Heart failure in COPD

Frans H. Rutten

Heart failure in COPD

Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht.
Thesis, with a summary in Dutch.
Proefschrift met een samenvatting in het Nederlands.

ISBN	90-9019750-8
Author	Frans Rutten
Cover design	Ena Rutten
Lay-out	Frances Verheij
Print	Febo druk BV, Enschede, the Netherlands

Heart failure in COPD

Hartfalen bij patiënten met chronisch obstructieve longziekte

(met een samenvatting in het Nederlands)

Proefschrift

Ter verkrijging van de graad van doctor aan de Universiteit Utrecht,
Op gezag van de Rector Magnificus, Prof. Dr. WH Gispen,
ingevolge het besluit van het College voor Promoties
in het openbaar te verdedigen op

Dinsdag 4 oktober 2005 des morgens te 10.30 uur

door

Frans Hendrik Rutten

Geboren 18 oktober 1959 te Venlo

Promotores

Prof. Dr. AW Hoes
Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, the Netherlands

Prof. Dr. DE Grobbee
Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, the Netherlands

Prof. Dr. J-WJ Lammers
Heart Lung Center, Department of Pulmonary Diseases, University Medical Center Utrecht, the Netherlands

The studies described in this thesis were supported by a grant from the Netherlands Heart Foundation (NHF, 48006), and the Netherlands Organisation for Scientific Research (NWO 904-61-144).

The author gratefully acknowledges financial support for publication of this thesis by the Julius Center for Health Sciences and Primary Care, and the Netherlands Heart Foundation.
Additional support was received from Roche Diagnostics Nederland BV, Almere.

Aan mijn moeder
Ter nagedachtenis aan mijn vader

Manuscripts based on the studies presented in this thesis

Chapter 2
Rutten FH, Grobbee DE, Hoes AW. Differences between general practitioners and cardiologists in diagnosis and management of heart failure: a survey in every-day practice. Eur J Heart Fail 2003;5:337-344.

Chapter 3
Rutten FH, Grobbee DE, Hoes AW. Diagnosis and management of heart failure: a questionnaire among general practitioners and cardiologists. Eur J Heart Fail 2003;5:345-348.

Chapter 4
Rutten FH, Cramer M-JM, Lammers J-WJ, Grobbee DE, Hoes AW. Heart failure and chronic obstructive pulmonary disease: an ignored combination? Submitted

Chapter 5
Rutten FH, Lammers J-WJ, Cramer M-JM, Zanen P, Sachs APE, Grobbee DE, Hoes AW. Heart failure and chronic obstructive pulmonary disease: common mechanisms and possible interactions. Submitted.

Chapter 6
Rutten FH, Cramer M-JM, Grobbee DE, Sachs APE, Kirkels JH, Lammers J-WJ, Hoes AW. Unrecognized heart failure in elderly patients with stable chronic obstructive pulmonary disease. Eur Heart J Advanced Access published April 2005.

Chapter 7
Rutten FH, Moons KGM, Cramer M-JM, Grobbee DE, Zuithoff NPA, Lammers J-WJ, Hoes AW. Recognising heart failure in elderly patients with stable chronic obstructive pulmonary disease in primary care: a cross-sectional diagnostic study. Accepted for publication BMJ.

Chapter 8
Rutten FH, Cramer M-JM, Zuithoff NPA, Lammers J-WJ, Verweij W, Grobbee DE, Hoes AW. Identifying heart failure in elderly patients with chronic obstructive pulmonary disease: comparison of natriuretic peptides. Submitted.

Chapter 9
Rutten FH, Vonken E-J, Cramer M-JM, Moons KGM, Veldhuis B, Lammers J-WJ, Grobbee DE, Mali PThM, Hoes AW. Value of cardiovascular magnetic resonance imaging in identifying heart failure in patients with stable chronic obstructive pulmonary disease. Submitted.

Contents

Chapter 1

Introduction

Introduction

Heart failure has gradually become one of the most prevalent cardiovascular disorders in Western Societies, notably in the elderly.[1;2] The prevalence of heart failure increases with age, and is 7-10% in those aged 65 years or over.[3] A further increase in the prevalence is expected in the near future[1;4] due to ageing of the population and more successful treatment of acute cardiac disease.[4] This implies that nowadays the 'average' Dutch general practitioner (with 2300 enlisted patients) currently takes care of at least 20 patients with heart failure.[5] Pharmacological and non-pharmacological treatment options have rapidly developed over the last decades, resulting in prognostic improvement.[6] The prognosis in terms of survival, however, remains relatively poor and is comparable with that of e.g. colon cancer.[7] Furthermore, heart failure has an important impact on quality of life and functional status and leads to considerable health-care costs.[8]

Heart failure guidelines

In the last decades many clinical guidelines have been published on the diagnosis and treatment of heart failure.[6;9-11] Most evidence regarding interventions in heart failure is drawn from randomised controlled trials. In these trials a rather selective population of relatively young (<70 years of age) males participated with heart failure in the presence of a reduced left ventricular ejection fraction (LVEF) < 40-45%). Participants had limited co-morbidity, and ischaemic heart disease was the most prominent underlying cause for their heart failure.[12;13] Heart failure patients in every-day practice are, however, often elderly (>70 years of age) female patients with heart failure in the presence of a preserved left ventricular ejection fraction ('isolated' diastolic heart failure) and relevant co-morbidity such as diabetes and chronic obstructive pulmonary disease (COPD). Long-lasting hypertension is an important underlying cause for their heart failure.[12]

The number of studies assessing the value of diagnostic strategies in patients suspected of heart failure is low compared to the abundance of therapeutic interventions. Moreover, many of these studies suffer from methodological problems. Often the diagnostic value of a 'single test' is assessed.[14-17] This does not agree with clinical practice where no diagnosis is ever based on one test, and the medical history including known morbidity always should play a prominent role.[18] Thus, the assessment of the value of diagnostic tests, e.g. natriuretic peptides, electrocardiography, chest X-ray, in addition to readily available diagnostic parameters from the clinical assessment requires a multivariate approach.[18]

Furthermore, many diagnostic studies were not performed in the relevant patient domain, i.e. those suspected of heart failure, and some studies even included large numbers of patients not suspected of the disease. The optimal diagnostic strategy to detect heart failure in suspected patients remains therefore largely unknown, notably in the every-day practice of older patients mentioned above.

In conclusion, present heart failure guidelines aim to be as 'evidence-based' as possible but there is a shortage of information regarding the optimal diagnostic assessment of patients suspected of heart failure and treatment of heart failure patients in every-day clinical practice, in particular elderly patients with relevant comorbidity. Since heart failure is mostly managed by general practitioners and cardiologists, it is of interest to compare these physicians in their every-day practice and opinions regarding diagnosis and treatment of heart failure.

Heart failure and chronic obstructive pulmonary disease

Information regarding the diagnosis and treatment of heart failure in the presence of important co-morbidities is scarce. This is especially true for chronic obstructive pulmonary disease (COPD).[11;19] Both heart failure and COPD are common in the elderly population[20-22] and both are on the increase.[2;23] Heart failure and COPD show an important overlap in signs and symptoms,[19] and elderly patients with dyspnoea face their physicians with the diagnostic challenge to determine whether the patient suffers from heart failure, COPD, both, or neither of the two. The possibility of concomitant presence of both diseases is underexposed in clinical practice and research. Since presence of one syndrome in the presence of the other has important therapeutic and prognostic implications, knowledge about possible concomitant prevalence is clinically relevant.

Both diseases have been studied extensively and separately; heart failure mainly in the domain of the cardiologist and COPD in the domain of the pulmonologist. Several studies provided some evidence that the syndromes often co-exist. Diagnostic studies showed that pulmonary dysfunction and use of pulmonary medication, for example, often coincide with unrecognised heart failure,[14;24;25] and that unrecognised heart failure appears to be common in COPD patients experiencing an exacerbation.[26] Earlier studies showed that left ventricular systolic dysfunction (LVSD) is rather common in COPD patients.[27-36] This was especially true for 'unselected' COPD patients (i.e. without exclusion of those known with heart disease) and in COPD patients with an exacerbation, although the prevalence rates differ considerably between studies.[28;33-36] So far, however, studies assessing

the prevalence of unrecognised heart failure in COPD patients in a stable phase of their disease are lacking.

There are reasons to suspect common mechanisms in the development of both diseases. First and foremost, tobacco smoking is an important common causal factor in both COPD and heart failure.[6;37] In addition, systemic and local atherosclerosis is possibly a common mechanism. Systemic and coronary atherosclerosis are established risk factors for heart failure,[6] and prospective studies showed that COPD was associated with an increased incidence of ischaemic coronary heart disease and carotid atherosclerotic plaque formation, independent of age, smoking, or other cardiovascular risk factors.[38-40] A third common pathway is systemic and local inflammation. COPD can be regarded as an inflammatory disease of the lungs,[37] but also systemic inflammation is present in COPD, irrespective of smoking status and disease stage.[41-43] Heart failure can be seen as an 'end-stage disease', with also inflammatory involvement.[44] Inflammation is an important feature in the atherosclerotic process.[45] Much is unclear, however, about how the mentioned mechanisms and possible interactions are involved in developing or promoting one disease in the presence of the other.

In conclusion, heart failure and COPD appear to coincide more often than generally acknowledged. Important information, however, is lacking regarding the exact prevalence of heart failure in (stable) COPD patients and vice versa. Moreover, the optimal diagnostic strategy to detect concomitant heart failure in COPD patients is not known. Tobacco smoking, inflammation and atherosclerosis are known to play an important role in the development of both diseases, but common pathways and possible interactions are not yet completely explored.

Research questions addressed in this thesis

- What is the current diagnostic and therapeutic management of heart failure patients by general practitioners and cardiologists, and how do the findings compare to available guidelines? This will be addressed in chapter 2.
- What is the opinion of general practitioners and cardiologists about diagnostic and therapeutic aspects regarding heart failure, and is this in line with existing guidelines? This issue will be addressed in chapter 3.
- What is the prevalence of heart failure and left ventricular systolic dysfunction in COPD patients based on the available literature, and what are the possible consequences for diagnosis and treatment of concomitant presence of heart failure and COPD? (Chapter 4).

- What are common mechanisms and interactions in the development of heart failure in COPD patients or vice versa? (Chapter 5).
- What is the prevalence of heart failure in patients with stable COPD? (Chapter 6).
- What is the optimal diagnostic strategy for recognising heart failure in COPD patients? (Chapter 7).
- Natriuretic peptide measurements are helpful in the diagnostic process of recognising heart failure. Are they also useful in detecting heart failure in COPD patients, and are there differences between the types of assays of natriuretic peptides? (Chapter 8).
- What is the (added) diagnostic value of cardiovascular magnetic resonance imaging in recognising heart failure in COPD patients? (Chapter 9).

References

1. Cowie MR, Mosterd A, Wood DA, Deckers JW, Poole-Wilson PA, Sutton GC *et al*. The epidemiology of heart failure. *Eur Heart J* 1997;18:208-25.
2. Hoes AW, Mosterd A, Grobbee DE. An epidemic of heart failure? Recent evidence from Europe. *Eur Heart J* 1998;19 Suppl L:L2-L9.
3. Hogg K, Swedberg K, McMurray J. Heart failure with preserved left ventricular systolic function; epidemiology, clinical characteristics, and prognosis. *J Am Coll Cardiol* 2004;43:317-27.
4. Murray CJ, Lopez AD. Evidence-based health policy: lessons from the Global Burden of Disease Study. *Science* 1996;274:740-3.
5. Hobbs FD, Davis RC, Lip GY. ABC of heart failure: Heart failure in general practice. *BMJ* 2000;320:626-9.
6. Remme WJ, Swedberg K. Guidelines for the diagnosis and treatment of chronic heart failure. *Eur Heart J* 2001;22:1527-60.
7. Hobbs FDR. Management of heart failure: evidence versus practice. Does current prescribing provide optimal treatment for heart failure patients? *Br J Gen Pract* 2000;50:735-42.
8. Stewart S, MacIntyre K, Capewell S, McMurray JJ. Heart failure and the aging population: an increasing burden in the 21st century? *Heart* 2003;89:49-53.
9. Hunt SA, Baker DW, Chin MH, Cinquegrani MP, Feldman AM, Francis GS *et al*. ACC/AHA Guidelines for the evaluation and management of chronic heart failure in the adult: executive summary. *Circulation* 2001;104:2996-3007.
10. Mosterd WL, Rosier PFWM, Balk AHMM, *et al* Multidisciplinaire richtlijn chronisch hartfalen. The Netherlands: Van Zuiden. Oktober 2002.

11. Rutten FH, Walma EP, Kruizinga GI, Bakx HCA, Van Lieshout J. NHG-Standaard Hartfalen, eerste herziening. *Huisarts en Wetenschap* 2005;48:64-76.

12. Rutten FH, Grobbee DE, Hoes AW. Differences between general practitioners and cardiologists in diagnosis and management of heart failure: a survey in every-day practice. *Eur J Heart Fail* 2003;5:337-44.

13. Lindenfeld J, Krause S, Salerno J. Where are all the women with heart failure? *J Am Coll Cardiol* 1997;30:1417-9.

14. Cowie MR, Struthers AD, Wood DA, Coats AJ, Thompson SG, Poole-Wilson PA *et al*. Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care. *Lancet* 1997;350:1349-53.

15. Davie AP, Francis CM, Love MP, Caruana L, Starkey IR, Shaw TR *et al*. Value of the electrocardiogram in identifying heart failure due to left ventricular systolic dysfunction. *BMJ* 1996;312:222.

16. Davie AP, Francis CM, Caruana L, Sutherland GR, McMurray JJ. Assessing diagnosis in heart failure: which features are any use? *QJM* 1997;90:335-9.

17. O'Neill TW, Barry M, Smith M, Graham IM. Diagnostic value of the apex beat. *Lancet* 1989;1:410-1.

18. Moons KG, Biesheuvel CJ, Grobbee DE. Test research versus diagnostic research. *Clin Chem* 2004;50:473-6.

19. Remes J, Miettinen H, Reunanen A, Pyörälä K. Validity of clinical diagnosis of heart failure in primary health care. *Eur Heart J* 1991;12:315-21.

20. Morrison LK, Harrison A, Krishnaswamy P, Kazanegra R, Clopton P, Maisel A. Utility of a rapid B-natriuretic peptide assay in differentiating congestive heart failure from lung disease in patients presenting with dyspnea. *J Am Coll Cardiol* 2002;39:202-9.

21. Eriksson H, Svardsudd K, Larsson B, Ohlson LO, Welin L, Tibblin G *et al*. Dyspnoea in a cross-sectional and a longitudinal study of middle-aged men: the Study of Men Born in 1913 and 1923. *Eur Heart J* 1987;8:1015-23.

22. Pratter MR, Curley FJ, Dubois J, Irwin RS. Cause and evaluation of chronic dyspnea in a pulmonary disease clinic. *Arch Intern Med* 1989;149:2277-82.

23. Pearson SB, Pearson EM, Mitchell JR. The diagnosis and management of patients admitted to hospital with acute breathlessness. *Postgrad Med J* 1981;57:419-24.

24. Wheeldon NM, MacDonald TM, Flucker CJ, McKendrick AD, McDevitt DG, Struthers AD. Echocardiography in chronic heart failure in the community. *Q J Med* 1993;86:17-23.

25. Davies M, Hobbs F, Davis R, Kenkre J, Roalfe AK, Hare R *et al*. Prevalence of left-ventricular systolic dysfunction and heart failure in the Echocardiographic Heart of England Screening study: a population based study. *Lancet* 2001;358:439-44.

26. McCullough PA, Hollander JE, Nowak RM, Storrow AB, Duc P, Omland T *et al*. Uncovering heart failure in patients with a history of pulmonary disease: rationale for the early use of B-type natriuretic peptide in the emergency department. *Acad Emerg Med* 2003;10:198-204.

27. Christianson LC, Shah A, Fisher VJ. Quantitative left ventricular cineangiography in patients with chronic obstructive pulmonary disease. *Am J Med* 1979;66:399-404.

28. Steele P, Ellis JH, Van D, Sutton F, Creagh E, Davies H. Left ventricular ejection fraction in severe chronic obstructive airways disease. *Am J Med* 1975;59:21-8.

29. Render ML, Weinstein AS, Blaustein AS. Left ventricular dysfunction in deteriorating patients with chronic obstructive pulmonary disease. *Chest* 1995;107:162-8.

30. Schena M, Clini E, Errera D, Quadri A. Echo-Doppler evaluation of left ventricular impairment in chronic cor pulmonale. *Chest* 1996;109:1446-51.

31. Vizza CD, Lynch JP, Ochoa LL, Richardson G, Trulock EP. Right and left ventricular dysfunction in patients with severe pulmonary disease. *Chest* 1998;113:576-83.

32. Boussuges A, Pinet C, Molenat F, Burnet H, Ambrosi P, Badier M *et al*. Left atrial and ventricular filling in chronic obstructive pulmonary disease. An echocardiographic and Doppler study. *Am J Respir Crit Care Med* 2000;162:670-5.

33. Kline LE, Crawford MH, MacDonald WJ, Schelbert H, Rourke RA, Moser KM. Noninvasive assessment of left ventricular performance in patients with chronic obstructive pulmonary disease. *Chest* 1977;72:558-64.

34. Berger HJ, Matthay RA, Loke J, Marshall RC, Gottschalk A, Zaret BL. Assessment of cardiac performance with quantitative radionuclide angiocardiography: right ventricular ejection fraction with reference to findings in chronic obstructive pulmonary disease. *Am J Cardiol* 1978;41:897-905.

35. MacNee W, Xue QF, Hannan WJ, Flenley DC, Adie CJ, Muir AL. Assessment by radionuclide angiography of right and left ventricular function in chronic bronchitis and emphysema. *Thorax* 1983;38:494-500.

36. Zema MJ, Masters AP, Margouleff D. Dyspnea: the heart or the lungs? Differentiation at bedside by use of the simple Valsalva maneuver. *Chest* 1984;85:59-64.

37. Pauwels RA, Buist AS, Ma P, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: National Heart, Lung, and Blood Institute and World Health Organization Global Initiative for Chronic Obstructive Lung Disease (GOLD): executive summary. *Respir Care* 2001;46:798-825.

38. Ebi K, Hawthorne VM, Rose G, Shipley MJ, Gillis CR, Hole DJ *et al.* Breathlessness, chronic bronchitis and reduced pulmonary function as predictors of cardiovascular disease mortality among men in England, Scotland and the United

States. *Int J Epidemiol* 1989;18:84-8.

39. Hole DJ, Watt GC, Davey S, Hart CL, Gillis CR, Hawthorne VM. Impaired lung function and mortality risk in men and women: findings from the Renfrew and Paisley prospective population study. *BMJ* 1996;313:711-5.

40. Zureik M, Kauffmann F, Touboul PJ, Courbon D, Ducimetiere P. Association between peak expiratory flow and the development of carotid atherosclerotic plaques. *Arch Intern Med* 2001;161:1669-76.

41. Sin DD, Man SF. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease. *Circulation* 2003;107:1514-9.

42. Dentener MA, Creutzberg EC, Schols AM, Mantovani A, van't Veer C, Buurman WA *et al*. Systemic anti-inflammatory mediators in COPD: increase in soluble interleukin 1 receptor II during treatment of exacerbations. *Thorax* 2001;56:721-6.

43. Oudijk EJ, Lammers JW, Koenderman L. Systemic inflammation in chronic obstructive pulmonary disease. *Eur Respir J Suppl* 2003;46:5s-13s.

44. Vasan RS, Sullivan LM, Roubenoff R, Dinarello CA, Harris T, Benjamin EJ *et al*. Inflammatory markers and risk of heart failure in elderly subjects without prior myocardial infarction: the Framingham Heart Study. *Circulation* 2003;107:1486-91.

45. Ross R. Atherosclerosis--an inflammatory disease. *N Engl J Med* 1999;340:115-26.

Chapter 2

Differences between general practitioners and cardiologists in diagnosis and management of heart failure: a survey in every-day practice

Frans H Rutten, Diederick E Grobbee, Arno W Hoes

Julius Center for Health Sciences and Primary Care
University Medical Center Utrecht

Eur J Heart Fail 2003;5:337-44

Abstract

Background Data on diagnosis and management of heart failure in every-day care are scarce.

Aims To compare general practitioners' and cardiologists' diagnostic work-up and management of patients with (suspected) heart failure.

Methods In a cross-sectional survey we studied a sample of 103 files of patients coded as heart failure in primary care (31 general practices), and 99 files of out-patients coded as heart failure from 9 hospitals in the Netherlands. We defined patients as heart failure 'GP patients', when they were managed by a general practitioner without co-treatment of a cardiologist.

Results Patients managed in general practice were older (mean age 79 years (SD 8.5) and more often female than 'cardiology patients' (mean age 64 years (SD 11.7)). Ischaemic heart disease (31 vs. 57%) was more prevalent in 'cardiology patients'. Additional investigations such as chest radiography (51% vs. 84%), electrocardiography (39% vs. 100%), and echocardiography (12% vs. 97%) were performed more often in 'cardiology patients'. Most patients received diuretics (85% vs.79%). Angiotensin-converting enzyme inhibitors (40% vs. 76%), β-blockers (9% vs. 30%), spironolactone (11% vs. 32%), and angiotensin-II receptor blockers (6% vs. 13%) were prescribed much more often to 'cardiology patients'.

Conclusion General practitioners more often treat elderly, female patients with heart failure than cardiologists. General practitioners use less additional investigations and prescribe less potentially beneficial medication, compared to cardiologists. Population characteristics only partly explain these differences, suggesting that physicians attitude has an important bearing on the uptake of treatment.

Introduction

Heart failure has gradually become one of the most prevalent cardiovascular disorders in Western societies, notably in the elderly.[1;2] A further increase in the prevalence of heart failure is expected in the near future due to the ageing population and more successful cardiovascular disease management. The last decade has produced important advances in chronic heart failure treatment and established the prognostic efficacy of some drugs, such as angiotensin converting enzyme inhibitors (ACE inhibitors), β-blockers, spironolactone and angiotensin-II receptor blockers in patients with heart failure due to left ventricular dysfunction. Less robust studies also show that patients with 'diastolic heart failure' are likely to benefit form the same type of drugs.[3-6]

Heart failure is a prevalent disease in the elderly, with frequent co-morbidities, and a frequently unfavourable outcome. Notwithstanding the public health importance of heart failure, available data on heart failure management in clinical practice are sparse. We do know, however, that current diagnostic and therapeutic management of heart failure in clinical practice is still far from optimal.[7-11] General practitioners especially show hesitation in making use of echocardiography as a diagnostic facility, resulting in diagnostic uncertainty.[12] Studies comparing every-day primary and secondary care, are rare.
We therefore studied the diagnostic and therapeutic management of heart failure in current primary and secondary care.

Methods

In a cross-sectional survey conducted in 2000, we visited 31 general practices (rural, urban, and suburban) and 9 hospitals in the Netherlands. We invited 19 general practices connected to the General Practice Network Utrecht (HNU); a computerised general practice network, co-ordinated by the Julius Center for Health Sciences and Primary Care, from the University Medical Center Utrecht, and 49 other general practices in the vicinity of Utrecht. All invited general practitioners routinely register their patient contacts in ELIAS (SMS Cendata Nieuwegein); a software package suitable for electronic registration of medical information.[13;14] The general practices consisted of both single-handed and group practices. All 19 general practices allied to the general practice network participated, together with 13 other general practices (overall response 63%). We included one academic, three middle size, and five smaller hospitals. The hospitals were selected at random. Only patients from the 'general' out-patient cardiology

department were eligible for our study; patients from any specialised heart failure out-patient department were excluded.

For the purpose of this study, heart failure was defined pragmatically as a coded diagnosis of heart failure. The first inclusion criterion was a coded diagnosis of heart failure recorded more than once (single episodes were excluded) by a general practitioner or cardiologist. We required more than one registration of the heart failure code in the patient files, to minimise the number of false positive diagnoses. The second inclusion criterion was a follow-up period of more than 3 months after initial registration of a coded heart failure diagnosis. This period was thought to be necessary for the physician to establish a complete diagnostic and therapeutic management regime. Finally, the third inclusion criterion was a period of 5 years or less between the initial diagnosis of heart failure and the date of the study.

We defined patients as 'GP patients' if they were never referred to a cardiologist or internist for (suspected) heart failure or if they were referred only once *for diagnostic reasons*. In general practice, we studied files from patients with the International Classification of Primary Care (ICPC) code K 77 (heart failure)[13] and in the cardiology out-patient department, files from patients with International Classification of Diseases, 9th edition (ICD-9) code 428 (heart failure).
Files of patients with an initial coded diagnosis of heart failure were scrutinised and all relevant information was extracted. In total 963 patients with an ICPC code K77 (heart failure) were identified in the 31 general practices. After application of inclusion and exclusion criteria, 103 patients remained. Of the excluded patients from general practice, 301 patients (31%) had been referred to a cardiologist and 9 (0.9%) to an internist for (suspected) heart failure. Another 135 patients (14%) had been referred to a cardiologist for other reasons. Also excluded were 308 patients for whom the ICPC code K 77 was only stated once in the patient files, and 32 patients for whom the initial ICPC code K77 was recorded more than five years before the date of our study. Another 75 patients were excluded because they had a follow-up period shorter than 3 months.

In addition, consecutive out-patient files of patients with ICD-9 code 428 (heart failure) from the 'general' out-patient cardiology department of nine different hospitals were scrutinised. After applying the previously mentioned inclusion and exclusion criteria, 11 patients with ICD-9 code 428 (heart failure) per hospital (in total 99 patients) were included in our study.
The following demographic, diagnostic, and treatment data were extracted from the patient notes: date of birth; sex; date of diagnosis of heart failure; referral to a

cardiologist or internist; signs and symptoms in the days prior to the diagnosis; additional diagnostic investigations (such as echocardiography) performed six months prior to diagnosis and during the year since diagnosis; comorbidity (including coronary heart disease (CHD) such as myocardial infarction, angina pectoris, and coronary revascularisation (percutaneous transluminal intervention (PTI)) or coronary artery bypass grafting (CABG); atrial fibrillation; valvular heart disease; chronic obstructive pulmonary disease (COPD); diabetes mellitus; stroke or transient ischaemic attack (TIA); physician contacts; prescriptions; counselling advice; co-treatment by other health care workers.
Approval of the study was obtained from the Ethics Committee of the University Medical Center Utrecht, the Netherlands.

Data analysis
Differences in proportions were assessed by χ^2 tests and differences between means by *t*-tests. All analyses were undertaken using SPSS for Windows version 9.0 (SPSS, Chicago, Ill, USA).

Results

Patient characteristics
The mean age of the general practice and cardiology patients was 79 (SD 8.5) and 64 (SD 11.7) years ($p<0.001$), respectively, and 42% vs. 78% ($p<0.001$) were male (Table 1). Patients with coded heart failure were seen by a physician approximately four times a year in both primary and secondary care. Ischaemic heart disease was more prevalent in 'cardiology' patients (31 vs. 57%, $p<0.001$). Hypertension (53 vs. 41%, $p=0.09$) and atrial fibrillation (23 vs. 16%, $p=0.20$) were somewhat more common in 'GP patients', although these differences were not statistically significant.

Diagnosis
Dyspnoea was the most frequently recorded complaint in both primary and secondary care patients at the time of diagnosis (Table 2). Paroxysmal nocturnal dyspnoea (32 vs. 14%, $p=0.003$), nocturnal cough (36 vs. 13%, $p<0.001$), and pulmonary crepitations (77 vs. 46%, $p<0.001$) were more often recorded in 'GP patients'. Anginal complaints (11 vs. 41%, $p<0.001$), heart murmurs (12 vs. 43%, $p<0.001$), a third heart sound (1 vs. 14%, $p<0.001$), and hepatomegaly (2 vs. 11%, $p=0.007$) were more often recorded in 'cardiology patients' (Table 2).

Chest radiography (51 vs. 84%, $p<0.001$), electrocardiography (ECG) (39%

Table 1 Characteristics of 202 heart failure coded patients; 103 patients treated by general practitioners and 99 treated by cardiologists

Characteristics	GP patients	Cardiology patients	p-value
Age at diagnosis of heart failure	79.2 (8.5)	64.2 (11.7)	<0.001
Male	42	78	<0.001
Time between diagnosis and initiation of the study	1.9 years	2.0 years	0.62
Consultations per year	4.1 (3.2)	3.5 (1.2)	0.06
NYHA I or II	83	75	0.13
Prior myocardial infarction	15	43	<0.001
History of angina pectoris	20	34	0.03
CABG	3	17	0.001
PTI	1	6	0.05
Ischaemic heart disease*	31	56	<0.001
Hypertension	53	41	0.09
Atrial fibrillation	23	16	0.20
COPD	27	26	0.88
Diabetes	18	21	0.62
Stroke/TIA	3	6	0.26
> 6 alcohol units/day	3	7	0.17

Values are means (S.D.) or percentages. S.D. is standard deviation

* Ischaemic heart disease is (prior) myocardial infarction, angina pectoris, coronary artery bypass grafting (CABG) or percutaneous transluminal intervention (PTI).

vs.100%, p<0.001), and echocardiography (12% vs. 97%, p<0.001) were performed more often in 'cardiology patients', as were other additional investigations, with the exception of laboratory and pulmonary function tests (Table 3). None of the patients in either the primary or secondary care setting underwent measurements of natriuretic peptides.

Laboratory, chest X-ray, electrocardiographic, and echocardiographic abnormalities

Except for anaemia, laboratory tests seldom showed any abnormalities. Chest X-rays showed abnormalities in a substantial proportion of the investigated patients (85 vs. 90%, p=0.32), in particular a cardiothoracic ratio >0.50 (40 vs. 70%,

Table 2 Symptoms and signs in 202 heart failure coded patients, at the time of diagnosing heart failure; 103 patients treated by general practitioners and 99 treated by cardiologists

History and physical examination	GP patients (%)	Cardiology patients (%)	p-value
Symptoms			
Dyspnoea	94	94	0.94
Orthopnoea	25	20	0.39
Paroxysmal nocturnal dyspnoea	32	14	0.003
Nocturnal coughing	36	13	<0.001
Nycturia	13	5	0.06
Fatigue	62	62	0.94
Anginal complaints	11	41	<0.001
Signs			
Pulmonary crepitations	77	46	<0.001
Tachycardia (>100 beats/minute)	17	21	0.39
Elevated jugular venous pressure	8	19	0.02
Third heart sound	1	14	<0.001
Heart murmurs	12	43	<0.001
Laterally displaced apex beat	6	11	0.18
Ankle oedema	37	22	0.02
Irregular pulse	29	14	0.01
Palpitations	14	9	0.31
Hepatomegaly	2	11	0.007

p=0.001) (Table 4). Electrocardiographic abnormalities were often observed, especially ST and/or T-wave abnormalities (68 vs. 91%, p=0.001), prior myocardial infarction (5 vs. 9%, p=0.42), left ventricular hypertrophy (13 vs. 20%, p=0.28), and atrial fibrillation (28 vs. 13%, p=0.04) (Table 4). During echocardiography heart valve dysfunction was often seen (50 vs. 64%, p=0.36), while signs of diastolic dysfunction (0 vs. 3%, p=0.54) and left ventricular hypertrophy (0 vs. 3%, p=0.54) were reported in a few cases only. A left ventricular ejection fraction (LVEF) <40% was recorded more often in 'cardiology patients' (17% vs. 48%, p=0.04) (Table 4).

Pharmaceutical and non-pharmaceutical treatment

At the time of the assessment of the patient files, the vast majority of patients

Table 3 Diagnostic investigations in 202 heart failure coded patients performed 6 months prior to diagnosis and during the 1 year since diagnosis; 103 patients treated by general practitioners and 99 treated by cardiologists

Investigation	GP patients (%)	Cardiology patients (%)	p-value
Laboratory investigations*	88	98	0.007
Chest radiography	51	84	<0.001
ECG	39	100	<0.001
Echocardiography	12	97	<0.001
Exercise ECG	2	28	<0.001
Coronary angiography	3	26	<0.001
Pulmonary function tests	5	6	0.70
Radionuclide ventriculography	1	14	<0.001
Stress-imaging	2	16	<0.001
Ambulant ECG/holter monitoring	0	12	<0.001

* The most prevalent laboratory investigations were haemoglobin (76 vs. 95%, p<0.001), serum creatinine (69 vs. 96%, p<0.001), serum glucose (71 vs. 92%, p<0.001), and serum potassium (46 vs. 89%, p<0.001). Thyroid stimulating hormone was analysed in a minority of the patients (34 vs. 21%, p=0.04), and neuropeptide levels such as BNP, NT-proBNP, or ANP, were not assessed at all.

received diuretics, especially loop diuretics, both in primary (85%) and secondary care (79%) (Table 5). ACE-inhibitors (40 vs. 76%, p<0.001), β-blockers (9 vs. 30%, p<0.001), spironolactone (11 vs. 32%, p<0.001), and angiotensin-II receptor blockers (6 vs. 13%, p=0.08) were prescribed more often in 'cardiology patients'. Only a minority of all patients using ACE-inhibitors received the (high) dosages used in randomised controlled trials (32 vs. 44%, p=0.20). In both the GP's and cardiologist's population, age differences (age < 70 years or ≥70 years) did not appear to play an important role in the prescription preferences (Table 6), nor in the rates of additional diagnostic investigations used (data not shown).

In patient files of both 'cardiology patients' and 'GP patients' there was little information about non-pharmaceutical treatment and advice (Table 7) or co-treatment by other health care workers. A (heart failure) nurse (in 16% of the 'cardiology patients' and 3% of the 'GP patients') was most frequently mentioned as a co-treating health-care worker (Table 8).

Table 4 Abnormalities on chest X-ray, ECG and echocardiography in heart failure coded patients; 103 patients treated by general practitioners and 99 treated by cardiologists

Investigation	GP patients	Cardiology patients	p-value
Chest X-ray	**(n=52)***	**(n=83)***	
Cardiothoracic ratio >0.50	21 (40%)	58 (70%)	0.001
Signs of redistribution	20 (38%)	36 (43%)	0.57
Pleural fluid	8 (15%)	8 (9.6%)	0.32
Signs of COPD	4 (7.7%)	2 (2.4%)	0.15
ECG	**(n=40)***	**(n=99)***	
Myocardial infarction	2 (5.0%)	9 (9.1%)	0.42
ST and/or T-wave abnormalities	27 (68%)	90 (91%)	0.001
Left ventricular hypertrophy	5 (13%)	20 (20%)	0.28
Atrial fibrillation	11 (28%)	13 (13%)	0.04
Left bundle branch block	0 (0%)	20 (20%)	0.002
Echocardiography	**(n=12)***	**(n=96)***	
Left ventricular EF** < 40%	2 (17%)	46 (48%)	0.04
Valvular abnormalities	6 (50%)	61 (64%)	0.36
Signs of diastolic dysfunction	0 (0%)	3 (3.1%)	0.54
Left ventricular hypertrophy	0 (0%)	3 (3.1%)	0.54

* Numbers are patients with available chest X-ray, ECG or echocardiography data.
** EF, ejection fraction

Discussion

Our study shows that there are major differences in the population coded as heart failure by general practitioners and cardiologists. The GP more often manages elderly and female patients, while cardiologists more often treat relatively young male patients with a history of ischaemic heart disease. The GP uses fewer additional diagnostic investigations, and less often prescribes 'evidence-based' morbidity and mortality reducing medication.

The differences in diagnostic and therapeutic management between the GP and cardiologist can only partly be explained by the large difference in age of the coded heart failure patients: patients aged < 70 years or ≥ 70 years are investigated and treated in a similar way by both health care providers. This suggests that the physician's attitude could have an important bearing on the uptake of treatment.

Table 5 Current medication in 202 heart failure coded patients; 103 patients treated by general practitioners and 99 treated by cardiologists

Medication	GP patients (%)	Cardiology Patients (%)	p-value
Loop diuretics	78	79	0.85
Any diuretic	85	79	0.22
ACE inhibitors	40	76	<0.001
ß-blockers	8.7	30	<0.001
Spironolactone	11	32	<0.001
Digoxin	18	22	0.40
Nitrates	6.8	14	0.09
Angiotensin-II-receptor blockers	5.8	13	0.08
Cordarone	0	4.0	0.04
Coumarins	6.8	29	<0.001
Aspirin	20	13	0.17
Calcium channel-antagonists	6.8	6.1	0.83
NSAIDs	7.8	8.1	0.93

In our study we aimed to compare the management of patients with (suspected) heart failure in primary and secondary care. For this reason, patients with ICPC code K77 (heart failure) in general practice, who were referred to a cardiologist (except those patients referred for a single diagnostic assessment) (in total 31%) were excluded, since in practice these patients are primarily treated by cardiologists and not general practitioners. This is a major difference compared to other recent practice studies,[10;11] and is an important reason for the relatively low number of additional diagnostic investigations such as echocardiography and lower prescription rates of potentially beneficial medication in 'GP patients'. Fewer additional investigations in GP patients compared to those managed by the cardiologist illustrates that the GPs' diagnosis of heart failure is based primarily on clinical judgement.[7;8] However, diagnosing heart failure based on clinical judgement alone is notoriously difficult and leads to considerable proportions of false-negative and false-positive diagnoses.[9;15]

Table 6 Medication according to age group in 202 heart failure coded patients; 103 patients treated by the general practitioner and 99 treated by cardiologists

Medication	<70 years			≥ 70 years		
	GP patients (n=12) (%)	Cardiology patients (n=53) (%)	p-value	GP patients (n=91) (%)	Cardiology patients (n=46) (%)	p-value
Loop diuretics	92	70	0.12	76	89	0.06
Any diuretic	92	70	0.12	85	89	0.47
ACE inhibitors	33	77	0.003	41	74	<0.001
ß-blockers	8.3	28	0.15	8.8	33	<0.001
Spironolactone	25	36	0.47	8.8	28	0.003
Digoxin	17	21	0.75	18	24	0.38
Nitrates	17	13	0.75	5.5	15	0.06
ARB#	0	9.4	0.27	6.6	17	0.05
Cordarone	0	3.8	0.50	0	4.3	0.05
Coumarins	0	28	0.04	7.7	30	<0.001
Aspirin	8.3	11	0.76	22	15	0.35
Calcium-blockers	0	9.4	9.27	7.7	2.2	0.19

ARB, angiotensin-II receptor blockers.

A limitation of our study is that we studied patients who had heart failure according to their physician, without confirming the diagnosis. We were, however, interested in current management in patients with (suspected) heart failure according to the GP or cardiologist, and our aim was not to study the incidence or prevalence of heart failure or the effects of interventions. Evidently, some patients, more often those in primary care, without heart failure have been coded and treated as heart failure patients. We are convinced, however, that this pragmatic choice did not bias our results. Moreover, by including only patients in whom a diagnosis of heart failure was coded at least twice we limited the number of false positives.

Since we performed a cross-sectional survey, using available patient files, data should be interpreted with the understanding that recording of investigations performed and their results may be incomplete. Because physicians are more likely to record abnormalities than normal findings, under-recording of normal findings is likely. We could only observe the prevalence of recording of clinical signs such as

Table 7 Non-drug treatment and counselling in 202 heart failure coded patients; 103 treated by the general practitioner and 99 treated by cardiologists

Treatment and counselling	GP patients	Cardiology patients	p-value
Treatment			
CABG *	1	1	0.97
PTI**	1	3	0.29
Heart transplantation	0	1	0.30
Valve replacement	0	1	0.27
Counselling			
Smoking cessation	11	18	0.06
Reduced salt intake	3	10	0.04
Weight reduction	9	14	0.26
Alcohol restriction	2	3	0.55
Physical activity	5	1	0.11
Education	5	13	0.03

* CABG, coronary artery bypass grafting.

** PTI , percutaneous transluminal intervention.

heart murmurs, a third heart sound and hepatomegaly in patients. Therefore, we do not know whether these clinical signs were less prevalent or less often assessed in GP patients. For similar reasons, participation rates for other health care workers and provision of life style advice are also likely to be underestimated. On the other hand, prospective surveys or questionnaires are likely to induce 'desirable' answers and this produces inflated estimates.

