1.01 - 1.06	0.0146	0.95	0.94 - 0.97	0.001
HTN-Rx use (%)†	1.86	1.48 - 2.35	0.0001	2.86	2.33 - 3.51	0.001
Decade‡:						
1950s	1.00	Referent group		1.00	Referent group	
1960s	0.63	0.51 - 0.78	0.0001	0.41	0.32 - 0.52	0.001
1970s	0.44	0.33 - 0.58	0.0001	0.23	0.17 - 0.31	0.001
1980s	0.40	0.27 - 0.58	0.0001	0.29	0.21 - 0.42	0.001

* Body mass index.
† Use of antihypertensive medication.
‡ 1950s used as reference.

Controlling for age and body mass index, the increase in use of antihypertensive medication and the temporal decline in prevalence of high blood pressure and electrocardiographic left ventricular hypertrophy remained highly significant (Table 5.2). Mean changes per decade, adjusted for age and body mass index, are presented for the variables studied in Tables 5.2-4.

Table 5.4. Temporal trends in prevalence and severity of electrocardiographic left ventricular hypertrophy. Men and women ages 45-74 years, age adjusted values.

Age 45-74 years	Men					Women				
Decade	1950s	1960s	1970s	1980s	Change*	1950s	1960s	1970s	1980s	Change*
Person-examinations	5,695	6,882	4,766	4,467		7,552	9,753	6,828	5,813	
ECG LVH (n)	222	217	110	123		208	202	88	95	
ECG LVH (%)	4.5	3.2	1.8	2.5	- 24% (-23%)	3.6	2.2	0.6	1.1	- 41% (-41%)
Mean voltage†	23.0	21.4	20.6	21.0	- 0.7 (-0.8)	23.8	22.0	19.3	20.0	-0.6 (-0.6)
Voltage criteria‡										
ECG LVH_{25} (%)	0.7	0.6	0.5	0.5	- 16% (-16%)	0.7	0.5	0.1	0.3	- 37% (-39%)
ECG LVH_{50} (%)	1.4	0.9	0.6	1.0	- 14% (-16%)	1.0	0.6	0.2	0.3	- 38% (-38%)
ECG LVH_{75} (%)	2.4	1.7	1.0	0.8	- 36% (-37%)	1.9	1.1	0.3	0.4	- 47% (-46%)
Repolarization§										
mildly abnormal	2.9	2.3	1.2	1.6	-81% (-80%)	2.2	1.4	0.3	0.7	- 64% (-65%)
severely abnormal	1.6	0.9	0.6	0.8	-78% (-77%)	1.4	0.9	0.3	0.4	- 63% (-63%)
severely / LVH_{total}	0.4	0.3	0.3	0.3		0.4	0.4	0.5	0.4	

* Mean change per decade, adjusted for age as well as for age and body mass index (in parentheses).

† Sum of RaVL and SV3.

‡ Voltage criteria: LVH_{25} 13 mV < RaVL + SV3 <= 18 mV.
LVH_{50} 18 mV < RaVL + SV3 <= 23 mV.
LVH_{75} RaVL + SV3 > 23 mV.

§ Repolarization: mildly abnormal — ST-T flattening, isolated ST depression or T wave inversion
severely abnormal — "strain" pattern - ST depression in association with inverted or biphasic T waves.

Discussion

We studied the impact of increasing use of antihypertensive medication on the prevalence of high blood pressure electrocardiographic left ventricular hypertrophy in a general population sample followed from 1950 to 1989. Our data indicate that the widespread introduction of antihypertensive medication over the past forty years has resulted in a decline in the prevalence of high blood pressure. The decline was particularly striking for stage III and IV high blood pressure. A concomitant decrease in the prevalence of hypertensive target organ damage, as assessed by ECG evidence of LVH, were observed. In addition, among those with left ventricular hypertrophy, mean voltage (RaVL plus SV3) declined.

Our data are in accordance with findings from the National Health and Nutrition Examination Survey (NHANES), 1981-1991, indicating that awareness, treatment and control of hypertension in the United States have improved over recent years.[6] NHANES data also indicated a general increase in body mass index of the American population from 1960 to 1991; this trend was observed for nearly all gender and age categories.[34]

Interestingly, in our study, age adjusted mean blood pressure levels (both diastolic and systolic) decreased appreciably in women, but conspicuously less so in men. This may be attributed to the fact that body mass index increased in men, whereas body mass index declined over time in women. A 10 pound increase in weight has been demonstrated to result in a 4.5 mmHg increase in systolic blood pressure.[35] Both the increase in obesity in men and decrease in women are consistent with previous reports of the Framingham Heart Study.[36] The increase in body mass index has been related to decreasing numbers of male smokers, the opposite occurring in women.[36,37]

Left ventricular hypertrophy and hypertension; risk factors, mechanisms and possible effects of modification.

Electrocardiographic left ventricular hypertrophy is an important risk factor for cardiovascular disease.[11,15,18,21] Left ventricular hypertrophy was reported to be the characteristic of the resting electrocardiogram that carried the highest risk for fatal coronary heart disease in a group of 7,682 men who were followed up for 12 years, conferring an 11.4 fold (95% confidence interval 5.4 - 22.2) increased hazard.[21] The mechanisms by which left ventricular hypertrophy is associated with increased risk for cardiovascular sequelae are not fully understood. Hypertrophy increases the oxygen requirement of the myocardium, which, in the setting of decreased supply due to atherosclerosis and decreased coronary reserve, imposes a hazard of ischemia. This is especially true when repolarization abnormalities are present.[38] Left ventricular hypertrophy also is associated with increased risk for arrhythmias[39-43] and sudden death.[13,44]

Blood pressure is a major determinant of left ventricular hypertrophy on the electrocardiogram (both in terms of voltage criteria and repolarization abnormalities).[15,17] Regression of electrocardiographic left ventricular hypertrophy has been observed in hypertensive patients in response to blood pressure treatment,[16,23,24,26,45,46] apparently reducing cardiovascular risk.[17] Over 43 million Americans have hypertension (defined as systolic blood pressure >= 140 mmHg, diastolic blood pressure >= 90 mmHg, or

treatment with antihypertensive medication) of whom about half are on drug treatment.[6] Since high blood pressure is one of the major risk factors for cardiovascular disease, it is a reasonable assumption that progress in the detection, treatment and control of hypertension has contributed substantially to the decline in coronary heart disease and stroke mortality.[2,8,9] According to one optimistic estimate, antihypertensive treatment accounted for 18% of the observed decline in coronary heart disease mortality rates in the period 1968-76.[10] The decline in prevalence, severity (in trems of voltage) and incidence of left ventricular hypertrophy in our population-based study can be interpreted as a favorable change in presence of a major cardiovascular risk factor and as such may have contributed to the decline in cardiovascular disease mortality rates, observed since the late 1960's.