Our study confirms earlier observations that GPs treat those patients (elderly and women) who are underrepresented in trials.[8] This is important in the interpretation of the differences observed with 'cardiology patients'. For example, the prevalence of 'diastolic heart failure' is higher in elderly female patients.[16;17] With 'diastolic heart failure' we mean both (symptoms of) heart failure with preserved left ventricular systolic function and 'pure' diastolic heart failure, which implies the demonstration of left ventricular diastolic dysfunction.[6] However, the exact contribution of 'diastolic heart failure' in the overall picture of heart failure is still not clear. Non-invasive assessment of diastolic dysfunction remains difficult and a consensus regarding the diagnostic criteria has not been agreed.[18] Moreover, tissue Doppler imaging has revealed that systolic abnormalities are present in about half

Table 8 Other medical health workers involved in the treatment of 202 heart failure coded patients; 103 patients treated by general practitioners and 99 treated by cardiologists

Medical health workers	GP patients	cardiology patients	p-value
Heart failure nurse	0	16	<0.001
District nurse	3	0	0.09
Dietician	4	3	0.75
Physiotherapist	0	0	-

of the patients with a left ventricular ejection fraction ≥ 50% and echocardiographic diastolic dysfunction.[19] One other study clearly showed that many patients suspected of having diastolic heart failure, had other explanations for their symptoms such as obesity or COPD.[20]
Moreover, at the time our study was performed, available heart failure guidelines in the Netherlands provided diagnostic and therapeutic advices for (suspected) heart failure, without making a clear distinction between 'systolic' and 'diastolic' heart failure. Although, there are only a few small clinical trials of the pharmacological treatment of patients with 'diastolic heart failure', treatment with ACE-inhibitors and β-blockers seems to be of prognostic benefit.[21;22] Apart from this, treatment of the possible causes of 'diastolic heart failure', i.e. myocardial ischaemia, hypertension, myocardial hypertrophy, and myocardial/pericardial constriction also implies that the physician can prescribe ACE-inhibitors, β-blockers and (low dose) diuretics.[6]

There is robust evidence that ACE-inhibitors, β-blockers, spironolactone, and angiotensin-II receptor blockers reduce morbidity and mortality when prescribed in combination with diuretics in patients with heart failure due to left ventricular systolic dysfunction.[23-29] An important reason for under-use of prognostically beneficial medication by the GP in patients with heart failure due to left ventricular systolic dysfunction could be diagnostic uncertainty.[10] Under-use of ACE-inhibitors in primary care was also observed in earlier studies from Great Britain.[7;8] Fear of the side effects of ACE-inhibitors seems to be of more importance for under-prescription by the GP than lack of knowledge of the possible beneficial effects.[30] Less than half of the patients in both primary and secondary care in our study were prescribed high dosages of ACE-inhibitor similar to those used in the major trials,[31] although high dosages are more effective in systolic heart failure without an important increase in side effects.[32] β-blockers were prescribed in only a

minority of patients coded as heart failure in our study. This is partly attributable to the fact that ß-blockers were contra-indicated in heart failure in the past and the necessity to start with a low dosage and up-titrate very slowly; a process which takes several weeks and leads to a short period of increased complaints in some patients.[26;27] A possible explanation for the under-use of spironolactone in our study is the under-representation of patients in NYHA class III or IV with a LVEF < 40% in our study; the population in which spironolactone, added to diuretics and an ACE-inhibitor, was proven to be effective.[29] Potentially harmful medication such as first generation calcium channel blockers and non-steroid anti-inflammatory drugs (NSAIDs)[33] was prescribed in only 6-8% of the patients. In our study patients of different ages were treated similarly by both health care providers. This is somewhat in contrast with a recently performed practice study which showed that patients in general practice with (suspected) heart failure aged over 75 years were treated less with ACE-inhibitors and β-blockers.[11]

Initially, we also intended to include patients from the internal medicine department in our survey. In the Netherlands, however, nearly all patients with (suspected) heart failure who are referred to the hospital or out-patient department are (co)treated by a cardiologist.

We conclude that heart failure patients managed by the general practitioner alone are more often elderly female patients compared to heart failure patients managed by the cardiologist. Fewer additional investigations and lower prescription rates of potentially beneficial medication in primary care are only partly explained by differences in population characteristics suggesting that the physicians attitude has an important bearing on the uptake of treatment. In both primary and secondary care diagnostic and therapeutic management of heart failure does not reflect current scientific evidence.

Acknowledgements

We thank the participating general practitioners, internists and cardiologists. In addition we want to thank Diana Balk, Renate Siebes and Peter Zuithoff for administrative assistance and statistical help, and Geert van der Heijden, PhD, for critical comments on earlier versions of the manuscript.
Financial support for this study was obtained from the Netherlands Heart Foundation, grant number 48006.

References

1. Cowie MR, Mosterd A, Wood DA, Deckers JW, Poole-Wilson PA, Sutton GC *et al*. The epidemiology of heart failure. *Eur Heart J* 1997;18:208-25.

2. Senni M, Tribouilloy CM, Rodeheffer RJ, Jacobsen SJ, Evans JM, Bailey KR *et al*. Congestive heart failure in the community: trends in incidence and survival in a 10-year period. *Arch Intern Med* 1999;159:29-34.

3. Senni M, Redfield MM. Heart failure with preserved systolic function. A different natural history? *J Am Coll Cardiol* 2001;38:1277-82.

4. Kostis JB, Davis BR, Cutler J, Grimm-RH J, Berge KG, Cohen JD *et al*. Prevention of heart failure by antihypertensive drug treatment in older persons with isolated systolic hypertension. SHEP Cooperative Research Group. *JAMA* 1997;278:212-6.

5. Banerjee P, Banerjee T, Khand A, Clark A, Cleland J. Diastolic heart failure: Neglected or misdiagnosed? *J Am Coll Cardiol* 2002;39:138-41.

6. Remme WJ, Swedberg K. Guidelines for the diagnosis and treatment of chronic heart failure. *Eur Heart J* 2001;22:1527-60.

7. Hood S, Taylor S, Roeves A, Crook AM, Tlusty P, Cohen J *et al*. Are there age and sex differences in the investigation and treatment of heart failure? A population-based study. *Br J Gen Pract* 2000;50:559-63.

8. Mair FS, Crowley TS, Bundred PE. Prevalence, aetiology and management of heart failure in general practice. *Br J Gen Pract* 1996;46:77-9.

9. Clarke KW, Gray D, Hampton JR. Evidence of inadequate investigation and treatment of patients with heart failure. *Br Heart J* 1994;71:584-7.

10. Cleland JG, Swedberg K, Cohen-Solal A, Cosin-Aguilar J, Dietz R, Follath F *et al*. The Euro Heart Failure Survey of the EUROHEART survey programme. A survey on the quality of care among patients with heart failure in Europe. *Eur J Heart Fail* 2000;2:123-32.

11. Cleland JG, Cohen S, Aguilar JC, Dietz R, Eastaugh J, Follath F *et al*. Management of heart failure in primary care (the IMPROVEMENT of Heart Failure Programme): an international survey. *Lancet* 2002;360:1631-9.

12. Mason J, Young P, Freemantle N, Hobbs FDR. Safety and costs of initiating angiotensin converting enzyme inhibitors for heart failure in primary care: analysis of induvidual patient data from studies of left ventricular dysfunction. *BMJ* 2000;321:1113-6.

13. Classification Committee of WONCA. ICHPPC-2 defined. International classification of primary care. UK: Oxford University Press, 1983.

14. Van der Lei J, Duisterhout JS, Westerhof HP, van der Does E, Cromme PV, Boon WM *et al*. The introduction of computer-based patient records in The Netherlands. *Ann Intern Med* 1993;119:1036-41.

15. Remes J, Miettinen H, Reunanen A, Pyörälä K. Validity of clinical diagnosis of heart failure in primary health care. *Eur Heart J* 1991;12:315-21.

16. Lindenfeld J, Krause S, Salerno J. Where are all the women with heart failure? *J Am Coll Cardiol* 1997;30:1417-9.

17. Davie AP, Francis CM, Caruana L, Sutherland GR, McMurray JJ. The prevalence of left ventricular diastolic filling abnormalities in patients with suspected heart failure. *Eur Heart J* 1997;18:981-4.

18. European Study Group on Diastolic Heart Failure. How to diagnose diastolic heart failure. *Eur Heart J* 1998;19:990-1003.

19. Yu CM, Lin H, Yang H, Kong SL, Zhang Q, Lee SW. Progression of systolic abnormalities in patients with "isolated" diastolic heart failure and diastolic dysfunction. *Circulation* 2002;105:1195-201.

20. Caruana L, Petrie MC, Davie AP, McMurray JJ. Do patients with suspected heart failure and preserved left ventricular systolic function suffer from "diastolic heart failure" or from misdiagnosis? A prospective descriptive study. *BMJ* 2000;321:215-8.

21. Aronow WS, Ahn C, Kronzon I. Effect of propranolol versus no propranolol on total mortality plus nonfatal myocardial infarction in older patients with prior myocardial infarction, congestive heart failure, and left ventricular ejection fraction > or = 40% treated with diuretics plus angiotensin-converting enzyme inhibitors. *Am.J Cardiol* 1997;80:207-9.

22. Aronow WS, Kronzon I. Effect of enalapril on congestive heart failure treated with diuretics in elderly patients with prior myocardial infarction and normal left ventricular ejection fraction. *Am J Cardiol* 1993;71:602-4.

23. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. *JAMA* 1995;273:1450-6.

24. Eccles M, Freemantle N, Mason J. North of England evidence based development project: guideline for angiotensin converting enzyme inhibitors in primary care management of adults with symptomatic heart failure. *BMJ* 1998;316:1369-75.

25. Lechat P, Packer M, Chalon S, Cucherat M, Arab T, Boissel JP. Clinical effects of beta-adrenergic blockade in chronic heart failure: a meta-analysis of double-blind, placebo-controlled, randomized trials. *Circulation* 1998;98:1184-91.

26. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999;353:9-13.

27. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999;353:2001-7.

28. Pitt B, Segal R, Martinez FA, Meurers G, Cowley AJ, Thomas I *et al*. Randomised

trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *Lancet* 1997;349:747-52.

29. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A *et al*. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999;341:709-17.

30. Houghton AR, Cowley AJ. Why are angiotensin converting enzyme inhibitors underutilised in the treatment of heart failure by general practitioners? *Int J Cardiol* 1997;59:7-10.

31. Remme WJ. Heart failure management: why evidence does not influence clinical practice. *Eur Heart J* 2000;2 (suppl I):115-21.

32. Massie BM, Armstrong PW, Cleland JG, Horowitz JD, Packer M, Poole W *et al*. Toleration of high doses of angiotensin-converting enzyme inhibitors in patients with chronic heart failure: results from the ATLAS trial. The Assessment of Treatment with Lisinopril and Survival. *Arch Intern Med* 2001;161:165-71.

33. Heerdink ER, Leufkens HG, Herings RM, Ottervanger JP, Stricker BH, Bakker A. NSAIDs associated with increased risk of congestive heart failure in elderly patients taking diuretics. *Arch Intern Med* 1998;158:1108-12.

Chapter 3

Diagnosis and management of heart failure: a questionnaire among general practitioners and cardiologists

Frans H Rutten, Diederick E Grobbee , Arno W Hoes

Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht

Eur J Heart Fail 2003;5:345-48

Background

Heart failure has gradually become one of the most prevalent cardiovascular disorders in Western Societies, notably in the elderly.[1;2] Notwithstanding the public health importance of heart failure, current management of heart failure in clinical practice seems far from optimal.[3-5] Data on perceptions,[6-8] diagnosis, and management of patients with heart failure in every day care are, however, scarce.[9] In particular, studies comparing primary and secondary care are virtually non-existent.[9]

Aims

To compare perceptions about heart failure diagnosis and management between cardiologists and general practitioners (GPs) in the Netherlands.

Methods

In the year 2000, 150 GPs in the Netherlands were sent a questionnaire. The general practices were located in the vicinity of Utrecht, were both urban and rural, and included single-handed and group practices. In total, 99 (62%) of the GPs participated. Forty-five (45%) of the participating GPs also took part in our study using patient files (see Chapter 2). All invited GPs routinely register their patient contacts in ELIAS (SMS Cendata Nieuwegein); a software package suitable for electronic registration of medical information. In addition, 58 cardiologists were sent a questionnaire. Cardiologists were selected at random from one academic, three middle size, and five smaller hospitals in the Netherlands. Thirty-six (62%) cardiologists participated. Twenty-four (67%) of the participating cardiologists also took part in our study on patient files (see Chapter 2).[10]
The questionnaire consisted of 21 questions, with dichotomous response options, concerning aspects on the diagnosis and management of heart failure.
The study was conducted as part of the Utrecht Heart Failure Organisation (UHFO) program. Approval of the study was obtained from the Ethics Committee of the University Medical Center Utrecht, the Netherlands.

Data analysis
Differences in proportions were assessed by means of χ^2 tests. All analyses were undertaken using SPSS for Windows version 9.0 (SPSS, Chicago, Ill, USA).

Table 1 Items from history taking and physical examination considered most important in patient suspected of heart failure by GPs and cardiologists

History	**GPs (%) (N=61)**	**Cardiologists (%) (N=36)**	**p-value**
Prior myocardial infarction	69	83	0.12
Hypertension	59	72	0.19
Valvular disease	38	47	0.36
Atrial fibrillation	25	2.8	0.005
Diabetes mellitus	18	19	0.86
COPD*	13	0	0.02
Symptoms			
Dyspnoea	81	97	0.03
Fatigue	53	56	0.77
Nycturia ≥ 2x	48	22	0.01
Paroxysmal nocturnal dyspnoea	36	8.3	0.003
Coughing	16	14	0.74
Weight loss	15	25	0.21
Anginal complaints	6.6	5.6	0.84
Orthopnoea	4.9	0	0.18
Signs			
Pulmonary crepitations	93	92	0.74
Peripheral oedema	90	81	0.18
Elevated JVP**	69	67	0.82
Hepatomegaly	43	31	0.24
Heart murmurs	16	36	0.03
Laterally displaced apex beat	16	22	0.48
Third heart sound	12	44	<0.001

* COPD, chronic obstructive pulmonary disease.

** JVP, jugular venous pressure.

Table 2 Investigations considered most important by GPs and cardiologists in suspected heart failure, in addition to history taking and physical examination

Investigations	GPs (%) (N=61)	Cardiologists (%) (N=36)	p-value
Chest X-ray	98	100	0.44
Reaction on diuretics	97	49	<0.001
Electrocardiography	85	94	0.17
Echocardiography	62	100	<0.001
(Other) laboratory tests	33	64	0.005
Exercise ECG	26	61	0.001
Stress-echo or stress-scintigraphy	16	47	0.001
Coronary angiography	15	81	<0.001
Radionuclide ventriculography	10	67	<0.001
Natriuretic peptides	4.9	28	0.001

Results

Prior myocardial infarction (69 vs. 83%) and hypertension (59 vs. 72%) are seen as important features in history by both GPs and cardiologists (Table 1). Of symptoms, dyspnoea (81 vs. 97%), and peripheral oedema (77 vs. 72%) are qualified as most important by both. Pulmonary crepitations (93 vs. 92%), peripheral oedema (90 vs. 81%), and an elevated jugular venous pressure (69 vs. 67%) are considered important signs (Table 1). In addition, cardiologists pay relatively more attention to heart murmurs (16 vs. 36%) and a third heart sound (12 vs. 44%) than GPs.

Chest radiography (98 vs. 100%) and electrocardiography (85 vs. 94%) are used most often as additional diagnostic investigations, in both primary and secondary care. As a subsequent diagnostic tool, GPs prefer a change in symptoms following test treatment with diuretics (97 vs. 49%) while cardiologists prefer (Doppler) echocardiography (62 vs. 100%) and coronary angiography (15 vs. 81%) (Table 2). Currently, both physicians do not regard natriuretic peptides as an important diagnostic tool in heart failure (Table 2).

As first choice medical treatment GPs prescribe diuretics (63 vs. 29%, p=0.001), while cardiologists primarily prefer a combination of ACE inhibitor and diuretics (32 vs. 63%, p=0.001). All cardiologists (100%), but only 35% of the GPs ever

Table 3 Additional drug treatment considered most important by GPs and cardiologists in patients with heart failure who remain symptomatic after initial treatment with a diuretic and ACE inhibitor

Treatment	GPs (%) (N=61)	Cardiologists (%) (N=36)	p-value
Increase dosage of diuretic	90	94	0.45
Add spironolactone	73	86	0.13
Add digoxin	70	64	0.54
Increase dosage of ACE inhibitor	68	86	0.05
Add a β-blocker	35	75	<0.001
Add another diuretic	30	36	0.54
Add an angiotensin-II receptor blocker	8.3	33	0.002

prescribe β-blockers for heart failure. In case of persisting symptoms in patients being treated with diuretics and ACE inhibitor, GPs add spironolactone and digoxin, while cardiologists also use β-blockers or angiotensin-II receptor blocker as additional therapy (Table 3).

There were no significant differences between GPs who participated in the patient files study (see Chapter 2) and the other GPs. Also, between cardiologists who participated in the patient files study and those who did not, answers to the questions in the questionnaire did not differ significantly. (Table 1,2,3)

Conclusion

Differences in opinions regarding diagnosis and management of heart failure between GPs and cardiologists primarily concern preferences in additional investigations and pharmacological interventions. GPs tend to diagnose heart failure on clinical grounds not making use of echocardiography facilities. This tendency has also observed in other studies.[7-9] Limited access to echocardiography for primary care patients is probably the most important explanation for this.

At the moment, natriuretic peptides do not play an important role in the diagnostic assessment in either primary or secondary care in the Netherlands, although studies have already shown their usefulness as a diagnostic tool in patients suspected of heart failure.[11-14]

Our study shows that GPs often rely on a 'positive' reaction following initiation of diuretics as a diagnostic tool. Although several heart failure guidelines, including the European Society of Cardiology (ESC) guideline mention improvement in symptomatology following appropriate therapy as an important diagnostic sign,[15] its diagnostic value is still unknown and should be assessed.

In contrast to cardiologists, most GPs consider monotherapy with diuretics an important option in heart failure treatment. In addition, GPs are reluctant to prescribe β-blocking agents.[8;16-19] Differences between primary and secondary care populations could play a role in these preferences of the GPs, because on average, primary care patients are 10-15 years older, are more often female,[3;4;8] and have more often 'diastolic' heart failure.

Acknowledgements

We thank the participating general practitioners, internists and cardiologists. In addition, we thank Diana Balk, Renate Siebes and Peter Zuithoff for administrative assistance and statistical help, and Geert van der Heijden, PhD, for critically reading the manuscript.
Financial support for this study was obtained from the Netherlands Heart Foundation, grant number 48006.

References

1. Cowie MR, Mosterd A, Wood DA, Deckers JW, Poole-Wilson PA, Sutton GC *et al*. The epidemiology of heart failure. *Eur Heart J* 1997;18:208-25.
2. Senni M, Tribouilloy CM, Rodeheffer RJ, Jacobsen SJ, Evans JM, Bailey KR *et al*. Congestive heart failure in the community: trends in incidence and survival in a 10-year period. *Arch Intern Med* 1999;159:29-34.
3. Cleland JG, Swedberg K, Cohen-Solal A, Cosin-Aguilar J, Dietz R, Follath F *et al*. The Euro Heart Failure Survey of the EUROHEART survey programme. A survey on the quality of care among patients with heart failure in Europe. *Eur J Heart Fail* 2000;2:123-32.
4. Hood S, Taylor S, Roeves A, Crook AM, Tlusty P, Cohen J *et al*. Are there age and

sex differences in the investigation and treatment of heart failure? A population-based study. *Br J Gen Pract* 2000;50:559-63.

5. Clarke KW, Gray D, Hampton JR. Evidence of inadequate investigation and treatment of patients with heart failure. *Br Heart J* 1994;71:584-7.

6. Hobbs FDR. Management of heart failure: evidence versus practice. Does current prescribing provide optimal treatment for heart failure patients? *Br J Gen Pract* 2000;50:735-42.

7. Edep ME, Shah NB, Tateo IM, Massie BM. Differences between primary care physicians and cardiologists in management of congestive heart failure: relation to practice guidelines. *J Am Coll Cardiol* 1997;30:518-26.

8. Hobbs FDR, Jones MI, Allan TF, Wilson S, Tobias R. European survey of primary care physician perceptions on heart failure diagnosis and management (Euro-HF). *Eur Heart J* 2000;21:1877-87.

9. Cleland JG, Cohen S, Aguilar JC, Dietz R, Eastaugh J, Follath F *et al*. Management of heart failure in primary care (the IMPROVEMENT of Heart Failure Programme): an international survey. *Lancet* 2002;360:1631-9.

10. Rutten FH, Grobbee DE, Hoes AW. Differences between general practitioners and cardiologists in diagnosis and management of heart failure: a survey in every-day practice. *Eur J Heart Fail* 2003;5:337-44.

11. Cowie MR, Struthers AD, Wood DA, Coats AJ, Thompson SG, Poole-Wilson PA *et al*. Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care. *Lancet* 1997;350:1349-53.

12. Landray MJ, Lehman R, Arnold I. Measuring brain natriuretic peptide in suspected left ventricular systolic dysfunction in general practice: cross-sectional study. *BMJ* 2000;320:985-6.

13. McClure SJ, Caruana L, Davie AP, Goldthorp S, McMurray JJV. Cohort study of plasma natriuretic peptides for identifying left ventricular systolic dysfunction in primary care. *BMJ* 2000;317:316-9.

14. Smith H, Pickering RM, Struthers A, Simpson I, Mant D. Biochemical diagnosis of ventricular dysfunction in elderly patients in general practice: observational study. *BMJ* 2000;320:906-8.

15. Remme WJ, Swedberg K. Guidelines for the diagnosis and treatment of chronic heart failure. *Eur Heart J* 2001;22:1527-60.

16. Lechat P, Packer M, Chalon S, Cucherat M, Arab T, Boissel JP. Clinical effects of beta-adrenergic blockade in chronic heart failure: a meta-analysis of double-blind, placebo-controlled, randomized trials. *Circulation* 1998;98:1184-91.

17. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A *et al*. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med*

1999;341:709-17.

18. Pitt B, Poole-Wilson P, Segal BL, Martinez F, Dickstein K, Camm AJ *et al*. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial-the Losartan Heart Failure Survival Study ELITE II. *Lancet* 2000;355:1582-7.

19. Pitt B, Segal R, Martinez FA, Meurers G, Cowley AJ, Thomas I *et al*. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *Lancet* 1997;349:747-52.

Chapter 4

Heart failure and chronic obstructive pulmonary disease: an ignored combination?

Frans H Rutten [1], Maarten-Jan M Cramer [2], Jan-Willem J Lammers [3], Diederick E Grobbee [1], Arno W Hoes [1]

[1] Julius Center for Health Sciences and Primary Care;
[2] Heart Lung Center Utrecht, Department of Cardiology;
[3] Heart Lung Center Utrecht, Department of Pulmonary Diseases;
University Medical Center Utrecht.

Submitted

Abstract

Aims To quantify the prevalence of heart failure and left ventricular systolic dysfunction (LVSD) in chronic obstructive pulmonary disease (COPD) patients and vice versa. Further, to discuss diagnostic and therapeutic implications of the co-existence of both syndromes.

Methods and results We performed a Medline search from 1966 to October 2004. The reported prevalence of LVSD among COPD patients varied considerably, with the highest prevalence (10-46%) among those with an exacerbation. One single study assessed the prevalence of heart failure in COPD patients. A prevalence of 21% of previously unknown heart failure was reported in patients with a history of COPD or asthma. We did not find any report on COPD in heart failure or LVSD patients.

Diagnosing heart failure in COPD patients or vice versa is complicated by overlap in signs and symptoms, and diminished diagnostic value of additional investigations.

In general, pulmonary and heart failure 'drug cocktails' can be administered safely to patients with concomitant COPD and heart failure, although (short acting) β2-adrenoreceptor agonists and digitalis have potentially deleterious effects on cardiac and pulmonary function, respectively.

Conclusion Although knowledge about the prevalence of concomitant heart failure in COPD patients and vice versa is scarce, it seems that the combined presence is rather common. In view of diagnostic and therapeutic implications more attention should be paid to the concomitant presence of both syndromes in clinical practice and research.

Introduction

Clinicians in both primary and secondary care are often confronted with elderly dyspnoeic patients.[1;2] Major causes for dyspnoea in the elderly are heart failure and chronic obstructive pulmonary disease (COPD),[3-5] and both are on the increase.[2;6] Both syndromes have been studied extensively, but largely separately, with COPD in the domain of the pulmonologist and heart failure in the domain of the cardiologist. Studies on the prevalence of heart failure in COPD patients or vice versa are scarce. Since presence of one syndrome in the presence of the other has important therapeutic implications, knowledge about the concomitant prevalence is clinically relevant.

Several studies provided some evidence that the syndromes often co-exist. Diagnostic studies showed that pulmonary dysfunction and use of pulmonary medication for example often coincide with unrecognised heart failure,[7-9] and that unrecognised heart failure is common in COPD patients experiencing an exacerbation.[10] Moreover, tobacco smoking is an important common etiologic factor in COPD and heart failure.

We hypothesised that the combination of heart failure and COPD is much more common than generally acknowledged. We reviewed the existing literature to estimate the prevalence of heart failure or left ventricular systolic dysfunction (LVSD) in COPD patients and vice versa. In addition, we discuss diagnostic and therapeutic implications of the co-existence of both syndromes.

Methods

A Medline search was conducted for 1966 to October 2004. We used the MESH terms 'pulmonary disease, chronic obstructive or COPD', 'heart failure, congestive', 'cor pulmonale', and 'dyspn(o)ea'. Additional references were retrieved by citation tracking of relevant publications. Only studies published in English were included in the analysis. To quantify the prevalence of heart failure or LVSD in COPD patients, we only included studies that reported left ventricular ejection fractions (LVEF) assessed by either echocardiography, radionuclide or angiographic ventriculography.

Ideally, the prevalence of heart failure or LVSD in COPD patients should be assessed in a representative sample of patients with *objective* evidence of COPD, with diagnostic measurements in *all* eligible patients, using state-of-the-art

methodology.[11] In case of COPD an adequately performed spirometric pulmonary function test with application of the GOLD criteria is presently considered the reference ('gold') standard.[12] Echocardiography is the cornerstone in the diagnostic assessment of heart failure, because of its ability to provide information about systolic and/or diastolic ventricular function, but echocardiography alone is not considered the reference ('gold') standard.[13] An acceptable proxy reference is the consensus of an outcome panel, that determines the presence or absence of heart failure by using all available diagnostic tests results, including echocardiography.[14]

Definitions

For COPD we used the definition of the Global Initiative for COPD ('GOLD'),[12] i.e. a disease state characterised by airflow limitation that is not fully reversible. A ratio of post-dilatory forced expiratory volume in one second divided by forced vital capacity (FEV1/FVC) < 70%, assessed by spirometry, confirms the presence of COPD, either with or without symptoms compatible with chronic pulmonary disease (cough, dyspnoea, sputum production). Heart failure was defined according to the European Society of Cardiology (ESC),[13] i.e. clinical symptoms and objective evidence of cardiac dysfunction (systolic and/or diastolic).
Left ventricular systolic dysfunction (LVSD) was defined as a LVEF < 50% assessed by echocardiography, radionuclide, or angiographic ventriculography.
'Isolated' right sided heart failure was defined as the presence of signs of right sided heart failure (i.e. elevated central venous pressure, peripheral oedema, and/or liver enlargement), increased right atrial pressure, and a LVEF > 50%.

The magnitude of the problem

Prevalence of heart failure or LVSD in COPD patients
We divided studies in those that excluded patients known with coronary artery disease and studies that did not, because the prevalence of heart failure is clearly influenced by presence or absence of coronary artery disease.
All 12 studies that excluded patients known with coronary artery disease included small numbers of participants, with mean ages ranging from 53-68 years. Nine of these 12 studies were performed in stable, mostly severe COPD patients. In four (comprising 98 COPD patients in total) of these nine studies the prevalence of LVSD (LVEF < 40-50%) was zero,[15-18] and in five studies (comprising 283 COPD patients in total) the prevalence of LVSD ranged from 3.8-16%.[19-23]

Three studies were performed in patients experiencing an exacerbation (worsening) of their COPD. One study, with only 10 COPD patients (all with pulmonary artery hypertension) reported zero patients with LVSD.[24] The other two studies (comprising 99 patients in total) reported a prevalence of 23% and 32% LVSD, respectively (Table 1).[25;26]

Six studies included 'unselected' COPD patients, that is, without exclusion of patients known with coronary artery disease. The mean age in these studies ranged from 59-74 years (Table 2). Five studies in more or less stable COPD patients showed prevalence rates of LVSD ranging from 10% (n=27) to 46% (n=37).[27-31] One study, a sub-study of the Breathing Not Properly (BNP) trial,[32] was performed in patients known with a history of asthma or COPD, who had acute dyspnoea, urging them to visit an emergency department.[10] Prevalence of LVSD (LVEF < 45%) in this study was 18%, and the prevalence of previously unknown heart failure was 20.9%. Importantly, however, in only 29% of all participants echocardiography was performed, and the diagnosis of heart failure was based on the opinion of two cardiologists.[10] They based their diagnosis on the heart failure scores of Framingham[33] and National Health and Nutrition Examination Survey (NHANES),[34] scores that only include elements from history, physical examination and chest radiography. In an unspecified sample of the participants additional information was available from electrocardiography or further cardiac testing.[10]

Prevalence of COPD in LVSD or heart failure patients

We could not find any report on prevalence of COPD in patients with LVSD or (a history of) heart failure. In five studies among patients with acute dyspnoea the presence of either COPD, heart failure, or both was assessed.[3;35-38] These studies included patients without a diagnosis of heart failure or COPD at the start of the investigations. Consequently, these studies were not included in our review.

Diagnostic difficulties

Recognising heart failure in the presence of COPD and vice versa is complicated by similarities in symptoms and physical findings.[39;40] Furthermore, chest radiography is less sensitive for detecting heart failure because the cardiothoracic ratio is adversely affected by hyperinflated lungs, and left ventricular dilatation can be masked by right ventricular enlargement caused by COPD.[41] Moreover, in severe COPD some degree of pulmonary congestion and even pulmonary oedema can be present on chest X-ray, without manifest heart failure.[40] Electrocardiographic abnormalities reported in COPD patients overlap with those

Table 1 Studies that assessed heart failure or LVSD in COPD patients, with exclusion of

First author	Christian son	Matthay	Olvey	Slutsky	Jardin	Yamaoka
Year of publication	1979	1980	1980	1980	1984	1987
Sample size	19	30	18	37	10	15
Patient population	Severe COPD	COPD	COPD	COPD	COPD, all PAH **	Stable, chronic COPD
Mean age	54	53	61	52	68	60
Reference test	Left VG	RVG	RVG	RVG	Echo	RVG + right VG
All patients reference test?	Yes	Yes	Yes	Yes	No [&]	Yes
Exclusion of overt CAD?	Yes, also exclusion of HT, DM	Yes, also exclusion of HT	Yes	Partly. In 8 patients heart disease	Yes	Yes, also exclusion of HT, renal or hepatic failure
LV SD	16% LVEF<45%	10% LVEF<50%	0% LVEF<50%	11% LVEF <45%	0% LVEF<45%	0% LVEF<50%
HF	NA	NA	NA	NA	NA	NA
Remarks	-	-	-	-	-	-

CAD, coronary artery disease; CP, cor pulmonale; DM, diabetes mellitus; HF, heart hypertension; RVG, radionuclide ventriculography; VG, angiographic ventriculography.

* In the study of Vizza, et al, 434 patients were evaluated for lung transplantation, 168

** patients experiencing an exacerbation or worsening of their dyspnoea.

[&] In the study of Jardin four (29%) patients, and in the study of Boussuges 18 (35%)

patients with overt coronary artery diseases

Song	Incalzi	Render	Schena	Vizza	Boussuges
1989	1990	1995	1996	1998	2000
29	22	77	30	168 *	34
Stable CP secondary to COPD	COPD **	Out Patients with COPD **	CP secondary to COPD	Severe COPD	Severe COPD
64	63	66	62	54	60
Left and right VG	RVG	RVG	Echo + right VG	Echo + RVG + right VG	Echo
Yes	Yes	Yes	Yes	No, in 94%	No [&]
Yes, also exclusion of HT	Yes, also exclusion of HT, DM, renal or hepatic failure	Yes	Yes, also exclusion of HT	Yes	Yes, also exclusion of HT
7% LVEF <50%	23% LVEF <50%	32% LVEF <40%	0% LVEF <40%	3.8% LVEF <45%	0% LVEF <50%
NA	NA	NA	NA	NA	NA
7 patients >50% coronary stenosis	-	All male smokers	-	-	-

failure; HT, hypertension; LV, left ventricular; NA, not assessed; PAH, pulmonary artery

patients with (end-stage) COPD. The other 266 patients had other pulmonary diseases;

patients were excluded because of technical insufficient echocardiograms.

seen in heart failure.[42;43] Natriuretic peptides such as B-type natriuretic peptide (BNP) and amino-terminal pro B-type natriuretic peptide (NT-proBNP) can help the clinician in differentiating COPD from heart failure in patients with acute dyspnoea.[36;38] However, natriuretic peptide levels can be increased in acute hypoxemic COPD, although not as high as in manifest heart failure, possibly due to pressure and/or volume load on the right ventricle.[44] Pulmonary function tests in patients with heart failure show intermediate reduction of pulmonary function at a level between healthy subjects and COPD patients.[35;45] Echocardiographic windows are limited by hyperinflated lungs and can complicate precise measurements in up to 10-30% of COPD patients.[7;18] Cardiovascular magnetic resonance imaging (CMR) could serve as an alternative for echocardiography in these patients, since CMR is not affected by hyperinflated lungs. Moreover, visualisation and measurements of the right ventricle are more easy and right ventricular function can be measured.[46-48] Disadvantages are the time-consuming data-acquisition and post-processing, and the higher cost of CMR compared to echocardiography.[48]

Therapeutic implications

Pulmonary medication influencing cardiac function

The most important treatment options for COPD are β2-adrenoreceptor agonists and anticholinergics. β2-adrenoreceptor agonists are not highly selective, and thus, β1-receptors predominantly present in myocardial tissue might also be activated. Increased stimulation of these myocardial β1-receptors may eventually accelerate the down regulation of these receptors with increased myocardial oxygen consumption and endogenous catecholamine production as a result.[49] A limited number of studies showed that oral and inhaled short-acting β2-adrenoreceptor agonists do seem to increase the risk of mortality and number of heart failure exacerbations in patients with left ventricular dysfunction.[49-51]

Currently, inhalation with long-acting β2-adrenoreceptor agonists are preferred in most COPD patients. These drugs are more quickly removed from myocardial and kidney β-receptors. Potentially deleterious cardiac effects are therefore less probable.[52]

Anticholinergics can (shortly) reduce acetylcholine release.[53] Potentially, these drugs could exert (adverse) cardiac effect conform atropine. Till now, no adverse influence on cardiac function has been described, but the numbers of reliable studies are small.[53]

Cardiovascular medication influencing pulmonary function

Treatment options of heart failure include diuretics, β-blocking agents, angiotensin-converting enzyme (ACE)-inhibitors, angiotensine-II-receptor blockers (ARB), aldosteron antagonists, and digitalis.

High dosages of diuretics can cause acid-base disturbances (metabolic alkalosis) in COPD patients and this may blunt the respiratory drive, but at normal dosages pulmonary function is not influenced by diuretics.[37,54]

Until recently, authors advised not to use β-blocking agents in case of COPD, notably in the presence of bronchospasm.[54-56] However, a recent systematic review revealed that β-blocking agents, at least cardio-selective ones, can be safely administered to COPD patients even in those patients with some bronchospasm with no or only small negative effects on pulmonary function.[57;58]

The renin-angiotensin system exerts its activity not only in the systemic circulation, but also in organ tissues, such as the lungs.[59] Angiotensin-II is a potent pulmonary airway constrictor. Therefore, ACE-inhibitors and ARBs confer potential benefit in treating patients with COPD by decreasing angiotensin-II levels and thus pulmonary obstruction.[54] ACE-inhibitors may have additional beneficial effects because they can also decrease pulmonary inflammation and pulmonary vascular constriction,[59] and ameliorate the alveolar membrane gas exchange.[60]

Aldosterone antagonists such as spironolactone can also have possibly positive effects on gas exchange, because aldosterone can damage the alveolar-capillary membrane.[61]

Digitalis may, however, reduce lung function because it can cause pulmonary vasoconstriction.[54]

Discussion

Our review of the literature shows that precise data about the prevalence of left ventricular systolic dysfunction (LVSD) or heart failure in patients with chronic obstructive pulmonary disease (COPD) or vice versa, are still lacking. The available data, however, suggest that in 'unselected' COPD patients (range 10-46%) and in COPD patients experiencing an exacerbation (23-32%) the prevalence of LVSD is common. LVSD is not very common (0-16%) in 'selected' COPD patients, that is, with exclusion of those with a history of coronary artery disease. The only study assessing (previously unknown) heart failure in patients with a history of COPD or asthma showed prevalence rates of 21%. To our knowledge, no study assessed the prevalence of COPD in patients with LVSD or heart failure.

Table 2 Studies that assessed heart failure or left ventricular systolic dysfunction in COPD, without exclusion of patients known with coronary artery disease

First author	Steele	Kline	Berger	Macnee	Zema	McCullough
Year of publication	1975	1977	1978	1983	1984	2003
Sample size	120	27	36	45	37	417
Patient population	Severe COPD	COPD, suspected LV dysfunction	Stable ambulatory COPD	Hypoxemic COPD	Suspected for COPD	History of COPD or asthma, with acute dyspnoea*
Mean age	60	62	67	59	61	62
Reference test	RVG	RVG, echo	RVG	RVG	RVG	2 cardiologists **
All patients reference test?	No. Only in 30%	No. Only 74% with echo studied	Yes	Yes	Yes	No. Echo in 29%
Exclusion of overt coronary artery disease?	No. 17% had CAD	No, but none of the patients had a history of prior MI	No. 9% known with CAD	No	Partly !	No. 30% had CAD
LVSD	21% LVEF< 40%	10% LVEF <40%	14% LVEF <40%	36% LVEF<50%	46% LVEF<50%	18% LVEF <45%
Heart failure	NA	NA	NA	NA	NA	21%
Remarks		No patients with LVEF <50% by echo				33% cor pulmonale^

CAD, coronary artery disease; ED, emergency department; NA, not assessed; NS, not stated; MI, myocardial infarction; RVG, radionuclide ventriculography; * patients *unknown* with heart failure, experiencing acute dyspnoea urging them to visit the emergency department; ** two cardiologists independently based the diagnosis of heart failure on the Framingham and NHANES scores. Additionally, echocardiogram (in 28.5% of the patients), and otherclinical tests were used when available for the diagnostic assessment of heart failure. ! Exclusion of coarctatio aortae, valve disease, atrial septal defect, and beta-blocker use;^ cor pulmonale was assessed clinically, that is, a history of obstructive or restrictive lung disease plus hepatic congestion or peripheral oedema on physical examination.

Diagnostic assessment of one disease in the presence of the other is complicated by overlap in signs and symptoms,[39;40] and a decreased sensitivity of additional tests such as chest X-ray, electrocardiography, but also echocardiography and pulmonary function testing. Multiple testing is necessary to establish whether a particular patient has heart failure, COPD, both, or neither. Natriuretic peptides[36;38] and cardiovascular magnetic resonance imaging[46-48] may be helpful in the diagnostic work-up. The best diagnostic strategy, however, to assess patients suspected of co-existence of both diseases remains to be determined. For this purpose diagnostic studies performed in an adequate patient domain are needed[62;63] collecting all relevant diagnostic test results from history, signs and symptoms, electrocardiography, chest X-ray, pulmonary function tests, natriuretic peptides, echocardiography, and cardiovascular magnetic resonance imaging. The results of (combinations of) these tests should than be compared to the presence of either or both diseases, ideally assessed by a multidisciplinary panel since a 'gold' reference standard for heart failure is lacking.