Study strengths and limitations

This was a longitudinal study of blood pressure levels, use of antihypertensive medication and hypertensive target organ damage in a general population sample of over 10,000 persons, contributing 51,756 person examinations. As such referral bias is less likely to have occurred than in hospital or clinic-based studies. Participants were examined at regular intervals and morbidity and mortality were continuously monitored. Measurements were carried out in a highly standardized way throughout the study period. Changing diagnostic techniques and non-random attrition, favoring continued participation of healthier persons,[47] may result in a certain degree of bias when analysing temporal trends within cohorts. Measurements of weight and blood pressure were done in a standardized manner that did not change over the study period. Information on the use of antihypertensive medication was routinely obtained. The electrocardiogram coding form that is filled out by the examining physicians underwent minor changes during the course of the study. It is conceivable that this affected the coding of electrocardiograms by the examining physicians. To minimize any potential bias we used a strict definition of electrocardiographic left ventricular hypertrophy, excluding mild forms of left ventricular hypertrophy (see Methods section). The study can be perceived as a dynamic cohort study, with participants entering upon reaching 45 years and leaving at 75 years; moreover, original Framingham cohort as well as Offspring Study participants were included. This should attenuate the possible effects of non random attrition.

Lastly, racial differences in prevalence of hypertension[6] and performance of electrocardiographic criteria for left ventricular hypertrophy have been reported[48]; since the Framingham Heart Study sample is predominately white, the results may not be applicable to other racial groups.

Our data do not prove that the improvement in blood pressure control caused the decline in prevalence of left ventricular hypertrophy in our general population sample. We can, however, conclude that these trends were concurrent and are consistent with a causal relation. The concomitant decline in severity of left ventricular hypertrophy provides further support.

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General discussion

The studies described in this thesis were prompted by the realization that heart failure will be an increasingly important public health problem in the decades to come.[1] Epidemiological information on heart failure, however, is scarce. The population-based Rotterdam Study, a single center, prospective follow-up study of 7,983 persons, aged 55 years or over, that started in 1990 provided a unique opportunity to gain more insight into the epidemiology of heart failure and neurohormonal regulation in presymptomatic heart failure.[2] An investigation of trends in hospital admissions for heart failure in the Netherlands from 1980 to 1993 and a longitudinal analysis of the effect of the increasing use of antihypertensive medication on the prevalence of electrocardiographic left ventricular hypertrophy in participants of the Framingham Heart Study complement the essentially cross-sectional Rotterdam Study analyses.

Epidemiology of heart failure

In a pilot study of 54 Rotterdam Study participants, scores that have previously been used to assess the presence of heart failure were evaluated. The diagnostic characteristics of the score that was subsequently used to estimate the prevalence of heart failure in the Rotterdam Study was found to compare favorably to previously used scores in population-based studies of heart failure. The prevalence of heart failure increased progressively with age, from 0.7% in persons aged 55 to 65 years to 11.7% in persons aged 85 to 95 years, and did not differ appreciably between men and women. The prevalence of left ventricular systolic dysfunction, assessed by echocardiography, however, was found to be higher in men (5.5%) than in women (2.2%). This finding supports a recent report from the Framingham Heart Study that heart failure resulting from diastolic dysfunction may be more common in women.[3]

Echocardiography is widely recommended as an essential tool in the evaluation and management of heart failure,[4-6] but its use has yet to become commonplace in population-based research. None of the heart failure scores used to date in population-based research comprised echocardiographic assessment. The usefulness of echocardiography in a population-based setting is underscored by our study of 1,980 Rotterdam Study participants in whom both electrocardiography and echocardiography was performed. Although it was recently suggested that echocardiographic examination could be withheld in subjects without major electrocardiographic abnormalities as only 6% (1 - sensitivity) of persons with LV systolic dysfunction would be missed,[7] our study indicated that withholding echocardiography in persons without major electrocardiographic abnormalities would result in a considerable underestimation of the prevalence of LV systolic dysfunction in population-based studies, with as much 46% of persons with LV dysfunction remaining unrecognized.

Age-adjusted hospitalization rates for heart failure rose 48% in men and 40% in women from 1980 to 1993, the number of readmissions being considerable (within a 2-year period 18% of the heart failure patients were admitted more than once). Analysis of Framingham Heart Study data indicated a decreasing prevalence of left ventricular hypertrophy, one of the strongest risk factors for heart failure, from 1950 to 1990 that may well be attributed to the increasing use of antihypertensive medication in the same period. Indeed, regardless of the importance of hypertension in the development of heart failure,[8] ischemic heart disease nowadays appears to be the most important cause of heart failure in the Western world.

Neurohormonal activation in presymptomatic heart failure

Information on presymptomatic heart failure is a prerequisite to develop strategies to postpone or prevent the onset of overt heart failure. Echocardiography was employed to select 80 Rotterdam Study participants with impaired LV systolic function, who subsequently underwent a comprehensive cardiovascular examination. The same examination was carried out in 80 controls sampled from the same population.

As such, this is the first population-based study to evaluate neurohormonal characteristics at rest and directly following peak exercise in persons with previously unknown LV dysfunction. Presymptomatic LV dysfunction is characterized particularly by an increase in atrial natriuretic peptide, at rest as well after exercise. Furthermore, the increase in norepinephrine upon exercise was smaller in persons with lower ejection fraction, suggesting a blunted sympathetic response to exercise in early stages of heart failure.

Clinical relevance and health care aspects

The observed prevalence of heart failure (4.2% in persons over 55 years of age) and the fact that age-adjusted hospitalization rates for heart failure almost doubled between 1980 and 1993 testify to the importance of heart failure as a public health problem.

Clinical trials have conclusively demonstrated that effective treatment is available for patients across the complete clinical spectrum of heart failure, from those with asymptomatic left ventricular systolic dysfunction to NYHA class IV heart failure patients.[9-11] The benefits of trials need to be translated to larger groups of patients, including those at increased risk of developing overt heart failure.

The neurohormones studied (norepinephrine, renin, aldosterone, arginine vasopressin, atrial natriuretic peptide and N-terminal atrial natriuretic peptide) do not appear to be useful to identify this group. The electrocardiogram alone may also be insufficient in identifying persons with impaired left ventricular function. Echocardiography, providing direct information on cardiac structure and function, therefore seems to be essential in the detection of (early) heart failure.

The observed increase in atrial natriuretic peptides in our study participants with impaired left ventricular systolic function demonstrates the importance of natriuretic peptides in the pathophysiology of heart failure. Modulation of the natriuretic peptide response in early heart failure may be a target for pharmacological intervention.

Recommendations for future research

Several areas of future research can be identified:

- *Improvement of prognosis.* Despite the positive results of large heart failure trials questions remain. The gain in life expectancy may be small, measured in months rather than years. A recent analysis from the Framingham Heart Study failed to demonstrate an improvement in survival following the onset of heart failure in a general population sample from 1950 - 1990.[12] This may be related to the fact that the mean age of participants in most trials is appreciably lower than 65 years, whereas the bulk of heart failure patients is older than 70 years. The benefits of treating patients with asymptomatic left ventricular dysfunction need confirmation, as it is conceivable that "... there may be only a small difference between asymptomatic patients treated preventively and those treated with careful follow-up and initiation of therapy if heart failure develops".[13,14] Furthermore, the field of diastolic heart failure remains largely unexplored in terms of optimal therapy and trials in persons older than 75 years are needed.

Prevention of physical inactivity and improvement of exercise capacity in heart failure patients is likely to be valuable in improving prognosis in heart failure.[15,16]

- The role of *Doppler echocardiography* needs to be more clearly defined. Assessment of left ventricular mass and dimensions, valvular abnormalities, left ventricular systolic and diastolic function appears to be warranted in heart failure patients. Whereas the importance of systolic function is widely recognized, the role of impaired diastolic filling of the left ventricle in heart failure, especially in elderly people, is increasingly being acknowledged.[17-20] Diastolic abnormalities may precede systolic dysfunction and the development of hypertrophy.[21] Furthermore, it has been suggested that diastolic function of the left ventricle correlates better with exercise capacity than systolic function.[22,23] Doppler echocardiography is useful in the assessment of diastolic and systolic function of the left ventricle non-invasively, although several methodological and technical problems have yet to be addressed. The age dependency of Doppler indices of mitral flow (chapter 2.4) as well as the phenomenon of pseudonormalization of E/A ratio hamper interpretation of diastolic function.[24] Methods to unmask pseudonormalization should be investigated.[25,26] The effect of regression to the mean should be appreciated when using echocardiography to detect LV systolic dysfunction in population-based studies (chapter 4); repeated echocardiographic measurements appear necessary.[27]

- *heart failure in general practice.* Most heart failure patients are diagnosed and treated by general practitioners (chapter 1).[28] Routine application of (Doppler) echocardiography in general practice is limited by costs and low accessibility of echocardiographic services. It would be worthwhile to evaluate the impact of open access echocardiography units on the outcome of heart failure treatment in general practice.[5] In addition pharmacoepidemiological studies in general practice appear warranted to translate the benefits of clinical trials to all heart failure patients.[29]

- *sudden death.* A considerable proportion of mortality in heart failure can be attributed to sudden death (chapter 1), regardless of severity of the syndrome. Investigation into determinants of sudden death appears useful.[30]

- *quality of life.* Heart failure usually is a chronic disease that impacts greatly on quality

of life. It is arguable whether traditional scores for the assessment of quality of life in cardiovascular disease can be easily translated to the situation of heart failure patients or that specifically developed heart failure quality of life scores should be used.[31,32]

- *non invasive estimation of pulmonary capillary wedge pressure and measurement of "novel" neurohormones*, e.g. brain natriuretic peptide, may be useful in the detection of asymptomatic left ventricular dysfunction and provide useful prognostic information in the early stages of heart failure.[33-35]

- *prevention of (re)hospitalizations for heart failure.* Hospitalizations form a major determinant of heart failure associated costs. Identification of modifiable factors precipitating hospital admissions, e.g. the use of non-steroidal anti-inflammatory drugs,[36] is important. It is conceivable that specially trained heart failure nurses can be instrumental in decreasing (re)admissions for heart failure.[37]

- *studies of incident heart failure* in the population at large should provide information on determinants of the occurrence of heart failure as well as on the usefulness of echocardiography in diagnosis and management of heart failure.[38]

- *noninvasive assessment of the neuroendocrine autonomic interface* by means of heart rate and blood pressure variability, as well as autonomic function tests may provide insight into the progression of disease.[39-41]

By prospectively following the large, unselected cohort of persons aged 55 years or older in whom cardiovascular baseline measurements were carried out, and a carefully selected group of 200 participants thereof, who underwent an extensive cardiovascular examination (including a symptom limited exercise test, determination of neurohormones at rest and peak exercise, Doppler echocardiography with provocation tests to unmask pseudonormalization of mitral flow, 24 hour Holter monitoring, autonomic function tests and a calibrated Valsalva maneuver for noninvasive estimation of the pulmonary capillary wedge pressure) the Rotterdam Study provides a unique framework for continuing research in the field of heart failure.

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Summary

Heart failure has been defined as "a complex clinical syndrome characterized by abnormalities of left ventricular function and neurohumoral regulation, which are accompanied by effort intolerance, fluid retention and reduced longevity". Heart failure is rapidly becoming one of the most prevalent cardiovascular disorders and the incidence of heart failure is expected to continue to increase. Despite the poor prognosis, and considerable economic impact on health services because of long-term pharmacological treatment and frequent hospitalizations associated with the syndrome, epidemiological data on heart failure are relatively scarce. The studies described in this thesis address several aspects of heart failure and its determinants from an epidemiological viewpoint.

In chapter 1 the current epidemiological knowledge about heart failure is reviewed in terms of definition, classification, prevalence, incidence, etiology, risk factors, prognosis, trends in hospital admissions and economic impact. The lack of a gold standard for the assessment of heart failure limits the comparability of studies performed to date, but some general conclusions can be drawn. The prevalence and incidence of heart failure rise strongly with age; the prevalence increases from approximately 1% in persons in their fifties to over 10% in persons older than 80 years. Ischemic heart disease is the most common cause of heart failure, although the role of hypertension in the development of heart failure should not be underestimated. Left ventricular hypertrophy is the strongest risk factor for the development of heart failure. Prognosis of heart failure is poor with a mortality rate 6 to 7 times that of the general population. The mortality one year following the onset of heart failure lies around 30%. The incidence of sudden death in heart failure patients is 5 times that of the general population. Despite documented benefits of pharmacological treatment in heart failure, the prognosis following the onset of heart failure did not improve from the 1950's to the 1980's in participants of the population-based Framingham Heart Study. Analysis of hospital registries demonstrates a large (up to 60%) increase in admission rates for heart failure from 1980 to 1990. The economic impact of heart failure is considerable and can largely be attributed to the costs related to hospitalization for the syndrome.

In chapter 2 currently used and new methods to classify and detect heart failure are evaluated. In chapter 2.1 six heart failure scores, based on symptoms and signs, were compared in non-hospitalized subjects to determine their usefulness in population- based research. The scores were applied to 54 participants of a population-based study. All underwent a complete medical examination, including chest X-ray, electrocardiography and Doppler echocardiography. Using all information available, a cardiologist, unaware of the results of the scores, clinically classified participants as having no, possible or definite heart failure. Sensitivity, specificity, predictive values and receiver operating characteristics were calculated, using the cardiologist's assessment as a gold standard. The cardiologist judged definite or possible heart failure to be present in 17 persons. All scores had a high sensitivity for the detection of definite heart failure, whereas the Study

of Men Born in 1913 and Walma's score had the highest sensitivity for the combination of possible and definite heart failure. Gheorgiade's and the Boston score had the highest positive predictive values. Five of the six scores we studied are broadly similar in the detection of heart failure. The Men Born in 1913 score relies heavily on the assessment of dyspnea, resulting in a relatively large number of false positives. In addition, the diagnostic characteristics of the newly developed Rotterdam Study heart failure score were evaluated and found to compare favorably to the other scores studied.
Although the scores are useful in detecting manifest heart failure, objective measurements of cardiac function appear necessary to reduce the false positive rate and accurately detect early stages of heart failure.