In general, pulmonary and heart failure 'drug-cocktails' can be administered safely to patients with concomitant COPD and heart failure, although (short acting) β2-adrenoreceptor agonists and digitalis have potentially deleterious effects on cardiac or pulmonary function, respectively.
Currently, much of the possible interactions between both syndromes are still unclear, and more extensive knowledge is important in view of the increasing prevalence of both diseases in the near future, the possibly common existence, and the potential benefit of adequate treatment.
To achieve this, closer co-operation between general practitioners, cardiologists and pulmonologists is necessary, both in practice and in research.

References

1. Mulrow CD, Lucey CR, Farnett LE. Discriminating causes of dyspnea through clinical examination. *J Gen Intern Med* 1993;8:383-92.
2. Pearson SB, Pearson EM, Mitchell JR. The diagnosis and management of patients admitted to hospital with acute breathlessness. *Postgrad Med J* 1981;57:419-24.
3. Morrison LK, Harrison A, Krishnaswamy P, Kazanegra R, Clopton P, Maisel A. Utility of a rapid B-natriuretic peptide assay in differentiating congestive heart failure from lung disease in patients presenting with dyspnea. *J Am Coll Cardiol* 2002;39:202-9.
4. Eriksson H, Svardsudd K, Larsson B, Ohlson LO, Welin L, Tibblin G *et al.*

Dyspnoea in a cross-sectional and a longitudinal study of middle-aged men: the Study of Men Born in 1913 and 1923. *Eur Heart J* 1987;8:1015-23.

5. Pratter MR, Curley FJ, Dubois J, Irwin RS. Cause and evaluation of chronic dyspnea in a pulmonary disease clinic. *Arch Intern Med* 1989;149:2277-82.

6. Hoes AW, Mosterd A, Grobbee DE. An epidemic of heart failure? Recent evidence from Europe. *Eur Heart J* 1998;19 Suppl L:L2-L9.

7. Wheeldon NM, MacDonald TM, Flucker CJ, McKendrick AD, McDevitt DG, Struthers AD. Echocardiography in chronic heart failure in the community. *Q J Med* 1993;86:17-23.

8. Cowie MR, Struthers AD, Wood DA, Coats AJ, Thompson SG, Poole-Wilson PA *et al*. Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care. *Lancet* 1997;350:1349-53.

9. Davies M, Hobbs F, Davis R, Kenkre J, Roalfe AK, Hare R *et al*. Prevalence of left-ventricular systolic dysfunction and heart failure in the Echocardiographic Heart of England Screening study: a population based study. *Lancet* 2001;358:439-44.

10. McCullough PA, Hollander JE, Nowak RM, Storrow AB, Duc P, Omland T *et al*. Uncovering heart failure in patients with a history of pulmonary disease: rationale for the early use of B-type natriuretic peptide in the emergency department. *Acad Emerg Med* 2003;10:198-204.

11. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM *et al*. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. *BMJ* 2003;326:41-4.

12. Pauwels RA, Buist AS, Ma P, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: National Heart, Lung, and Blood Institute and World Health Organization Global Initiative for Chronic Obstructive Lung Disease (GOLD): executive summary. *Respir Care* 2001;46:798-825.

13. Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M *et al*. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. *Eur Heart J* 2005;26:1115-40.

14. Moons KG, Grobbee DE. When should we remain blind and when should our eyes remain open in diagnostic studies? *J Clin Epidemiol* 2002;55:633-6.

15. Olvey SK, Reduto LA, Stevens PM, Deaton WJ, Miller RR. First pass radionuclide assessment of right and left ventricular ejection fraction in chronic pulmonary disease. Effect of oxygen upon exercise response. *Chest* 1980;78:4-9.

16. Yamaoka S, Yonekura Y, Koide H, Ohi M, Kuno K. Noninvasive method to assess cor pulmonale in patients with chronic obstructive pulmonary disease. *Chest* 1987;92:10-7.

17. Schena M, Clini E, Errera D, Quadri A. Echo-Doppler evaluation of left ventricular impairment in chronic cor pulmonale. *Chest* 1996;109:1446-51.

18. Boussuges A, Pinet C, Molenat F, Burnet H, Ambrosi P, Badier M *et al*. Left atrial and ventricular filling in chronic obstructive pulmonary disease. An echocardiographic and Doppler study. *Am J Respir Crit Care Med* 2000;162:670-5.

19. Christianson LC, Shah A, Fisher VJ. Quantitative left ventricular cineangiography in patients with chronic obstructive pulmonary disease. *Am J Med* 1979;66:399-404.

20. Matthay RA, Berger HJ, Davies RA, Loke J, Mahler DA, Gottschalk A *et al*. Right and left ventricular exercise performance in chronic obstructive pulmonary disease: radionuclide assessment. *Ann Intern Med* 1980;93:234-9.

21. Slutsky RA, Ackerman W, Karliner JS, Ashburn WL, Moser KM. Right and left ventricular dysfunction in patients with chronic obstructive lung disease. Assessment by first-pass radionuclide angiography. *Am J Med* 1980;68:197-205.

22. Song GJ, Oldershaw PJ. Left ventricular dysfunction in obstructive lung disease: an echocardiographic and angiographic study of cor pulmonale patients with decreased mitral E-F slope. *Int J Cardiol* 1989;25:47-53.

23. Vizza CD, Lynch JP, Ochoa LL, Richardson G, Trulock EP. Right and left ventricular dysfunction in patients with severe pulmonary disease. *Chest* 1998;113:576-83.

24. Jardin F, Gueret P, Prost JF, Farcot JC, Ozier Y, Bourdarias JP. Two-dimensional echocardiographic assessment of left ventricular function in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1984;129:135-42.

25. Incalzi RA, Pistelli R, Fuso L, Cocchi A, Bonetti MG, Giordano A. Cardiac arrhythmias and left ventricular function in respiratory failure from chronic obstructive pulmonary disease. *Chest* 1990;97:1092-7.

26. Render ML, Weinstein AS, Blaustein AS. Left ventricular dysfunction in deteriorating patients with chronic obstructive pulmonary disease. *Chest* 1995;107:162-8.

27. Kline LE, Crawford MH, MacDonald WJ, Schelbert H, Rourke RA, Moser KM. Noninvasive assessment of left ventricular performance in patients with chronic obstructive pulmonary disease. *Chest* 1977;72:558-64.

28. Zema MJ, Masters AP, Margouleff D. Dyspnea: the heart or the lungs? Differentiation at bedside by use of the simple Valsalva maneuver. *Chest* 1984;85:59-64.

29. Steele P, Ellis JH, Van D, Sutton F, Creagh E, Davies H. Left ventricular ejection fraction in severe chronic obstructive airways disease. *Am J Med* 1975;59:21-8.

30. Berger HJ, Matthay RA, Loke J, Marshall RC, Gottschalk A, Zaret BL. Assessment of cardiac performance with quantitative radionuclide angiocardiography: right ventricular ejection fraction with reference to findings in chronic obstructive

pulmonary disease. *Am J Cardiol* 1978;41:897-905.

31. MacNee W, Xue QF, Hannan WJ, Flenley DC, Adie CJ, Muir AL. Assessment by radionuclide angiography of right and left ventricular function in chronic bronchitis and emphysema. *Thorax* 1983;38:494-500.

32. Maisel A. B-type natriuretic peptide levels: diagnostic and prognostic in congestive heart failure: what's next? *Circulation* 2002;105:2328-31.

33. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. *N Engl J Med* 1971;285:1441-6.

34. Schocken DD, Arrieta MI, Leaverton PE, Ross EA. Prevalence and mortality rate of congestive heart failure in the United States. *J Am Coll Cardiol* 1992;20:301-6.

35. McNamara RM, Cionni DJ. Utility of the peak expiratory flow rate in the differentiation of acute dyspnea. Cardiac vs pulmonary origin. *Chest* 1992;101:129-32.

36. Davis M, Espiner E, Richards G, Billings J, Town I, Neill A *et al*. Plasma brain natriuretic peptide in assessment of acute dyspnoea. *Lancet* 1994;343:440-4.

37. Ailani RK, Ravakhah K, DiGiovine B, Jacobsen G, Tun T, Epstein D *et al*. Dyspnea differentiation index: A new method for the rapid separation of cardiac vs pulmonary dyspnea. *Chest* 1999;116:1100-4.

38. Nielsen LS, Svanegaard J, Klitgaard A, Egeblad H. N-terminal pro-brain natriuretic peptide for discriminating between cardiac and non-cardiac dyspnoea. *Eur J Heart Fail* 2004;6:63-70.

39. Remes J, Miettinen H, Reunanen A, Pyörälä K. Validity of clinical diagnosis of heart failure in primary health care. *Eur Heart J* 1991;12:315-21.

40. Rao BS, Cohn KE, Eldridge FL, Hancock EW. Left ventricular failure secondary to chronic pulmonary disease. *Am J Med* 1968;45:229-41.

41. Gehlbach BK, Geppert E. The pulmonary manifestations of left heart failure. *Chest* 2004;125:669-82.

42. Baljepally R, Spodick DH. Electrocardiographic screening for emphysema: the frontal plane P axis. *Clin Cardiol* 1999;22:226-8.

43. Harrigan RA, Jones K. ABC of clinical electrocardiography. Conditions affecting the right side of the heart. *BMJ* 2002;324:1201-4.

44. Lang CC, Coutie WJ, Struthers AD, Dhillon DP, Winter JH, Lipworth BJ. Elevated levels of brain natriuretic peptide in acute hypoxaemic chronic obstructive pulmonary disease. *Clin Sci (Lond)* 1992;83:529-33.

45. Guazzi M, Pontone G, Brambilla R, Agostoni P, Reina G. Alveolar--capillary membrane gas conductance: a novel prognostic indicator in chronic heart failure. *Eur Heart J* 2002;23:467-76.

46. Grothues F, Smith GC, Moon JC, Bellenger NG, Collins P, Klein HU *et al*.

Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. *Am J Cardiol* 2002;90:29-34.

47. Grothues F, Moon JC, Bellenger NG, Smith GS, Klein HU, Pennell DJ. Interstudy reproducibility of right ventricular volumes, function, and mass with cardiovascular magnetic resonance. *Am Heart J* 2004;147:218-23.

48. Pennell DJ, Sechtem UP, Higgins CB, Manning WJ, Pohost GM, Rademakers FE *et al*. Clinical indications for cardiovascular magnetic resonance (CMR): Consensus Panel report. *Eur Heart J* 2004;25:1940-65.

49. Au DH, Udris EM, Fan VS, Curtis JR, McDonell MB, Fihn SD. Risk of mortality and heart failure exacerbations associated with inhaled beta-adrenoceptor agonists among patients with known left ventricular systolic dysfunction. *Chest* 2003;123:1964-9.

50. Hirono O, Kubota I, Minamihaba O, Fatema K, Kato S, Nakamura H *et al*. Left ventricular diastolic dysfunction in patients with bronchial asthma with long-term oral beta2-adrenoceptor agonists. *Am Heart J* 2001;142:E11.

51. Jenne JW. Can oral beta2 agonists cause heart failure? *Lancet* 1998;352:1081-2.

52. Cazzola M, Di Perna F, Noschese P, Vinciguerra A, Calderaro F, Girbino G *et al*. Effects of formoterol, salmeterol or oxitropium bromide on airway responses to salbutamol in COPD. *Eur Respir J* 1998;11:1337-41.

53. Casaburi R, Mahler DA, Jones PW, Wanner A, San PG, ZuWallack RL *et al*. A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. *Eur Respir J* 2002;19:217-24.

54. Aronow WS. Treatment of heart failure in older persons. Dilemmas with coexisting conditions: diabetes mellitus, chronic obstructive pulmonary disease, and arthritis. *Congest Heart Fail* 2003;9:142-7.

55. Kotlyar E, Keogh AM, Macdonald PS, Arnold RH, McCaffrey DJ, Glanville AR. Tolerability of carvedilol in patients with heart failure and concomitant chronic obstructive pulmonary disease or asthma. *J Heart Lung Transplant* 2002;21:1290-5.

56. Gheorghiade M, Colucci WS, Swedberg K. Beta-blockers in chronic heart failure. *Circulation* 2003;107:1570-5.

57. Salpeter SR, Ormiston TM, Salpeter EE, Poole PJ, Cates CJ. Cardioselective beta-blockers for chronic obstructive pulmonary disease: a meta-analysis. *Respir Med* 2003;97:1094-101.

58. Salpeter SR, Ormiston TM, Salpeter EE. Cardioselective beta-blockers in patients with reactive airway disease: a meta-analysis. *Ann Intern Med* 2002;137:715-25.

59. Forth R, Montgomery H. ACE in COPD: a therapeutic target? *Thorax* 2003;58:556-8.

60. Guazzi M. Alveolar-capillary membrane dysfunction in heart failure: evidence of a

pathophysiologic role. *Chest* 2003;124:1090-102.

61. Agostoni P, Magini A, Andreini D, Contini M, Apostolo A, Bussotti M *et al*. Spironolactone improves lung diffusion in chronic heart failure. *Eur Heart J* 2005;26:159-64.

62. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM *et al*. The STARD statement for reporting studies of diagnostic accuracy: explanation and elaboration. *Clin Chem* 2003;49:7-18.

63. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM *et al*. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Standards for Reporting of Diagnostic Accuracy. *Clin Chem* 2003;49:1-6.

Chapter 5

Heart failure and chronic obstructive pulmonary disease: common mechanisms and possible interactions

Frans H Rutten [1], Jan-Willem J Lammers [2] , Maarten-Jan M Cramer [3], Pieter Zanen [2] , Alfred PE Sachs [1], Diederick E Grobbee [1], Arno W Hoes [1]

[1] Julius Center for Health Sciences and Primary Care;
[2] Heart Lung Center Utrecht, Department of Pulmonary Diseases;
[3] Heart Lung Center Utrecht, Department of Cardiology; University Medical Center Utrecht

Submitted

Abstract

Aim To assess common mechanisms and possible interactions in the collective occurrence of heart failure and chronic obstructive pulmonary disease (COPD).
Methods and results We performed a Medline search from 1966 to October 2004. The relation between COPD and heart failure seems multi-factorial, with tobacco smoking as a major common causal factor. Systemic and local inflammation, and systemic and possibly local atherosclerosis are common mechanisms in COPD and heart failure. Whenever COPD or heart failure is present, different mechanical, sympathetic, hypoxic, and metabolic mechanisms may trigger the development or promote mutual progression.
Conclusion Further studies on common mechanisms in COPD and heart failure are worthwhile because these interactions may point at new preventive, therapeutic, and prognostic options for both COPD and heart failure patients.

Introduction

COPD and heart failure have been studied extensively, but largely separately, with COPD in the domain of the pulmonologist and heart failure in the domain of the cardiologist. Reliable data on the prevalence of heart failure in COPD patients are scarce, but prevalence rates of about 20% have been reported,[1] while, to our knowledge, data about the prevalence of COPD in heart failure patients are lacking altogether.[2] Findings in patients with acute dyspnoea at emergency departments show that 5-20% has concomitant heart failure and COPD.[3-5]

There is some evidence that both syndromes are related. First, heart failure and COPD share an important common causal factor, tobacco smoking. Next, prospective studies have shown that COPD is associated with an increased incidence of ischaemic heart disease and carotid atherosclerotic plaque formation, independent of age, smoking, or other cardiovascular risk factors.[6-8] Atherosclerotic coronary artery disease is the most important risk factor for heart failure.[9] It is, however, largely unclear which common mechanisms play a role and which interactions can trigger the development or promote progression of the one syndrome in the presence of the other.
We reviewed the existing literature to identify possible mechanisms and interactions.

Methods

A Medline search was conducted for 1966 to October 2004. We used the following MESH terms 'pulmonary disease, chronic obstructive or COPD', 'heart failure, congestive', 'cor pulmonale', and 'dyspnoea'. Additional references were retrieved by citation tracking of relevant publications. Only studies published in English were included in the analysis.

Results

Common mechanisms in COPD and heart failure
Risk factors for COPD include smoking status, host factors and environmental exposures. In 90% of the COPD patients tobacco smoking is the most important causal factor.[10] The best known host factor is the rare hereditary α-1-antitrypsin deficiency and the most important environmental risk factor are passive smoking and occupational related, such as mine working and working in dusty environment.[11] Apart from pulmonary inflammation, also systemic inflammation is

present in COPD, irrespective of smoking status and disease stage.[12-14]
The key pathogenetic mechanism in the lung is activation of macrophages and bronchial infiltration with granulocytes. These inflammatory cells release proteinases and oxidants. When insufficiently counterbalanced by anti-proteinases and oxidant scavengers this may lead to chronic pulmonary inflammation and fibrosis of peripheral airways (chronic obstructive bronchiolitis) as well as destruction of lung parenchyma, and as a result, lead to emphysema with loss of elastic recoil.[10]
Major risk factors for heart failure are ischaemic heart disease and hypertension.[9] Heart failure can be seen as an 'end-stage disease' with haemodynamic, neurohormonal, but also inflammatory involvement.[15] Systemic atherosclerosis and coronary atherosclerosis are the underlying cause of ischaemic vascular disease and ischaemic heart disease, respectively.[16] Tobacco smoking is a known risk factor for atherosclerosis and may induce systemic inflammation.
Thus, local and systemic inflammation by itself or induced by tobacco smoking is an important common mechanism in the development of heart failure and COPD.[8]

Also atherosclerosis seems a common mechanism with possible inducement of inflammation and/or tobacco smoking. Atherosclerosis shows features of inflammation with endothelial dysfunction as a starting point.[17] Important causes of this endothelial dysfunction leading to atherosclerosis include elevated low density lipoproteines levels, but also free radicals generated for instance by smoking and hypertension.[17;18] Hypertension may also increase formation of hydrogen peroxide which has pro-inflammatory properties.[17] Persistent low-grade systemic inflammation (such as in COPD)[14] is believed to be one of the centrepieces in atherosclerotic clot formation.[17] Apart from these inflammatory and/or smoking factors, arterial wall hypoxia may induce atherosclerosis.[19;20] Smoking, hypertension, hyperlipidemia, and diabetes can impair erythrocyte deformability and increase oxygen affinity while decreasing oxygen capacity of haemoglobin. This may result in decreased arterial wall oxygen delivery causing arterial wall hypoxia. A cascade of changes may follow with an increased release of growth factors, intimal wall proliferation and platelet adherence, all inducing atherosclerosis.[19]

Whether the above mentioned atherosclerotic mechanisms only apply to systemic and coronary arteries, or also to the pulmonary arteries, is unclear. The pulmonary arterial circulation seems to be 'a no man's land', neither studied by pulmonologists nor cardiologists. Still there is some support that pulmonary arterial atherosclerosis is of influence. For instance, one study reported that pulmonary arterial

atherosclerosis was a common autopsy finding and that it was positively correlated with COPD, and aortic and coronary atherosclerosis.[21] Another study showed central pulmonary artery lesions in about half of the patients with stable COPD, detected with transoesopheal echocardiography.[22] Pulmonary arterial atherosclerosis (with or without pulmonary arterial wall hypoxia) could possibly induce alveolar-capillary membrane dysfunction by affecting the capillary endothelium of this membrane. Alveolar-capillary dysfunction could further induce pulmonary changes leading to COPD. Alternatively, alveolar-capillary membrane dysfunction could lead to (periodic) hypoxemia which may further promote local (pulmonary and coronary) and systemic atherosclerosis, and increase cardiac work load (Figure 1).

At a later stage in the progression of both COPD and heart failure, metabolic mechanisms play an important role, with metabolic modulation,[23] generalised muscle dysfunction,[24] and eventually chronic wasting and cachexia as an end-result in both syndromes.[25]

Interactions between COPD and heart failure

Pulmonary hyperinflation and hypoxemia are the main mechanisms by which COPD can influence ventricular function (Table 1). A number of possible pathways has been put forward in the literature.

(A) Bronchial obstruction can increase intrinsic positive end-expiratory pressure, especially during exercise, and thus limit venous blood return.[26;27] This may reduce right and left ventricular preload[26] and thus negatively influence ventricular function.

(B) Systemic vasodilatation is common.[26;28] This may reduce venous blood return[26] and negatively influence ventricular function.

(C) Several processes such as increased thoracic pressures, increased respiratory effort, hypoxemia, and hypercapnia can induce generalised sympathetic over-activity, which eventually cause sympathetic nervous impairment of the myocardium by down regulation and reduction of the density of β-adrenoreceptors.[29] Increased generalised sympathetic activity leads to increased heart rates and (short-term) contractility, vasoconstriction, activation of the renin-angiotensin system, and direct cardiotoxicity with myocyte apoptosis and focal myocardial necrosis.[30;31] This results in fluid retention, increased left ventricular wall stress, and eventually this leads to myocardial hypertrophy, decreased contractility, and myocardial damage,[31] and thus to decreased left ventricular function.

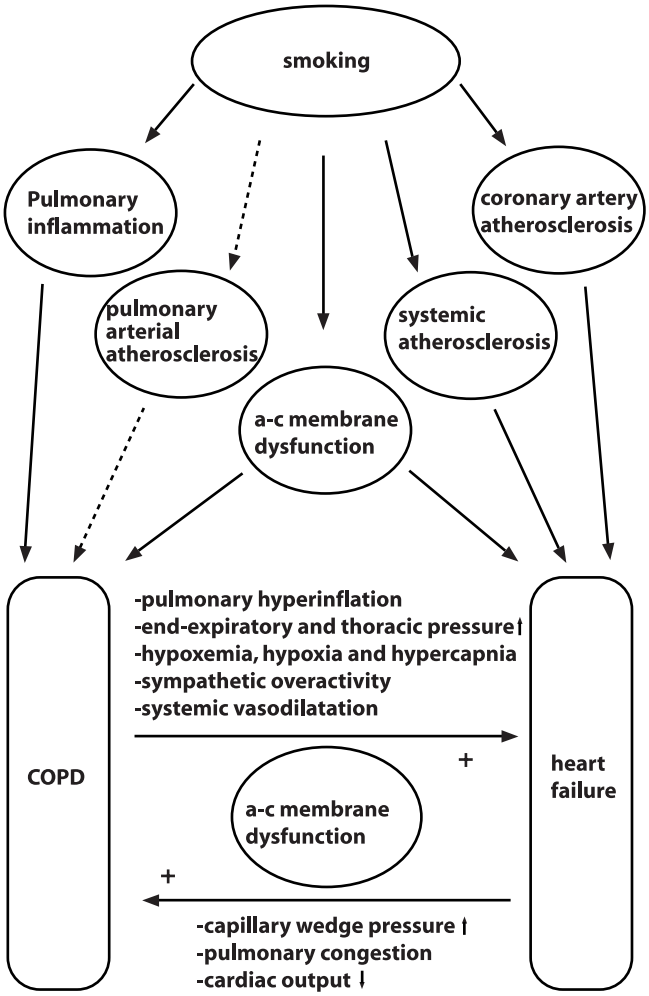


Figure 1

(D) Hyperinflation implies increased longitudinal tension in the alveolar wall.[32] Some of this tension may be transmitted to the pulmonary capillary wall and cause structural changes and damage of this wall. These ultra-structural changes of the alveolar-capillary membrane may cause leakage, that is, 'stress failure'.[32;33] Stress failure can result in high-permeability pulmonary oedema [32] and a decrease in oxygen diffusion capacity, with ventilation-perfusion mismatch as a result. When extensive, the diffusion disorder causes hypoxemia and may adversely influence ventricular function (see pathways (E), (F), and (G)).

Table 1 Pathophysiological changes in COPD with influence on cardiac function: possible pathways

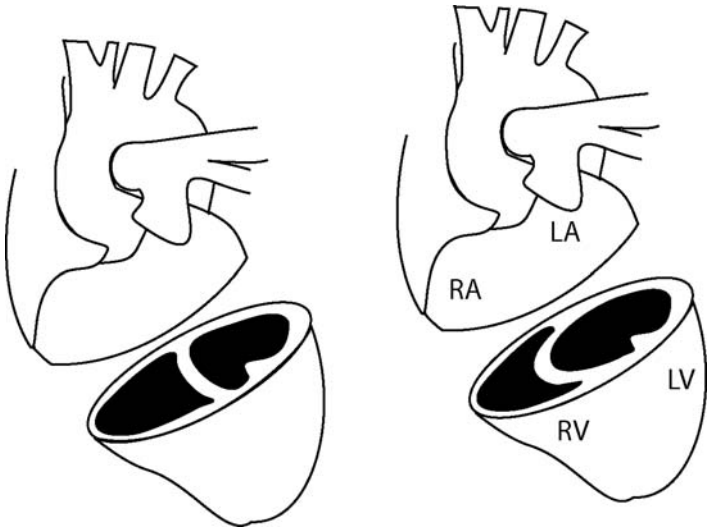
A	Positive end-expiratory Pressure ↑	=>	Venous blood return ↓	=>	Reduced RV and LV preload
B	Systemic vasodilatation	=>	Venous blood return ↓	=>	Reduced RV and LV preload
C	Thoracic pressure ↑, Respiratory effort ↑, hypoxia, hypercapnia	=>	Generalised sympathetic overactivity and eventually down regulation and density ↓ of cardiac ß-adrenoreceptors	=>	Heart rate ↑ and short term contractility ↑, vasoconstriction, renin-angiotensin system ↑, cardiotoxicity, eventually leading to myocardial hypertrophy and damage, and contractility ↓
D	Hyperinflation, lung volume ↑	=>	Pulmonary capillary wall stress ↑ and capillary leakage	=>	high-permeability pulmonary oedema and diffusion capacity↓, resulting in hypoxemia. See further pathways E, F, G
E	Hypoxemia	=>	Myocyte hypoxia	=>	Impaired relaxation and contraction of RV and LV
F	Hypoxemia	=>	Polycythaemia leading to serum viscosity ↑ and pulmonary thrombo-embolism	=>	RV dilatation and hypertrophy due to RV workload ↑ resulting in 'isolated right ventricular failure' and/or left ventricular dysfunction by diastolic flattening of the intraventricular septum
G	Hypoxemia induces Hypoxic pulmonary vasoconstriction and pulmonary vascular bed 'remodelling'	=>	Pulmonary hypertension, Pulmonary vascular resistance ↑	=>	RV dilatation and hypertrophy due to RV workload ↑ resulting in 'isolated right ventricular failure' and/or left ventricular dysfunction by diastolic flattening of the intraventricular septum

Table 2 Pathophysiological changes in heart failure with influence on pulmonary function: possible pathways

A	Capillary wedge pressure ↑	=>	Vascular bed 'remodelling' and thickening of the capillary membrane	=>	Diffusion capacity ↓ (restrictive dysfunction)
B	Pulmonary congestion	=>	Distance between alveolar gas and red blood cells ↑	=>	Diffusion capacity ↓ (restrictive dysfunction)
C	Pulmonary congestion	=>	Peribronchiolar oedema and distended pulmonary arterioles	=>	airways narrowing (obstructive dysfunction)
D	Cardiac output ↓	=>	(respiratory) muscle blood flow ↓	=>	(respiratory) muscle weakness (restrictive dysfunction)
E	Cardiac output ↓	=>	pulmonary perfusion ↓	=>	Pulmonary dead space ↑ (restrictive dysfunction)
F	Pulmonary congestion	=>	Decreased lung compliance and eventually interstitial fibrosis	=>	Inspiratory capacity ↓ Total lung capacity ↓ (restrictive dysfunction)

(E) Hypoxemia may lead to myocyte hypoxia and herewith impaired active relaxation and contraction of both cardiac ventricles.[34]
(F) Hypoxemia may also induce secondary polycythaemia, resulting in increased serum viscosity and increased risk of pulmonary thromboembolism.[35] Pulmonary thromboembolism can result in a ventilation-perfusion mismatch and pulmonary artery hypertension, and hence increased work load of the right ventricle, resulting in cor pulmonale and right sided heart failure. By diastolic bulging or flattening of the interventricular septum to the left, left ventricular function can also be negatively influenced (see pathway (G)).

Figure 2 Diastolic bulging/ intraventricular septum flattening and normal situation of the ventricles



diastolic bulging/intraventricular normal septum flattening

(G) Hypoxemia induces alveolar hypoxia and pulmonary vasoconstriction which eventually leads to 'remodelling' of the pulmonary vascular bed.[35] This 'remodelling' consists of diversion of blood flow from areas of regional alveolar hypoxia to better ventilated areas of the lung[35] plus medial hypertrophy of muscular pulmonary arteries and proliferation of vascular smooth muscle into the normally non-muscular vessels of the pulmonary circulation.[35] When extensive parts of the lungs are involved, these changes result in pulmonary arterial hypertension and increased pulmonary vascular resistance, [36] and herewith increased workload of the right ventricle [37]. Small increments in pulmonary artery pressure are associated with decrease in right ventricular stroke volume,[36] and dilatation and hypertrophy of the right ventricle.[38] These right ventricular changes (cor pulmonale) can lead to right sided heart failure. Because the right and left ventricles are coupled within the pericardial space, right ventricular dilatation and hypertrophy can lead to diastolic bulging or flattening of the interventricular septum to the left and changes in the shape of the left ventricle (reduction of the septum-lateral wall axis) (Figure 2).[39-41] This leads to a disorganised isovolumatic

relaxation and subsequent impaired left ventricular filling.[26;42;43] This septal flattening persists partly during systole and adversely affects left ventricular systolic function.[44-46]

It is difficult to decide which of the above mentioned mechanical ((A), (D), (F), (G)), sympathetic ((B), (C)), and/or hypoxic ((E), (F), (G)) pathways is clinically most relevant. The mentioned pathways seem most applicable to patients with severe COPD. At an earlier stage in COPD, changes in the alveolar-capillary membrane and the adjacent vascular bed could already adversely affect cardiac ventricular function because this membrane is responsible for intensified oxygen and circulation interchange.[33] (See Figure 1) Before 'stress failure' of this membrane occurs (as mentioned in pathway (D)), lesser degrees of dysfunction of the membrane with locally activated neurohumoral and cytotoxic factors could adversely affect oxygen gas exchange.[33] A cascade starting in the capillaries and peri-capillary vascular bed could result, with negative effect on local oxygen transport and eventually diminished delivery of oxygen to the whole body, including the heart.

Is left ventricular systolic function enhanced in COPD?
Several studies in severe COPD patients (GOLD class III) including patients with cor pulmonale have reported non-depressed or even enhanced left ventricular systolic function. [47-51] These studies, however, were performed in a highly selected population of relative young COPD patients (mean ages 54-68 years) without any overt co-existing cardiac disease at the time of study. Importantly, in cases with normal or enhanced left ventricular systolic function, other cardiac abnormalities were detectable such as left ventricular hypertrophy, signs of restricted left ventricular diastolic function, and right ventricular enlargement.[47;48] Eventually, these cardiac abnormalities will reduce (left) ventricular function and lead to heart failure.

Another hypothesis is that the 'only' way in which COPD could induce heart failure would be by development of cor pulmonale, eventually resulting in 'isolated' right sided heart failure, without substantially affecting the left ventricle.[37;52;53] This was also based on the same selected young, severe COPD patients with prior exclusion of overt cardiac disease. However, most COPD patients are elderly with concomitant (often sub-clinical) cardiovascular diseases.[1;6;54] As discussed above, however, in these elderly patients other mechanisms are likely to induce left ventricular dysfunction usually before right sided dysfunction develops.

Impact of heart failure on pulmonary function

Decreased cardiac output and pulmonary congestion are most likely pathways whereby heart failure may lead to restriction (diminished vital capacity) (Table 2).[55] A number of possible pathways has been put forward in the literature.

(A) Heart failure leads to increased pulmonary capillary wedge pressure. This can induce pulmonary vascular bed 'remodelling', resulting in arteriolar wall hypertrophy.[32] Next, it may also induce a gradual thickening of the capillary membrane of the alveolar-capillary membrane, leading to a reduction of the diffusion capacity of this membrane[56-60] and result in ventilation-perfusion mismatch[61] and restrictive dysfunction of the lungs.

(B) In heart failure pulmonary congestion with interstitial and peri-bronchiolar oedema increases the distance between alveolar gas and the pulmonary arterioles and herewith decrease diffusion capacity. [56] This results in ventilation-perfusion mismatch [61] and restrictive dysfunction of the lungs.

(C) Pulmonary congestion with peri-bronchiolar oedema and distension of pulmonary arterioles can also increase airways narrowing and resistance, thereby inducing bronchial obstruction.[59;60;62;63]

(D) Decreased cardiac output leads to diminished muscle blood flow, and thus to muscle weakness. Respiratory, accessory respiratory, and diaphragmatic muscles are affected most, leading to impaired respiratory function.[57;61;64-67]

(E) With decreased cardiac output pulmonary perfusion is reduced. This can lead to perfusion-ventilation mismatch and increased pulmonary dead space, [65] resulting in a restrictive dysfunction. [65;68]

(F) Pulmonary congestion and possibly cardiomegaly can compress the basal pulmonary segments, and adversely affect alveolar-capillary gas exchange in the basal lung segments. Also restrictive dysfunction is induced because of decreased inspiratory and total lung capacity, [61;62] decreased lung compliance, [69] and eventually local interstitial fibrosis. [61]

The alveolar-capillary membrane (pathways (A) and (B)) seems to be the first to be affected adversely by cardiac dysfunction.[33] In a later stage mechanical (pathways (C) and (F)), and hypoxic factors (pathways (D) and (E)) further decrease the alveolar-capillary membrane function and can induce both restrictive and obstructive pulmonary dysfunction.

Discussion

A review of the literature lends support to the view that COPD and heart failure are closely related in several ways, with tobacco smoking as a central common causal

factor. Systemic and local inflammation, but also systemic and possibly local atherosclerosis are inter-related with smoking and additional common mechanisms. Whenever COPD or heart failure is present, mechanical, sympathetic, hypoxic, and metabolic interactions may trigger development or promote the other syndrome. An important starting point seems to be the dysfunction of the alveolar-capillary membrane. This dysfunction may result in decreased oxygen supply, and (in more severe cases) sympathetic and structural changes in both heart and lungs.

At the moment, much of the interrelations between both syndromes remain unexplored, and more extensive knowledge is needed in view of the increase in the prevalence of heart failure and COPD[70] as well as the combined presence of the two.[71] Moreover, insight in common mechanisms and possible interactions may point at new preventive, therapeutic, and prognostic options for both syndromes.

References

1. McCullough PA, Hollander JE, Nowak RM, Storrow AB, Duc P, Omland T *et al*. Uncovering heart failure in patients with a history of pulmonary disease: rationale for the early use of B-type natriuretic peptide in the emergency department. *Acad Emerg Med* 2003;10:198-204.
2. Rutten FH, Cramer MJM, Lammers J-WJ, Zanen P, Grobbee DE, Hoes AW. Heart failure and chronic obstructive pulmonary disease: an ignored combination? *submitted* 2005.
3. Morrison LK, Harrison A, Krishnaswamy P, Kazanegra R, Clopton P, Maisel A. Utility of a rapid B-natriuretic peptide assay in differentiating congestive heart failure from lung disease in patients presenting with dyspnea. *J Am Coll Cardiol* 2002;39:202-9.
4. McNamara RM, Cionni DJ. Utility of the peak expiratory flow rate in the differentiation of acute dyspnea. Cardiac vs pulmonary origin. *Chest* 1992;101:129-32.
5. Ailani RK, Ravakhah K, DiGiovine B, Jacobsen G, Tun T, Epstein D *et al*. Dyspnea differentiation index: A new method for the rapid separation of cardiac vs pulmonary dyspnea. *Chest* 1999;116:1100-4.
6. Ebi K, Hawthorne VM, Rose G, Shipley MJ, Gillis CR, Hole DJ *et al*. Breathlessness, chronic bronchitis and reduced pulmonary function as predictors of cardiovascular disease mortality among men in England, Scotland and the United States. *Int J Epidemiol* 1989;18:84-8.
7. Hole DJ, Watt GC, Davey S, Hart CL, Gillis CR, Hawthorne VM. Impaired lung function and mortality risk in men and women: findings from the Renfrew and Paisley prospective population study. *BMJ* 1996;313:711-5.

8. Zureik M, Kauffmann F, Touboul PJ, Courbon D, Ducimetiere P. Association between peak expiratory flow and the development of carotid atherosclerotic plaques. *Arch Intern Med* 2001;161:1669-76.

9. Remme WJ, Swedberg K. Guidelines for the diagnosis and treatment of chronic heart failure. *Eur Heart J* 2001;22:1527-60.

10. Pauwels RA, Buist AS, Ma P, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: National Heart, Lung, and Blood Institute and World Health Organization Global Initiative for Chronic Obstructive Lung Disease (GOLD): executive summary. *Respir Care* 2001;46:798-825.

11. Siafakas NM, Vermeire P, Pride NB, Paoletti P, Gibson J, Howard P *et al*. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). The European Respiratory Society Task Force. *Eur Respir J* 1995;8:1398-420.

12. Sin DD, Man SF. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease. *Circulation* 2003;107:1514-9.

13. Dentener MA, Creutzberg EC, Schols AM, Mantovani A, van't Veer C, Buurman WA *et al*. Systemic anti-inflammatory mediators in COPD: increase in soluble interleukin 1 receptor II during treatment of exacerbations. *Thorax* 2001;56:721-6.

14. Oudijk EJ, Lammers JW, Koenderman L. Systemic inflammation in chronic obstructive pulmonary disease. *Eur Respir J Suppl* 2003;46:5s-13s.

15. Vasan RS, Sullivan LM, Roubenoff R, Dinarello CA, Harris T, Benjamin EJ *et al*. Inflammatory markers and risk of heart failure in elderly subjects without prior myocardial infarction: the Framingham Heart Study. *Circulation* 2003;107:1486-91.

16. Agmon Y, Khandheria BK, Meissner I, Petterson TM, O'Fallon WM, Wiebers DO *et al*. C-reactive protein and atherosclerosis of the thoracic aorta: a population-based transesophageal echocardiographic study. *Arch Intern Med* 2004;164:1781-7.

17. Ross R. Atherosclerosis--an inflammatory disease. *N Engl J Med* 1999;340:115-26.

18. Witztum JL. The oxidation hypothesis of atherosclerosis. *Lancet* 1994;344:793-5.

19. Simanonok JP. Non-ischemic hypoxia of the arterial wall is a primary cause of atherosclerosis. *Med Hypotheses* 1996;46:155-61.

20. Martin JF, Booth RF, Moncada S. Arterial wall hypoxia following thrombosis of the vasa vasorum is an initial lesion in atherosclerosis. *Eur J Clin Invest* 1991;21:355-9.

21. Moore GW, Smith RR, Hutchins GM. Pulmonary artery atherosclerosis: correlation with systemic atherosclerosis and hypertensive pulmonary vascular disease. *Arch Pathol Lab Med* 1982;106:378-80.

22. Russo A, De Luca M, Vigna C, De R, V, Pacilli M, Lombardo A *et al*. Central pulmonary artery lesions in chronic obstructive pulmonary disease: A

transesophageal echocardiography study. *Circulation* 1999;100:1808-15.

23. Mann DL. Mechanisms and models in heart failure: A combinatorial approach. *Circulation* 1999;100:999-1008.

24. Gosker HR, Lencer NH, Franssen FM, van der Vusse GJ, Wouters EF, Schols AM. Striking similarities in systemic factors contributing to decreased exercise capacity in patients with severe chronic heart failure or COPD. *Chest* 2003;123:1416-24.

25. Schols AM. Nutritional and metabolic modulation in chronic obstructive pulmonary disease management. *Eur Respir J Suppl* 2003;46:81s-6s.

26. Boussuges A, Pinet C, Molenat F, Burnet H, Ambrosi P, Badier M *et al*. Left atrial and ventricular filling in chronic obstructive pulmonary disease. An echocardiographic and Doppler study. *Am J Respir Crit Care Med* 2000;162:670-5.

27. Aldrich TK, Hendler JM, Vizioli LD, Park M, Multz AS, Shapiro SM. Intrinsic positive end-expiratory pressure in ambulatory patients with airways obstruction. *Am Rev Respir Dis.* 1993;147:845-9.

28. Casiglia E, Pavan L, Marcato L, Leopardi M, Pizziol A, Salvador P *et al*. Subjects with obstructive pulmonary disease tend to be chronically vasodilated. *Clin Sci (Lond)* 1998;95:287-94.