In chapter 2.2 the use of the routine 12 lead electrocardiogram in the detection of left ventricular systolic dysfunction was studied in 1,980 Rotterdam Study participants (mean age 65.5 years (SD 7.5), 45% men). Although the electrocardiogram was found to have a high negative predictive value to detect left ventricular systolic dysfunction, withholding echocardiography in persons without major electrocardiographic abnormalities would result in a considerable underestimation of left ventricular systolic dysfunction (sensitivity only 54%). Thus echocardiography remains an essential tool to detect left ventricular systolic dysfunction in population-based studies.

Multifrequency bioimpedance measurement has been proposed as a safe and efficient method to estimate volumes of extracellular and total body water. In chapter 2.3 its use in the assessment of heart failure, a clinical syndrome with retention of water as one of its key features, was studied in 54 Rotterdam Study participants (mean age 66 years, SD 6, 20 men). Biompedance measurements were performed in all subjects and a comprehensive cardiovascular examination was carried out to allow a cardiologist, who was unaware of biompedance results, to assess the presence of heart failure. Five participants were judged to have heart failure. None of them was receiving treatment for heart failure at the time of the study. After adjustment for gender, height and age, both extracellular (1.2 liters, 95% CI 0.2 - 2.3) and total body water (3.3 liters, 95% CI 0.0 - 6.7) was higher in the heart failure group. Using age, gender and height adjusted cut-off values of 14.9 liters (extracellular water) and 36.4 liters (total body water) specificity for the detection of heart failure was 0.65 and 0.59 respectively, at a sensitivity of 0.80. It is concluded that multifrequency bioimpedance measurements can detect increases in volume of both extracellular and total body water in persons with heart failure. The use of bioimpedance measurements to detect heart failure as well as its role in the monitoring of changes in fluid status following initiation of treatment merits further investigation.

The contribution of diastolic dysfunction to cardiac diseases, especially heart failure, is increasingly being recognized. Mitral flow velocity, although not providing direct information on intracardiac pressures, is used widely for indirect noninvasive assessment of diastolic function. Cross-sectional studies have demonstrated age to be the predominant determinant of diastolic flow indexes. As cross-sectional studies may give a biased estimate of true change, for example as a result of survivor bias, cross-sectional estimates of change in mitral flow parameters with age were compared to longitudinally obtained estimates (chapter 2.4). In 500 Rotterdam Study participants (age 61.9 $\pm$ 4.0

years) mitral flow was measured and linear regression analysis was performed to obtain cross-sectional estimates of change. Those estimates were compared to longitudinal estimates in 50 participants (age 61.7 ± 4.0 years) who were re-examined approximately one year after their baseline visit. Adjustments were made for differences in previously identified determinants of mitral flow. Longitudinal estimates of annual change in peak early (E) mitral flow velocity (-0.060 m/s), peak late (A) mitral flow velocity (0.024 m/s) and peak mitral flow E/A ratio (-0.132) were much larger than estimated cross-sectionally (-0.001 m/s, 0.007 m/s and -0.014, respectively). In this first study to prospectively evaluate changes in mitral flow indices with increasing age, longitudinal estimates of annual change in diastolic indexes were much larger than estimated by a cross-sectional analysis. Survivor bias, due to increased mortality in persons with decreased E/A ratio (observed in hypertension, hypertrophic cardiomyopathy and coronary artery disease) may partially explain the observed difference between longitudinal and cross-sectional estimates.

In chapter 3.1 the prevalence of heart failure and left ventricular (LV) systolic dysfunction in the general population is studied, relating symptoms and signs to the presence of echocardiographic left ventricular dysfunction. In 5,540 participants of the Rotterdam Study (age 68.9 ± 8.7 years, 2,251 men) aged 55-95 years, the presence of heart failure was determined by assessment of symptoms and signs (shortness of breath, ankle edema and pulmonary crepitations) and use of heart failure medication. In 2,267 subjects (age 65.7 ± 7.4 years, 1,028 men) fractional shortening was measured. The overall prevalence of heart failure was 4.2% (95% C.I. 3.3-5.1) and did not differ between men and women. The prevalence increased with age, with the exception of the highest age group in men. LV systolic function had a normal distribution, was on average somewhat higher in women and did not decrease appreciably with age. The age adjusted prevalence of LV systolic dysfunction (fractional shortening $<= 25\%$) was approximately 2.5 times higher in men (5.5%, 95% C.I. 4.1-7.0) than in women (2.2%, 95% C.I. 1.4-3.2). Only 29% of participants with LV systolic dysfunction was classified as having heart failure, and 60% of persons with LV systolic dysfunction had no shortness of breath, ankle edema or crepitations. It is concluded that the prevalence of heart failure is appreciable in the general population and does not differ markedly between men and women. The prevalence of LV systolic dysfunction lies around 3.7% and is more frequently observed in men than in women. The majority of persons with LV systolic dysfunction show none of the cardinal symptoms of heart failure and can be regarded as having asymptomatic LV systolic dysfunction.

In chapter 3.2 the trend in hospitalization rates for heart failure in The Netherlands from 1980 to 1993 is studied. All hospital admissions in The Netherlands with a principal discharge diagnosis of heart failure were analyzed. In addition, individual records of heart failure patients from a subset of 7 hospitals were analyzed to estimate the frequency and timing of readmissions. The total number of discharges for men increased from 7,377 in 1980 to 13,022 in 1993, and for women from 7,064 to 12,944. From 1980 through 1993 age adjusted discharge rates rose 48% for men and 40% for women. Age adjusted in-hospital mortality for heart failure decreased from 19% in 1980 to 15% in 1993. For all

age groups in-hospital mortality for men was higher than for women. The average length of hospitalisation in 1993 was 14.0 days for men and 16.4 days for women. A review of individual patient records from a 6% sample of all hospital admissions in The Netherlands indicated that within a 2-year period 18% of the heart failure patients were admitted more than once, and 5% more than twice. In conclusion, for both men and women a pronounced increase in age adjusted discharge rates for heart failure was observed in The Netherlands from 1980 to 1993. Readmissions were a prominent feature among heart failure patients. Higher survival rates after acute myocardial infarction and the longer survival of patients with heart disease, including heart failure, may have contributed to the observed increase. The importance of advances in diagnostic tools and of possible changes in admission policy remain uncertain.

Neurohormonal activation is an important characteristic of heart failure. Insight into its role in the transition of asymptomatic LV dysfunction to overt heart failure is important to develop (therapeutic) strategies to postpone or prevent the onset of symptomatic heart failure. The aim of the study described in chapter 4 was to assess neurohormonal characteristics of persons at an increased risk of developing heart failure, to gain insight in the phase preceding overt heart failure. In 160 participants of the population-based Rotterdam Study, 80 with impaired left ventricular function (age 62.6 $\pm$ 4.0 years, ejection fraction 41% $\pm$ 7) and 80 controls (age 61.2 $\pm$ 3.7 years, ejection fraction 70% $\pm$ 8), plasma norepinephrine, renin, aldosterone, arginin vasopressine and (N-terminal) atrial natriuretic peptide (ANP) were measured at rest and after a maximal exercise test. Multivariate regression analysis, adjusting for age and gender, demonstrated a strong inverse relation of ANP and a positive relation of exercise norepinephrine to ejection fraction. Only the atrial natriuretic peptides were found to have a positive association to left atrial diameter, highly significant for ANP and less so for N-ANP. Additional adjustment for the use diuretics, ß blockers or ACE inhibitors did not appreciably change the results. All neurohormones increased significantly following exercise, the increase in norepinephrine was smaller in persons with lower ejection fraction. Diuretics were associated with higher norepinephrine, renin and aldosterone concentrations. In persons on ß blockers norepinephrine, ANP and N-ANP were higher, whereas renin was lower. In those who used ACE inhibitors both renin and (N)-ANP were higher. It is concluded that presymptomatic heart failure appears to be characterized particularly by an increase of ANP and a blunted response of the sympathetic system to exercise. Stimulation of ANP response or use of ANP degradation inhibitors may constitute a pathophysiologically sound approach to the treatment of early heart failure.

Hypertension and electrocardiographic left ventricular hypertrophy are important determinants of the occurrence of heart failure. In chapter 5 a study examining temporal trends in the use of antihypertensive medication and the effects of antihypertensive medication on prevalence of high blood pressure and electrocardiographic evidence of left ventricular hypertrophy, is described. Use of antihypertensive medication, blood pressure levels and electrocardiographic LVH were assessed in 10,333 original and offspring participants of the Framingham Heart Study aged 45 - 75 years who contributed 51,756 person examinations from 1950 to 1989. The generalized estimating equation method was

used to test for trends in use of antihypertensive medication, prevalence of high blood pressure and electrocardiographic LVH. Use of antihypertensive medication increased progressively from the 1950's to the 1980's; from 2.3% to 24.6% in men, and from 5.7% to 27.7% in women. The age adjusted prevalence of systolic blood pressure of at least 160 mm Hg or diastolic blood pressure of 100 mm Hg or higher, declined from 18.5% to 9.2% in men, and 28.0 to 7.7% in women during the study period. This was accompanied by an age adjusted decline in prevalence of electrocardiographic LVH (from 4.5% to 2.5% in men and from 3.6% to 1.1% in women). These findings support the notion that the widespread introduction of antihypertensive medication has resulted in reduced prevalence of high blood pressure and concomitant declines in the prevalence and severity of hypertensive target organ damage in the general population. Our observations may help to explain the decrease in cardiovascular disease mortality observed since the late 1960's.

In the general discussion the implications of the studies described in this thesis are addressed and recommendations for future research provided.

Samenvatting

Hartfalen is een aandoening die zich moeilijk laat omschrijven. De commissie die in 1994 de consensus hartfalen van het Centraal Begeleidingsorgaan voor de Intercollegiale Toetsing (CBO) voorbereidde, omschreef hartfalen als een "cardiaal bepaalde (pomp)functiestoornis met daarbij behorende symptomen". Patiënten met hartfalen zijn snel vermoeid, kortademig bij lichte inspanning en houden vocht vast (bijvoorbeeld in de benen). Hartfalen heeft vele oorzaken, waarvan coronairlijden (vernauwing van de kransslagaderen van het hart) en hypertensie (hoge bloeddruk) de belangrijkste zijn. De prognose van hartfalen is slecht, met een vijfjaarsoverleving die veelal lager is dan die van kwaadaardige aandoeningen.

Hartfalen is in het algemeen een chronische aandoening. Met de verschuiving van acute naar chronische ziekten in de Westerse wereld, lijkt het aannemelijk dat hartfalen in de komende jaren een belangrijk volksgezondheidsprobleem zal worden. Mensen met coronairlijden leven langer dan voorheen, de sterfte bij hartinfarcten neemt af, de mogelijkheden om patiënten met hartfalen in een vroeg stadium op te sporen en te behandelen zijn toegenomen. Voorts zou de behandeling van hoge bloeddruk mogelijk leiden tot uitstel, niet afstel, van het optreden van hartfalen en eist ook de vergrijzing zijn tol. Al deze factoren zullen waarschijnlijk bijdragen aan een toename van het aantal mensen met hartfalen in onze samenleving.

Ondanks het feit dat hartfalen vaak voorkomt, een slechte prognose heeft, en gepaard gaat met aanzienlijke kosten (met name door ziekenhuisopnamen) zijn slechts weinig epidemiologische gegevens over hartfalen voorhanden. Het Erasmus Gezondheid en Ouderen (ERGO) onderzoek, een grootschalig bevolkingsonderzoek bij 7.983 bewoners van de Rotterdamse wijk Ommoord ouder dan 55 jaar, bood een uitgelezen kans epidemiologische aspecten van hartfalen alsmede kenmerken van vroege stadia van hartfalen te bestuderen. De resultaten van onderzoekingen op het gebied van hartfalen bij deelnemers aan het ERGO onderzoek worden in dit proefschrift beschreven, gecompleteerd door een onderzoek naar het aantal ziekenhuisopnamen in Nederland wegens hartfalen in de periode 1980 - 1993 en een onderzoek naar de invloed van het toenemende gebruik van antihypertensieve medicijnen op het vóórkomen van hypertrofie (vergroting) van de linker hartkamer in de periode 1950 - 1989. Linker ventrikel hypertrofie is een belangrijke risicofactor voor het optreden van hartfalen. Het laatstgenoemde onderzoek werd uitgevoerd bij deelnemers aan de Framingham Heart Study (USA), het langstlopende bevolkingsonderzoek naar hart- en vaatziekten ter wereld.

In hoofdstuk 1 wordt een overzicht gegeven van de epidemiologie van hartfalen op grond van een uitgebreid literatuuronderzoek. Definitie, classificatie, prevalentie, incidentie, etiologie, risicofactoren, trends in ziekenhuisopnamen en economische gevolgen van hartfalen komen aan de orde. Het ontbreken van een gouden standaard voor het vaststellen van de aan- of afwezigheid van hartfalen bemoeilijkt de onderlinge vergelijkbaarheid van onderzoeken, maar desondanks kan een aantal conclusies worden getrokken. De prevalentie en incidentie van hartfalen nemen sterk toe bij het ouder

worden; de prevalentie stijgt van ongeveer 1% bij mensen tussen de 50 en 60 jaar tot meer dan 10% bij mensen ouder dan 80 jaar. Coronairlijden is de belangrijkste oorzaak van hartfalen, alhoewel de rol van hoge bloeddruk in het ontstaan van hartfalen niet onderschat moet worden. De prognose van personen met hartfalen is slecht; de sterfte van patiënten met hartfalen ligt zes tot zeven maal hoger dan die van leeftijdsgenoten zonder hartfalen. Binnen één jaar na het ontstaan van hartfalen overlijdt 30% van de patiënten. Voorts komt plotselinge dood vijf maal zo vaak voor bij hartfalenpatiënten als bij gezonde leeftijdsgenoten. Alhoewel grote onderzoeken hebben aangetoond dat medicamenteuze behandeling van hartfalen het aantal ziekenhuisopnamen wegens hartfalen vermindert en de levensverwachting verlengt, bleek uit een analyse van de Framingham Heart Study dat de prognose van hartfalen niet verbeterd is tussen 1950 en 1990. De volksgezondheidsuitgaven voor hartfalen zijn aanzienlijk en worden voornamelijk bepaald door frequente ziekenhuisopnamen. Het aantal ziekenhuisopnamen wegens hartfalen is fors (tot ± 60%) toegenomen tussen 1980 en 1990.