29. Sakamaki F, Satoh T, Nagaya N, Kyotani S, Nakanishi N, Ishida Y. Abnormality of left ventricular sympathetic nervous function assessed by (123)I-metaiodobenzylguanidine imaging in patients with COPD. *Chest* 1999;116:1575-81.

30. Mark AL. Sympathetic dysregulation in heart failure: mechanisms and therapy. *Clin Cardiol* 1995;18:I3-I8.

31. Jackson G, Gibbs CR, Davies MK, Lip GY. ABC of heart failure. Pathophysiology. *BMJ* 2000;320:167-70.

32. West JB, Mathieu C. Stress failure of pulmonary capillaries: role in lung and heart disease. *Lancet* 1992;340:762-7.

33. Guazzi M. Alveolar-capillary membrane dysfunction in heart failure: evidence of a pathophysiologic role. *Chest* 2003;124:1090-102.

34. Vitarelli A, Gheorghiade M. Diastolic heart failure: standard Doppler approach and beyond. *Am J Cardiol* 1998;81:115G-21G.

35. Klinger JR, Hill NS. Right ventricular dysfunction in chronic obstructive pulmonary disease. Evaluation and management. *Chest* 1991;99:715-23.

36. Burghuber O, Bergmann H, Silberbauer K, Hofer R. Right ventricular performance in chronic air flow obstruction. *Respiration* 1984;45:124-30.

37. Fishman AP. State of the art: chronic cor pulmonale. *Am Rev Respir Dis* 1976;114:775-94.

38. Morrison DA, Adcock K, Collins CM, Goldman S, Caldwell JH, Schwarz MI. Right ventricular dysfunction and the exercise limitation of chronic obstructive pulmonary

disease. *J Am Coll Cardiol* 1987;9:1219-29.

39. Gabinski C, Courty G, Besse P, Castaing R. [Left ventricular function in chronic obstructive lung disease]. *Bull Physiopathol Respir* 1979;15:755-72.

40. Weber KT, Janicki JS, Shroff S, Fishman AP. Contractile mechanics and interaction of the right and left ventricles. *Am J Cardiol* 1981;47:686-95.

41. Dittrich HC, Chow LC, Nicod PH. Early improvement in left ventricular diastolic function after relief of chronic right ventricular pressure overload. *Circulation* 1989;80:823-30.

42. Stojnic BB, Brecker SJ, Xiao HB, Helmy SM, Mbaissouroum M, Gibson DG. Left ventricular filling characteristics in pulmonary hypertension: a new mode of ventricular interaction. *Br Heart J* 1992;68:16-20.

43. Tutar E, Kaya A, Gulec S, Erta¦ F, Erol C, Ozdemir O *et al*. Echocardiographic evaluation of left ventricular diastolic function in chronic cor pulmonale. *Am J Cardiol* 1999;83:1414-7, A9.

44. Brinker JA, Weiss JL, Lappe DL, Rabson JL, Summer WR, Permutt S *et al*. Leftward septal displacement during right ventricular loading in man. *Circulation* 1980;61:626-33.

45. Guzman PA, Maughan WL, Yin FC, Eaton LW, Brinker JA, Weisfeldt ML *et al*. Transseptal pressure gradient with leftward septal displacement during the Mueller manoeuvre in man. *Br Heart J* 1981;46:657-62.

46. Santamore WP, Gray L. Significant left ventricular contributions to right ventricular systolic function. Mechanism and clinical implications. *Chest* 1995;107:1134-45.

47. Jardin F, Gueret P, Prost JF, Farcot JC, Ozier Y, Bourdarias JP. Two-dimensional echocardiographic assessment of left ventricular function in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1984;129:135-42.

48. Davies H, Overy HR. Left ventricular function in cor pulmonale. *Chest* 1970;58:8-14.

49. Murphy ML, Adamson J, Hutcheson F. Left ventricular hypertrophy in patients with chronic bronchitis and emphysema. *Ann Intern Med* 1974;81:307-13.

50. Williams JF, Childress RH, Boyd DL, Higgs LM, Behnke RH. Left ventricular function in patients with chronic obstructive pulmonary disease. *J Clin Invest* 1968;47:1143-53.

51. Kachel RG. Left ventricular function in chronic obstructive pulmonary disease. *Chest* 1978;74:286-90.

52. Frank MJ, Weisse AB, Moschos CB, Levinson GE. Left ventricular function, metabolism, and blood flow in chronic cor pulmonale. *Circulation* 1973;47:798-806.

53. Steele P, Ellis JH, Van D, Sutton F, Creagh E, Davies H. Left ventricular ejection fraction in severe chronic obstructive airways disease. *Am J Med* 1975;59:21-8.

54. Kjoller E, Kober L, Iversen K, Torp-Pedersen C. Importance of chronic obstructive pulmonary disease for prognosis and diagnosis of congestive heart failure in patients with acute myocardial infarction. *Eur J Heart Fail* 2004;6:71-7.

55. Mohnssen SR, Weisman IM, Zeballos RJ, Hall A, Wasserman K, Tavel ME. Heart or lung disease: determining the primary cause for dyspnea on exertion. *Chest* 1998;113:1705-10.

56. Assayag P, Benamer H, Aubry P, de P, Brochet E, Besse S *et al*. Alteration of the alveolar-capillary membrane diffusing capacity in chronic left heart disease. *Am J Cardiol* 1998;82:459-64.

57. Puri S, Baker BL, Dutka DP, Oakley CM, Hughes JM, Cleland JG. Reduced alveolar-capillary membrane diffusing capacity in chronic heart failure. Its pathophysiological relevance and relationship to exercise performance. *Circulation* 1995;91:2769-74.

58. Naum CC, Sciurba FC, Rogers RM. Pulmonary function abnormalities in chronic severe cardiomyopathy preceding cardiac transplantation. *Am Rev Respir Dis* 1992;145:1334-8.

59. Wright RS, Levine MS, Bellamy PE, Simmons MS, Batra P, Stevenson LW *et al*. Ventilatory and diffusion abnormalities in potential heart transplant recipients. *Chest* 1990;98:816-20.

60. Siegel JL, Miller A, Brown LK, DeLuca A, Teirstein AS. Pulmonary diffusing capacity in left ventricular dysfunction. *Chest* 1990;98:550-3.

61. Dimopoulou I, Daganou M, Tsintzas OK, Tzelepis GE. Effects of severity of long-standing congestive heart failure on pulmonary function. *Respir Med* 1998;92:1321-5.

62. Nanas S, Nanas J, Papazachou O, Kassiotis C, Papamichalopoulos A, Milic E *et al*. Resting lung function and hemodynamic parameters as predictors of exercise capacity in patients with chronic heart failure. *Chest* 2003;123:1386-93.

63. Chua TP, Coats AJ. The lungs in chronic heart failure. *Eur Heart J* 1995;16:882-7.

64. McParland C, Krishnan B, Wang Y, Gallagher CG. Inspiratory muscle weakness and dyspnea in chronic heart failure. *Am Rev Respir Dis* 1992;146:467-72.

65. Russell SD, McNeer FR, Higginbotham MB. Exertional dyspnea in heart failure: a symptom unrelated to pulmonary function at rest or during exercise. Duke University Clinical Cardiology Studies (DUCCS) Exercise Group. *Am Heart J* 1998;135:398-405.

66. Hammond MD, Bauer KA, Sharp JT, Rocha RD. Respiratory muscle strength in congestive heart failure. *Chest* 1990;98:1091-4.

67. Mancini DM, Henson D, LaManca J, Levine S. Respiratory muscle function and dyspnea in patients with chronic congestive heart failure. *Circulation* 1992;86:909-18.

68. Ries AL, Gregoratos G, Friedman PJ, Clausen JL. Pulmonary function tests in the detection of left heart failure: correlation with pulmonary artery wedge pressure. *Respiration* 1986;49:241-50.

69. Clark AL, Swan JW, Laney R, Connelly M, Somerville J, Coats AJ. The role of right and left ventricular function in the ventilatory response to exercise in chronic heart failure. *Circulation* 1994;89:2062-9.

70. Murray CJ, Lopez AD. Evidence-based health policy--lessons from the Global Burden of Disease Study. *Science* 1996;274:740-3.

71. Rutten FH, Cramer MJ, Grobbee DE, Sachs AP, Kirkels JH, Lammers JW *et al*. Unrecognized heart failure in elderly patients with stable chronic obstructive pulmonary disease. *Accepted Eur Heart J 2005*.

Chapter 6

Unrecognised heart failure in elderly patients with stable chronic obstructive pulmonary disease

Frans H Rutten [1], Maarten-Jan M Cramer [2], Diederick E Grobbee [1] , Alfred PE Sachs [1], Johannes H Kirkels [2], Jan-Willem J Lammers [3], Arno W Hoes [1]

[1] Julius Center for Health Sciences and Primary Care;
[2] Heart Lung Center Utrecht, Department of Cardiology;
[3] Heart Lung Center Utrecht, Department of Pulmonary; Diseases;
University Medical Center Utrecht.

Eur Heart J Advanced Access published April 2005

Abstract

Aims To establish the prevalence of unrecognised heart failure in elderly patients with a diagnosis of chronic obstructive pulmonary disease, in a stable phase of their disease.

Methods and Results In a cross-sectional study, patients ≥65 years of age, classified as chronic obstructive pulmonary disease (COPD) by their general practitioner, and not known with a cardiologist-confirmed diagnosis of heart failure, were invited to our out-patient clinic. Four hundred and five participants underwent an extensive diagnostic work-up, including medical history and physical examination, followed by chest radiography, electrocardiography, echocardiography, and pulmonary function tests. As reference (i.e. 'gold') standard the consensus opinion of an expert panel was used. The panel based the diagnosis of heart failure on all available results from the diagnostic assessment, guided by the diagnostic principles of the European Society of Cardiology (ESC) for heart failure (i.e., symptoms and echocardiographic systolic and/or diastolic dysfunction). The diagnosis of COPD was based on the diagnostic criteria of the Global Initiative (GOLD) for COPD.

Of 405 participating patients with a diagnosis of COPD, 83 (20.5%, 95% C.I. 16.7-24.8) had previously unrecognised heart failure (42 patients systolic, and 41 'isolated' diastolic, and none 'isolated' right sided heart failure). In total 244 (60.2%) patients had COPD according to the GOLD criteria and 50 (20.5%, 95% C.I. 15.6-26.1) patients combined with unrecognised heart failure.

Conclusion Unrecognised heart failure is very common in elderly patients with stable COPD. Closer co-operation between general practitioners, pulmonologists, and cardiologists is necessary to improve detection and adequate treatment of heart failure in this large patient population.

Introduction

Heart failure and chronic obstructive pulmonary disease (COPD) are both common diseases in the elderly.[1;2] They have an important impact on quality of life and functional status, show high morbidity and mortality rates, and lead to considerable health-care costs. Although both diseases have been studied extensively, information about the prevalence of heart failure in stable COPD patients is lacking.

The diagnosis of heart failure is fraught with difficulties, notably in the early phases of the syndrome and in the presence of certain comorbidities. This is particularly true for COPD, as recognition of heart failure in these patients is hampered by similarities in signs and symptoms. Importantly, co-existence of COPD and heart failure is plausible in view of overlap in risk factors, notably smoking. Echocardiography is essential for establishing the diagnosis of heart failure. Accessibility to this diagnostic facility, however, is limited for primary care patients, and echocardiography is not part of the standard investigational protocol of pulmonologists.

It seems therefore plausible that a considerable proportion of patients with a diagnosis of COPD have concomitant heart failure, which remains unrecognised by primary care physicians or pulmonologists. In addition, due to similarities in symptoms, some COPD patients may be misclassified and in fact have heart failure.
Earlier studies suggested that the use of pulmonary medication often coincides with unrecognised heart failure,[3;4] and that the prevalence of heart failure can be as high as 20-30% in those COPD patients who are referred for an acute exacerbation.[5;6] However, information is lacking on the prevalence of heart failure in the much larger population of patients with stable COPD.
We assessed the prevalence of unrecognised heart failure in elderly patients, who were in a stable phase of their disease, diagnosed as COPD by their general practitioner.

Methods

Participants
Fifty-one primary care practices, located in the vicinity of Utrecht, the Netherlands, agreed to participate in this study, executed between April 2001 and June 2003. In total, 14,069 subjects aged 65 years or over were registered within these practices,

which routinely register patient contacts electronically.[7] In this sample of primary care practices, inner-city, urban, suburban, and rural communities are represented. All patients aged 65 years or over with an International Classification of Primary Care (ICPC) code R 91 (chronic bronchitis) or R 95 (COPD or emphysema) were eligible.[8] These ICPC codes are based on symptoms (dyspnoea, cough, or sputum production) and in the case of R95, additionally on pulmonary changes on the chest radiograph.[8] Identification of eligible subjects from the computerised patient files of the general practitioners was performed by a single general practitioner (F.H.R.), using a standardised extraction form. In total, 1,716 patients met these criteria. In 98 (5.7%) patients, heart failure had already been diagnosed, that is, heart failure confirmed by a cardiologist, with evidence of left ventricular dysfunction from echocardiography. Because we were interested in the prevalence of previously unrecognised heart failure, these 98 patients were excluded. Another 432 (25.2%) patients were excluded because of severe psychiatric disorders, immobility, or terminal illness. In total, 1,186 patients were invited by a letter signed by their own general practitioner and 405 (34%) patients agreed to participate. The most often mentioned reasons for not participating were a recent check-up by a specialist and time involved in the diagnostic program. In none of these patients was suspected heart failure the reason for the recent specialist check-up. Of all 1,716 subjects, patient characteristics were extracted anonymised from the computerised patient files of the general practitioners, with special attention for cardiovascular diseases and co-morbidity.
The Ethics Committee of the University Medical Center Utrecht, the Netherlands approved the study protocol, and all participants gave written informed consent.

Diagnostic procedures
Each of the 405 participants was investigated during a single three hours session at our out-patient department. A standardised questionnaire was administered to participants to obtain additional information on complaints and smoking habits. Present medication use was asked for and checked (participants had to take medication boxes with them). Presence of angina pectoris and shortness of breath was assessed by means of the World Health Organisation (WHO) questionnaires.[9] Data on co-morbidities were acquired by scrutinising the computerised data files of the participating general practitioners, including available letters from hospital specialists.
Body-mass index was calculated as weight (kg)/height $(m)^2$. A standardised physical examination was carried out by one general practitioner (F.H.R.). A standard 12-lead electrocardiogram (ECG) was recorded and classified according to the Minnesota coding criteria,[9] by a single cardiologist (M-J.C.). Postero-

anterior and lateral plane chest radiographs were taken in standing position according to standard radiological criteria and described by one of three radiologists, who were blinded to clinical data. Blood samples were taken and analysed the same day, and after centrifugation specimens of serum and plasma were stored at –70 ° Celsius.

Cardiac function

Echocardiographic studies were performed using a Philips Sonos 5500 imaging system (Andover, MA, USA) by two cardiac sonographers. All echocardiographic images were interpreted by a single cardiologist (M-J.C.), who was blinded to clinical data. Parameters from Doppler analysis, M-mode echocardiography, and 2D transthoracic echocardiography were used. Where image quality was sufficient, the left-ventricular ejection fraction was calculated from the endocardial surface tracings in the apical four chamber view and two chamber view, using Simpson's rule (disc summation method).[10] Alternatively, the endocardial surface of the left ventricle was traced at end-systole and end-diastole. The ejection fraction was then calculated using the single plane area-length method.[11]

In 185 patients ejection fraction could be assessed by one of these quantitative methods. In the remaining 219 patients left-ventricular systolic function was assessed semiquantatively by the 2D visual estimate method ('eyeballing').[12] The accuracy of this visual method has been validated previously.[13] In 42 (10.4%) patients echocardiographic view was of poor quality. In one patient the image quality did not allow any estimation of LVEF. Valve regurgitation was graded semiquantitatively, and in case of aortic stenosis the pressure gradient was assessed. Left atrial volume was assessed by the biplane area-length method from apical four- and two-chamber views.[14] The normal value was indexed for body surface area. As cut-off values for normal and definitely increased left atrial volume index 28 ml/m² and 32 ml/m² were used, respectively.[14;15] With pulsed-wave Doppler echocardiography mitral inflow and pulmonary venous inflow was assessed. From the mitral inflow profile, the E- and A-wave velocity and E-deceleration time were measured and E/A velocity ratio was calculated. The flow velocities of the left or right upper pulmonary vein were recorded, and the ratio of systolic to diastolic forward flow (S/D ratio) was calculated. Diastolic function was categorised as normal, impaired relaxation (grade I), pseudonormal filling (grade II), or restrictive filling (grade III) by a combination of transmitral and pulmonary flow patterns and left atrial volume indexes.[16-18] (Appendix).

We measured the peak velocity of the tricuspid regurgitant signal with continuous-wave Doppler and calculated the systolic pulmonary artery pressure with the modified Bernoulli equation.[19]

Pulmonary function

A fixed-volume body plethysmograph (Masterlab Jaeger, Würzburg, Germany) was used to measure lung volumes and airway resistance, and a Masterscreen for measuring alveolar volume and diffusion capacity of the lung for carbon monoxide using a single-breath method. In the analysis, the choice of the best test out of three was based on the highest sum of forced expiratory volume in one second (FEV1) and forced vital capacity (FVC).[2] A bronchodilator reversibility test was performed by inhalation of two puffs of 20 μg ipatropium bromide by an inhalation chamber. Measurements were performed after an interval of at least 30 minutes. Baseline spirometric measurement was performed in all patients. In five (1.2%) patients we were not able to perform postdilatory spirometric measurements or body box measurements. CO-diffusion could not be assessed in 42 (10.4%) patients because of low values of FEV1.

Diagnostic criteria

Heart failure was assessed by an expert panel of two cardiologists, a pulmonologist, and a general practitioner. The panel used all available diagnostic information, including echocardiography and pulmonary function tests. First, the panel classified heart failure as definite, probable, or no heart failure. For those with definite or probable heart failure, the most probable cause of heart failure according to the panel was notified. As a guide, the panel used the diagnostic principles formulated by the European Society of Cardiology (ESC), that is, symptoms of heart failure and objective evidence of cardiac dysfunction.[1] Importantly, objective evidence of cardiac dysfunction in our study was defined as echocardiographic ventricular (systolic and/or diastolic) dysfunction. Systolic heart failure was defined as the presence of symptoms in combination with an LVEF ≤ 45%. 'Isolated' diastolic heart failure was defined as echocardiographic diastolic dysfunction (grade I, II or III) (Appendix) in combination with LVEF >45%. These echocardiographic parameters had to be present in combination with (i) symptoms and signs of heart failure [20] or (ii) symptoms and a combination of two of the following items: hypertension, echocardiographic left ventricular hypertrophy, atrial fibrillation or anginal complaints.[21] Additionally, these symptoms and/or signs should not, or insufficiently, be explained by COPD.[22] 'Isolated' right sided heart failure was defined as signs of right sided heart failure, LVEF >45%, and increased right atrial pressure estimated from the respiratory variation in diameter of the caval vein and/or right-ventricular dysfunction assessed semiquantatively by the 2D visual estimate method ('eyeballing').

Presence of definite COPD was assessed by the panel according to the recent GOLD criteria.[2;23] A spirometrically assessed ratio of a postdilatory FEV1/FVC <

70% confirmed the presence of definite COPD, either with or without complaints compatible with COPD (cough, dyspnoea, sputum production). Other pulmonary diseases were classified by the panel, using information from patient's history, pulmonary function tests, and chest radiography.

Data analysis
We calculated age- and sex-specific prevalence of heart failure. Prevalence estimates are given for 10 years age groups, and for men and women separately. Binomial confidence intervals (95%) were calculated for prevalence estimates. Prevalence was calculated as the number of cases of heart failure divided by the number of participants. Any data with a skewed distribution were summarised as medians with interquartile ranges. Data were analysed using SPSS Windows version 11.0 (SPSS Inc., Chicago, IL, USA).

Results

The mean age of the participants was 73.0 (S.D. 5.3) years, and 55% were male. Participants were comparable in cardiovascular co-morbidity to eligible non-responders and to those who were excluded because of severe psychiatric disorders, immobility, or terminal illness, although participants were somewhat younger (Table 1). Patients who were excluded because they were known with documented heart failure had much more cardiovascular co-morbities than participants.

In 83 patients, previously unrecognised heart failure was discovered (prevalence 20.5%, 95% C.I. 16.7-24.8). Of these patients, 33 had heart failure only, whereas in 50, heart failure and definite COPD were both present. Of the 83 heart failure patients, 42 (50.6%) had systolic, and 41 (49.4%) had 'isolated' diastolic, and none had right sided heart failure. Of those with systolic heart failure, 32 (76.2%) had an LVEF $\leq$ 40%, and 10 (23.8%) an LVEF between 40% and 45%. Another 47 (11.6%) patients were classified as having *possible* heart failure by the expert panel: eight patients as having systolic, 37 as having 'isolated' diastolic, and two patients as having possible right sided heart failure. In total 130 (32.1%, 95% C.I. 27.6-36.9) patients were classified as heart failure or possible heart failure by the panel.

Age- and sex-specific prevalence data of systolic and diastolic heart failure are shown in Table 2. The overall prevalence of heart failure was somewhat higher in men. The prevalence of heart failure increased with age in women, but not in men.

Table 1 Characteristics of patients aged ≥65 years with a general practitioner's diagnosis of COPD. Values are percentages, unless stated otherwise

			Excluded patients (N=530)	
Characteristics	**Participants (N=405)**	**Non-responders (N=781)**	**Severe psychiatric disorder, immobility, or terminal illness (N=432)**	**Documented heart failure (N=98)**
Mean (SD) age in years	73.0 (5.3)	74.9 (7.8)	77.5 (7.0)	76.9 (6.2)
Male	55.1	53.8	40.7	62.2
Ischaemic heart disease [a]	20.2	24.3	23.6	50.0
Hypertension	35.8	37.3	41.4	48.0
Diabetes mellitus	10.4	12.8	14.4	24.5
Stroke/TIA	5.2	7.8	13.2	14.3
Atrial fibrillation	8.4	9.1	11.6	51.0
Valvular disease	3.5	4.7	4.2	29.6
Peripheral arterial disease	6.9	6.5	6.9	15.3
Thyroid disease	3.7	5.3	4.0	6.1

SD, standard deviation. TIA= transient ischaemic attack.

[a] Ischaemic heart disease = prior myocardial infarction, angina pectoris, coronary artery bypass grafting or percutaneous coronary intervention.

Systolic heart failure was most common in younger male patients, whereas 'isolated' diastolic heart failure was most common in elderly women. Definite COPD was diagnosed in 244 (60.2%) participants. In 194 patients, only COPD was present and in 50 patients concomitant heart failure was present. Therefore, the prevalence of heart failure in definite COPD was 20.5% (95% C.I. 15.6-26.1). Of the patients with neither heart failure nor COPD, the following pulmonary diagnoses were established by the panel: persisting asthma (20 patients), bronchiectasis (four patients), scarring on chest radiograph due to tuberculosis (four patients), prior pulmonary embolism (two patients), and alveolitis (one patient).

Table 2 Prevalence of systolic and 'isolated' diastolic heart failure by age and sex. Numbers with percentages and 95% confidence intervals (95%CI)

	Systolic heart failure (N=42)	'Isolated' diastolic heart failure (N=41)	All heart failure (N=83)
Males			
Age (years)			
65-74 (n=150)	26 (17.3% (11.6-24.4))	11 (7.3% (3.7-12.7))	37 (24.7% (18.0-32.4))
≥75 (n=73)	9 (12.3% (5.8-22.1))	5 (6.8% (2.3-15.3))	14 (19.2% (10.9-30.1))
All ages (n=223)	35 (15.7% (11.1-21.1))	16 (7.2% (4.2-11.4))	51 (22.9% (17.5-28.9))
Females			
Age (years)			
65-74 (n=112)	4 (3.6% (1.0-8.9))	7 (6.3% (2.5-12.5))	11 (9.8% (5.0-16.9))
≥75 (n=70)	3 (4.3% (0.9-12.0))	18 (25.7% (16.0-37.6))	21 (30.0% (19.6-42.1))
All ages (n=182)	7 (3.8% (1.6-7.8))	25 (13.7% (9.1-19.6))	32 (17.6% (12.3-23.9))
All males and females			
Age (years)			
65-74 (n=262)	30 (11.5% (7.9-15.9))	18 (6.9% (4.1-10.6))	48 (18.3% (13.8-23.5))
≥75 (n=143)	12 (8.4% (4.4-14.2))	23 (16.1% (10.5-23.2))	35 (24.5% (17.7-32.4))
All ages (n=405)	42 (10.4% (7.6-13.8))	41 (10.1% (7.4-13.5))	83 (20.5% (16.7-24.8))

Seven females and three males were aged 85 years or over.

Table 3 Baseline characteristics of 405 patients with a GP's diagnosis of COPD

Characteristics	All patients N=405	HF only N=33	HF+COPD N=50	COPD only N=194	Neither N=128
Demographic data					
Mean (SD) age in years	73.0 (5.3)	74.0 (5.9)	73.7 (5.3)	73.3 (5.0)	71.8 (5.6)
Male	55.1	45.5	72.0	67.5	32.0
Median (25-75 percentile) pack years of smoking	14.5 (0.0-37.8)	9.6 (0.0-30.3)	27.0 (0.6-53.7)	22.7 (1.4-43.9)	0.75 (0.0-27.1)
History					
Ischaemic heart disease[a]	20.5	27.3	38.0	19.1	14.1
Hypertension	35.8	51.5	36.0	28.9	42.2
Diabetes mellitus	10.4	15.2	14.0	7.2	12.5
Signs & Symptoms					
Dyspnoea	96.5	97.0	100	98.5	92.2
Orthopnoea or PND	26.7	33.3	28.0	24.2	28.1
Fatigue	62.2	75.8	72.0	64.4	60.9
Heart rate (beats/minute)	76.5 (14.1)	76.5 (17.2)	82.4 (14.8)	76.0 (12.9)	74.9 (14.2)
BMI (weight/m²)	26.7 (4.2)	29.3 (4.0)	27.2 (3.6)	25.6 (3.9)	27.4 (4.3)
Systolic blood pressure (mmHg)	151.7 (18.3)	153.2 (16.1)	150.1 (24.0)	150.9 (17.4)	153.2 (17.7)
Diastolic blood pressure (mmHg)	83.5 (10.4)	86.6 (8.7)	83.2 (13.0)	82.0 (10.2)	85.0 (9.5)

Values are percentages, means values (SD), or median (25th-75th percentile).

HF, heart failure; PND, paroxysmal nocturnal dyspnoea; BMI, body mass index (weight (kg)/length (m)²).

[a] Ischaemic heart disease = prior myocardial infarction, angina pectoris, coronary artery bypass grafting or percutaneous coronary intervention.

Table 4 Results of additional investigations of 405 patients with a general practitioner's diagnosis of COPD

Additional measurements	All patients N=405	HF only N=33	HF+COPD N=50	COPD only N=194	Neither N=128
Cardiothoracic ratio	0.48 (0.05)	0.52 (0.04)	0.49 (0.05)	0.46 (0.05)	0.49 (0.05)
Pulmonary fluid [a]	2.7%	9.1%	4.0%	1.0%	3.1%
Abnormal ECG [b]	35.3%	60.6%	64.0%	26.8%	30.5%
- Myocardial infarction	31 (7.7%)	2 (6.1%)	13 (26.0%)	12 (6.2%)	4 (3.1%)
- Left bundle branch block	63 (15.6%)	9 (27.3%)	18 (36.0%)	20 (10.3%)	16 (12.5%)
- LVH	24 (5.9%)	1 (3.0%)	7 (14.0%)	10 (5.2%)	6 (4.7%)
- Atrial fibrillation	22 (5.4%)	3 (9.1%)	5 (10.0%)	11 (5.7%)	3 (2.3%)
- ST and/or T-wave changes	92 (22.7%)	14 (42.4%)	17 (34.0%)	33 (17.0%)	28 (21.9%)
- sinus tachycardia	9 (2.2%)	2 (6.1%)	4 (8.0%)	0 (0%)	3 (2.3%)
LVEF	57.2 (9.8)	48.9 (12.8)	45.1 (14.7)	59.6 (6.3)	60.6 (5.1)
FEV1/FVC ratio [c]	64.4 (14.2)	77.3 (5.4)	57.4 (10.4)	55.0(10.8)	78.0(6.0)

Values are in n (%), mean (SD). Cardiothoracic ratio, four missings (due to lobectomy); LVEF one missing.

[a] Pulmonary fluid: pleural fluid, interlobular, alveolar or interstitial fluid, or redistribution on chest radiograph.

[b] Abnormal ECG: abnormal Q-waves fitting in the diagnosis of (prior) myocardial infarction, left bundle branch block (complete or incomplete), left ventricular hypertrophy (LVH), atrial fibrillation, ST and/or T-wave changes (non-specific or suggestive for myocardial ischaemia), and sinus tachycardia. More than one electrocardiographic diagnosis per patient is possible.

[c] FEV1/FVC ratios are postdilatory values of the ratios of forced expiratory volume in one second and forced vital capacity. In five cases with missing postdilatory values, pre-dilatory values were used.

In Table 3, demographic details are provided for participants with heart failure only, heart failure plus COPD, COPD only, or neither heart failure nor COPD. COPD patients were more often males, with a higher number of pack years of smoking, although a history of ischaemic heart disease, hypertension and diabetes mellitus were more prevalent in heart failure patients. Most participants in all four categories reported dyspnoea and fatigue. Apart from increased cardiothoracic ratio and decreased LVEF, about 60% of the patients with heart failure showed abnormalities on ECG (i.e. abnormal Q-waves, left bundle branch block, left ventricular hypertrophy, ST and/or T-wave changes, or sinus tachycardia). These ECG abnormalities were more common in heart failure patients than in those with COPD only (Table 4). Of all participants, 148 (36.5%) patients had a normal ECG, whereas 16 (19.3%) patients with heart failure had a normal ECG. The 33 patients who were wrongly classified by their general practitioner as having COPD, but were actually suffering from heart failure, were more often female than heart failure patients with concomitant COPD. Half of these 33 patients had hypertension, and a third reported complaints of orthopnoea or paroxysmal nocturnal dyspnoea. They also reported less pack years of smoking and prevalence of chest radiographic abnormalities compared to heart failure patients with concomitant COPD.

According to the panel, ischaemic heart diseases were the most prominent possible causes for systolic heart failure, whereas hypertension, left ventricular hypertrophy, and atrial fibrillation were the most common possible causes for 'isolated' diastolic heart failure (Table 5). The number of patients with heart failure due to clinically significant valvular disease (3.6%) was low. Most heart failure patients were in New York Heart Association (NYHA) functional class II and III (Table 5).

Discussion

To our knowledge, this is the first study to show that unrecognised heart failure is very common (20.5%) in elderly patients with a general practitioner's diagnosis of chronic obstructive pulmonary disease, in a stable phase of their disease. Also, in patients with definite chronic obstructive pulmonary disease according to the GOLD-criteria (244 patients (60.2%)), the prevalence rate of unrecognised heart failure is 20.5%. None of the heart failure patients had 'isolated' right sided heart failure, only 2 (0.5%) patients had possible 'isolated' right sided heart failure. Inclusion of patients with established heart failure (who were not invited to participate), would yield an estimate of heart failure of 26% in unselected primary care COPD patients in a stable phase of their disease. The prevalence of heart failure in stable COPD patients is therefore about four times as high compared to

Table 5 Possible causes of heart failure and NYHA classification according to the panel in 83 heart failure patients [a]

	Systolic heart failure (N=42)	'Isolated' diastolic heart failure (N=41)	All heart failure (N=83)
Possible causes of heart failure			
Prior myocardial infarction	14 (33%)	2 (4.9%)	16 (19%)
Other ischaemic heart disease [b]	17 (41%)	7 (17%)	24 (29%)
Hypertension	13 (31%)	27 (66%)	40 (48%)
Left ventricular hypertrophy	2 (4.8%)	7 (17%)	9 (11%)
Atrial fibrillation	4 (9.5%)	6 (15%)	10 (12%)
Valvular disease	1 (2.4%)	2 (4.9%)	3 (3.6%)
NYHA class			
NYHA I	1 (2.4%)	0 (0%)	1 (1.2%)
NYHA II	17 (40%)	12 (29%)	29 (35%)
NYHA III	18 (43%)	24 (49%)	42 (51%)
NYHA IV	6 (14%)	4 (9.8%)	10 (12%)

[a] The panel could adjudge more than one possible cause.

[b] Other ischaemic heart disease: angina pectoris, coronary artery bypass grafting or percutaneous coronary intervention (PCI).

subjects aged 65 years or over in the population at large.[24]

Presence of COPD is generally considered a complicating factor in the diagnostic assessment of patients suspected of heart failure, but COPD patients are not considered a high risk group for developing heart failure.[1] The reasons for the high prevalence of heart failure among COPD patients we found in our study remain speculative, but the increased prevalence rates of atherosclerosis found in COPD patients and the impressive smoking status of these patients are likely to be important, as both smoking and atherosclerosis are known risk factors for developing ischaemic heart disease and heart failure. COPD can also lead to

(periods of) hypoxemia and hypercapnia, and to (periods of) pressure changes in the right ventricle and therefore increased wall stress in the interventricular septum which may further promote heart failure. The lack of right sided heart failure in our study is probably attributable to the fact that right ventricular contractility remains relatively normal in COPD, even in the presence of pulmonary hypertension,[25] and right ventricular dysfunction may only occur in end-stage COPD.[26]

A recent subgroup analysis of the Breathing Not Properly-study revealed a remarkably similar prevalence of previously unrecognised heart failure of 20.9% for patients (mean age 62 years) with a history of COPD or asthma.[6] However, these were patients experiencing an exacerbation of their COPD or asthma, urging them to visit an Emergency Department with acute dyspnoea. Moreover, the assessment of heart failure differed from our study. The diagnosis of heart failure was established by two cardiologists, using the Framingham and NHANES score as reference standard,[27] with echocardiographic information available in only 29% of the patients.

In our study about 50% of all heart failure patients had 'isolated' diastolic heart failure, with higher prevalence rates in elderly women. These findings are comparable with findings in population-based studies.[28;29] Our findings that a history of myocardial infarction or other ischaemic heart disease were most often mentioned as possible cause for systolic heart failure, whereas hypertension, left ventricular hypertrophy and atrial fibrillation were more often implicated in 'isolated' diastolic heart failure were in concordance with other studies.[1]

Because our study was restricted to elderly patients, we had to consider changes in echocardiographic parameters associated with ageing such as reduced early diastolic filling, increased late diastolic filling, and reduced myocardial diastolic velocities.[30;31] Also, we had to consider that Doppler measurements of diastolic function are influenced by loading conditions of the heart.[32] Because we studied patients in stable conditions, however, echocardiographic results were possibly less hampered by loading conditions. To optimise classification of 'isolated' diastolic heart failure we added a combination of relevant clinical parameters to echocardiographic signs of diastolic dysfunction.[33] This may have influenced the expert panel in their allocation of the possible cause for heart failure in the individual patient.

Work-up bias (verification bias) was eliminated from our study, since all subjects underwent all diagnostic tests necessary to classify heart failure and COPD. To

prevent work-up bias, we also choose not to use clinical data of non-participants to establish presence or absence of heart failure, because these data were available in a minority of non-participants only.

The presence of heart failure was established by consensus evaluation, using all available diagnostic information.[29;34] This is an established method as reference standard, since a true 'gold' standard is lacking for assessing heart failure.[34] Moreover, earlier studies have shown that panel diagnosis in establishing heart failure was highly reproducible.[35] This method seems more valid than more easily applicable reference standards such as the Framingham score, [27] Boston score, [36] or NHANES score,[37] because these scores are only based on diagnostic information from signs and symptoms, electrocardiography, and chest radiography, and do not include information from echocardiography. Because of overlapping signs and symptoms,[38;39] these scores may lead to an overestimation of the prevalence of heart failure in COPD patients. The panel was guided by the ESC principles of heart failure (i.e. symptoms and objective evidence of cardiac dysfunction). Importantly, however, objective evidence of cardiac dysfunction was defined in our study as echocardiographical ventricular (systolic and/or diastolic) dysfunction. Therefore, patients with, for example, dyspnoea and atrial fibrillation or valvular disease, but with a normal ventricular function on echocardiography were not considered as heart failure patients in our study.

The response rate (34%) in our study may seem modest, but was only slightly lower than in population-based studies assessing heart failure in the elderly.[28;40] Because we invited diseased elderly patients in a stable phase of their disease (i.e. patients with a diagnosis of COPD), and only excluded patients with severe psychiatric disease, immobility or terminal illness, lower response rates could be expected because many elderly patients with rather high levels of disability were invited. Although we, inevitably, studied a selection of available COPD patients, selection bias in our prevalence estimates of unrecognised heart failure seems limited, because relevant and known cardiovascular risk factors for heart failure and co-morbidities of participants were only slightly lower in participants than in non-responders and patients who were excluded because of severe psychiatric disorder, immobility, or terminal illness. Patients who were excluded because they were known with documented heart failure, however, had clearly increased cardiovascular co-morbidity compared to participants in our study. Because we were interested in the prevalence of *unrecognised* heart failure, differences in patient characteristics between patients excluded because of documented heart failure and participants, however, do not bias our prevalence estimation. In all,

owing to this patient selection, the prevalence of unrecognised heart failure in the population of elderly COPD patients at large is even somewhat higher than our estimate. Importantly, the clinical applicability of our results is high, we studied those patients who were able to undergo the relevant diagnostic investigations, and therefore, we studied those COPD patients in whom treatment is likely to be initiated in everyday practice.

Although inadequate echocardiographic views can hamper diagnostic assessment especially in COPD patients with their large thoracic cavities filled with air,[4] the image quality in our study was poor in only about 10% of the patients, and an estimation of left ventricular ejection fraction was impossible in one single patient.

The high prevalence of unrecognised heart failure in stable COPD patients in our study provides some evidence in favour of screening of this large group of patients. Although performing echocardiography in all elderly COPD patients is not feasible, more easily applicable tests, such as natriuretic peptide measurements could be helpful in the diagnostic assessment of stable COPD patients. Natriuretic peptide measurements have already shown to be useful in the diagnostic assessment of patients suspected of heart failure, [34] in patients with acute dyspnoea, [41] and in patients with a history of pulmonary disease who experience acute dyspnoea.[6] However, the exact role of these measurements in the diagnostic process in stable COPD patients, in addition to other easily available diagnostic information such as history, physical examination and ECG, remains to be determined. We do aim to study the additional diagnostic value of natriuretic peptides in our patient population by analysing stored serum and plasma samples, but these data are not yet available.

In 32% of the patients neither heart failure nor COPD could explain the patient's complaints. This rather large proportion was due to the fact that our study focussed on detecting heart failure and COPD and not on investigating all possible causes for the complaints in these patients. Moreover, some of these patients had possibly heart failure, and 31 (7.7%) patients had other pulmonary diseases than COPD, notably persisting asthma.
In conclusion, our findings support the view that unrecognised heart failure is very common in elderly patients with stable COPD. Adequate treatment of heart failure, in particular in its early stages, may alleviate symptoms, delay progression, and improve prognosis.[1] Closer co-operation between general practitioners, pulmonologists and cardiologists is necessary to optimise management of this large population of patients.

Acknowledgements

We wish to thank the participating patients, general practitioners, and their assistants, including the general practices connected to the General Practice Network Utrecht (HNU), the sonographers, especially Elly Lutgert-Hagman, the pulmonology technicians, and Pieter Zanen, lung physiologist. Peter Zuithoff helped us with the data management. The study was funded by a research grant (number 904-61-144) of the Netherlands Organisation for Scientific Research (NWO).

Appendix Doppler echocardiographic criteria used for classification of diastolic function

	Normal (elderly adults)	**Impaired relaxation (grade I)**	**Pseudonormal filling (grade II)**	**Restrictive filling (grade III)**
E/A (cm/s)	0.75<E/A<1.5	E/A ≤ 0.75	0.75<E/A<1.5	E/A ≥ 1.5
DT (ms)	150<DT<240	≥ 240	150<DT<240	DT ≤ 150
IVRT (ms)	60<IVRT<110	≥ 110	60<IVRT<110	IVRT ≤ 60
S/D	≥ 1	≥ 1	< 1	< 1
LA volume index (ml/m²)	≤ 28	28-32	≥ 32	≥ 32

E/A, early-to-atrial left ventricular filling ratio; DT, deceleration time; IVRT, isovolumetic relaxation time; S/D, systolic-to-diastolic pulmonary venous flow ratio; LA volume index, left atrial volume indexed for body surface area

References

1. Remme WJ, Swedberg K. Guidelines for the diagnosis and treatment of chronic heart failure. *Eur Heart J* 2001;22:1527-60.

2. Pauwels RA, Buist AS, Ma P, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: National Heart, Lung, and Blood Institute and World Health Organization Global Initiative for Chronic Obstructive Lung Disease (GOLD): executive summary. *Respir Care* 2001;46:798-825.

3. Remes J, Miettinen H, Reunanen A, Pyörälä K. Validity of clinical diagnosis of heart failure in primary health care. *Eur Heart J* 1991;12:315-21.

4. Wheeldon NM, MacDonald TM, Flucker CJ, McKendrick AD, McDevitt DG, Struthers AD. Echocardiography in chronic heart failure in the community. *Q J Med* 1993;86:17-23.

5. Render ML, Weinstein AS, Blaustein AS. Left ventricular dysfunction in deteriorating patients with chronic obstructive pulmonary disease. *Chest* 1995;107:162-8.

6. McCullough PA, Hollander JE, Nowak RM, Storrow AB, Duc P, Omland T, McCord J, Herrmann HC, Steg PG, Westheim A, Knudsen LW, Abraham WT, Lamba S, Wu AH, Perez A, Clopton P, Krishnaswany P, Kazanegra R, Maisel AS. Uncovering heart failure in patients with a history of pulmonary disease: rationale for the early use of B-type natriuretic peptide in the emergency department. *Acad Emerg Med* 2003;10:198-204.

7. Van der Lei J, Duisterhout JS, Westerhof HP, Van der Does, Cromme PV, Boon WM, Van Bemmel JH. The introduction of computer-based patient records in The Netherlands. *Ann Intern Med* 1993;119:1036-41.

8. Classification Committee of WONCA. *International classification of primary care*. UK: Oxford University Press; 1983.

9. Rose GA, Blackburn, H. *Cardiovascular Survey Methods*. Geneva: World Health Organisation; 1982.

10. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, Gutgesell H, Reichek N, Sahn D, Schrittger I. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr* 1989;2:358-67.

11. Folland ED, Parisi AF, Moynihan PF, Jones DR, Feldman CL, Tow DE. Assessment of left ventricular ejection fraction and volumes by real-time, two-dimensional echocardiography. A comparison of cineangiographic and radionuclide techniques. *Circulation* 1979;60:760-6.

12. Quinones MA, Waggoner AD, Reduto LA, Nelson JG, Young JB, Winters WL,

Ribeiro LG, Miller RR. A new, simplified and accurate method for determining ejection fraction with two-dimensional echocardiography. *Circulation* 1981;64:744-53.

13. Willenheimer RB, Israelsson BA, Cline CM, Erhardt LR. Simplified echocardiography in the diagnosis of heart failure. *Scand Cardiovasc J* 1997;31:9-16.

14. Tsang TS, Barnes ME, Gersh BJ, Bailey KR, Seward JB. Left atrial volume as a morphophysiologic expression of left ventricular diastolic dysfunction and relation to cardiovascular risk burden. *Am J Cardiol* 2002;90:1284-9.

15. Moller JE, Hillis GS, Oh JK, Seward JB, Reeder GS, Wright RS, Park SW, Bailey KR, Pellikka PA. Left atrial volume: a powerful predictor of survival after acute myocardial infarction. *Circulation* 2003;107:2207-12.

16. Garcia MJ, Thomas JD, Klein AL. New Doppler echocardiographic applications for the study of diastolic function. *J Am Coll Cardiol* 1998;32:865-75.

17. Nishimura RA, Tajik AJ. Evaluation of diastolic filling of left ventricle in health and disease: Doppler echocardiography is the clinician's Rosetta Stone. *J Am Coll Cardiol* 1997;30:8-18.

18. Oh JK, Appleton CP, Hatle LK, Nishimura RA, Seward JB, Tajik AJ. The noninvasive assessment of left ventricular diastolic function with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr* 1997;10:246-70.

19. Schena M, Clini E, Errera D, Quadri A. Echo-Doppler evaluation of left ventricular impairment in chronic cor pulmonale. *Chest* 1996;109:1446-51.

20. Zile MR. Heart failure with preserved ejection fraction: is this diastolic heart failure? *J Am Coll Cardiol* 2003;41:1519-22.

21. Vasan RS, Benjamin EJ, Levy D. Congestive heart failure with normal left ventricular systolic function. Clinical approaches to the diagnosis and treatment of diastolic heart failure. *Arch Intern Med* 1996;156:146-57.

22. Caruana L, Petrie MC, Davie AP, McMurray JJ. Do patients with suspected heart failure and preserved left ventricular systolic function suffer from "diastolic heart failure" or from misdiagnosis? A prospective descriptive study. *BMJ* 2000;321:215-8.

23. Fabbri LM, Hurd SS. Global Strategy for the Diagnosis, Management and Prevention of COPD: 2003 update. *Eur Respir J* 2003;22:1-2.

24. Hogg K, Swedberg K, McMurray J. Heart failure with preserved left ventricular systolic function; epidemiology, clinical characteristics, and prognosis. *J Am Coll Cardiol* 2004;43:317-27.

25. Biernacki W, Flenley DC, Muir AL, MacNee W. Pulmonary hypertension and right ventricular function in patients with COPD. *Chest* 1988;94:1169-75.

26. Kohama A, Tanouchi J, Hori M, Kitabatake A, Kamada T. Pathologic involvement

of the left ventricle in chronic cor pulmonale. *Chest* 1990;98:794-800.

27. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. *N Engl J Med* 1971;285:1441-6.

28. Mosterd A, Hoes AW, de Bruyne MC, Deckers JW, Linker DT, Hofman A, Grobbee DE. Prevalence of heart failure and left ventricular dysfunction in the general population; The Rotterdam Study. *Eur Heart J* 1999;20:447-55.

29. Kitzman DW, Gardin JM, Gottdiener JS, Arnold A, Boineau R, Aurigemma G, Marino EK, Lyles M, Cushman M, Enright PL. Importance of heart failure with preserved systolic function in patients > or = 65 years of age. CHS Research Group. Cardiovascular Health Study. *Am J Cardiol* 2001;87:413-9.

30. Oxenham H, Sharpe N. Cardiovascular aging and heart failure. *Eur J Heart Fail* 2003;5:427-34.

31. Tighe DA, Vinch CS, Hill JC, Meyer TE, Goldberg RJ, Aurigemma GP. Influence of age on assessment of diastolic function by Doppler tissue imaging. *Am J Cardiol* 2003;91:254-7.

32. Vasan RS, Benjamin EJ. Diastolic heart failure-no time to relax. *N Engl J Med* 2001;344:56-9.

33. Petrie MC, Hogg K, Caruana L, McMurray JJ. Poor concordance of commonly used echocardiographic measures of left ventricular diastolic function in patients with suspected heart failure but preserved systolic function: is there a reliable echocardiographic measure of diastolic dysfunction? *Heart* 2004;90:511-7.

34. Cowie MR, Struthers AD, Wood DA, Coats AJ, Thompson SG, Poole-Wilson PA, Sutton GC. Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care. *Lancet* 1997;350:1349-53.

35. Cowie MR, Wood DA, Coats AJ, Thompson SG, Poole-Wilson PA, Suresh V, Sutton GC. Incidence and aetiology of heart failure; a population-based study. *Eur Heart J* 1999;20:421-8.

36. Carlson KJ, Lee DC, Goroll AH, Leahy M, Johnson RA. An analysis of physicians' reasons for prescribing long-term digitalis therapy in outpatients. *J Chronic Dis* 1985;38:733-9.

37. Schocken DD, Arrieta MI, Leaverton PE, Ross EA. Prevalence and mortality rate of congestive heart failure in the United States. *J Am Coll Cardiol* 1992;20:301-6.

38. Harrigan RA, Jones K. ABC of clinical electrocardiography. Conditions affecting the right side of the heart. *BMJ* 2002;324:1201-4.

39. Himelman RB, Struve SN, Brown JK, Namnum P, Schiller NB. Improved recognition of cor pulmonale in patients with severe chronic obstructive pulmonary disease. *Am J Med* 1988;84:891-8.

40. Redfield MM, Jacobsen SJ, Burnett JC, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community:

appreciating the scope of the heart failure epidemic. *JAMA* 2003;289:194-202.

41. Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, Omland T, Storrow AB, Abraham WT, Wu AH, Clopton P, Steg PG, Westheim A, Knudsen CW, Perez A, Kazanegra R, Herrmann HC, McCullough PA. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med* 2002;347:161-7.

Chapter 7

Recognising heart failure in elderly patients with stable chronic obstructive pulmonary disease in primary care: a cross-sectional diagnostic study

Frans H Rutten [1], Karel GM Moons [1], Maarten-Jan M Cramer [2], Diederick E Grobbee [1], Nicolaas PA Zuithoff [1], Jan-Willem J Lammers [3], Arno W Hoes [1]

[1] Julius Center for Health Sciences and Primary Care;
[2] Heart Lung Center Utrecht, Department of Cardiology;
[3] Heart Lung Center Utrecht, Department of Pulmonary Diseases;
University Medical Center Utrecht.

Accepted BMJ

Abstract

Objective To determine which clinical items provide diagnostic information in recognising heart failure in primary care patients with stable chronic obstructive pulmonary disease (COPD), and whether easily available tests provide added diagnostic information.
Design A cross-sectional diagnostic study.
Setting 405 (34% of the eligible) patients underwent a systematic diagnostic work-up, including clinical assessment, blood tests (including amino-terminal pro B-type natriuretic peptide (NT-proBNP)), electrocardiography, chest radiography, echocardiography, and pulmonary function tests. The consensus opinion of an expert panel was used as reference test for heart failure. The panel used all available results from the diagnostic assessment, excluding NT-proBNP. The diagnostic value of independent predictors for heart failure was quantified using multivariate logistic modelling in combination with area under the receiver operating characteristic curves (ROC-area).
Participants Patients ≥65 years of age, classified as COPD by their general practitioner, and without a cardiologist-confirmed diagnosis of heart failure.
Main outcome measures Independent predictors for concomitant heart failure in primary care patients with stable COPD.
Results Eighty-three (20.5%) of the 405 enrolled COPD patients had a new diagnosis of concomitant heart failure. Independent clinical predictors for concomitant heart failure were a history of ischaemic heart disease, body mass index, laterally displaced apex beat, and heart rate. The ROC-area of the multivariate model with these four predictors was 0.70 (95% CI 0.64-0.76). The ROC area of NT-proBNP as single test was 0.72 (95%CI 0.66-0.79). Addition of NT-proBNP to the reduced 'clinical model' had the largest added diagnostic value, with a significant increase of the ROC-area to 0.77 (95% CI 0.71-0.83), followed by electrocardiography (ROC-area 0.75; 95% CI 0.69-0.81).
Conclusions A limited number of easily available items from history and physical examination, with addition of NT-proBNP and/or electrocardiography can increase the confidence of the clinician about presence or absence of concomitant heart failure in the individual primary care patient with stable COPD.

Introduction

A diagnosis of heart failure in primary care is notoriously difficult, notably in the early phases of the syndrome and in the presence of chronic obstructive pulmonary disease (COPD).[1] Recognition of co-morbid heart failure in COPD patients is hampered by similarities in signs and symptoms, and overlap in risk factors such as tobacco smoking. Echocardiography is essential to definitively establish the diagnosis of heart failure. Accessibility to this diagnostic facility, however, is limited for primary care patients in many countries.[2] In addition, high-quality echocardiographic measurements are more difficult to obtain in COPD patients.[3] Recently, natriuretic peptides showed to be useful in the diagnostic assessment of patients suspected of heart failure,[4;5] but also in acute dyspoeic patients.[6] Also, in patients with acute dyspnoea and a history of COPD or asthma, natriuretic peptides appeared to be useful to recognise or rule out heart failure.[7] However, diagnostic studies to determine the presence of heart failure in patients with stable COPD are lacking.

Most diagnostic studies, including those on the diagnosis of heart failure, are limited to single test evaluations.[8;9] In clinical practice, however, hardly any diagnosis is set by a single test. For example, patient history and physical examination are always considered before additional tests are ordered. Thus, studies are needed that use multivariable approaches to quantify which diagnostic tests truly contribute to the recognition of heart failure.[9;10]

We quantified which items from history and physical examination are potential diagnostic indicators of the presence of heart failure in primary care patients with stable COPD. We also assessed whether easily available additional tests such as electrocardiography, chest radiography, and amino-terminal pro B-type natriuretic peptide, provide added diagnostic value beyond history taking and physical examination.

Methods

Study population

In total, 51 primary care practices agreed to participate in this cross-sectional study that was executed between April 2001 and June 2003. All practices routinely registered their patient contacts electronically.[11] All subjects aged 65 years or over with a registered International Classification of Primary Care (ICPC) code R 91 (chronic bronchitis) or R 95 (COPD or emphysema)[12] were eligible. These ICPC

codes are based on symptoms (dyspnoea, cough, or sputum production) and in case of R95 also on pulmonary changes on the chest radiograph.[12] Patients with a cardiologist-confirmed diagnosis of heart failure were excluded, and patients with severe psychiatric disorders, immobility, or terminal illness were judged unsuitable to approach. In total 1,186 eligible patients were invited by a letter signed by their own general practitioner, and 405 (34%) patients agreed to participate, and signed informed consent. Patient characteristics of all 1,186 eligible patients were extracted anonymised from the computerised patient files of the general practitioners with special attention for cardiovascular and pulmonary co-morbidity. The study was approved by the Medical Ethical Committee of the University Medical Center Utrecht, the Netherlands.

Diagnostic work-up

All 405 participants were investigated during a single 3 hours session at our out-patient clinic. They underwent a systematic diagnostic work-up including patient history, physical examination, electrocardiography (ECG), chest radiography, blood tests, pulmonary function tests, and echocardiography.

Data on co-morbidities were acquired by scrutinising the computerised data files of the general practitioners, including available letters from hospital specialists. Patient history and physical examination were carried out by the same physician (F.H.R.). A standardised questionnaire was used to obtain information on symptoms, smoking habits and medication use. A standardised physical examination included measurement of jugular venous pressure and palpation of the apex beat in supine and lateral position. Patients with unmeasurable jugular venous pressure (n=13) were counted as having a non elevated jugular venous pressure, and patients with impalpable apex beat (n=165) were counted as undisplaced apex beat. Blood samples were taken and analysed the same day. Eight patients had missing values for C-reactive protein (CRP). After centrifugation, specimens of serum and plasma were stored at –70° Celsius. Serum levels of amino-terminal pro B-type natriuretic peptide (NT-proBNP) were measured using a non-competitive immunoradiometric assay (Roche Inc., Mannheim, Germany), for all participants in a single batch. Two patients had missing values for NT-proBNP.

A standard 12-lead electrocardiogram was recorded and classified according to the Minnesota coding criteria,[13] by a single cardiologist (M-J.M.C.). Chest radiographs were subsequently taken using standard procedures and classified by one of three radiologists. Cardiothoracic ratio was not measurable in four patients due to lobectomy. Lung volumes, bronchodilator responses, airway resistance, alveolar volume and diffusion capacity of the lung for carbon monoxide were measured using a fixed-volume body plethysmograph and Masterscreen (Masterlab Jaeger,

Würzburg, Germany). Classification was performed by a single pulmonologist (J-W.J.L.).
Finally, echocardiographic studies were performed by two well trained cardiac sonographers using a Philips Sonos 5500 imaging system (Andover, Mass., USA) and interpreted by a single experienced cardiologist (M-J.M.C.). Parameters from Doppler analysis, M-mode echocardiography, and two-dimensional transthoracic echocardiography were used. The left-ventricular ejection fraction was calculated using Simpson's rule (disc summation method),[14] the single plane area-length method,[15] or semiquantatively by the two dimensional visual estimate method ('eyeballing').[16] In 42 (10.4%) image quality was poor, and in one patient the image quality did not allow any estimation of left-ventricular ejection fraction. Left atrial volume was assessed by the volume prolated ellipsoid method.[17] With pulsed-wave Doppler the E- and A-wave velocity, and E-deceleration time were measured and E/A velocity ratio was calculated. The flow velocities of the left or right upper pulmonary vein were recorded, and the ratio of systolic to diastolic forward flow was calculated. Diastolic function was categorised as normal, impaired relaxation, pseudonormal filling, or restrictive filling by a combination of transmitral and pulmonary flow patterns and left atrial volumes.[18-20] A random sample of 41 (10%) of the digitally stored echocardiograms was re-presented to the same cardiologist (M-J.M.C.) after completion of the patient inclusion, blinded to the original results. Only in two cases disagreement existed (Cohen's kappa (κ =0.90)) when the cardiologist had to redecide about presence or absence of systolic or 'isolated' diastolic dysfunction. In both cases the disagreement was between 'normal' and impaired relaxation (grade I diastolic dysfunction).
Chest radiographs, pulmonary function tests, electrocardiograms, and echocardiograms were interpreted by physicians blinded to all other data.

Presence or absence of heart failure
Ideally, in diagnostic accuracy studies the final diagnosis is made by a (single) reference test, without knowledge of the results of the test(s) under study.[9;21-23] Although echocardiography is a cornerstone in the diagnosis of heart failure, it is still considered imperfect as reference test (i.e. 'gold' standard).[2] The best alternative for diagnostic accuracy studies of diseases lacking an established reference, is the use of consensus diagnosis as reference.[9;22;23] In our study, the presence or absence of heart failure was determined by an expert panel, in agreement with previous studies. [4;6;24] The panel consisted of two cardiologists, a pulmonologist and a general practitioner. The panel decided on the basis of consensus, and in case no consensus was reached the majority decided whether the case definition was met. In case of equality of votes (which was the case in five

patients), the majority decision of the two cardiologists and general practitioner was applied. The panel used all available patient information from the diagnostic assessment including echocardiographic results, except NT-proBNP results.
Patients with heart failure according to the panel were further classified as systolic, 'isolated' diastolic, or 'isolated' right sided heart failure. For a full case definition of systolic heart failure an echocardiographic left-ventricular ejection fraction ≤ 45% was obligatory in combination with presence of symptoms indicative of heart failure (i.e. orthopnoea, paroxysmal nocturnal dyspnoea, fatigue, peripheral oedema, nycturia ≥ 2 times a night, or any combination of these symptoms). To fulfill the definition of 'isolated' diastolic ventricular dysfunction, echocardiographic diastolic dysfunction and left-ventricular ejection fraction >45% was obligatory. Echocardiographic diastolic abnormalities had to be present in combination with (i) indicative symptoms and signs (i.e. peripheral or pulmonary fluid retention and/or elevated jugular venous pressure) of heart failure, [25] or (ii) indicative symptoms and echocardiographic left ventricular hypertrophy, atrial fibrillation, or anginal complaints,[26] to satisfy the full case definition of 'isolated' diastolic heart failure.
'Isolated' right-sided heart failure was defined as an increased right atrial pressure, estimated from the respiratory variation in diameter of the caval vein, and/or right ventricular dysfunction assessed semiquantatively by the two-dimensional visual estimate method, and a left-ventricular ejection fraction >45%.

Data analysis
The relation of each studied diagnostic test with the presence or absence of heart failure was quantified using univariate logistic regression analysis. Those with a p-value <0.15 were subsequently included in multivariate logistic regression analyses to determine their independent contribution to the diagnosis of heart failure. In the analyses the chronology in which investigations are performed in practice was followed,[8;23] and first all findings from patient history and physical examination were included. This 'clinical model' was then reduced by excluding variables (one by one) from the model with p-values > 0.15 based on the likelihood ratio test, yielding a reduced clinical model. Then the laboratory tests (i.e., NT-proBNP and C-reactive protein), ECG, and chest radiograph were added (first separately, and then in different combinations) to quantify their added diagnostic value, again using the likelihood ratio test at a p-value of 0.15. Echocardiographic variables were not evaluated on their independent diagnostic value because the study was conducted with a view to primary care and pulmonary care where echocardiography is not routinely available. Moreover, echocardiography would likely receive an overriding weight in the consensus judgement (i.e. diagnostic

outcome assessment), and thus could overrule the contribution of all other tests in the multivariable analysis.[23]
The ability of models to discriminate between patients with and without heart failure was estimated using the area under the receiver operating characteristic curve (ROC-area).[27] The ROC-area can range from 0.5 (no discrimination, like flipping a coin) to 1.0 (perfect discrimination).
There were in total 14 missing values in nine subjects (two NT-proBNP, eight C-reactive protein, four cardiothoracic ratio). Missing data usually do not occur at random. It has been shown that deleting subjects with a missing value (so called 'complete case analysis') commonly leads to biased results and surely to a loss of power.[27-29] To decrease bias and increase statistical efficiency, it is advised to impute these missings.[27-29] Accordingly, we imputed our missing data using the regression method as available in SPSS software (version 11.0). The imputation was based on the correlation between each variable with missing values and all other variables as estimated from the 391 (97%) complete subjects.

Results

Eligible patients participating in the study (n=405, 34%) were 1.9 years younger than non-responders (n=781, 66%) and overall somewhat less diseased (Table 1). The median age of the study population was 73 (SD 5.3) years, and 55% were male. In 83 (20.5%) patients the consensus panel set a new diagnosis of heart failure. Half of these patients had systolic heart failure (42), half (41 patients) had 'isolated' diastolic heart failure, and none had 'isolated' right sided heart failure. Of the 41 patients classified as 'isolated' diastolic heart failure, all had the above mentioned indicative symptoms; in 22 patients together with indicative signs of heart failure, in four patients with atrial fibrillation, in eight patients with echocardiographic left ventricular hypertrophy (LVH), in two patients with anginal complaints, and in five patients together with a combination of atrial fibrillation, LVH, or anginal complaints.

The reproducibility of the panel diagnosis of heart failure was assessed by re-presentation to the panel (blinded to the original decision) of a random sample of 41 (10%) patients. Disagreement occurred in one case only (Cohen's kappa κ=0.92). This patient had moderate-severe dyspnoea, indicative symptoms and signs of heart failure, atrial fibrillation, and a slightly impaired echocardiographic left ventricular ejection fraction of 45-50% and a normal diastolic function. This case was originally classified as non-heart failure and after re-presentation as a heart failure case.

Table 1 Characteristics of eligible patients with a general practitioner's diagnosis of COPD, participating and not participating in the study. Values are numbers (%) unless stated otherwise

Characteristics	Study population	Non-participants	p-value
Age (mean) in years (SD)	73.0 (5.3)	74.9 (7.8)	<0.001
Male	223 (55.1)	420 (53.8)	0.67
Ischaemic heart disease*	82 (20.2)	190 (24.3)	0.11
Hypertension	145 (35.8)	291 (37.3)	0.62
Diabetes mellitus	42 (10.4)	100 (12.8)	0.22
Stroke/TIA	21 (5.2)	61 (7.8)	0.09
Atrial fibrillation	34 (8.4)	71 (9.1)	0.69
Valvular disease	14 (3.5)	37 (4.7)	0.30
Other chronic pulmonary diseases^	94 (23.2)	190 (24.3)	0.67
Co-treated by cardiologist	63 (15.6)	158 (20.2)	0.05
Co-treated by pulmonologist	135 (33.3)	241 (30.9)	0.39

SD, standard deviation; TIA, transient ischaemic attack.

* Presence of ischaemic heart disease including myocardial infarction, angina pectoris, coronary artery bypass grafting (CABG), or percutaneous coronary intervention (PCI).

^ Presence of pulmonary diseases other than COPD, including (persisting) asthma, pulmonary cancer, bronchiectasis, tuberculosis, alveolitis, sarcoidosis, idiopathic pulmonary fibrosis, pulmonary hypertension, and pneumothorax. None of the eligible patients had an α-1 antitrypsin deficiency.

Of all participants, only three patients had a S3-gallop, and 11 patients had signs of pulmonary fluid on chest X-ray. One participant had a serum creatinine concentration greater than 200 μmol/l (i.e. 243 μmol/l), and no participant had a blood urea greater than 20 mmol/l.

Univariate associations are presented in Table 2. Electrocardiographic abnormalities were more common in those with heart failure, mostly ST and/or T-wave abnormalities (22.7%), left bundle branch block (complete or incomplete) (16.1%), and Q-waves suggesting a prior myocardial infarction (7.7%). Results from pulmonary function tests were largely similar in patients with and without heart failure, and 60.2% of the participants had a ratio of forced expiratory volume in one second and forced vital capacity (FEV1/FVC) <70% (Table 2).

Of the variables from history and physical examination, a history of ischaemic heart disease, laterally displaced apex beat, body mass index (BMI), and heart rate were independent predictors of presence of heart failure (Table 3). The ROC-area of this reduced clinical model was 0.70 (95% CI 0.64-0.76). Cardiovascular medication (e.g. diuretics or angiotensin-converting enzyme (ACE) inhibitors) was not an independent predictor of the presence or absence of heart failure. NT-proBNP (odds ratio (OR)=1.06 per 5 pmol/l) was the best diagnostic test when applied without information from the clinical assessment (ROC-area of NT-proBNP only was 0.72 (95% CI 0.66-0.79)). The performance of a model including the clinical items and NT-proBNP was significantly better (ROC-area 0.77 (95% CI 0.71-0.83) (Table 4). Added to the 'clinical model' electrocardiography increased the ROC-area to 0.75, C-reactive protein to 0.73, and cardiothoracic ratio (CTR) on chest radiograph to 0.73 (Table 4). Given the 'clinical+NT-proBNP' model, electrocardiography (OR= 2.76; 95% CI 1.54-4.94, p=0.001) marginally increased the ROC-area further to 0.78. C-reactive protein (OR= 1.03 per mg/l ; 95% CI 1.00-1.07, p=0.09) and cardiothoracic ratio (OR= 1.05 ; 95% CI 1.00-1.07, p=0.11), showed no material increase in the ROC-area when added to the 'clinical+NT-proBNP+ECG' model.

Discussion

A history of ischaemic heart disease, laterally displaced apex beat, body mass index, and heart rate are independent diagnostic indicators of the presence or absence of concomitant heart failure in elderly primary care patients with stable COPD. Elevated NT-proBNP and abnormalities on ECG may further improve the diagnostic accuracy. The added value of C-reactive protein or cardiothoracic ratio on chest radiograph is limited. To our knowledge, this is the first study to determine the collective value of symptoms, signs, and additional testing to establish a diagnosis of heart failure in COPD patients in primary care.

To appreciate the results, some methodological aspects need to be discussed. First, the diagnosis of heart failure misses a true 'gold' standard. We used the consensus diagnosis method to assess the final diagnosis of heart failure in line with a range of previous studies.[4;6;9;23] A potential disadvantage of this reference method is the possibility of incorporation bias,[23;30-32] because the reference standard (panel diagnosis) is not independent from all the tests studied. The effect of the incorporation bias can, however, be judged afterwards as it commonly leads to overestimation of the diagnostic value of the tests under study. Withholding results of crucial tests from the panel, however, leads to prevalent misclassification in the

Table 2 Characteristics of the study population according to presence or absence of heart failure. Values are numbers (percentages) unless stated otherwise

Characteristics	HF present (N=83)	HF absent (N=322)	Odds ratio (95% CI)	p-value
Patient history				
Age (years) §§	74 (69-78)	72 (69-76)	1.04 (1.00-1.09) §	0.07
Pack years of smoking* §§	25.0 (1.1-41.7)	15.0 (0.0-38.1)	1.01 (1.00-1.02) §	0.04
Ischaemic heart disease **	28 (33.7)	55 (17.1)	2.47 (1.44-4.24)	0.001
Cardiovascular comorbidity***	51 (61.4)	144 (44.7)	1.97 (1.20-3.23)	0.007
Orthopnoea or paroxysmal noct. dyspnoea	25 (30.1)	83 (25.8)	1.24 (0.73-2.11)	0.43
Nycturia (≥ 2x)	45 (54.2)	130 (40.4)	1.75 (1.08-2.84)	0.02
Medication				
Diuretics	29 (34.9)	71 (22.0)	1.90 (1.13-3.20)	0.02
ACE-inhibitors	22 (26.5)	50 (15.5)	1.96 (1.11-3.48)	0.02
Physical examination				
Body mass index (kg/m²) §§§	28.1 (3.9)	26.3 (4.2)	1.10 (1.04-1.17) §	0.001
Heart rate (beat/minute) §§§	80.0 (15.9)	75.6 (13.5)	1.02 (1.01-1.04) §	0.01
Pulmonary sounds ¶	31 (37.3)	97 (30.1)	1.38 (0.84-2.29)	0.21
Elevated jugular venous pressure	26 (31.3)	75 (23.3)	1.56 (0.91-2.66)	0.10
Laterally displaced apex beat	22 (26.5)	48 (14.9)	2.06 (1.16-3.66)	0.01
Peripheral oedema	22 (26.5)	54 (16.8)	1.79 (1.01-3.16)	0.04

Continued on next page

Table 2 (Continued from previous page)

Characteristics	HF present (N=83)	HF absent (N=322)	Odds ratio (95% CI)	p-value
Additional tests				
NT-pro-BNP (pmol/l) §§	28.9 (15.1-95)	13.2 (8.3-23.3)	1.01 (1.01-1.02) §	<0.001
C-reactive protein (mg/ml) §§	5.0 (3.0-10.0)	3.0 (3.0-6.0)	1.05 (1.02-1.09) §	0.001
Cardiothoracic ratio chest X-ray §§§	0.50 (0.05)	0.47 (0.05)	1.10 (1.05-1.15) §	<0.001
Abnormal ECG #	52 (62.7%)	91 (28.3%)	4.26 (2.57-7.07)	<0.001
FEV1 as % of expected ## §§§	81.7 (24.2)	83.7 (25.9)	0.74 (0.28-1.91)	0.53
FEV1/FVC ## §§§	65.3 (13.1)	64.1 (14.4)	1.01 (0.99-1.02)	0.50
FEV1/FVC < 70% ##	50 (60.2)	194 (60.2)	1.00 (0.61-1.64)	1.00

§ = odds ratio per unit change, §§ = median (IQR), §§§ = mean (SD).

* Pack years of cigarette smoking in current and past smokers.

** Presence of ischaemic heart disease (IHD) including myocardial infarction, angina pectoris, percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG).

*** Presence of diabetes mellitus, hypertension, stroke or peripheral arterial disease.

¶ Crackles, including crepitations, and wheezing.

Abnormalities on electrocardiogram fitting in the diagnosis of (prior) myocardial infarction (abnormal Q-waves), complete or incomplete left bundle branch block, left ventricular hypertrophy, atrial fibrillation, ST and/or T-wave abnormalities, and sinus tachycardia.

Post-dilatory spirometric measurements were used. In 5 cases with missing values due to interruption of pulmonary measurements, pre-dilatory values were used. For expected values of the forced expiratory volume in 1 second (FEV1), the recommendations of the European Respiratory Society (ERS) were used. [54]

Table 3 Variables from history and physical examination with an independent contribution to the diagnosis of heart failure in patients with a general practitioner's diagnosis of COPD

Variables 'Clinical model'	Odds ratio (95% CI)	p-value
History of ischaemic heart disease	2.16 (1.28-3.64)	0.004
Body mass index per kg/m²	1.11 (1.04-1.18)	0.001
Laterally displaced apex beat	2.34 (1.28-4.29)	0.006
Heart rate per 10 beats/minute	1.26 (1.06-1.49)	0.009
ROC-area *	0.70 (0.64-0.76)	

* ROC-area= area under the receiver operating characteristic curve

outcome (final diagnosis) with invalid estimates of the diagnostic value of the tests under study. Therefore, we specifically chose to include most tests under study in the consensus judgement. Importantly, however, echocardiography is the cornerstone of the diagnostic assessment of heart failure, and this test was only used for assessing the outcome, and not assessed as a diagnostic test, to prevent overestimation of its diagnostic value. In fact, any incorporation bias is likely to be small, since most diagnostic determinants we studied were not crucial in the panel decision process. Furthermore, incorporation bias does not apply to NT-proBNP, as this test was not included in the consensus diagnosis. Finally, in earlier studies as in our study it is shown that a panel diagnosis for establishing heart failure is highly reproducible,[33;34] and it is, as stated by the Standards for Reporting of Diagnostic Accuracy (STARD) initiative, the best proxy reference in case of lack of an irreproachable 'gold' standard.[21]

Another issue regards the definition of diastolic heart failure. The echocardiographic variables needed to establish the diagnosis of diastolic heart failure remain subject to debate. Therefore, we added clinical variables to increase the diagnostic accuracy of echocardiographic criteria, as suggested by others.[26;35]

The definitions of test results in our study were chosen to minimise indeterminate results of tests under study.[30] Only presence of increased jugular venous pressure or a laterally displaced apex beat were not assessable in a material number of patients. However, by counting indeterminate as 'not present' rather than 'present', overestimation of the diagnostic value was avoided.

Table 4 Contribution of diagnostic tests to the diagnosis of heart failure in patients with a general practitioner's diagnosis of COPD

Variables	Odds ratio (95% CI)*	p-value*	AUC (95% CI)
Single diagnostic test			
NT-proBNP (per 5 pmol/l)	1.06 (1.03-1.08)	<0.001	0.72 (0.66-0.79)
Clinical model plus single additional test			
'clinical' + NT-proBNP (per 5 pmol/l)	1.05 (1.03-1.07)	<0.001	0.77 (0.71-0.83)
'clinical' + ECG**	3.69 (2.17-6.29)	<0.001	0.75 (0.69-0.81)
'clinical' + CRP (per mg/ml)	1.05 (1.02-1.08)	0.003	0.73 (0.67-0.79)
'clinical' + CT-ratio	1.08 (1.02-1.13)	0.005	0.73 (0.67-0.79)
Multiple additional test			
'clinical' + NT-proBNP' +ECG	2.76 (1.54-4.94)	0.001	0.78 (0.72-0.84)

'Clinical' = clinical model with a history of ischaemic heart disease, body mass index, laterally displaced apex beat, and heart rate.

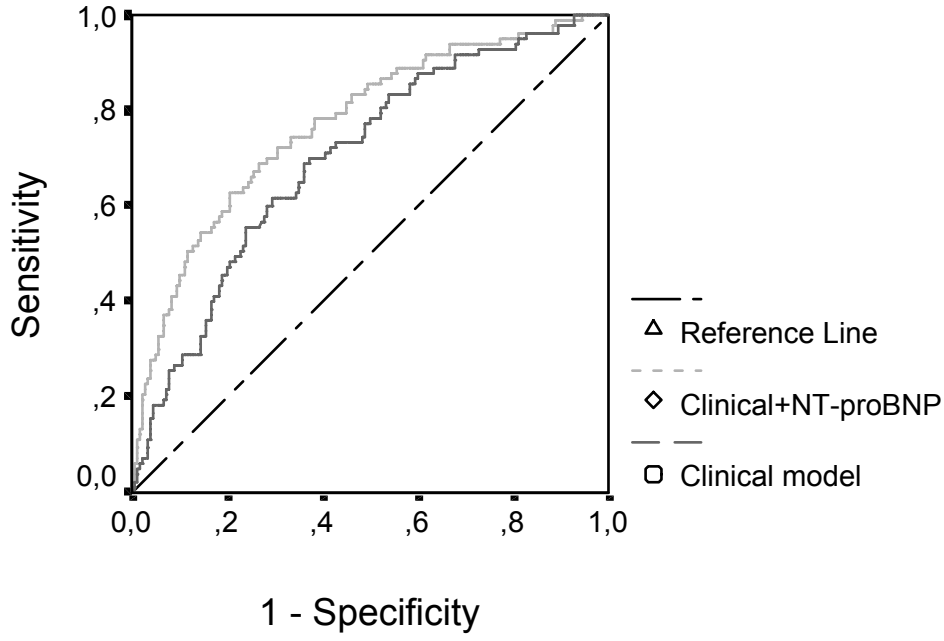
* Odds ratios and p-values are given for the added test (Italic), and not for the clinical variables (see Table 2).

** ECG = Abnormalities on electrocardiogram fitting in the diagnosis of (prior) myocardial infarction (abnormal Q-waves), complete or incomplete left bundle branch block, left ventricular hypertrophy, atrial fibrillation, ST and/or T-wave abnormalities, and sinus tachycardia.

The potential added diagnostic contribution of tests was estimated by the likelihood ratio test rather than the increase in ROC-area. This was done because the ROC-area is a rank-order statistic and less sensitive for detecting small changes in diagnostic value between (reduced and extended) models.[27;36] Accordingly, electrocardiographic results (and to a lesser extent chest radiography and C-reactive protein) were considered to have added value beyond history, physical examination and NT-proBNP, even though the ROC-area increased only marginally.

Most independent tests for the presence or absence of concomitant heart failure in patients with COPD in our study, have also been reported in studies among patients primarily suspected of heart failure.[4;5;10;37-42] Particularly, a history of ischaemic heart disease, or rather prior myocardial infarction, is an established diagnostic

Figure ROC-curves for the ability to determine the presence or absence of heart failure in elderly patients with a GP's diagnosis of COPD



indicator of heart failure presence. Similarly this applies to a laterally displaced apex beat, although the apex beat is impalpable in a substantial number of patients.[43] The diagnostic value of heart rate is controversial.[10] Perhaps the use of medication such as beta-sympathicometic inhalator drugs often used by COPD patients, may partly explain this finding. Our study is the first study to show that a high body mass index is independently related to the presence of heart failure in COPD patients. Overweight, i.e. BMI $\geq$ 30, was already known to be a risk factor for the development of heart failure.[44] C-reactive protein has not been examined for its diagnostic value before, although it is known to be related to atherosclerosis and an adverse prognosis in ischaemic heart disease.[45]

Importantly, the natriuretic peptide NT-proBNP was a powerful diagnostic test for heart failure in COPD patients. The overall diagnostic accuracy of the natriuretic peptide measurements in detecting heart failure in our study was lower than in previous studies including patients suspected of heart failure [4] and patients with acute dyspnoea visiting an emergency department, [6;46] but higher than levels

reported in community screening studies with systolic and/or diastolic dysfunction as the outcome.[47;48] The most obvious reason for these differences in diagnostic accuracy are the difference in the populations studied.[47] We studied patients with a GP diagnosis of COPD, unknown with a cardiologist-confirmed diagnosis of heart failure. New detected heart failure cases were therefore in an early stage of their disease. Moreover, our participants were in a stable phase. These aspects make it plausible that the concentrations of NT-proBNP are lower than, for instance, in patients suffering from acute dyspnoea (acute increase in intracardiac pressure) or suspected of heart failure by the GP, [48;49] because NT-proBNP production in the ventricles of the heart increase in response to increased intracardiac volume or pressure. Moreover, COPD patients without heart failure in our study had a median NT-proBNP concentration of 13.2 pmol/l (IQR 8.3-23.3), which is at the upper level of the suggested 'normal' range of 8.2-13.3 pmol/l.[50] Also other studies provided an indication that COPD patients without heart failure can have increased natriuretic peptide levels, possibly by some degree of right ventricular wall stress.[51;52]

The response rate (34%) in our study may seem modest, but was only slightly lower than in population-based studies assessing heart failure in the elderly.[24;53] Because we invited diseased elderly patients in a stable phase of their disease (i.e. patients with a diagnosis of COPD) lower response rates could be expected because we invited many patients with rather high levels of disability. Although we, inevitably, studied a selection of available COPD patients, selection *bias* seems limited because relevant and known cardiovascular risk factors for heart failure and co-morbidities were only slightly lower in participants than in non-responders. Importantly, the clinical applicability of our results is high, because we included those patients who were able to undergo the relevant diagnostic investigations, and therefore, we studied those COPD patients in whom treatment is likely to be initiated in everyday practice.