In hoofdstuk 2 wordt een aantal methoden om hartfalen te ontdekken en classificeren beschreven. In hoofdstuk 2.1 worden zes scores vergeleken om de aanwezigheid van hartfalen aan te tonen. De scores werden toegepast op 54 deelnemers aan het ERGO onderzoek. Alle deelnemers werden uitgebreid cardiovasculair onderzocht (inclusief thoraxfoto, electrocardiogram en Doppler echocardiografie). Op grond van alle verzamelde gegevens beoordeelde een cardioloog, onbekend met de hartfalen scores, of al dan niet sprake was van hartfalen. Gebaseerd op het oordeel van de cardioloog als gouden standaard werden sensitiviteit, specificiteit, voorspellende waarden en ROC curven bepaald. Volgens de cardioloog hadden 17 deelnemers mogelijk (12) of zeker (5) hartfalen. Alle scores hadden een hoge sensitiviteit voor de aanwezigheid van zeker hartfalen. De score gebruikt in de Zweedse "Study of Men Born in 1913" en Walma's score hadden de hoogste sensitiviteit voor de combinatie van mogelijk en zeker hartfalen. Gheorgiade's en de Boston score hadden de hoogste positief voorspellende waarde voor de aanwezigheid van hartfalen. De zes onderzochte scores, met uitzondering van de "Men Born in 1913" score, waren redelijk vergelijkbaar wat betreft hun diagnostische eigenschappen. De "Men Born in 1913" score vertrouwt erg op de beoordeling van kortademigheid en leidt daardoor nog al eens tot fout positieve bevindingen. Tenslotte werd de hartfalen score die later werd toegepast in het prevalentie onderzoek bij ERGO deelnemers bestudeerd. De ERGO hartfalen score kon de vergelijking met andere tot op heden gebruikte hartfalen scores goed doorstaan. Geconcludeerd wordt dat, ondanks het nut van de beoordeelde scores om manifest hartfalen aan te tonen, objectieve beoordeling van de cardiale functie (bijvoorbeeld door Doppler echocardiografie) nodig is om het aantal fout positieve bevindingen bij toepassing van de hartfalenscores terug te brengen en om vroege stadia van hartfalen op het spoor te komen.

In hoofdstuk 2.2 wordt de mogelijkheid bestudeerd om op grond van afwijkingen op het routine electrocardiogram de aanwezigheid van systolische dysfunctie van de linker hartkamer aan te tonen. Dit onderzoek gebeurde bij 1.980 deelnemers aan het ERGO onderzoek (gemiddelde leeftijd 65.5 ± 7.5 jaar, 45% mannen). Alhoewel het electrocardiogram een hoge negatief voorspellende waarde heeft, zou achterwege laten van

echocardiografie bij mensen zonder electrocardiografische afwijkingen leiden tot een aanzienlijke onderschatting van het vóórkomen van systolische dysfunctie van de linker hartkamer (sensitiviteit slechts 54%). Derhalve lijkt echocardiografie aangewezen om dysfunctie van het hart op te sporen in bevolkingsonderszoeken.

Met bioimpedantiemetingen is het mogelijk de hoeveelheid intra -en extracellulair water in het lichaam te meten. Omdat hartfalen wordt gekenmerkt door een toename van de hoeveelheid lichaamswater, werd bij 54 ERGO deelnemers (gemiddelde leeftijd 66 ± 6 jaar, 20 mannen) onderzocht of bioimpedantie metingen van nut zijn bij hartfalen (hoofdstuk 2.3). Alle 54 deelnemers werden uitgebreid onderzocht door een cardioloog, die op grond van zijn bevindingen en aanvullend onderzoek (electrocardiogram, thoraxfoto, echocardiografie) bepaalde of al dan niet sprake was van hartfalen. De cardioloog was niet op de hoogte van resultaten van de bioimpedantiemetingen. Bij vijf deelnemers, die niet behandeld werden voor hartfalen, was sprake van hartfalen. Na correctie voor verschillen in leeftijd, geslacht en lengte bleek zowel de hoeveelheid extracellulair (1.2 liter, 95% BI 0.2 - 2.3) als totale hoeveelheid lichaamswater (3.3 liter, 95% BI 0.0 - 6.7) bij de groep deelnemers met hartfalen groter dan bij deelnemers zonder hartfalen.

Bij grenswaarden van 14.9 liter (extracellulair water) en 36.4 liter (totaal lichaamswater) was de specificiteit voor het aantonen van hartfalen respectievelijk 0.65 en 0.59, bij een sensitiviteit van 0.8. De conclusie luidt dat bioimpedantie metingen een verschil in zowel de hoeveelheid extracellulair als totaal lichaamswater kunnen aantonen tussen een groep mensen met en zonder hartfalen. Nader onderzoek naar de mogelijke rol van bioimpedantiemetingen bij het vaststellen van de aanwezigheid van hartfalen en het vervolgen van veranderingen in lichaamswater na het starten van behandeling lijkt nuttig.

Het belang van diastolische dysfunctie bij cardiale aandoeningen, met name hartfalen, wordt in toenemende mate erkend. Metingen van de bloedstroom over de mitralis kleppen, de zogenaamde mitraal flow, worden, alhoewel ze geen direkte informatie geven over de drukken in het hart, vaak gebruikt om noninvasief de diastolische functie van het hart te beoordelen. Cross-sectionele onderzoeken hebben aangetoond dat leeftijd een belangrijke invloed heeft op de mitraal flow. Cross-sectionele onderzoeken kunnen echter een vertekend beeld van de werkelijkheid geven, bijvoorbeeld als gevolg van survivor bias. Daarom werden cross-sectionele schattingen van de jaarlijkse verandering in mitraal flow waarden vergeleken met longitudinaal verkregen waarden (hoofdstuk 2.4). Bij 500 deelnemers aan het ERGO onderzoek (gemiddelde leeftijd 61.9 ± 4.0 jaar) werd de mitraal flow gemeten. Met lineaire regressie werden cross-sectionele schattingen van jaarlijkse verandering in mitraal flow verkregen. Deze schattingen werden vergeleken met longitudinale waarden in een groep van 50 ERGO deelnemers (gemiddelde leeftijd 61.7 ± 4.0 jaar) die ongeveer een jaar na hun deelname aan het eerste ERGO onderzoek opnieuw werden onderzocht. De longitudinale bepaalde jaarlijkse veranderingen in piek vroege (E) mitraal flow snelheid (-0.060 m/s), piek late (A) mitraal flow snelheid (0.024 m/s) en de ratio van vroege / late (E/A) snelheid (-0.132) waren veel groter dan op grond van de cross-sectionele veranderingen werd geschat (-0.001 m/s, 0.007 m/s en -0.014, respectievelijk). Derhalve blijkt uit dit onderzoek, waarbij voor het eerst longitudinale bevindingen met cross-sectionele schattingen werden vergeleken, dat de jaarlijkse

verandering in mitraal flow waarden hoger is dan werd aangenomen op basis van cross-sectionele schattingen. Survivor bias, doordat mensen met een lage E/A ratio (zoals bijvoorbeeld wordt gevonden bij hoge bloeddruk, hypertrofische cardiomyopathy en coronair lijden) een hogere sterfte hebben, zou het gevonden verschil tussen cross-sectionele en longitudinale bevindingen ten dele kunnen verklaren.

In hoofdstuk 3.1 wordt het vóórkomen (de prevalentie) van hartfalen en systolische dysfunctie van de linker hartkamer in de algemene bevolking beschreven. Bij 5.540 deelnemers aan het ERGO onderzoek (gemiddelde leeftijd 68.9 ± 8.7 jaar, 2.251 mannen) werd de aan- of afwezigheid van hartfalen vastgesteld aan de hand van bevindingen bij anamnese en lichamelijk onderzoek (kortademigheid, enkeloedeem en crepitaties bij auscultatie van de longen), alsmede door na te gaan of zij medicijnen voor hartfalen gebruikten. Bij 2.267 deelnemers (gemiddelde leeftijd 65.7 ± 7.4 jaar, 1.028 mannen) werd de fractionele verkorting van de linker hartkamer met M-mode echocardiografie bepaald als afgeleide maat voor ejectiefractie van de linker hartkamer. De prevalentie van hartfalen in deze groep mensen ouder dan 55 jaar was 4.2% (95% BI 3.3 - 5.1) en verschilde niet wezenlijk tussen mannen en vrouwen. Hartfalen kwam vaker voor in oudere leeftijdsgroepen. De systolische functie van de linker hartkamer (gemeten als fractionele verkorting) had een normale verdeling in de onderzochte groep, lag gemiddeld wat hoger bij vrouwen dan bij mannen, en nam niet duidelijk af in oudere leeftijdsgroepen. Gecorrigeerd voor leeftijdsverschillen kwam systolische dysfunctie ongeveer twee keer zo vaak voor bij mannen (5.5 95% BI 4.1 - 7.0) als bij vrouwen (2.2%, 95 BI 1.4 - 3.2). Slechts 29% van de deelnemers met systolische dysfunctie bleek hartfalen te hebben, en bij maar liefst 60% van de personen met systolische dysfunctie bleek geen sprake te zijn van kortademigheid, enkeloedeem of crepitaties. Ongeveer 3.7% van de bevolking ouder dan 55 jaar heeft echocardiografische aanwijzingen voor systolische dysfunctie. Systolische dysfunctie komt vaker voor bij mannen dan bij vrouwen. De meerderheid van de mensen met systolische dysfunctie heeft geen klachten of symptomen passend bij hartfalen en kan derhalve beschouwd worden als hebbende asymptomatische dysfunctie van de linker hartkamer.

In hoofdstuk 3.2 komt de stijging van het aantal ziekenhuisopnamen wegens hartfalen in Nederland aan de orde. Het aantal opnamen steeg van 7.377 in 1980 tot 13.022 in 1993 voor mannen, en voor vrouwen van 7.064 tot 12.944. Gecorrigeerd voor verschillen in leeftijdsopbouw van de bevolking bedraagt de stijging 48% (mannen), respectievelijk 40% (vrouwen). In dezelfde periode daalde de sterfte in het ziekenhuis bij patiënten opgenomen wegens hartfalen van 19% tot 15%. De gemiddelde ligduur in 1993 was 14 dagen voor mannen en 16.4 dagen voor vrouwen. Voorts blijkt dat 18% van de patiënten binnen twee jaar wordt heropgenomen wegens hartfalen. De stijging van het aantal ziekenhuisopnamen voor hartfalen wordt waarschijnlijk deels verklaard door de dalende sterfte na een hartinfarct en de verbeterde overleving van mensen met hart -en vaatziekten in het algemeen. De rol van verbeterde diagnostiek van hartfalen en veranderingen in opnamebeleid blijft vooralsnog onduidelijk.

Neurohormonale activatie is een belangrijk kenmerk van hartfalen. Kennis van de rol van neurohormonen bij de overgang van asymptomatische dysfunctie van het hart naar

manifest hartfalen is noodzakelijk om, al dan niet medicamenteus, het optreden van hartfalen uit stellen of zelfs geheel te voorkomen. Het doel van het in hoofdstuk 4 beschreven onderzoek was het verkrijgen van inzicht in neurohormonale kenmerken van mensen met een verhoogde kans op hartfalen. Hiertoe werden 160 ERGO deelnemers uitgebreid onderzocht; 80 personen met verminderde functie van de linker hartkamer (leeftijd 62.6 ± 4.0 jaar, ejectiefractie 41% ± 7) en 80 controlepersonen (leeftijd 61.2 ± 3.7 jaar, ejectiefractie 70% ± 8). Voor en na een maximale inspanningstest werd de concentratie van de volgende neurohormonen gemeten: plasma norepinephrine, renine, aldosteron, vasopressine, atriaal natriuretisch peptide (ANP) en N-eindstandig atriaal natriuretisch peptide (n-ANP). Bij multivariate regressie analyse bleek dat, na correctie voor verschillen in leeftijd en geslacht, ANP waarden hoger waren bij deelnemers met een verminderde ejectiefractie en dat hogere norepinephrine waarden na inspanning gerelateerd waren aan een hogere ejectiefractie. De waarden van de natriuretische peptiden bleken samen te hangen met de doorsnede van de linker boezem. Dit was met name het geval voor atriaal natriuretisch peptide.

Correctie voor gebruik van medicijnen die neurohormonen kunnen beïnvloeden, zoals diuretica, ß-blockers en ACE-remmers had geen grote invloed op de resultaten. Alle neurohormonen stegen na het verrichten van de inspanningstest, alleen was de stijging van norepinephrine minder uitgesproken voor mensen met een verminderde ejectiefractie. Geconcludeerd wordt dat de vroege fase van hartfalen gekenmerkt wordt door een stijging van atriaal natriuretisch peptide en een verminderde respons van het sympathische zenuwstelsel op inspanning. Medicijnen die ingrijpen op de natriuretische peptiden zouden mogelijk een rol kunnen hebben in de behandeling van vroege stadia van hartfalen.