In conclusion, a number of easily obtained clinical parameters and a few additional diagnostic investigations, notably natriuretic peptide and/or electrocardiography may improve the detection of concomitant heart failure in primary care patients with COPD. The use of these parameters increases the confidence about presence or absence of heart failure, and will help to decide about the need for additional echocardiography or treatment in COPD patients.

Acknowledgement

We thank the participating patients, general practitioners, and their assistants, including the general practices connected to the General Practice Network Utrecht (HNU), the cardiac sonographers Elly Lutgert-Hagman and Ineke Kasteleijn, the pulmonology technicians, especially Paul Munnik, and Pieter Zanen, lung physiologist. Frances Verheij assisted us with the data management. The study was funded by a research grant (number 904-61-144) of the Netherlands Organisation for Scientific Research (NWO). We thank Roche Inc. (Mannheim, Germany) for supplying the assays for analysis of NT-proBNP.

References

1. Remes J, Miettinen H, Reunanen A, Pyörälä K. Validity of clinical diagnosis of heart failure in primary health care. *Eur Heart J* 1991;12:315-21.
2. Remme WJ, Swedberg K. Guidelines for the diagnosis and treatment of chronic heart failure. *Eur Heart J* 2001;22:1527-60.
3. Boussuges A, Pinet C, Molenat F, Burnet H, Ambrosi P, Badier M *et al*. Left atrial and ventricular filling in chronic obstructive pulmonary disease. An echocardiographic and Doppler study. *Am J Respir Crit Care Med* 2000;162:670-5.
4. Cowie MR, Struthers AD, Wood DA, Coats AJ, Thompson SG, Poole-Wilson PA *et al*. Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care. *Lancet* 1997;350:1349-53.
5. Landray MJ, Lehman R, Arnold I. Measuring brain natriuretic peptide in suspected left ventricular systolic dysfunction in general practice: cross-sectional study. *BMJ* 2000;320:985-6.
6. Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P *et al*. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med* 2002;347:161-7.
7. McCullough PA, Hollander JE, Nowak RM, Storrow AB, Duc P, Omland T *et al*. Uncovering heart failure in patients with a history of pulmonary disease: rationale for the early use of B-type natriuretic peptide in the emergency department. *Acad Emerg Med* 2003;10:198-204.
8. Moons KG, van Es GA, Michel BC, Buller HR, Habbema JD, Grobbee DE. Redundancy of single diagnostic test evaluation. *Epidemiology* 1999;10:276-81.
9. Moons KG, Biesheuvel CJ, Grobbee DE. Test research versus diagnostic research. *Clin Chem* 2004;50:473-6.

10. Nielsen OW, Hansen J, Hilden J, Larsen ST, Svanegaard J. Risk assessment of left ventricular systolic dysfunction in primary care: cross sectional study evaluating a range of diagnostic tests. *BMJ* 2000;320:220-4.

11. Van der Lei J, Duisterhout JS, Westerhof HP, Van der Does E, Cromme PV, Boon WM *et al*. The introduction of computer-based patient records in The Netherlands. *Ann Intern Med* 1993;119:1036-41.

12. Classification Committee of WONCA. International classification of primary care. Oxford University Press 1983.

13. Rose GA, Blackburn H. Cardiovascular Survey Methods. World Health Organisation. Geneva 1982.

14. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H *et al*. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr* 1989;2:358-67.

15. Folland ED, Parisi AF, Moynihan PF, Jones DR, Feldman CL, Tow DE. Assessment of left ventricular ejection fraction and volumes by real-time, two-dimensional echocardiography. A comparison of cineangiographic and radionuclide techniques. *Circulation* 1979;60:760-6.

16. Quinones MA, Waggoner AD, Reduto LA, Nelson JG, Young JB, Winters WL *et al*. A new, simplified and accurate method for determining ejection fraction with two-dimensional echocardiography. *Circulation* 1981;64:744-53.

17. Sanfilippo AJ, Abascal VM, Sheehan M, Oertel LB, Harrigan P, Hughes RA *et al*. Atrial enlargement as a consequence of atrial fibrillation. A prospective echocardiographic study. *Circulation* 1990;82:792-7.

18. Garcia MJ, Thomas JD, Klein AL. New Doppler echocardiographic applications for the study of diastolic function. *J Am Coll Cardiol* 1998;32:865-75.

19. Nishimura RA,Tajik AJ. Evaluation of diastolic filling of left ventricle in health and disease: Doppler echocardiography is the clinician's Rosetta Stone. *J Am Coll Cardiol* 1997;30:8-18.

20. Oh JK, Appleton CP, Hatle LK, Nishimura RA, Seward JB, Tajik AJ. The noninvasive assessment of left ventricular diastolic function with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr* 1997;10:246-70.

21. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM *et al*. The STARD statement for reporting studies of diagnostic accuracy: explanation and elaboration. *Clin Chem* 2003;49:7-18.

22. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM *et al*. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Standards for Reporting of Diagnostic Accuracy. *Clin Chem* 2003;49:1-6.

23. Moons KG, Grobbee DE. When should we remain blind and when should our eyes remain open in diagnostic studies? *J Clin Epidemiol* 2002;55:633-6.

24. Mosterd A, Hoes AW, de Bruyne MC, Deckers JW, Linker DT, Hofman A *et al*. Prevalence of heart failure and left ventricular dysfunction in the general population; The Rotterdam Study. *Eur Heart J* 1999;20:447-55.

25. Zile MR, Gaasch WH, Carroll JD, Feldman MD, Aurigemma GP, Schaer GL *et al*. Heart failure with a normal ejection fraction: is measurement of diastolic function necessary to make the diagnosis of diastolic heart failure? *Circulation* 2001;104:779-82.

26. Vasan RS, Benjamin EJ, Levy D. Congestive heart failure with normal left ventricular systolic function. Clinical approaches to the diagnosis and treatment of diastolic heart failure. *Arch Intern Med* 1996;156:146-57.

27. Harrell FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996;15:361-87.

28. Greenland S,.Finkle WD. A critical look at methods for handling missing covariates in epidemiologic regression analyses. *Am J Epidemiol* 1995;142:1255-64.

29. Little RJA. Regression with missing X's: a review. *J Am Stat Assoc* 1992;87:1227-37.

30. Whiting P, Rutjes AW, Dinnes J, Reitsma J, Bossuyt PM, Kleijnen J. Development and validation of methods for assessing the quality of diagnostic accuracy studies. *Health Technol Assess* 2004;8:iii1-iii4.

31. Ransohoff DF, Feinstein AR. Problems of spectrum and bias in evaluating the efficacy of diagnostic tests. *N Engl J Med* 1978;299:926-30.

32. Clinical epidemiology; a basic science for clinical medicine. Boston: Little, Brown and Co., 1985.

33. Cowie MR, Wood DA, Coats AJ, Thompson SG, Poole-Wilson PA, Suresh V *et al*. Incidence and aetiology of heart failure; a population-based study. *Eur Heart J* 1999;20:421-8.

34. Wright SP, Doughty RN, Pearl A, Gamble GD, Whalley GA, Walsh HJ *et al*. Plasma amino-terminal pro-brain natriuretic peptide and accuracy of heart-failure diagnosis in primary care: a randomized, controlled trial. *J Am Coll Cardiol* 2003;42:1793-800.

35. Zile MR. Heart failure with preserved ejection fraction: is this diastolic heart failure? *J Am Coll Cardiol* 2003;41:1519-22.

36. Hosmer DW, Lemeshow S. Applied logistic regression. New York: 1989.

37. Davie AP, Francis CM, Caruana L, Sutherland GR, McMurray JJ. Assessing diagnosis in heart failure: which features are any use? *QJM* 1997;90:335-9.

38. Gillespie ND, McNeill G, Pringle T, Ogston S, Struthers AD, Pringle SD. Cross sectional study of contribution of clinical assessment and simple cardiac investigations to diagnosis of left ventricular systolic dysfunction in patients admitted with acute dyspnoea. *BMJ* 1997;314:936-40.

39. Smith H, Pickering RM, Struthers A, Simpson I, Mant D. Biochemical diagnosis of ventricular dysfunction in elderly patients in general practice: observational study. *BMJ* 2000;320:906-8.

40. Morgan S, Smith H, Simpson I, Liddiard GS, Raphael H, Pickering RM *et al*. Prevalence and clinical characteristics of left ventricular dysfunction among elderly patients in general practice setting: cross sectional survey. *BMJ* 1999;318:368-72.

41. Rihal CS, Davis KB, Kennedy JW, Gersh BJ. The utility of clinical, electrocardiographic, and roentgenographic variables in the prediction of left ventricular function. *Am J Cardiol* 1995;75:220-3.

42. Gottdiener JS, Arnold AM, Aurigemma GP, Polak JF, Tracy RP, Kitzman DW *et al*. Predictors of congestive heart failure in the elderly: the Cardiovascular Health Study. *J Am Coll Cardiol* 2000;35:1628-37.

43. Heckerling PS, Wiener SL, Wolfkiel CJ, Kushner MS, Dodin EM, Jelnin V *et al*. Accuracy and reproducibility of precordial percussion and palpation for detecting increased left ventricular end-diastolic volume and mass. A comparison of physical findings and ultrafast computed tomography of the heart. *JAMA* 1993;270:1943-8.

44. Kenchaiah S, Evans JC, Levy D, Wilson PW, Benjamin EJ, Larson MG *et al*. Obesity and the risk of heart failure. *N Engl J Med* 2002;347:305-13.

45. Lloyd-Jones DM, Levy D. C-reactive protein in the prediction of cardiovascular events. *N Engl J Med* 2003;348:1059-61.

46. Lainchbury JG, Campbell E, Frampton CM, Yandle TG, Nicholls MG, Richards AM. Brain natriuretic peptide and n-terminal brain natriuretic peptide in the diagnosis of heart failure in patients with acute shortness of breath. *J Am Coll Cardiol* 2003;42:728-35.

47. Vasan RS, Benjamin EJ, Larson MG, Leip EP, Wang TJ, Wilson PW *et al*. Plasma natriuretic peptides for community screening for left ventricular hypertrophy and systolic dysfunction: the Framingham heart study. *JAMA* 2002;288:1252-9.

48. Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR, Burnett JC, Jr. Plasma brain natriuretic peptide to detect preclinical ventricular systolic or diastolic dysfunction: a community-based study. *Circulation* 2004;109:3176-81.

49. Troughton RW, Frampton CM, Yandle TG, Espiner EA, Nicholls MG, Richards AM. Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations. *Lancet* 2000;355:1126-30.

50. Cowie MR, Jourdain P, Maisel A, Dahlstrom U, Follath F, Isnard R *et al*. Clinical applications of B-type natriuretic peptide (BNP) testing. *Eur Heart J* 2003;24:1710-8.

51. Lang CC, Coutie WJ, Struthers AD, Dhillon DP, Winter JH, Lipworth BJ. Elevated levels of brain natriuretic peptide in acute hypoxaemic chronic obstructive pulmonary disease. *Clin Sci (Lond)* 1992;83:529-33.

52. Troughton RW, Prior DL, Pereira JJ, Martin M, Fogarty A, Morehead A *et al*. Plasma B-type natriuretic peptide levels in systolic heart failure: importance of left ventricular diastolic function and right ventricular systolic function. *J Am Coll Cardiol* 2004;43:416-22.

53. Redfield MM, Jacobsen SJ, Burnett JC, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *JAMA* 2003;289:194-202.

54. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J* 1993;16 *Suppl*:5-40.

Chapter 8

Identifying heart failure in elderly patients with chronic obstructive pulmonary disease: comparison of natriuretic peptides

Frans H Rutten [1], Maarten-Jan M Cramer [2], Nicolaas PA Zuithoff [1], Jan-Willem J Lammers [3], Wim Verweij [4], Diederick E Grobbee [1], Arno W Hoes [1]

[1] Julius Center for Health Sciences and Primary Care;
[2] Heart Lung Center Utrecht, Department of Cardiology;
[3] Heart Lung Center Utrecht, Department of Pulmonary Diseases;University Medical Center Utrecht.
[4] SALTRO, Department of Clinical Chemistry, PO Box 9300, 3506 GH Utrecht, the Netherlands.

Submitted

Abstract

Background Studies that compare the diagnostic utility of different natriuretic peptide measurements to identify heart failure in patients with chronic obstructive pulmonary disease (COPD) are lacking.
Aim To compare the diagnostic ability of different natriuretic peptide measurements in recognising or ruling out heart failure in elderly patients with stable COPD.
Methods A random sample of 200 patients of a cohort of 405 patients aged ≥ 65 years with a general practitioner's diagnosis of COPD, and unknown with heart failure, underwent an extensive diagnostic work-up. Presence or absence of heart failure was established by a panel that used all available diagnostic results, excluding natriuretic peptide measurements. The ability of two types of B-type natriuretic peptide (BNP Centaur and BNP AxSYM) and plasma and serum measurements of the amino-terminal fragment of pro-BNP (NT-proBNP) to detect heart failure was estimated using the area under the receiver operating characteristic curves (ROC-area). For 'commonly used' cut-off levels positive and negative predictive values and sensitivity and specificity were calculated. After logaritmic transformation, Pearson's correlation coefficients between types of NT-proBNP and BNP measurements were calculated.
Results The ROC-areas did not differ significantly and ranged from 0.68 (95%CI 0.60-0.73) for BNP AxSYM to 0.73 (95%CI 0.64-0.81) for serum NT-proBNP. For 'commonly used' cut-off levels of 14.75 pmol/l (125 pg/ml) for NT-proBNP and 28.8 pmol/l (100 pg/ml) for BNP, the positive predictive value and specificity of NT-proBNP was lower and the negative predictive value and sensitivity higher than for the BNPs. All types of natriuretic peptides identified significantly better systolic than 'isolated' diastolic heart failure. Pearson's correlation between log transformed serum and plasma NT-proBNP was 0.998 ($p<0.001$), and between BNP Centaur and BNP AxSYM 0.818 ($p<0.001$).
Conclusions NT-proBNP, BNP Centaur and BNP AxSYM are comparable in their ability to identify or rule out previously unknown heart failure in the difficult to assess population of stable COPD patients. The natriuretic peptides better predict systolic than 'isolated' diastolic heart failure in this population.

Introduction

Heart failure is a complex clinical syndrome and the clinical diagnosis is notoriously difficult in elderly patients with co-morbid chronic obstructive pulmonary disease (COPD) due to overlap in signs and symptoms.[1] In search for more easily available diagnostic tests than echocardiography, natriuretic peptides showed to be useful in the diagnostic assessment of patients suspected of heart failure,[2;3] and in patients with acute dyspnoea.[4] Studies assigned to assess the diagnostic utility of natriuretic peptides in detecting heart failure in COPD patients, however, are scarce.[5]

Most diagnostic studies with natriuretic peptides are performed with either B-type natriuretic peptide (BNP) or the amino-terminal fragment of pro-BNP (NT-proBNP). Few data, however, are available on comparative performance of these assays in clinical decision-making.[6;7]
Both natriuretic peptides are split products of pro-BNP, the precursor of biologically active BNP. NT-proBNP and BNP are both stable and can easily be detected and quantified by immunometric assays in serum or plasma. The molecular weight of these natriuretic peptides differ, and because NT-proBNP is not cleared actively, it has a longer half-life and plasma levels 2-10 times as high as BNP.[8] Whether these biological differences between NT-proBNP and BNP have diagnostic implications remains unknown. In addition, it is unclear whether plasma and serum measurements of NT-proBNP are interchangeable. The latter is important in view of the discrepancies in the recommendations of the producer (Roche Inc.) and clinical practice regarding NT-proBNP assessment. [9;10]

We compared the diagnostic ability of two assay systems of BNP (Centaur and AxSYM), and plasma versus serum NT-proBNP in identifying or ruling out heart failure in the diagnostically difficult population of stable elderly patients with a general practitioner's diagnosis of COPD.

Methods

Participants
In this cross-sectional study, 200 patients aged 65 years or over, with a general practitioner's diagnosis of COPD, and unknown with a cardiologist-confirmed diagnosis of heart failure, were enrolled in the study. This was a random sample of a total study population of 405 elderly patients with a GP's diagnosis of COPD, in a stable phase of their disease.[11] The study was conducted between April 2001 and

June 2003.
The Medical Ethical Committee of the University Medical Center Utrecht, the Netherlands, approved the study protocol and all participants gave written informed consent.

Diagnostic work-up
All participants underwent an extensive diagnostic work-up at our out-patient clinic including patient history, physical examination, electrocardiography, chest radiography, laboratory measurements, pulmonary function tests, and echocardiography. Standard 12-lead electrocardiograms (ECG) were recorded and classified according to the Minnesota coding criteria.[12] Chest radiographs were taken according to standard radiological criteria. Blood samples were taken and analysed the same day, and after centrifugation specimens of serum and plasma were stored at –70 degrees Celsius. Lung function measurements were performed with a fixed-volume body plethysmograph and Masterscreen (Masterlab Jaeger, Würzburg, Germany). Finally, echocardiographic studies were performed by two experienced cardiac sonographers using a Philips Sonos 5500 imaging system (Andover, MA., USA) and interpreted by a single cardiologist (M-J.M.C.) specialised in echocardiography. Parameters from Doppler analysis, M-mode echocardiography, and two-dimensional transthoracic echocardiography were used. Detailed information about the echocardiographic assessment can be found elsewhere.[11]

Natriuretic peptide measurements
At the end of the study, NT-proBNP and BNP levels were measured for all patients in a single batch, after frozen specimen were thawed. NT-proBNP was measured with an automated non-competitive immunoradiometric assay (Roche Inc., Mannheim, Germany) on an Elecsys 1010 analyser. In our study both EDTA-plasma and serum were analysed. During the process of analysis, we accidentally omitted laboratory measurements of one serum and eight plasma assays of NT-proBNP. Results are given in pmol/l. For convertion to pg/ml one has to multiply by 8.457. For plasma BNP measurements we used the automated Abbott AxSYM BNP immuno assay (Abbott Inc., Park Ill, USA) and Bayer Centaur BNP immuno assay (Bayer Inc., Leverkusen, Germany), using the Advia Centaur analyser. Results are given in pmol/l. For convertion to pg/ml, one has to multiply by 3.467.

Presence or absence of heart failure
In our study, the presence or absence of heart failure was determined by an expert panel, in agreement with previous studies.[2;4;13] The panel consisted of two

cardiologists, a pulmonologist and a general practitioner. They used all available diagnostic information, except natriuretic peptide measurements.
Patients with heart failure according to the panel were further classified as systolic or 'isolated' diastolic heart failure. A patient was classified as systolic heart failure when indicative symptoms of heart failure (i.e. orthopnoea, paroxysmal nocturnal dyspnoea, fatigue, peripheral oedema, nycturia ≥ 2 times a night, or any combination of these symptoms) were present in combination with an echocardiographic left-ventricular ejection fraction ≤ 45%. A patient was classified as 'isolated' diastolic heart failure when echocardiographic diastolic dysfunction and left-ventricular ejection fraction >45% were present in combination with (i) indicative symptoms and signs (i.e. peripheral or pulmonary fluid retention and/or elevated jugular venous pressure) of heart failure, [14] or (ii) indicative symptoms and echocardiographic left ventricular hypertrophy, atrial fibrillation, or anginal complaints.[15] Dyspnoea was present in nearly all (96.5%) participants and could therefore not be regarded as indicative symptom for heart failure in this patient population.

Data analysis
The association between NT-proBNP and BNP and the presence or absence of previously unrecognised heart failure was quantified applying univariate logistic regression analysis. The ability of NT-proBNP and BNP to discriminate between patients with and without heart failure was estimated using the area under the receiver operating characteristic curve (ROC-area). [16] The ROC-area can range from 0.5 (no discrimination, like flipping a coin) to 1.0 (perfect discrimination). 'Commonly used' cut-off levels for NT-proBNP and BNP [17] were used to calculate positive and negative predictive values, and sensitivity and specificity, with 95% confidence intervals.
Because natriuretic peptide measurements had a skewed distribution, natural logarithmic transformation was applied before assessing Pearson's correlation coefficient. All data showed a Gaussian distribution after log transformation. Bland-Altman plots were applied to investigate the influence of natriuretic peptide levels on the observed differences between natriuretic peptide assays.[18]

Results

The mean age of the participants was 73 (SD 5.4) years, and 58% were male. Baseline demographics and clinical characteristics are presented in Table 1. In 51 (25.5%) participants previously unrecognised heart failure was diagnosed by the panel. Twenty-nine had (14.5%) systolic, and 22 (11%) 'isolated' diastolic heart

failure. Of the participants 118 (59.0%) were classified as COPD according to the GOLD criteria[19] (a ratio of the post-dilatory forced expiratory volume in 1 second and forced vital capacity (FEV1/FVC) <70 %). The other 82 (41.0%) patients were classified as 'bronchitis' (GOLD 0; complaints of dyspnoea, cough, and/or sputum production, and a FEV1/FVC ≥ 70%). Of the patients with COPD according to GOLD, 37 (31.4%) had mild COPD (GOLD I), 64 (54.2%) moderate (GOLD II), and 17 (14.4%) severe COPD (GOLD III).[20] The prevalence of heart failure (approximately 25%) was comparable between patients in different GOLD classes (0-III). One participant had a serum creatinine concentration greater than 200 μmol/l (i.e. 243 μmol/l), and no participant had a blood urea greater than 20 mmol/l.

Median values of all types of natriuretic peptide measurements differed significantly between those with and without heart failure (Table 2). Median serum levels of NT-proBNP (15.5 pmol/l, IQR 9.3-30.6) were 0.96 pmol/l higher than plasma levels of NT-proBNP. Median plasma levels of BNP AxSYM (13.2 pmol/l, IQR 5.6-19.3) were 3.57 pmol/l higher than the levels of BNP Centaur. Patients with systolic heart failure had higher natriuretic peptide levels and ROC-area's than those with 'isolated' diastolic heart failure (Table 2). Of the heart failure patients, men and those aged >75 years had higher natriuretic peptide levels than women and patients aged 65-75 years, respectively, without significant differences in the ROC-areas (data not shown).

The ROC-areas of the four natriuretic peptide measurements did not differ significantly, but was highest for NT-proBNP measured in serum (0.73 (95% CI 0.64-0.81), and lowest for BNP AxSYM (0.68 (95% CI 0.60-0.73) (Table 2, figure 1). All four natriuretic peptide measurements showed ROC-areas around 0.60 for establishing presence or absence of 'isolated' diastolic heart failure, and ROC-areas of 0.75-0.80 for systolic heart failure (Table 2).

When applying 'commonly used' cut off values of 14.75 pmol/l (125 pg/ml) for NT-proBNP, and 28.8 pmol/l (100 pg/ml) for BNP,[17] the negative predictive value and sensitivity was highest for NT-proBNP, and the positive predictive value and specificity was highest for BNP measurements. All natriuretic peptide assays had a negative predictive value of 80% or over (Table 3). After log transformation the Pearson's correlation coefficients between measurements of NT-proBNP in serum and plasma were very high (r = 0.998, p<0.001). Also the correlation between BNP AxSYM (Abbott Inc.) and BNP Centaur (Bayer Inc.) (r =0.818, p<0.001) was high (Table 4). Correlation between NT-proBNP measured in serum and BNP AxSYM

Table 1 Characteristics of 200 patients with a general practitioner's diagnosis of COPD. Values are numbers (percentages) unless stated otherwise

Characteristics	Participants (N=200)
Age (years) §	73.1 (5.4)
Male gender	116 (58.0)
Pack years of smoking * §§	18.0 (0.0-37.5)
Medication	
Diuretics (including spironolactone)	43 (21.5)
ACE inhibitors or Angiotensin II blockers	52 (26.0)
β-blockers	25 (12.5)
Patient history	
Ischaemic heart disease **	67 (33.5)
Diabetes mellitus	22 (11.0)
Hypertension	74 (37.0)
Dyspnoea	195 (97.5)
Orthopnoea or paroxysmal nocturnal dyspnoea	52 (26.0)
Physical examination	
Pulmonary sounds***	77 (38.5)
Elevated jugular venous pressure	45 (22.5)
Laterally displaced apex beat	44 (22.0)
Peripheral oedema	37 (18.5)
Test results	
Cardiothoracic ratio on chest X-ray §	0.48 (0.05)
Abnormal ECG #	74 (37.0)
Left ventricular ejection fraction §	55.9 (11.1)
FEV1/FVC ratio ## §	65.1 (14.6)
FEV1 as % expected ### §	84.1 (24.7)

§ , indicates mean (SD); §§, median (25th-75th percentile); *, pack years of cigarette smoking in current and past smokers; **, presence of ischaemic heart disease (IHD) including myocardial infarction, angina pectoris, percutaneous coronary intervention (PCI), or coronary bypass grafting (CABG); ***, pulmonary sounds include course crackles (rhonchi), fine crackles (crepitations) and wheezing; # , abnormalities on electrocardiogram fitting in the diagnosis of (prior) myocardial infarction (abnormal Q-waves), complete or incomplete left bundle branch block, left ventricular hypertrophy, atrial fibrillation, ST and/or T-wave abnormalities, and sinus tachycardia; ##, FEV1 /FVC ratio = the ratio of post-dilatory FEV1 and forced vital capacity; ### FEV1 as % expected, forced expiratory volume in one second. For expected values of FEV1, the recommendations of the European Respiratory Society were used. [30] In 2 patients with missing values, pre-dilatory measurements were used.

Table 2 Serum and plasma NT-proBNP measurements and BNP measurements (AxSYM and Centaur) in 200 patients with a general practitioner's diagnosis of COPD and their association with presence or absence of heart failure. Values are medians (25-75 percentiles) unless stated otherwise

Variables	HF present (N=51)	HF absent (N=149)	Odds ratio (95% CI) [§]	p-value	ROC-area (95% CI)
NTproBNP se* [#] (51; 148)	28.7 (15.1-101.9)	13.8 (8.5-24.8)	1.009 (1.004-1.015)	0.001	0.73 (0.64-0.81)
Systolic HF (29)	66.1 (20.0-185.6)		1.011 (1.005-1.016)	<0.001	0.80 (0.70-0.89)
Diastolic HF (21)	20.4 (9.6-56.2)		1.003 (0.996-1.009)	0.385	0.62 (0.49-0.74)
NTproBNP pl* [$] (49: 143)	26.0 (14.3-95.9)	12.3 (7.9-23.1)	1.010 (1.004-1.016)	0.001	0.72 (0.63-0.81)
Systolic HF (28)	59.4 (16.1-172.0)		1.012 (1.006-1.019)	<0.001	0.79 (0.69-0.89)
Diastolic HF (21)	18.9 (8.6-58.0)		1.003 (0.996-1.011)	0.341	0.62 (0.49-0.75)
*BNP AxSYM** (51; 149)	18.7 (11.5-54.5)	11.2 (5.0-22.9)	1.019 (1.008-1.029)	<0.001	0.68 (0.60-0.73)
Systolic HF (29)	38.6 (12.4-92.0)		1.024 (1.012-1.035)	<0.001	0.75 (0.64-0.85)
Diastolic HF (22)	17.4 (7.9-30.9)		1.005 (0.987-1.023)	0.617	0.60 (0.50-0.71)
BNP Centaur* (51; 149)	15.9 (8.3-38.1)	8.4 (5.3-14.0)	1.031 (1.014-1.048)	<0.001	0.69 (0.61-0.78)
Systolic HF (29)	25.8 (11.7-60.7)		1.039 (1.020-1.058)	<0.001	0.77 (0.66-0.87)
Diastolic HF (22)	13.1 (6.2-23.3)		1.011 (0.985-1.038)	0.410	0.60 (0.47-0.73)

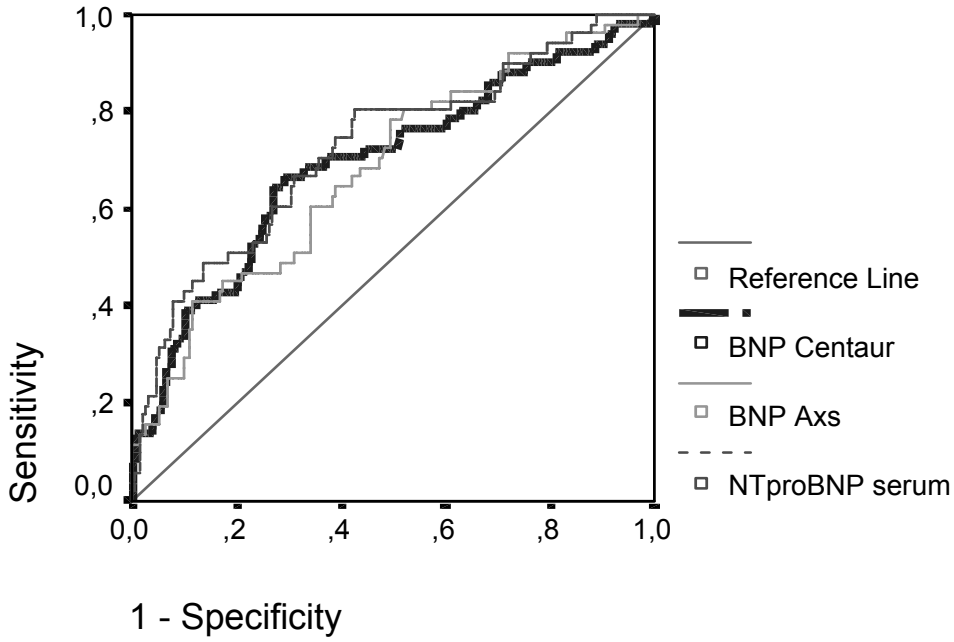
HF, heart failure; ROC, receiver operating characteristic; 95% CI, 95% Confidence Interval;
[§] per unit increase; * in pmol/l; [#] one missing; [$] 8 missings; (x: x) number of patients with and without heart failure.

Table 3 Sensitivity, specificity, positive and negative predictive value of NT-proBNP serum and plasma, BNP Centaur, and BNP AxSYM in a single test evaluation using 'common' cut-off levels of 14.75 pmol/l (125 mg/ml) for NT-proBNP and 28.8 pmol/l (100 mg/ml) for BNP

Variables	HF present (N=51)	HF absent (N=149)	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
NT-proBNP serum						
≥ 14.75 pmol/l	41	63	0.80 (0.67-0.90)	0.57 (0.49-0.66)	0.39 (0.30-0.49)	0.89 (0.81-0.95)
< 14.75 pmol/l	10	85				
NT-proBNP plasma						
≥ 14.75 pmol/l	35	55	0.71 (0.57-0.83)	0.62 (0.53-0.70)	0.39 (0.29-0.50)	0.86 (0.78-0.92)
< 14.75 pmol/l	14	88				
BNP AxSYM						
≥ 28.8 pmol/l	22	25	0.43 (0.29-0.58)	0.83 (0.76-0.89)	0.47 (0.32-0.62)	0.81 (0.74-0.87)
< 28.8 pmol/l	29	124				
BNP Centaur						
≥ 28.8 pmol/l	18	15	0.35 (0.22-0.50)	0.90 (0.84-0.94)	0.55 (0.36-0.72)	0.80 (0.73-0.86)
< 28.8 pmol/l	33	134				

95% CI, 95% Confidence Interval; NT-proBNP serum 1 missing; NT-proBNP plasma 8 missings.

Figure 1 ROC-curves of NT-proBNP serum, BNP Centaur, and BNP AxSYM for the ability to determine the presence or absence of heart failure in elderly patients with a GP's diagnosis of COPD



(r =0.744, p<0.001) was somewhat lower.

The Bland-Altman plots showed that differences were small between log transformed NT-proBNP serum and plasma levels, with consistently higher levels for serum measurements (figure 2a). Differences between log transformed BNP AxSYM and Centaur were less small, with higher levels for BNP AxSYM (Figure 2b). The Bland-Altman plot showed that for higher BNP levels, BNP Centaur tends to be higher than BNP AxSYM (figure 2b). Log transformed serum measurements of NT-proBNP were consistently higher than plasma BNP measurements (figure 2c and 2d).

Table 4 Pearson's correlation coefficients between natural logaritmic transformed natriuretic peptide measurements

	NT-proBNP plasma	BNP Centaur	BNP AxSYM
NT-proBNP serum*	0.998, p<0.001	0.915, p<0.001	0.744, p<0.001
NT-proBNP plasma**	-	0.916, p<0.001	0.762, p<0.001
BNP Centaur	-	-	0.818, p<0.001

* indicates 1 missing; ** 8 missings

Natriuretic peptide levels were not influenced by the severity of COPD (according to the GOLD-classification). With increasing severity of left ventricular dysfunction (decreasing levels of LV ejection fraction), however, natriuretic peptide levels increased, with a significant difference between LVEF ≤ 30% and other LV ejection fractions (figure 3a and 3b).

Discussion

Our study shows that measurements of different assay systems of the natriuretic peptides NT-proBNP and BNP are helpful diagnostic indicators for detecting previously unknown heart failure in elderly patients with a primary care diagnosis of chronic obstructive pulmonary disease (COPD). The four assay systems of natriuretic peptides were overall comparable in their ability to detect or rule out heart failure in these patients. In addition, serum and EDTA-plasma measurements of NT-proBNP (Roche Inc.) were interchangeable because the differences were very small differences and without clinical significance. The diagnostic ability of the four assay systems was good for detecting systolic heart failure, and rather poor for detecting 'isolated' diastolic heart failure. Natriuretic peptide levels were influenced by left ventricular ejection fraction (severity of LV dysfunction), but not by the GOLD-classification (severity of COPD).

The overall diagnostic accuracy of the natriuretic peptide measurements in detecting heart failure in our study was lower than in previous studies in patients suspected of heart failure [2] or in patients with acute dyspnoea visiting an emergency department.[4;6] The most obvious reason for the lower diagnostic accuracy in our study is the difference in population studied.[21] We studied COPD patients in a stable phase of their disease. Therefore, it is plausible that participants overall had lower intracardiac pressures than for example patients with acute dyspnoea (acute increase in intracardiac pressure), or suspected of heart failure

Figure 2a Bland-Altman plots of natural log-transformed levels of NT-proBNP serum and plasma with standard deviation

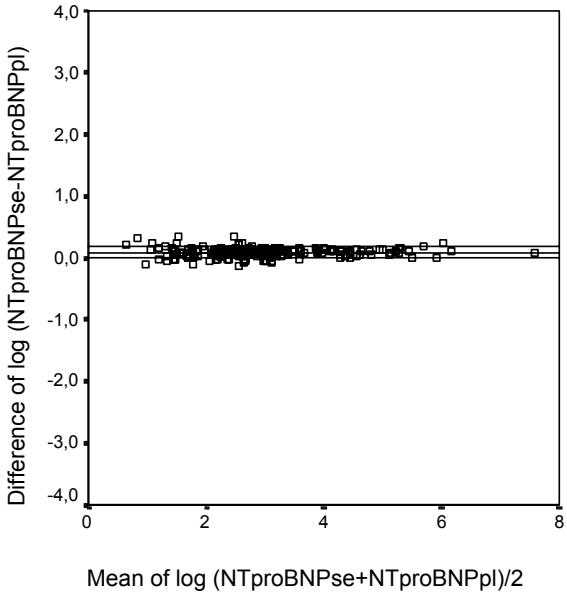


Figure 2b Bland-Altman plots of natural log-transformed levels of BNP Centaur and AxSYM with standard deviation

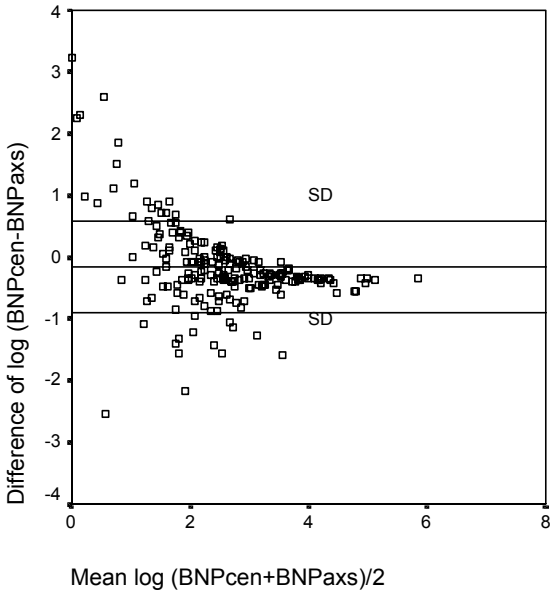


Figure 2c Bland-Altman plots of natural log-transformed levels of NT-proBNP serum and BNP AxSYM with standard deviation

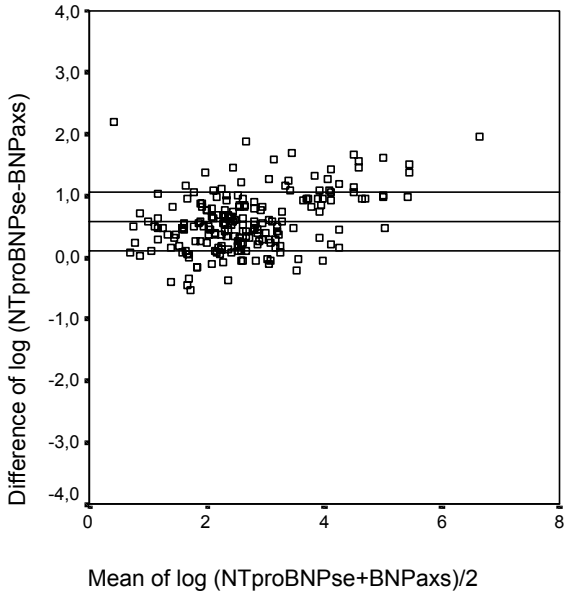


Figure 2d Bland-Altman plots of natural log-transformed levels of NT-proBNP serum and BNP Centaur with standard deviation

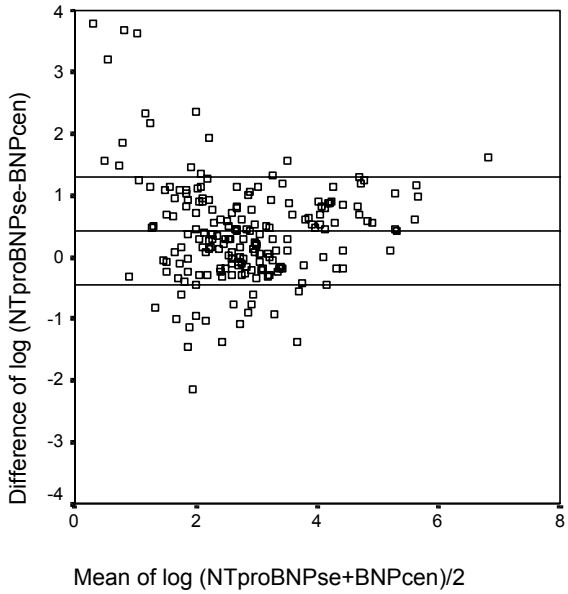
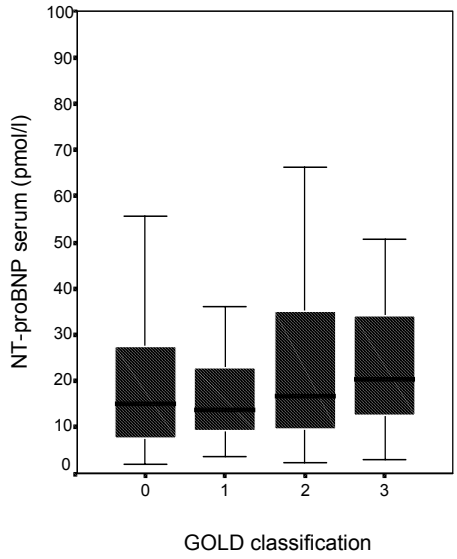
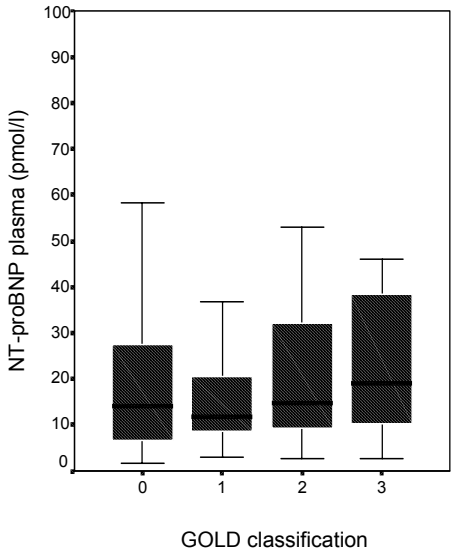
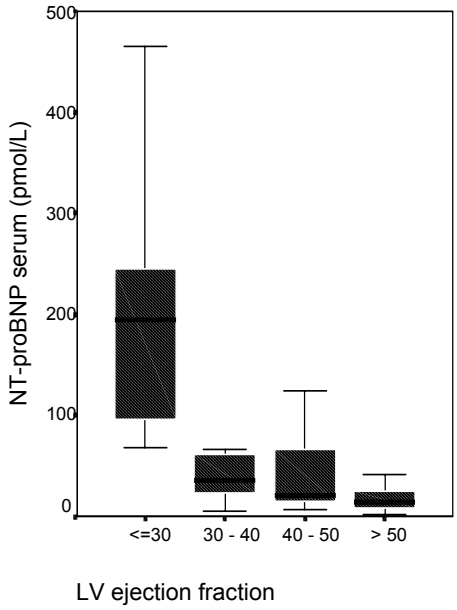