Hypertensie en electrocardiografisch aangetoonde hypertrofie van de linker hartkamer zijn belangrijke determinanten van het optreden van hartfalen. In hoofdstuk 5 worden trends in het gebruik van bloeddrukverlagende middelen beschreven en wordt nagegaan of het toenemende gebruik van deze middelen gepaard is gegaan met lagere bloeddrukken en vermindering van het percentage linkerkamer hypertrofie in de algemene bevolking. Dit onderzoek werd uitgevoerd bij 10.333 deelnemers van 45 tot 75 jaar oud aan de Framingham Heart Study in de Verenigde Staten, die in totaal 51.576 maal onderzocht werden tussen 1950 en 1989. Het gebruik van bloeddrukverlagende medicijnen steeg fors; van 2.3% in de vijftiger jaren tot 24.6% in de jaren tachtig bij mannen, en van 5.7% tot 27.7% bij vrouwen. De voor verschillen in leeftijd gecorrigeerde bloeddrukwaarden vertoonden een daling. Waar in de jaren vijftig nog 18.5% van de mannen een systolische bloeddruk hoger dan 160 mmHg of een diastolische bloedddruk hoger dan 100 mmHg had, was dit percentage in de tachtiger jaren 9.2%. Bij vrouwen waren de corresponderende waarden 28.0% en 7.7%. Hiermee gepaard ging een daling van het vóórkomen van electrocardiografische linker kamer hypertrofie van 4.5% tot 2.5% (mannen) en 3.6% tot 1.1% (vrouwen). Deze bevindingen ondersteunen de veronderstelling dat het toenemende gebruik van bloeddrukverlagende middelen heeft geleid tot een afname van het vóórkomen van eindorgaanschade (hypertrofie) van het hart ten gevolge van hoge bloeddruk. Het is voorstelbaar dat dit ook ten dele de sedert eind jaren zestig waargenomen daling in sterfte aan hart- en vaatziekten verklaart.

Tenslotte worden in de algemene discussie de voornaamste bevindingen van de in dit proefschrift beschreven onderzoeken in perspectief geplaatst en suggesties gedaan voor nader hartfalenonderzoek. Hartfalen is een vaak voorkomende aandoening, zowel bij mannen als bij vrouwen. Het feit dat, in absolute zin, het aantal opnamen wegens hartfalen in Nederlandse ziekenhuizen bijna verdubbelde tussen 1980 en 1993 geeft aan dat hartfalen een groeiend volksgezondheidsprobleem is. Grootschalige onderzoeken hebben aangetoond dat de prognose van patiënten met hartfalen kan worden verbeterd en dat het aantal ziekenhuisopnamen verminderd kan worden. Het is van belang dat alle hartfalenpatiënten hiervan profiteren, inclusief de mensen met een verhoogde kans op het krijgen van manifest hartfalen. Een aantal onderzoeken in dit proefschrift richtte zich met name op de laatste groep. De onderzochte neurohormonen (norepinephrine, renine, aldosteron, vasopressine, atriaal natriuretisch peptide en N-eindstandig atriaal natriuretisch peptide) lijken niet van nut bij het opsporen van mensen met een verhoogde kans op het krijgen van hartfalen (mensen met verminderde functie van de linker hartkamer). Evenmin lijkt het electrocardiogram op zichzelf voldoende informatie te bieden om deze groep te identificeren. Doppler echocardiografisch onderzoek, waarmee zowel informatie over de structuur als de functie van het hart verkregen wordt, lijkt daarom de aangewezen methode om mensen met asymptomatische dysfunctie van het hart op te sporen.

De verhoogde waarde van (N-eindstandig) atriaal natriuretisch peptide bij deelnemers aan ons onderzoek met een verminderde functie van de linker hartkamer weerspiegelt de belangrijke pathofysiologische rol van natriuretische peptiden bij hartfalen. Het lijkt aangewezen de rol van pharmacologische beïnvloeding van de natriuretische peptiden in vroege stadia van hartfalen nader te onderzoeken.

Toekomstig hartfalen onderzoek dient zich ondermeer te richten op verbetering van de prognose van hartfalen, hartfalen in de huisartsenpraktijk, het voorkómen van (her)opnames wegens hartfalen, kwaliteit van leven bij hartfalenpatiënten, terugdringen van de sterfte door plotselinge dood bij mensen met hartfalen, determinanten van het optreden van hartfalen, de rol van Doppler echocardiografie, neurohormonen, en non-invasieve bepaling van de pulmonale wiggedruk bij het vaststellen en vervolgen van hartfalen, alsook de wisselwerking tussen neurohormonen en het autonome zenuwstelsel.

Het ERGO onderzoek biedt voldoende mogelijkheden om in ieder geval een aantal van genoemde onderzoeken uit te voeren.

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Nawoord

Dit proefschrift is tot stand gekomen op het Instituut voor Epidemiologie en Biostatistiek en het Thoraxcentrum (afdeling Cardiologie) van de Erasmus Universiteit Rotterdam. Naast medewerkers van beide afdelingen hebben ook anderen een bijdrage geleverd aan dit proefschrift. Een aantal personen wil ik graag noemen.

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Lieve Birgitta, zikomo kwambiri.

Curriculum Vitae

Arend Mosterd was born on February 28, 1964 in Amersfoort, The Netherlands. He graduated in 1982 at the "Johan van Oldenbarnevelt Gymnasium" (secondary school) in Amersfoort. In the same year he started his medical training at Utrecht University. During his medical studies he was a teaching assistant in anatomy and physiology for 2nd year medical students, conducted a research project "A pilot study of the kinematic behaviour of a total condylar knee prosthesis" at the Biomechanics Section, Department of Orthopaedics, St. Radboud Hospital, Nijmegen, The Netherlands (Prof. Dr Ir R. Huiskes, Dr Ir L. Blankevoort, June 1985 - July 1986), worked in primary health care projects of the Salesian Mission in Venezuela and Peru (November 1986 - February 1987) and did clinical rotations in medicine and cardiology at Harvard Medical School, Boston, USA (April-July 1988). He successfully passed the Foreign Medical Graduate Examination in the Medical Sciences (FMGEMS) (1980 - 1990). In 1990 he obtained his medical degree and started working as a junior doctor in medicine in the Red Cross Hospital in the Hague (Dr D. Overbosch). In December 1991 he began the studies described in this thesis at the Department of Epidemiology and Biostatistics (Prof. Dr A. Hofman and Prof. Dr D.E. Grobbee) and Thoraxcenter, Department of Cardiology (Prof. Dr J.R.T.C. Roelandt, Dr J.W. Deckers), University Hospital "Dijkzigt" of Erasmus University, Rotterdam. He collaborated in the Rotterdam Study and received his training as an epidemiologist. He has been registered as an epidemiologist since July 1993. He was a member of the committee that prepared the "Dutch Heart Failure Consensus Meeting" in June 1994. In 1994 he was a participant of the Ten Day International Teaching Seminar on Cardiovascular Disease Epidemiology and Prevention in La Coruña, Spain. From September 1994 to June 1995 he worked as a research fellow at the Framingham Heart Study, Framingham, Massachusetts, USA (Dr D. Levy).
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