Figure 3 a Severity of COPD according to GOLD classification, and LV ejection fraction in relation to NTproBNP serum and plasma levels







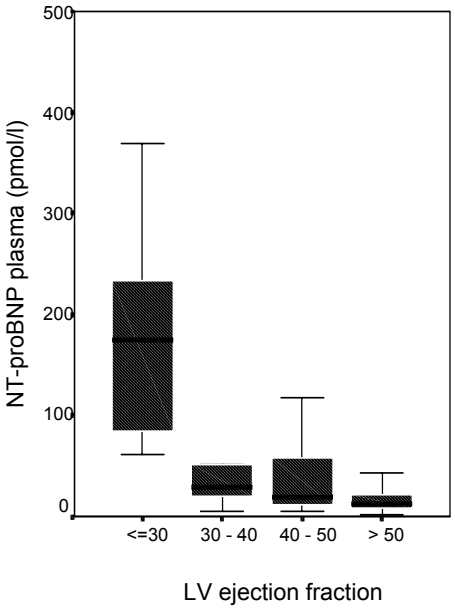
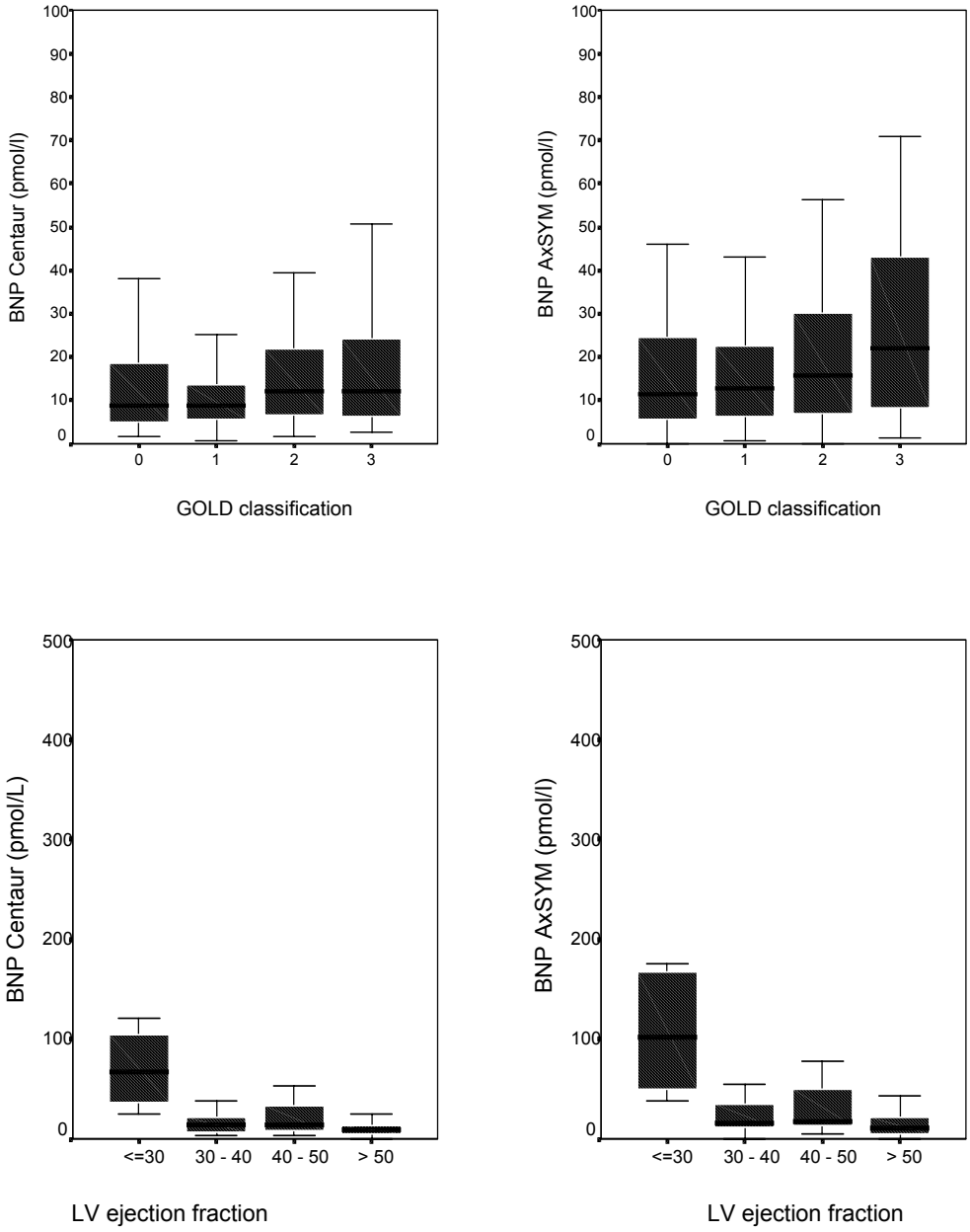


Figure 3 b Severity of COPD according to GOLD classification, and LV ejection fraction in relation to plasma BNP Centaur and BNP AxSYM levels



(recent increase in dyspnoea and most often signs of overfilling). Because the production of natriuretic peptides by the myocytes in the ventricles is dependent of the intracardiac pressure, lower concentrations of natriuretic peptides could be expected in our population.[22;23] Another factor that decreased the discriminatory ability ('contrast') of natriuretic peptides between those with and without heart failure was the relatively high median natriuretic peptide levels (at the upper level or even above that of the suggested 'normal' range) of the COPD patients without heart failure.[17] Also earlier studies provided an indication that COPD patients without heart failure can have increased natriuretic peptide levels, possibly by some degree of right ventricular wall stress.[24;25]

The diagnostic accuracy of all tested natriuretic peptides was significantly lower for detecting diastolic than systolic heart failure. An earlier study showed already that the diagnostic accuracy of (NT-pro)BNP was lower for detecting diastolic dysfunction than systolic dysfunction.[22] Since the increase of (NT-pro)BNP is not only positively correlated with intracardiac pressures, but also with severity of heart failure,[7] lower predictability of diastolic compared to systolic heart failure could be expected in our population.

Since our aim was to study possible differences in diagnostic performance between available natriuretic peptide assay systems, the exact role of these measurements in the complete diagnostic process of detecting heart failure in elderly COPD patients was not assessed. To address this issue, a study in a larger population sample is needed in which findings from history and physical examination should be included to determine the *additional* value of natriuretic peptides.[26]

The presence of heart failure was established by consensus evaluation, using all available diagnostic information.[2;27] This is an established method as reference standard, since a true 'gold' standard is lacking for assessing heart failure.[2] Moreover, earlier studies have shown that panel diagnosis in establishing heart failure were highly reproducible.[28]

In conclusion, NT-proBNP and BNP measurements did not differ significantly in their diagnostic abilities in detecting or ruling out previously unknown heart failure in elderly COPD patients. The diagnostic value for detecting or ruling out systolic heart failure was considerably higher than for 'isolated' diastolic heart failure. The overall diagnostic utility of natriuretic peptides in our difficult to assess population of elderly COPD patients was moderate, but could serve as a screening instrument to detect those patients who need further echocardiographic assessment. With

application of natriuretic peptides by primary care physicians and pulmonologist in COPD patients, a substantial number of patients with unknown heart failure can be detected and eventually offered adequate heart failure treatment that can alleviate symptoms, delay progression, and improve prognosis.[29]

Acknowledgement

We thank the participating patients, general practitioners, and their assistants, including the general practices connected to the General Practice Network Utrecht (HNU), the cardiac sonographers Elly Lutgert-Hagman and Ineke Kasteleijn, the pulmonology technicians, especially Paul Munnik, and Pieter Zanen, the lung physiologist. Frances Verheij assisted us with the data management. SALTRO, the department of clinical chemistry was helpful with the blood analyses. We thank Roche Inc. (Mannheim, Germany), Abbott Inc. (Illinois, USA), and Bayer Inc. (Leverkusen, Germany) for supplying the assays for analysis of NT-proBNP, BNP AxSYM and BNP Centaur, respectively.
The study was funded by research grant number 904-61-144 of the Netherlands Organisation for Scientific Research (NWO).

References

1. Remes J, Miettinen H, Reunanen A, Pyörälä K. Validity of clinical diagnosis of heart failure in primary health care. *Eur Heart J* 1991;12:315-21.
2. Cowie MR, Struthers AD, Wood DA, Coats AJ, Thompson SG, Poole-Wilson PA *et al*. Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care. *Lancet* 1997;350:1349-53.
3. Landray MJ, Lehman R, Arnold I. Measuring brain natriuretic peptide in suspected left ventricular systolic dysfunction in general practice: cross-sectional study. *BMJ* 2000;320:985-6.
4. Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P *et al*. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med* 2002;347:161-7.
5. McCullough PA, Hollander JE, Nowak RM, Storrow AB, Duc P, Omland T *et al*. Uncovering heart failure in patients with a history of pulmonary disease: rationale for the early use of B-type natriuretic peptide in the emergency department. *Acad Emerg Med* 2003;10:198-204.
6. Lainchbury JG, Campbell E, Frampton CM, Yandle TG, Nicholls MG, Richards AM. Brain natriuretic peptide and n-terminal brain natriuretic peptide in the diagnosis of heart failure in patients with acute shortness of breath. *J Am Coll*

Cardiol 2003;42:728-35.

7. Rodeheffer RJ. Measuring plasma B-type natriuretic peptide in heart failure: good to go in 2004? *J Am Coll Cardiol* 2004;44:740-9.

8. Hunt PJ, Yandle TG, Nicholls MG, Richards AM, Espiner EA. The amino-terminal portion of pro-brain natriuretic peptide (Pro-BNP) circulates in human plasma. *Biochem Biophys Res Commun.* 1995;214:1175-83.

9. Roche Diagnostics GmbH. Elecsys NT-proBNP [Package Insert]. Mannheim, Germany: Roche Diagnostics GmbH, 2002.

10. Van der Merwe DE, Henley R, Lane G, Field R, Frenneaux M, Dunstan F *et al*. Effect of different sample types and stability after blood collection of N-terminal pro-B-type natriuretic peptide as measured with Roche Elecsys system. *Clin Chem* 2004;50:779-80.

11. Rutten FH, Cramer MJM, Grobbee DE, Sachs APE, Kirkels JH, Lammers J-WJ *et al*. Unrecognized heart failure in elderly patients with stable chronic obstructive pulmonary disease. *Eur Heart J in press*.

12. Rose, GA and Blackburn, H. Cardiovascular Survey Methods. World Health Organisation. Geneva 1982.

13. Mosterd A, Hoes AW, de Bruyne MC, Deckers JW, Linker DT, Hofman A *et al*. Prevalence of heart failure and left ventricular dysfunction in the general population; The Rotterdam Study. *Eur Heart J* 1999;20:447-55.

14. Zile MR, Gaasch WH, Carroll JD, Feldman MD, Aurigemma GP, Schaer GL *et al*. Heart failure with a normal ejection fraction: is measurement of diastolic function necessary to make the diagnosis of diastolic heart failure? *Circulation* 2001;104:779-82.

15. Vasan RS, Benjamin EJ, Levy D. Congestive heart failure with normal left ventricular systolic function. Clinical approaches to the diagnosis and treatment of diastolic heart failure. *Arch Intern Med* 1996;156:146-57.

16. Harrell FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996;15:361-87.

17. Cowie MR, Jourdain P, Maisel A, Dahlstrom U, Follath F, Isnard R *et al*. Clinical applications of B-type natriuretic peptide (BNP) testing. *Eur Heart J* 2003;24:1710-8.

18. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;1:307-10.

19. Pauwels RA, Buist AS, Ma P, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: National Heart, Lung, and Blood Institute and World Health Organization Global Initiative for Chronic Obstructive Lung Disease (GOLD): executive summary.

Respir Care 2001;46:798-825.

20. Fabbri LM, Hurd SS. Global Strategy for the Diagnosis, Management and Prevention of COPD: 2003 update. *Eur Respir J* 2003;22:1-2.

21. Vasan RS, Benjamin EJ, Larson MG, Leip EP, Wang TJ, Wilson PW *et al*. Plasma natriuretic peptides for community screening for left ventricular hypertrophy and systolic dysfunction: the Framingham heart study. *JAMA* 2002;288:1252-9.

22. Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR, Burnett JC, Jr. Plasma brain natriuretic peptide to detect preclinical ventricular systolic or diastolic dysfunction: a community-based study. *Circulation* 2004;109:3176-81.

23. Troughton RW, Frampton CM, Yandle TG, Espiner EA, Nicholls MG, Richards AM. Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations. *Lancet* 2000;355:1126-30.

24. Lang CC, Coutie WJ, Struthers AD, Dhillon DP, Winter JH, Lipworth BJ. Elevated levels of brain natriuretic peptide in acute hypoxaemic chronic obstructive pulmonary disease. *Clin Sci (Lond)* 1992;83:529-33.

25. Troughton RW, Prior DL, Pereira JJ, Martin M, Fogarty A, Morehead A *et al*. Plasma B-type natriuretic peptide levels in systolic heart failure: importance of left ventricular diastolic function and right ventricular systolic function. *J Am Coll Cardiol* 2004;43:416-22.

26. Moons KG, Biesheuvel CJ, Grobbee DE. Test research versus diagnostic research. *Clin Chem* 2004;50:473-6.

27. Kitzman DW, Gardin JM, Gottdiener JS, Arnold A, Boineau R, Aurigemma G *et al*. Importance of heart failure with preserved systolic function in patients > or = 65 years of age. CHS Research Group. Cardiovascular Health Study. *Am J Cardiol* 2001;87:413-9.

28. Cowie MR, Wood DA, Coats AJ, Thompson SG, Poole-Wilson PA, Suresh V *et al*. Incidence and aetiology of heart failure; a population-based study. *Eur Heart J* 1999;20:421-8.

29. Remme WJ, Swedberg K. Guidelines for the diagnosis and treatment of chronic heart failure. *Eur Heart J* 2001;22:1527-60.

30. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J* 1993;16 *Suppl*:5-40.

Chapter 9

Value of cardiovascular magnetic resonance imaging in identifying heart failure in patients with stable chronic obstructive pulmonary disease

Frans H Rutten [1], Evert-Jan Vonken [2], Maarten-Jan M Cramer [3], Karel GM Moons [1], Brigitta Veldhuis [2], Jan-Willem J Lammers [4], Diederick E Grobbee [1], Willem PThM Mali [2], Arno W Hoes [1]

[1] *Julius Center for Health Sciences and Primary Care;*
[2] *Department of Radiology;*
[3] *Heart Lung Center Utrecht, Department of Cardiology;*
[4] *Heart Lung Center Utrecht, Department of Pulmonary Diseases;*
University Medical Center Utrecht

Submitted

Abstract

Background Information about the diagnostic value of cardiovascular magnetic resonance imaging (CMR) in detecting heart failure is scarce, and virtually lacking in patients with a diagnosis of chronic obstructive pulmonary disease (COPD).
Aim To determine which results from CMR provide (additional) diagnostic information for identifying heart failure in patients with stable COPD.
Methods Participants were recruited from a cohort of 405 patients aged 65 years or over, with a general practitioner's diagnosis of COPD. After an extensive diagnostic assessment, the diagnosis of heart failure was established by an expert panel, using all available diagnostic information, including echocardiography, but without natriuretic peptide measurements (amino-terminal pro B-type natriuretic peptide). In a nested case-control study design, 37 COPD patients with heart failure (cases) and a random sample of 41 COPD patients without heart failure (controls) received additional CMR measurements within three weeks from the panel meeting, before therapy was eventually changed. The diagnostic value of CMR measurements for heart failure was quantified using univariate and multivariate logistic modelling and area under the receiver operating characteristic curves (ROC-area) analyses.
Results Of the CMR measurements, left ventricular ejection fraction (LVEF) < 45% had the best test characteristics with a positive predictive value of 1.0 (95% CI 0.92-1.0), and a negative predictive value of 0.87 (95% CI 0.83-0.90). A 'CMR' model based on CMR parameters only (LVEF, indexed left and right atrial volume, and left ventricular end-systolic diameter) had an ROC-area of 0.88. These CMR measurements had significantly more additional diagnostic value beyond clinical signs and symptoms (ROC-area 0.91) than NT-proBNP (ROC-area 0.80), or electrocardiography (ROC-area 0.77). Further addition of NT-proBNP or electrocardiography had no independent value beyond the diagnostic model based on signs, symptoms, and CMR parameters.
Conclusions CMR is the test with the highest diagnostic value in identifying heart failure in stable COPD patients, and could be an attractive alternative for echocardiography in these notoriously difficult to investigate group of patients, although an important price difference should be kept in mind.

Introduction

Heart failure (HF) is a common syndrome in the elderly, affecting those aged 65 years or over in about 7-10%.[1] Heart failure can be difficult to diagnose in the presence of chronic obstructive pulmonary disease (COPD) due to overlap in signs and symptoms.[2] Echocardiography is considered to be the cornerstone investigation in heart failure, but high-quality echocardiographic measurements are more difficult to obtain in COPD patients.[3;4] Moreover, criteria for echocardiographic left ventricular diastolic dysfunction are still debated.[5-8] Importantly, echocardiographic diastolic measurements are dependent on loading conditions, heart rate, and systolic function, and 'normal' values vary considerable with age.[9] Cardiovascular magnetic resonance imaging (CMR) has the unique potential of a 3-dimensional function analysis with great accuracy and reproducibility.[10] It has unlimited access to the thoracic cavity, is independent of geometric assumptions,[11] and the right ventricle and left ventricular diastolic function can be assessed in more detail compared to echocardiography.[12] Thus, cardiovascular magnetic resonance imaging could serve as an alternative to echocardiography in the diagnostic assessment of heart failure in COPD patients.

Although CMR is time-consuming and expensive, the diagnostic advantages could be substantial when assessing presence or absence of heart failure, especially in patients with COPD with their decreased echogenicity. Diagnostic studies of CMR in heart failure are scarce. To our knowledge, studies assessing the role of CMR in the diagnostic assessment of heart failure in COPD patients are lacking.[13]

We assessed the value of CMR in identifying heart failure in elderly stable COPD patients. We also assessed the diagnostic value of CMR in addition to signs and symptoms compared to the added value of electrocardiography and/or natriuretic peptide measurements to the clinical assessment.

Methods

Study population

Participants were recruited from a cohort of 405 patients aged 65 years or over, with a general practitioner's diagnosis of COPD and in a stable phase of their disease. For the present analysis, a nested case-control design was used to efficiently reduce the number of CMR measurements without loss of diagnostic accuracy.[14] In this design, CMR measurements are performed in cases (COPD patients with heart failure) and in a random sample of the remainder of the original

study population (controls; COPD patients without heart failure). Since the 'true' disease status of the whole original cohort is known, there is no selection or work-up or verification bias in this design.[14] To obtain valid estimates of the diagnostic accuracy regarding CMR measurements controls and cases should be weighted by the sample fraction, i.e. the proportion of the COPD patients with or without heart failure that is sampled.[15] For the present nested case-control study, 45 consecutive COPD patients with heart failure (cases) and a random sample of 46 patients of the population of COPD patients without heart failure (controls) were invited to re-visit our out-patient clinic for CMR measurements. Of the COPD patients with heart failure, six refused (two were claustrophobic, and four did not show up) and one patient had a technically incomplete session. Of the controls three patients did not show up. Thus, in 81 patients CMR measurements were performed. However, in three patients (in one case and two controls) adequate short-axis CMR measurements were not available, thus eventually 78 participants (37 COPD patients with heart failure (cases) and 41 COPD patients without heart failure (controls) were included in the present analyses.
The study was executed between April 2001 and June 2003, and approved by the Medical Ethical Committee of the University Medical Center Utrecht, the Netherlands.All participants gave written informed consent.

Diagnostic work-up
All 405 participants in the original cohort underwent an extensive diagnostic work-up, including medical history and physical examination, laboratory tests (including measurements of amino-terminal pro B-type natriuretic peptide (NT-proBNP)), chest radiography, electrocardiography, echocardiography, and pulmonary function tests. Detailed information about the diagnostic procedure has been published elsewhere.[16] The panel classified 83 (20.5%) COPD patients of the original cohort as heart failure (42 systolic, and 41 'isolated' diastolic heart failure).[16]

Cardiovascular Magnetic Resonance Imaging (CMR) in cases and controls
CMR studies were performed on a 1.5 Tesla Philips Intera (Philips Medical Systems, Best, the Netherlands) within three weeks of the diagnostic work-up, without intermediate change in medication between the diagnostic work-up and CMR measurements to ensure optimal comparability between the tests under study. CMR imaging was performed with patients in the supine position, using a five-element phased-array cardiac coil and a vector-electrocardiogram for ECG gating.[17]
All acquisitions were obtained during breath holding in expiration. Localising scout images were followed by breath-hold cine acquisitions. Multiple-slice series,

parallel to the mitral valve were acquired covering the heart in 10-14 short-axis slices using the steady-state free precession imaging sequence (SSFP) technique. Slices of 8 mm thickness, without interslice gap were used with one slice acquired per breath hold in 25 phases/cardiac cycle.
Imaging analysis was performed off-line using commercially available software (Philips Easy Vision release 4 cardiac package, the Netherlands). Endocardial and epicardial contours were traced manually at end-diastole. The papillary muscles were attributed to the ventricular blood pool and excluded from the myocardial mass.
From the stack of contiguous short-axis cine-images the myocardial volume from each slice was summed to obtain the total volume by using the modified Simpson's rule. Multiplying this volume by the specific density of myocardial tissue (1.05 g/cm³) gave the left ventricular mass.[18] This technique has been validated, with high accuracy and reproducibility.[19;20]
A single investigator, blinded to clinical data and echocardiographic measurements performed the quantitative image analyses.

Presence or absence of heart failure: 'reference standard'
As there is no established, single reference method available for heart failure, presence or absence of heart failure in the original cohort of COPD patients was determined by an expert panel.[21-23] This is the conform previous studies and methodological guidelines.[21;23-26] The panel consisted of two cardiologists, a pulmonologist and a general practitioner. They used all available patient information including echocardiographic results, but without NT-proBNP results, to prevent incorporation bias of this diagnostic test.
Systolic heart failure was defined as a LVEF ≤ 45% in the presence of symptoms indicative of heart failure (i.e. orthopnoea, paroxysmal nocturnal dyspnoea, fatigue, peripheral oedema, nycturia ≥ 2 times a night, or any combination of these symptoms). 'Isolated' diastolic heart failure was defined as echocardiographic diastolic dysfunction, a LVEF > 45%, and either (i) indicative symptoms (see above) and signs (i.e. pulmonary or peripheral oedema, or elevated jugular venous pressure) of heart failure, or (ii) indicative symptoms of heart failure and echocardiographic left ventricular hypertrophy, atrial fibrillation, anginal complaints, or any combination of these additional findings.[27]
Eventually, the panel classified 83 (20.5%) COPD patients of the original cohort as heart failure (42 systolic and 41 'isolated' diastolic).[16]

Data analysis
We first quantified the association between potential diagnostic parameters

obtained from CMR and the outcome (presence or absence of heart failure), according to the panel as the reference standard, using univariate logistic regression analysis. The diagnostic accuracy of each CMR variable was assessed by calculating sensitivity, specificity, positive and negative predictive values. Because we used a nest case-control study design, with a fraction of the cases (with heart failure), and controls (without heart failure), calculations of sensitivity, specificity, positive and negative predictive values were corrected for sampling fractions. Thus by multiplying the number of cases by 2.24 (83/37) and the number of controls by 7.85 (322/41) for the controls we constructed new two by two tables to calculate diagnostic accuracy parameters.[15]

Multivariable logistic regression was then used to quantify the independent contribution of each of the CMR variables to the diagnosis of heart failure. The 'CMR model' was reduced by excluding variables from the model with p-values > 0.15, using the log likelihood ratiotest.[28] The ability of this model and all other models in the analysis to discriminate between patients with and without heart failure was estimated, using the area under the receiver operating characteristic curve (ROC-area).[28] The ROC-area can range from 0.5 (no discrimination, like flipping a coin) to 1.0 (perfect discrimination).

Finally, the contribution of this 'CMR model' to findings from patient history and physical examination was estimated by adding CMR parameters to a 'clinical model' including the independent clinical variables from the initial cohort of 405 patients (i.e. history of ischaemic heart disease, body mass index, laterally displaced apex beat, heart frequency).[27] Also NT-proBNP and the ECG were added (first separately, and then in combination) to the 'clinical model' to quantify their added diagnostic value. We accounted for the dependency between the different models as each model was estimated using the same subjects.[29;30]

Date were analysed using SPSS Windows version 12.0 (SPSS Inc., Chicago, Il, USA).

Results

The mean age of the participants undergoing CMR measurements was 73.1 (SD 5.2), and 65% were male. Baseline demographics and clinical characteristics of the 37 cases and 41 controls are presented in Table 1. In COPD patients with heart failure (cases) the median NT-proBNP level was 42.6 pmol/l (360.3 pg/ml) (IQR 14.8-90.6 pmol/l), and 63% showed abnormalities on the electrocardiogram. Corresponding figures for COPD patients without heart failure (controls) were 13.3 pmol/l (112.5 pg/ml) (IQR 8.3-17.8 pmol/l) and 29%, respectively (Table1). The

Table 1 COPD patients with heart failure (cases) and COPD patients without heart failure (controls) in whom CMR measurements were performed. Values are numbers (percentages) unless stated otherwise

Characteristics	HF present (cases; N=37)		HF absent (controls; N=41)	
Age (years)[§]	74.4	(5.2)	71.9	(5.0)
Male gender	23	(62.5)	28	(68.3)
Pack years smoking [§§*]	16.3	(0.75-40.5)	12.2	(0.0-40.3)
Ischaemic heart disease**	15	(40.5)	13	(31.7)
Hypertension	18	(48.6)	13	(31.7)
Diabetes mellitus	5	(13.5)	4	(9.8)
Use of diuretics	16	(43.2)	6	(14.6)
Use of ACE inhibitors or Angiotensin-II blockers	13	(35.1)	9	(22.0)
Use of β-blockers	5	(13.5)	2	(4.9)
Orthopnoea or paroxysmal nocturnal dyspnoea	12	(32.4)	9	(22.0)
Body surface area (m²) [§]	1.96	(0.20)	1.87	(0.16)
Body mass index (weight/m²) [§]	28.3	(3.9)	25.2	(4.3)
Heart rate (beats/minute) [§]	80.7	(13.1)	72.5	(12.4)
Systolic blood pressure (mmHg) [§]	147.2	(21.7)	147.7	(17.7)
Diastolic blood pressure (mmHg) [§]	83.1	(11.7)	83.5	(8.0)
Laterally displaced apex beat	8	(19.5)	7	(18.9)
Elevated jugular venous pressure	10	(27.8)	12	(29.3)
Peripheral oedema	9	(22.0)	11	(29.7)
Cardiothoracic ratio chest X-ray [§]	0.49	(0.05)	0.46	(0.04)
Abnormal ECG ***	23	(62.5)	12	(29.3)
NT-proBNP (pmol/l) [§§]	42.6	(14.8-90.6)	13.3	(8.3-17.8)
FEV1/FVC [#]	64.7	(14.7)	63.4	(13.7)
FEV1 as % of expected [#]	82.8	(24.6)	86.3	(26.3)

[§], mean (SD); [§§], median (25-75 percentile); * , pack years of cigarette smoking in current and past smokers; **, presence of ischaemic heart disease including myocardial infarction, angina pectoris, percutaneous coronary intervention, or coronary artery bypass grafting; ***, abnormal ECG , abnormalities on ECG fitting in the diagnosis of (prior) myocardial infarction (abnormal Q-waves), complete or incomplete left bundle branch block, left ventricular hypertrophy, atrial fibrillation, ST and/or T-wave changes, and sinus tachycardia according to the Minnesota code.FEV1, forced expiratory volume in 1 second, FVC, forced vital capacity. [#] Post-dilatory spirometric measurements were used. For expected values of the FEV1, the recommendations of the European Respiratory Society (ERS) were used. [42]

Table 2 Comparison between CMR and echocardiographic measurements in 78 COPD participants with heart failure (cases) and without heart failure (controls). Values are means (standard deviation (SD)) unless stated otherwise

Measurements	CMR		Echocardiography	
	HF present (37 cases)	HF absent (41 controls)	HF present (37 cases)	HF absent (41 controls)
LV ejection fraction (%)	48.2 (14.0)	60.6 (6.1)	45.4 (12.3)	58.6 (4.7)
LV end-systolic diameter (mm)	40.0 (10.6)	32.4 (4.1)	37.0 (9.9)	28.0 (4.9)
LV end-diastolic diameter (mm)	53.6 (7.6)	49.7 (4.0)	53.6 (8.0)	48.2 (4.8)
LV mass index (g/m²) *$	72.8 (19.1)	61.2 (12.5)	112.2 (32.3)	84.8 (18.3)
E/A ratio	0.91 (0.47)	1.36 (1.41)	0.68 (0.18)	0.83 (0.26)
RA volume index (ml/m²) *	22.4 (9.1)	26.4 (9.8)	NA	NA
LA volume index (ml/m²) *	31.7 (12.9)	27.3 (6.9)	43.0 (15.3)	33.6 (15.3)

NA, not assessed; E/A, early-to atrial left ventricular filling ratio. * Index values are values divided by body surface area. Body surface area (BSA) was calculated using the DuBois equation (BSA = 0.007184 (Weight in kg $^{0.425}$ x Height in cm$^{0.725}$). [43]

$ With CMR measurement of indexed left ventricular mass the papillary muscles were excluded from the myocardial mass. For echocardiographic LV mass the Devereux formula was used:LV mass (g) = 0.8 [1.04 (LV internal diameter+interventricular septum thickness+posterior wall thickness)³ - (LV internal diameter)³]+ 0.6 with all measurements made at end-systole.[44]

Missings: left ventricular end-diastolic diameter (CMR one, echo six), left ventricular end-diastolic diameter (CMR one, echo 17), left ventricular mass (CMR one, echo nine), E/A ratio (CMR nine, echo eight), right atrial volume (CMR one, not assessed by echo), and left atrial volume (CMR two, echo two).

Table 3 Univariate and multivariate analysis of the CMR measurements of the study population (n=78) according to presence or absence of heart failure.

CMR measurements	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
LV ejection fraction (%)	0.89 (0.84-0.94)	<0.001	0.78 (0.65-0.94)	0.007
LV end-systolic diameter (mm)	1.14 (1.06-1.23)	<0.001	0.88 (0.69-1.13)	0.321
LV end-diastolic diameter (mm)	1.12 (1.03-1.22)	0.006	0.88 (0.69-1.11)	0.266
LV mass index (g/m²) *	1.07 (1.02-1.13)	0.003	1.07 (0.98-1.16)	0.129
E/A ratio	0.43 (0.13-1.38)	0.068	0.70 (0.21-2.30)	0.555
RA volume index (ml/m²) *	0.95 (0.90-1.01)	0.068	0.87 (0.78-0.99)	0.027
LA volume index (ml/m²) *	1.05 (0.99-1.11)	0.070	1.08 (0.99-1.18)	0.102

* Index values are values divided by body surface area. Body surface area (BSA) was calculated using the DuBois equation (BSA = 0.007184 (Weight in kg $^{0.425}$ x Height in cm$^{0.725}$). [43]

Table 4 Sensitivity, specificity, positive and negative predictive value of the parameters obtained from cardiovascular magnetic resonance imaging (CMR). Values are corrected for sampling fractions in a nested case-control design

Variables	HF present	HF absent	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
LVEF						
< 45%	36	0	0.43 (0.33-0.55)	1.0 (0.99-1.0)	1.0 (0.92-1.0)	0.87 (0.83-0.90)
≥ 45%	47	322				
LVESd						
≥ 40 mm	47	31	0.58 (0.47-0.69)	0.90 (0.87-0.93)	0.60 (0.49-0.71)	0.90 (0.86-0.93)
< 40 mm	34	290				
LVEDd						
≥ 55 mm	34	39	0.42 (0.31-0.53)	0.88 (0.84 -0.91)	0.47 (0.35-0.59)	0.86 (0.82-0.89)
< 55 mm	47	283				
Indexed LV mass*						
≥ 70 g/m²	40	47	0.50 (0.39-0.61)	0.85 (0.810.89)	0.46 (0.35-0.57)	0.87 (0.83-0.91)
< 70 g/m²	40	275				
E/A						
≤ 0.75 or ≥ 1.5	36	133	0.54 (0.41-0.66)	0.57 (0.51-0.62)	0.21 (0.15-0.28)	0.85 (0.79-0.89)
0.75 <x <1.5	31	173				

Continued on next page

Table 4 *Continued from previous page*

Variables	HF present	HF absent	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
Indexed RA volume*						
< 24 ml/m²	60	149	0.77 (0.66-0.86)	0.54 (0.48-0.59)	0.29 (0.23-0.35)	0.91 (0.86-0.94)
≥ 24 ml/m²	18	173				
Indexed LA volume*						
≥ 32 ml/m²	36	86	0.43 (0.33-0.55)	0.73 (0.68-0.78)	0.30 (0.22-0.38)	0.83 (0.78-0.87)
< 32 ml/m²	47	235				

95% CI = 95% Confidence Interval.

* Index values are values divided by body surface area. Body surface area (BSA) was calculated using the DuBois equation (BSA = 0.007184 (Weight in kg $^{0.425}$ x Height in cm$^{0.725}$). [43]

Left ventricular end-diastolic diameter 1 missing, left ventricular end-diastolic diameter 1 missing, left ventricular mass 1 missing, E/A ratio 9 missings, right atrial volume 1 missing, left atrial volume 2 missings.

Table 5 Contribution of CMR parameters to the diagnosis of heart failure beyond clinical variables compared to the added value of ECG and NT-proBNP in COPD patients

Variables	ROC-area (95% CI)	Odds ratio (95% CI)*	p-value*
'clinical' model only	0.75 (0.64-0.86)		
'CMR' model only	0.88 (0.80-0.97)		
LV ejection fraction		0.76 (0.65-0.90)	0.001
LV end-systolic diameter		0.84 (0.70-1.01)	0.038
RA volume/ m²		0.89 (0.81-0.97)	0.010
LA volume/ m²		1.08 (1.00-1.16)	0.044
Single additional test to clinical model			
'clinical' + 'CMR' model	0.91 (0.84-0.97)		
LV ejection fraction		0.75 (0.63-0.90)	0.002
LV end-systolic diameter		0.82 (0.66-1.02)	0.078
RA volume/ m²		0.89 (0.81-0.97)	0.006
LA volume/ m²		1.09 (1.01-1.18)	0.022
'clinical' + NT-proBNP (per pmol/l)	0.80 (0.70-0.90)	1.01 (1.01-1.02)	0.084
'clinical' + ECG**	0.77 (0.66-0.87)	2.43 (0.87-6.83)	0.092

'Clinical' model included a history of ischaemic heart disease, body mass index, laterally displaced apex beat, and heart rate based on previous analysis of the full cohort [27];

*, all odds ratios and p-values are given, except of the variables included in the clinical model;

**, ECG, abnormalities on electrocardiogram fitting in the diagnosis of (prior) myocardial infarction (abnormal Q-waves), complete or incomplete left bundle branch block, left ventricular hypertrophy, atrial fibrillation, ST and/or T-wave abnormalities, and sinus tachycardia. The 'CMR model' had 3 missing.

pulmonary function tests showed that the severity of the COPD of the majority of the participants was mild or moderate.

Results from CMR measurements are compared to echocardiographic parameters in Table 2. Measurements of LV ejection fraction, and LV end-systolic and end-diastolic diameters were comparable. With echocardiography higher levels of left

ventricular mass and left atrial volume were measured than with CMR (Table 2). Patients with heart failure had increased left atrial volume and decreased right atrial volume with CMR compared to COPD patients without heart failure (Table 2). Right ventricular dimensions measured with CMR did not differ significantly between COPD patients with or without heart failure (data not shown). None of the participants had aortic valve disease, three had grade 2/4 mitral valve insufficiency, and three grade 2/4 tricuspid valve insufficiency (data not shown).

Univariate analyses of CMR measurements are shown in Table 3. In the single test evaluation of these CMR measurements, LVEF at a cut-off level of 45% showed the best test characteristics with a positive predictive value of 1.0 (95% CI 0.92-1.0) and a negative predictive value of 0.87 (95% CI 0.83-0.90) (Table 4).

Multivariable analysis of CMR measurements are also shown in Table 3. The best reduced 'CMR' model included the following items: LV end-systolic diameter, LVEF, and indexed RA and LA volume, with an ROC-area of 0.88 (95% CI 0.79-0.97) (Table 5).

In Table 5, the diagnostic values of the CMR parameters, ECG, and NT-proBNP beyond clinical information are presented. While the ROC-area of the 'clinical model' (signs and symptoms) was only 0.75, adding CMR parameters increased the ROC-area significantly to 0.91. This was significantly higher than addition of ECG (ROC-area 0.77) or NT-proBNP (ROC-area 0.80) to the clinical model. Adding ECG or NT-proBNP to the 'clinical+CMR model' provided no further diagnostic information.

Discussion

Our study is the first to show that cardiovascular magnetic resonance imaging (CMR) measurements are very valuable in detecting unrecognised heart failure in stable mild to moderate severe COPD patients. A 'CMR' model including measurements of LVEF, indexed left and right atrial volume, and left ventricular end-systolic dimensions had a ROC-area of 0.88 for determining presence or absence of heart failure, with the consensus diagnosis of the panel as the reference standard. Beyond a diagnostic model including signs and symptoms only (ROC-area 0.75), the CMR parameters had by far the highest additional diagnostic value compared to more easily available diagnostic tests such as ECG (ROC-area 0.77) and natriuretic peptide measurements (ROC-area 0.80).

To appreciate the results, some methodological aspects need to be discussed. First, the diagnosis of heart failure misses an irreproachable reference ('gold') standard. Therefore, we used the consensus diagnosis method to assess the final diagnosis of heart failure, as is common in diagnostic heart failure studies, and conform method guidelines.[21;23-25;31] Earlier studies have shown that panel diagnosis for establishing heart failure is highly reproducible.[27;32;33] The major disadvantage of this reference method, however, is the risk of incorporation bias,[25;34-36] because the reference standard is not independent from the tests studied. This disadvantage was decreased in our study because all patient information was considered by the expert panel, including the tests under study, except NT-proBNP. The potential for incorporation bias did not apply to NT-proBNP and CMR because results of these tests were not included in the consensus diagnosis. Furthermore, echocardiographic measurements were not considered as tests under study. This, because echocardiography weighed heavily in the consensus evaluation: echocardiographic (systolic or diastolic) ventricular dysfunction was obligatory to fulfill the criteria for a heart failure case.[25] Finally, results from clinical evaluation, ECG, chest X-ray, and blood tests (which were forwarded to the expert panel) provide only 'pieces of information' to an array of more or less equally contributing tests.[25] Therefore, incorporation bias and thus overestimation of the value of these tests is likely to be minimal.[25]

By using the consensus diagnosis including the important contribution of echocardiography to the diagnostic outcome (i.e. presence or absence of heart failure) the diagnostic value of CMR measurements can by definition not be higher than the echocardiographic assessment. This is somewhat at odds with studies comparing CMR and echocardiography, showing that CMR measurements are more precise and reproducible than echocardiographic measurements.[11;37] Before CMR can be considered as a potentially new reference standard of heart failure, it should show at least a good performance when compared to the currently established reference standard (i.e. the expert panel).

A second issue is the definition of diastolic heart failure. There are persisting concerns about establishing the diagnosis of 'isolated' diastolic heart failure on echocardiographic measurements. [8;38;39] CMR seems to be better equipped to assess diastolic dysfunction than echocardiography,[12] and can provide more precise three dimensional measurements without geometric assumptions.[10] Our study showed that CMR measurements indicative of diastolic dysfunction such as LA volume and E/A ratio were of diagnostic value to detect heart failure. With addition of more detailed and specialised CMR measurements of diastolic ventricular function,

such as analysis of diastolic velocity and volume flow, and global and regional analysis of myocardial strain, the assessment of diastolic function can be further increased.[12]

An interesting observation in our study was that in patients with heart failure the mean right atrial volume was decreased, while the mean left atrial volume increased compared to COPD patients without heart failure. A possible explanation for this phenomenon could be that in an early phase of heart failure increase in left atrial volume leads to a decrease in right atrial volume. Importantly, however, LA volume and RA volume had an independent contribution to the diagnosis of heart failure (Table 3).

Our study showed that some CMR measurements produced comparable results to echocardiography, such as LVEF, LV end-systolic and end-diastolic diameter, while other parameters differed widely (indexed LV mass and LA volume, and E/A ratio). An important reason for this difference is that with echocardiography geometrical assumptions are necessary to measure LV mass and left atrial volume, and E/A ratios are assessed differently by CMR than with echocardiography. Moreover, left ventricular mass assessed by CMR was artificially less because the papillary muscles were excluded from the myocardial mass. For measurements without geometrical assumptions (LV end-systolic and end-diastolic diameter), and LV ejection fraction the differences between CMR and echocardiographic measurements were small. In all, measurements of CMR and echocardiography are therefore not interchangeable.[10]

Our study clearly showed that CMR is a promising test in recognising heart failure in COPD patients either as a single diagnostic tool or in addition to information from history taking and physical examination. The added value of other tests such as ECG and NT-proBNP was considerably lower. Disadvantages of CMR include the acquisition time, limited availability and the price (approximately 5.5 times the price of echocardiography).[40]

The acquisition time will probably decrease further by new sequences yielding real-time acquisition without the need for breath-holding.[41]

In conclusion, CMR is a powerful tool in detecting or excluding heart failure among stable COPD patients. In cases of uninterpretable echocardiographic measurements, which is not uncommon in this difficult to asses patient population, CMR could certainly serve as an alternative. Further study on more detailed

assessment of diastolic and right sided heart function with CMR seems worthwhile to further increase its diagnostic yield.

Acknowledgement

We thank the participating patients and general practitioners, including the general practices connected to the General Practice Network Utrecht (HNU), the sonographers, especially Elly Lutgert-Hagman and Ineke Kasteleijn and the CMR technicians Niels Blanken, Greet Bouwman, and Marianne Nagtegaal. We thank Frances Verheij and Peter Zuithoff for their assistance in data management, and Lennart Bongartz for his work on the post-processing of CMR measurements.
The study was funded by a research grant (number 904-61-144) of the Netherlands Organisation for Scientific Research (NWO).
We thank Roche Inc. (Mannheim, Germany) for supplying the assays for analysis of NTproBNP.

References

1. Hogg K, Swedberg K, McMurray J. Heart failure with preserved left ventricular systolic function; epidemiology, clinical characteristics, and prognosis. *J Am Coll Cardiol* 2004;43:317-27.
2. Remes J, Miettinen H, Reunanen A, Pyörälä K. Validity of clinical diagnosis of heart failure in primary health care. *Eur Heart J* 1991;12:315-21.
3. Boussuges A, Pinet C, Molenat F, Burnet H, Ambrosi P, Badier M *et al*. Left atrial and ventricular filling in chronic obstructive pulmonary disease. An echocardiographic and Doppler study. *Am J Respir Crit Care Med* 2000;162:670-5.
4. Wheeldon NM, MacDonald TM, Flucker CJ, McKendrick AD, McDevitt DG, Struthers AD. Echocardiography in chronic heart failure in the community. *Q J Med* 1993;86:17-23.
5. Vasan RS, Levy D. Defining diastolic heart failure: a call for standardized diagnostic criteria. *Circulation* 2000;101:2118-21.
6. Grossman W. Defining diastolic dysfunction. *Circulation* 2000;101:2020-1.
7. Zile MR. Heart failure with preserved ejection fraction: is this diastolic heart failure? *J Am Coll Cardiol* 2003;41:1519-22.
8. Petrie MC, Hogg K, Caruana L, McMurray JJ. Poor concordance of commonly used echocardiographic measures of left ventricular diastolic function in patients with suspected heart failure but preserved systolic function: is there a reliable echocardiographic measure of diastolic dysfunction? *Heart* 2004;90:511-7.

9. Vasan RS, Benjamin EJ. Diastolic heart failure--no time to relax. *N Engl J Med* 2001;344:56-9.

10. Bellenger NG, Burgess MI, Ray SG, Lahiri A, Coats AJ, Cleland JG *et al.* Comparison of left ventricular ejection fraction and volumes in heart failure by echocardiography, radionuclide ventriculography and cardiovascular magnetic resonance; are they interchangeable? *Eur Heart J* 2000;21:1387-96.

11. Bellenger NG, Grothues F, Smith GC, Pennell DJ. Quantification of right and left ventricular function by cardiovascular magnetic resonance. *Herz* 2000;25:392-9.

12. Paelinck BP, Lamb HJ, Bax JJ, van der Wall EE, de Roos A. Assessment of diastolic function by cardiovascular magnetic resonance. *Am Heart J* 2002;144:198-205.

13. Remme WJ, Swedberg K. Guidelines for the diagnosis and treatment of chronic heart failure. *Eur Heart J* 2001;22:1527-60.

14. Lijmer JG, Mol BW, Heisterkamp S, Bonsel GJ, Prins MH, van der Meulen JH *et al.* Empirical evidence of design-related bias in studies of diagnostic tests. *JAMA* 1999;282:1061-6.

15. Essebag V, Genest J, Jr., Suissa S, Pilote L. The nested case-control study in cardiology. *Am Heart J* 2003;146:581-90.

16. Rutten FH, Cramer MJM, Grobbee DE, Sachs APE, Kirkels JH, Lammers J-WJ *et al.* Unrecognized heart failure in elderly patients with stable chronic obstructive pulmonary disease. *Eur Heart J 2005, in press*.

17. Chia JM, Fischer SE, Wickline SA, Lorenz CH. Performance of QRS detection for cardiac magnetic resonance imaging with a novel vectorcardiographic triggering method. *J Magn Reson Imaging* 2000;12:678-88.

18. Myerson SG, Montgomery HE, World MJ, Pennell DJ. Left ventricular mass: reliability of M-mode and 2-dimensional echocardiographic formulas. *Hypertension* 2002;40:673-8.

19. Germain P, Roul G, Kastler B, Mossard JM, Bareiss P, Sacrez A. Inter-study variability in left ventricular mass measurement. Comparison between M-mode echography and MRI. *Eur Heart J* 1992;13:1011-9.

20. Bottini PB, Carr AA, Prisant LM, Flickinger FW, Allison JD, Gottdiener JS. Magnetic resonance imaging compared to echocardiography to assess left ventricular mass in the hypertensive patient. *Am J Hypertens* 1995;8:221-8.

21. Cowie MR, Struthers AD, Wood DA, Coats AJ, Thompson SG, Poole-Wilson PA *et al.* Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care. *Lancet* 1997;350:1349-53.

22. Mosterd A, Hoes AW, de Bruyne MC, Deckers JW, Linker DT, Hofman A *et al.* Prevalence of heart failure and left ventricular dysfunction in the general population; The Rotterdam Study. *Eur Heart J* 1999;20:447-55.

23. Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P *et al.*

Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med* 2002;347:161-7.

24. Moons KG, Biesheuvel CJ, Grobbee DE. Test research versus diagnostic research. *Clin Chem* 2004;50:473-6.

25. Moons KG, Grobbee DE. When should we remain blind and when should our eyes remain open in diagnostic studies? *J Clin Epidemiol* 2002;55:633-6.

26. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM *et al*. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Standards for Reporting of Diagnostic Accuracy. *Clin Chem* 2003;49:1-6.

27. Rutten FH, Moons KGM, Cramer MJM, Grobbee DE, Zuithoff NPA, Lammers J-WJ *et al*. Recognising heart failure in elderly patients with stable chronic obstructive pulmonary disease in primary care: a cross-sectional diagnostic study. *Accepted BMJ 2005.*

28. Harrell FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996;15:361-87.

29. Moons KG, van Es GA, Deckers JW, Habbema JD, Grobbee DE. Limitations of sensitivity, specificity, likelihood ratio, and bayes' theorem in assessing diagnostic probabilities: a clinical example. *Epidemiology* 1997;8:12-7.

30. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988;44:837-45.

31. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM *et al*. The STARD statement for reporting studies of diagnostic accuracy: explanation and elaboration. *Clin Chem* 2003;49:7-18.

32. Cowie MR, Wood DA, Coats AJ, Thompson SG, Poole-Wilson PA, Suresh V *et al*. Incidence and aetiology of heart failure; a population-based study. *Eur Heart J* 1999;20:421-8.

33. Wright SP, Doughty RN, Pearl A, Gamble GD, Whalley GA, Walsh HJ *et al*. Plasma amino-terminal pro-brain natriuretic peptide and accuracy of heart-failure diagnosis in primary care: a randomized, controlled trial. *J Am Coll Cardiol* 2003;42:1793-800.

34. Whiting P, Rutjes AW, Dinnes J, Reitsma J, Bossuyt PM, Kleijnen J. Development and validation of methods for assessing the quality of diagnostic accuracy studies. *Health Technol Assess* 2004;8:iii1-iii, 4.

35. Ransohoff DF, Feinstein AR. Problems of spectrum and bias in evaluating the efficacy of diagnostic tests. *N Engl J Med* 1978;299:926-30.

36. Clinical epidemiology; a basic science for clinical medicine. Boston: Little, Brown

and Co., 1985.

37. Grothues F, Smith GC, Moon JC, Bellenger NG, Collins P, Klein HU *et al*. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. *Am J Cardiol* 2002;90:29-34.

38. Caruana L, Petrie MC, Davie AP, McMurray JJ. Do patients with suspected heart failure and preserved left ventricular systolic function suffer from "diastolic heart failure" or from misdiagnosis? A prospective descriptive study. *BMJ* 2000;321:215-8.

39. Vasan RS, Benjamin EJ, Levy D. Congestive heart failure with normal left ventricular systolic function. Clinical approaches to the diagnosis and treatment of diastolic heart failure. *Arch Intern Med* 1996;156:146-57.

40. Pennell DJ, Sechtem UP, Higgins CB, Manning WJ, Pohost GM, Rademakers FE *et al*. Clinical indications for cardiovascular magnetic resonance (CMR): Consensus Panel report. *Eur Heart J* 2004;25:1940-65.

41. Reeder SB, Faranesh AZ. Ultrafast pulse sequence techniques for cardiac magnetic resonance imaging. *Top.Magn Reson Imaging* 2000;11:312-30.

42. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J* 1993;16 *Suppl*:5-40.

43. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. 1916. *Nutrition* 1989;5:303-11.

44. Devereux RB, Casale PN, Kligfield P, Eisenberg RR, Miller D, Campo E *et al*. Performance of primary and derived M-mode echocardiographic measurements for detection of left ventricular hypertrophy in necropsied subjects and in patients with systemic hypertension, mitral regurgitation and dilated cardiomyopathy. *Am J Cardiol* 1986;57:1388-93.

Chapter 10

General discussion

General discussion

The central theme of this thesis was heart failure in the presence of chronic obstructive pulmonary disease (COPD). The major findings we presented were:

- The high prevalence of unrecognised heart failure in elderly stable COPD patients (20.5%).
- Natriuretic peptides are useful as diagnostic predictors in this population, but perform less than in other patient domains (i.e. patients suffering from acute dyspnoea[1] or patients suspected of heart failure[2])
- With application of easily assessable parameters, cardiovascular magnetic resonance (CMR) imaging performed well as a diagnostic predictor of presence or absence of heart failure in this population.

Clinical consequences of the high prevalence of heart failure in COPD

One out of five COPD patients aged 65 years or over has unrecognised heart failure, which is about 4 times as high as to be expected in a general population of elderly subjects.[3] Detecting patients with unknown heart failure is worthwhile because drugs and other treatment options are available that favourably affect prognosis.[4] As COPD is common in the elderly, with a prevalence of 10-15% in those aged 65 years or over, clinicians face important diagnostic dilemmas. Both general practitioners and pulmonologists are confronted by this problem, and intensified co-operation between these physicians and the cardiologist is necessary to optimise the management of these patients. One possible solution is a joint out-patient clinic run by a pulmonologist and a cardiologist, where dyspnoeic patients can be referred to by the general practitioner for a (one-stop) diagnostic check-up. Another solution would be that pulmonary function tests, natriuretic peptide measurements, and echocardiography become more widely available to allow a 'patient-centred' approach in all dyspnoeic patients, without restrictions imposed by dividing lines between primary and secondary care, and between pulmonologists and cardiologists. This option, however, will require some additional training of the involved physicians.

Should we screen all elderly COPD patients for presence of heart failure?

Echocardiography remains the cornerstone investigation in the diagnostic assessment of heart failure.[4] Widespread application of this facility, however, is hampered by the limited number of echocardiographs and qualified cardiosonographers. Moreover, accessibility to this diagnostic facility is limited for elderly immobilised patients in primary care, and echocardiography is not part of the standard investigational protocol of pulmonologists.

Natriuretic peptides are insufficient as a single screening test, although they are a good starting point. They are easily measured, inexpensive, and are becoming increasingly available. Natriuretic peptides (e.g. B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP)) all have shown to be good predictors of presence or absence of heart failure in patients suffering from acute dyspnoea,[1] or patients suspected of heart failure.[2] Our study showed, however, that the overall diagnostic accuracy of natriuretic peptides is only moderate in elderly stable COPD patients, although the diagnostic performance was better than reported in community screening studies with systolic and/or diastolic dysfunction as the outcome.[5;6] A major reason for a lower diagnostic performance in our study was the limited 'contrast' between patients with and without heart failure. Because (NT-pro)BNP production in the ventricles increases in response to increased intracardiac volume or pressure, lower levels in our stable population could be expected than for instance in patients suffering from acute dyspnoea (who may have an acute increase in intracardiac volume or pressure). Moreover, the median levels of (NT-pro)BNP in COPD patients without heart failure in our study were at the upper level of normal, possibly due to some degree of right ventricular wall stress.[7;8]

Although worthwhile in principle, a straightforward approach to screening by one of the two most appropriate diagnostic tests is not yet possible in this population. A feasible option would be to measure (NT-pro)BNP in all elderly COPD patients with subsequently echocardiography in those with increased values to confirm the diagnosis, and to assess whether treatable causes of heart failure are present. Still, the clinician has to bear in mind the logistic problems regarding echocardiography mentioned above, and the fact that exact cut-off values for (NT-pro)BNP have not yet been established.[9] Moreover, it has to be realised that these cut-off values are also influenced by age, gender, and the population under study.[5;6]

When should CMR be used as a diagnostic tool in COPD patients?

High-quality echocardiographic measurements are more difficult to obtain in COPD patients due to hyperinflation of the lungs.[10;11] Still, in our study in only 10% of the participants the echocardiographic view was of poor quality. The performance of other diagnostic tests than echocardiogram and (NT-pro)BNP is also less in COPD patients. Overlap in signs and symptoms, and in abnormalities found on electrocardiography[12;13] and chest X-ray[14;15] make these tests less specific when assessing heart failure in COPD patients.

Cardiovascular magnetic resonance (CMR) imaging appears to offer a diagnostic tool which is unaffected by the presence of COPD. It has the unique potential of 3-dimensional function analysis with great accuracy and reproducibility,[16] with unlimited access to the thoracic cavity, and independence of geometric assumptions.[17] Our study was the first to show that easily assessable parameters of CMR are powerful predictors of the presence of heart failure in COPD patients. More sophisticated applications in COPD patients are possible with CMR, with more thorough assessment of diastolic function and visualisation of the right side of the heart.[18] However, CMR is currently still a relatively rare resource, has longer acquisition time, and an important cost difference with echocardiography at a price of 5.5 times that of echocardiography.[19] Therefore, at present, CMR seems to be an option only in those COPD patients who have a poor echocardiographic acoustic window.

Is COPD also a vascular disease?

The pulmonary effects of tobacco smoking are well known, with chronic pulmonary inflammation and eventually fibrosis of peripheral airways as well as destruction of lung parenchyma.[20] That COPD is positively correlated with systemic inflammation[21;22] and atherosclerosis[23] is also established. However, whether pulmonary arterial atherosclerosis plays an important role in the promotion or progression of the disease process is currently not known.

The pulmonary arterial vascular bed, from the pulmonary artery till the alveolar-capillary membrane, has so far been a 'no man's land', hardly studied by pulmonologists or cardiologists. In the light of the above mentioned mechanisms of tobacco smoking, (systemic) atherosclerosis, and pulmonary and systemic inflammation, with their interrelation and their amplifying effects, pulmonary arterial atherosclerosis is an obvious additional mechanism. Arguments for a pulmonary arterial atherosclerosis hypothesis in literature are, however, scarce. One study reported pulmonary artery atherosclerosis as a common autopsy finding with positive correlation with COPD, but also with aortic and coronary atherosclerosis.[24] Another study showed that in about half of the patients with stable COPD central pulmonary artery lesions are detectable with transoesophageal echocardiography.[25]

Pulmonary arterial atherosclerosis could possibly induce alveolar-capillary membrane dysfunction, because the capillary endothelium of this membrane is the terminus of the pulmonary arterial vascular bed. As the alveolar-capillary dysfunction is the centrepiece of blood oxygenation, dysfunction of this membrane

can further induce pulmonary, but also cardiac and systemic changes by (periodic) hypoxemia. Hypoxemia can cause cellular hypoxia with all types of dysfunction as a result. Notably, arterial wall hypoxia can be induced, which is another causal factor in the development of atherosclerosis.[26;27]

Future clinical research

Diagnostic studies are urgently needed to improve the assessment of presence or absence of heart failure in COPD patients, but also in other high risk populations such as patients with diabetes or renal dysfunction. Detailed assessment of CMR in COPD patients seems worthwhile, with special attention for the right side of the heart and application of more sophisticated measurements. We also need studies that determine whether joint out-patient clinics for dyspnoeic patients have advantages compared to regular service. Further research targeted on exploring the interrelations between both syndromes could possibly indicate new therapeutic options.

Of special interest are studies that target on pharmacological interventions directed against (systemic and/or pulmonary) atherosclerosis or alveolar-capillary membrane dysfunction in patients with (developing) COPD. By considering COPD a 'vascular disease' a number of drugs known for their cardiovascular activity could (speculatively) be useful for patients with (developing) COPD. These therapeutic options are the more challenging because in patients with COPD no drugs are currently available that clearly increase survival.

One could think about drugs with positive effects on the endothelium and atherosclerotic plaque-stabilising drugs. Another target could be the alveolar-capillary membrane. ACE-inhibitors can stabilise atherosclerotic plaques, but also ameliorate the alveolar membrane gas exchange.[28] Moreover, they can decrease pulmonary inflammation and pulmonary vascular constriction.[29] Another way of action of ACE-inhibitors is by the renin-angiotensin system. This system exerts its activity not only in the systemic circulation, but also in organ tissues, such as the lungs.[29] Angiotensin-II is, for instance, a potent pulmonary airway constrictor. Therefore, ACE-inhibitors, but also angiotensin-II receptor blockers may improve pulmonary obstruction by decreasing angiotensin-II levels.[30] Also aldosteron-antagonists such as spironolactone have possible positive effects on the gas exchange over the alveolar-capillary membrane.[31]

Theoretically, even β-blockers could have a place in treating patients with (developing) COPD. Until recently, it was advised not to use β-blocking agents in

case of COPD, notably in the presence of bronchospasm.[30;32;33] However, a recent systematic review revealed that β-blocking agents, at least cardio-selective ones, can be safely administered to COPD patients even in those patients with some bronchospasm, with no or only small negative effects on pulmonary function.[34;35] β-blocking agents have a positive effect on the atherosclerotic process, [36] but they also can counter-act the increased generalised sympathetic activity found in COPD.[37]

These treatment options are based on pathophysiologic reasoning, with still important knowledge gaps. The possible effects of the drugs are still rather speculative. A starting point for further investigating these treatment options could be case-control studies using pharmacological data-bases. Next, and as a realistic option, clinical trials with anti-atherosclerotic drugs in COPD patients could be initiated.

References

1. Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P *et al*. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med* 2002;347:161-7.
2. Cowie MR, Struthers AD, Wood DA, Coats AJ, Thompson SG, Poole-Wilson PA *et al*. Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care. *Lancet* 1997;350:1349-53.
3. Hogg K, Swedberg K, McMurray J. Heart failure with preserved left ventricular systolic function; epidemiology, clinical characteristics, and prognosis. *J Am Coll Cardiol* 2004;43:317-27.
4. Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M *et al*. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. *Eur Heart J* 2005;26:1115-40.
5. Vasan RS, Benjamin EJ, Larson MG, Leip EP, Wang TJ, Wilson PW *et al*. Plasma natriuretic peptides for community screening for left ventricular hypertrophy and systolic dysfunction: the Framingham heart study. *JAMA* 2002;288:1252-9.
6. Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR, Burnett JC, Jr. Plasma brain natriuretic peptide to detect preclinical ventricular systolic or diastolic dysfunction: a community-based study. *Circulation* 2004;109:3176-81.
7. Lang CC, Coutie WJ, Struthers AD, Dhillon DP, Winter JH, Lipworth BJ. Elevated levels of brain natriuretic peptide in acute hypoxaemic chronic obstructive pulmonary disease. *Clin Sci (Lond)* 1992;83:529-33.

8. Troughton RW, Prior DL, Pereira JJ, Martin M, Fogarty A, Morehead A *et al*. Plasma B-type natriuretic peptide levels in systolic heart failure: importance of left ventricular diastolic function and right ventricular systolic function. *J Am Coll Cardiol* 2004;43:416-22.

9. Cowie MR, Jourdain P, Maisel A, Dahlstrom U, Follath F, Isnard R *et al*. Clinical applications of B-type natriuretic peptide (BNP) testing. *Eur Heart J* 2003;24:1710-8.

10. Boussuges A, Pinet C, Molenat F, Burnet H, Ambrosi P, Badier M *et al*. Left atrial and ventricular filling in chronic obstructive pulmonary disease. An echocardiographic and Doppler study. *Am J Respir Crit Care Med* 2000;162:670-5.

11. Wheeldon NM, MacDonald TM, Flucker CJ, McKendrick AD, McDevitt DG, Struthers AD. Echocardiography in chronic heart failure in the community. *Q J Med* 1993;86:17-23.

12. Baljepally R, Spodick DH. Electrocardiographic screening for emphysema: the frontal plane P axis. *Clin Cardiol* 1999;22:226-8.

13. Harrigan RA, Jones K. ABC of clinical electrocardiography. Conditions affecting the right side of the heart. *BMJ* 2002;324:1201-4.

14. Gehlbach BK, Geppert E. The pulmonary manifestations of left heart failure. *Chest* 2004;125:669-82.

15. Rao BS, Cohn KE, Eldridge FL, Hancock EW. Left ventricular failure secondary to chronic pulmonary disease. *Am J Med* 1968;45:229-41.

16. Bellenger NG, Burgess MI, Ray SG, Lahiri A, Coats AJ, Cleland JG *et al*. Comparison of left ventricular ejection fraction and volumes in heart failure by echocardiography, radionuclide ventriculography and cardiovascular magnetic resonance; are they interchangeable? *Eur Heart J* 2000;21:1387-96.

17. Bellenger NG, Grothues F, Smith GC, Pennell DJ. Quantification of right and left ventricular function by cardiovascular magnetic resonance. *Herz* 2000;25:392-9.

18. Paelinck BP, Lamb HJ, Bax JJ, van der Wall EE, de Roos A. Assessment of diastolic function by cardiovascular magnetic resonance. *Am Heart J* 2002;144:198-205.

19. Pennell DJ, Sechtem UP, Higgins CB, Manning WJ, Pohost GM, Rademakers FE *et al*. Clinical indications for cardiovascular magnetic resonance (CMR): Consensus Panel report. *Eur Heart J* 2004;25:1940-65.

20. Pauwels RA, Buist AS, Ma P, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: National Heart, Lung, and Blood Institute and World Health Organization Global Initiative for Chronic Obstructive Lung Disease (GOLD): executive summary. *Respir Care* 2001;46:798-825.

21. Sin DD, Man SF. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic in-

flammation in chronic obstructive pulmonary disease. *Circulation* 2003;107:1514-9.

22. Oudijk EJ, Lammers JW, Koenderman L. Systemic inflammation in chronic obstructive pulmonary disease. *Eur Respir J Suppl* 2003;46:5s-13s.

23. Zureik M, Kauffmann F, Touboul PJ, Courbon D, Ducimetiere P. Association between peak expiratory flow and the development of carotid atherosclerotic plaques. *Arch Intern Med* 2001;161:1669-76.

24. Moore GW, Smith RR, Hutchins GM. Pulmonary artery atherosclerosis: correlation with systemic atherosclerosis and hypertensive pulmonary vascular disease. *Arch Pathol Lab Med* 1982;106:378-80.

25. Russo A, De Luca M, Vigna C, De R, V, Pacilli M, Lombardo A *et al*. Central pulmonary artery lesions in chronic obstructive pulmonary disease: A transesophageal echocardiography study. *Circulation* 1999;100:1808-15.

26. Simanonok JP. Non-ischemic hypoxia of the arterial wall is a primary cause of atherosclerosis. *Med Hypotheses* 1996;46:155-61.

27. Martin JF, Booth RF, Moncada S. Arterial wall hypoxia following thrombosis of the vasa vasorum is an initial lesion in atherosclerosis. *Eur J Clin.Invest* 1991;21:355-9.

28. Guazzi M. Alveolar-capillary membrane dysfunction in heart failure: evidence of a pathophysiologic role. *Chest* 2003;124:1090-102.

29. Forth R, Montgomery H. ACE in COPD: a therapeutic target? *Thorax* 2003;58:556-8.

30. Aronow WS. Treatment of heart failure in older persons. Dilemmas with coexisting conditions: diabetes mellitus, chronic obstructive pulmonary disease, and arthritis. *Congest Heart Fail* 2003 9 :142-7.

31. Agostoni P, Magini A, Andreini D, Contini M, Apostolo A, Bussotti M *et al*. Spironolactone improves lung diffusion in chronic heart failure. *Eur Heart J* 2005;26:159-64.

32. Kotlyar E, Keogh AM, Macdonald PS, Arnold RH, McCaffrey DJ, Glanville AR. Tolerability of carvedilol in patients with heart failure and concomitant chronic obstructive pulmonary disease or asthma. *J Heart Lung Transplant* 2002;21:1290-5.

33. Gheorghiade M, Colucci WS, Swedberg K. Beta-blockers in chronic heart failure. *Circulation* 2003;107:1570-5.

34. Salpeter SR, Ormiston TM, Salpeter EE, Poole PJ, Cates CJ. Cardioselective beta-blockers for chronic obstructive pulmonary disease: a meta-analysis. *Respir Med* 2003;97:1094-101.

35. Salpeter SR, Ormiston TM, Salpeter EE. Cardioselective beta-blockers in patients with reactive airway disease: a meta-analysis. *Ann Intern Med* 2002;137:715-25.

36. Bondjers G. Anti-atherosclerotic effects of beta-blockers. *Eur Heart J* 1994;15 Suppl C:8-15.

37. Sakamaki F, Satoh T, Nagaya N, Kyotani S, Nakanishi N, Ishida Y. Abnormality of left ventricular sympathetic nervous function assessed by (123)I-metaiodobenzylguanidine imaging in patients with COPD. *Chest* 1999;116:1575-81.

Summary

Summary

In the introduction (**Chapter one)** we discuss that, notwithstanding the clinical importance of heart failure, relevant information about the optimal diagnostic process and evidence-based treatment of every-day heart failure patients is still lacking. For example, the therapeutic approach of the large group of elderly patients with a preserved left ventricular ejection fraction ('isolated' diastolic heart failure) is not well established. Furthermore, diagnostic and therapeutic studies often excluded patients with relevant comorbidity, such as diabetes and chronic obstructive pulmonary disease (COPD). In The Netherlands, but also in other European countries, most heart failure patients, in particular older patients with multiple comorbidities, are diagnosed and managed in primary care. Moreover, echocardiography, the cornerstone in the diagnostic assessment is not easily accessible for patients from primary care, especially when immobilised. Differences in accessibility to diagnostic procedures such as echocardiography and in patient 'spectrum' of primary care physicians compared to cardiologists play an important role in the perceptions of heart failure management and the adjustment to available guidelines.

In our practice study in **Chapter two** we show that general practitioners (GPs) and cardiologists differ regarding the diagnostic assessment and treatment of heart failure patients. In our practice study we assessed primary care patients with a diagnosis of heart failure, *not* co-treated by a cardiologist. This is an important difference with other practice studies which compared the management of GPs and cardiologists. In these studies conducted in the same time-period, many 'primary care' patients with heart failure were co-treated by a cardiologist.

'GP heart failure patients' in our study were much older and more often female than 'cardiologist heart failure patients'. The GPs diagnosed heart failure most often on the basis of signs and symptoms, with echocardiography performed in only 12% of the patients, while almost all (97%) cardiology patients underwent echocardiography. 'GP heart failure patients' were less often prescribed angiotensin-converting enzyme (ACE) inhibitors and β-blockers than 'cardiologist heart failure patients' (40 versus 76%, 9 versus 30%, respectively). Fear of side effects of ACE inhibitors by GPs, and difficulties with up-titrating the dosages of β-blockers were important reasons for under-prescription of these prognostically beneficial drugs.

In **Chapter three**, we describe the differences in opinion between GPs and cardiologists regarding diagnosis and management of heart failure. In general, there

were no major differences regarding history taking and physical examination, although cardiologist judged auscultation of the heart as more useful than GPs. Chest X-ray and electrocardiography are regarded as useful in the diagnostic assessment by both physicians. As additional diagnostic test, GPs preferred test treatment with diuretics, and cardiologists echocardiography. Natriuretic peptide measurements were not yet within the diagnostic scope of both physicians at the moment our study was executed (in the year 2000). GPs preferred mono-therapy with diuretics and are reluctant to start β-blockers, while cardiologist prefer the combination of angiotensin-converting enzyme inhibitors (ACE-inhibitors) and diuretics as starting treatment, and tend to prescribe β-blockers more often than GPs.

As already mentioned in chapter one, co-morbidities are of crucial importance in the diagnosis and management of the large group of elderly heart failure patients. Especially COPD is an important co-morbidity because it complicates the diagnostic assessment and its presence may influence prognosis and the choice of therapy. Moreover, there are indications in the literature that heart failure and COPD often coincide.

We therefore performed a literature review to retrieve more detailed information about the prevalence of heart failure in COPD or vice versa, and the diagnostic and therapeutic consequences of concomitant presence of both diseases. In **Chapter four** the results of the review are reported. We could only find one study that assessed the prevalence of (unrecognised) heart failure in patients with (a history of) COPD or asthma. A prevalence of 21% of previously unknown heart failure was reported. Importantly, however, these were patients with acute dyspnoea necessitating them to visit an emergency department. Only 29% of the participants had an echocardiography, and definite presence of either asthma or COPD was not assessed in this study. Several other studies reported the prevalence of left ventricular systolic dysfunction (and thus not 'heart failure') among COPD patients. The reported prevalence varied considerably, with the highest prevalence (10-46%) among COPD patients experiencing an exacerbation (acute dyspnoea). We could not find any report on the prevalence of COPD in heart failure patients or patients with left ventricular systolic dysfunction.

Apart from similarities in signs and symptoms, recognising heart failure in the presence of COPD or vice versa is complicated by decreased diagnostic value of the chest X-ray and electrocardiography. Precise measurements with echocardiography can also be hampered by hyperinflated lungs in COPD patients.

Regarding treatment of concomitant heart failure and COPD, pulmonary and heart failure 'drug cocktails' can in general be administered safely to patients with both diseases, although, (short acting) β2-adrenoreceptor agonists and digitalis have potentially deleterious effects on cardiac and pulmonary function, respectively.

In **Chapter five** we reviewed the literature for etiological and pathophysiological pathways involved in the development of heart failure in the presence of COPD or vice versa. The relationship between COPD and heart failure seems multi-factorial, with tobacco smoking as a common etiologic factor. Local and systemic inflammation, and possibly local and systemic atherosclerosis are common pathways. An important starting point for both diseases seems to be dysfunction of the alveolar-capillary membrane, resulting in decreased oxygen diffusion, and (in more severe cases) sympathetic, and structural changes in heart and lungs, which could promote the development of COPD and heart failure. In more severe cases of COPD or heart failure, different mechanical, sympathetical, hypox(em)ic, and metabolic mechanisms can further aggravate or induce the other syndrome. At the moment, much of the interrelations between both syndromes is still unknown. In particular, the role of pulmonary arterial atherosclerosis requires further study.

In **Chapter six** we assessed the prevalence of previously unknown heart failure in elderly patients with a GP diagnosis of COPD, in a stable phase of their disease. All 405 participants underwent an extensive systematic diagnostic work-up, and the consensus opinion of an expert panel was used as reference test for heart failure. The panel used all available results from the diagnostic assessment, excluding NT-proBNP. Of 405 participating patients with a diagnosis of COPD, 83 (20.5%, 95% CI 16.7-24.8) had previously unrecognised heart failure (42 patients systolic, and 41 'isolated' diastolic, and none 'isolated' right sided heart failure). In total 244 (60.2%) patients had COPD according to the GOLD criteria; in 50 (20.5%, 95% CI 15.6-26.1) patients combined with unrecognised heart failure. To our knowledge, this was the first study to show that unrecognised heart failure is very common (20.5%) in elderly patients with COPD in a stable phase of their disease. Inclusion of patients with established heart failure (who were not invited to participate), would yield an estimate of heart failure of 26% in unselected primary care COPD patients. The prevalence of heart failure in stable COPD patients is therefore about four times as high as in subjects aged 65 years or over in the population at large.

In **Chapter seven** the value of symptoms and signs and additional tests, such as chest X-ray, electrocardiography, and natriuretic peptides (NT-proBNP) in

diagnosing heart failure in COPD patients was assessed. Independent predictors for the presence of heart failure were quantified in the before mentioned 405 COPD patients, using multivariate logistic modelling in combination with area under the receiver operating characteristic curves (ROC-area).
Independent clinical determinants of the presence of concomitant heart failure were a history of ischaemic heart disease, body mass index, laterally displaced apex beat, and heart rate. The ROC-area of this multivariate 'clinical model' with these four predictors was 0.70 (95% CI 0.64-0.76). The ROC area of NT-proBNP as single test was 0.72 (95% CI 0.66-0.79). Addition of NT-proBNP to the 'clinical model' had the largest added diagnostic value, with a significant increase of the ROC-area to 0.77 (95% CI 0.71-0.83), followed by electrocardiography (ROC-area 0.75; 95% CI 0.69-0.81). Thus, a limited number of easy available items from history and physical examination, with addition of NT-proBNP and/or electrocardiography can increase the confidence of the clinician about the presence or absence of concomitant heart failure in the individual primary care patient with stable COPD.

To our knowledge, this was the first study to determine the collective value of symptoms, signs, and additional testing to establish a diagnosis of heart failure in COPD patients in primary care. The overall diagnostic accuracy of the natriuretic peptide measurements in detecting heart failure in our study was lower than in previous studies including patients suspected of heart failure or in patients with acute dyspnoea visiting an emergency department. The most obvious reason for this lower diagnostic accuracy are differences in the populations studied.

In **Chapter eight** we compared the diagnostic utility of different natriuretic peptides in a random sample of 200 COPD patients. NT-proBNP, BNP Centaur and BNP AxSYM are comparable in their ability to identify or rule out previously unrecognised heart failure in elderly COPD patients. Overall, the different assay systems of natriuretic peptides were comparable in their ability to detect or rule out heart failure in these patients. The diagnostic ability of the natriuretic peptides was considerably higher for systolic than for 'isolated' diastolic heart failure. In patients with 'isolated' diastolic heart failure who are stable and assessed in rest, overfilling (volume overload) or increased cardiac filling pressures can not be expected. This is the major reason for the lower diagnostic ability of (NT-pro)BNP in our stable COPD population, because (NT-pro)BNP levels are positively correlated to intraventricular pressure or volume. Severity of COPD had no influence on (NT-pro)BNP levels, while the degree of left ventricular dysfunction clearly did.

In **Chapter nine** we assessed the (added) diagnostic value of cardiovascular magnetic resonance (CMR) imaging in a nested-case control study of 37 COPD patients with heart failure, and 41 COPD patients without heart failure. Presence of heart failure was assessed by a panel using all available diagnostic information, except NT-proBNP and CMR results. Of the CMR measurements, left ventricular ejection fraction (LVEF) < 45% had the best test characteristics with a positive predictive value of 1.0 (95% CI 0.92-1.0), and a negative predictive value of 0.87 (95% CI 0.83-0.90). CMR was the test with the highest diagnostic value in identifying heart failure in COPD patients, with an ROC-area of 0.88 (0.80-0.97). When added to information from history taking and physical examination, the added diagnostic value of CMR was higher than that of electrocardiography or natriuretic peptide measurements. CMR is therefore a powerful diagnostic tool for assessing presence or absence of heart failure. In cases of an uninterpretable echocardiography it could certainly serve as an alternative.

In the general discussion (**Chapter ten**) we further discuss the clinical consequences of our findings and future perspectives. In some detail we discuss the therapeutic implications of regarding COPD as a 'vascular disease'.

Intensified co-operation in practice and research between GPs, cardiologists, and pulmonologists is certainly needed to further explore common pathways and treatment options to increase the prognosis of this patient population.

Samenvatting

Samenvatting

In de introductie (**hoofdstuk 1**) wordt gesteld dat ondanks de klinische relevantie van hartfalen er nog steeds gebrek aan informatie bestaat over het optimale diagnostische traject en de beste therapie bij de 'alledaagse' patiënt met hartfalen. Zo is bijvoorbeeld de beste behandeling van de grote groep oudere patiënten met een behouden linker ventrikel ejectiefractie ('geïsoleerd' diastolisch hartfalen) nog onbekend. Daarnaast zijn patiënten met relevante comorbiditeit zoals diabetes mellitus en chronisch obstructieve longziekte (COPD) vaak uitgesloten bij de beschikbare diagnostische en therapeutische studies. In Nederland, maar ook in andere Europese landen worden de meeste patiënten met hartfalen, met name de oudere patiënten met relevante comorbiditeit, gediagnosticeerd en behandeld in de eerste lijn. Echocardiografie, de hoeksteen in de diagnostiek van hartfalen, is minder toegankelijk voor patiënten in de huisartspraktijk, zeker voor diegenen die minder mobiel zijn. Verschillen in toegankelijkheid van diagnostische faciliteiten zoals echocardiografie en verschillen in het 'patiëntenspectrum' tussen de eerste- en tweedelijn spelen een belangrijke rol bij de perceptie van hartfalen en het volgen van de beschikbare richtlijnen door huisartsen en cardiologen.

In **hoofdstuk 2** laten we zien dat huisartsen en cardiologen verschillen wat betreft hun diagnostisch beleid en de behandeling van patiënten met hartfalen. In dit praktijkonderzoek werden patiënten in de huisartspraktijk met een ICPC-code hartfalen en die *niet* (mee)behandeld werden door een cardioloog bestudeerd en vergeleken met een groep hartfalenpatiënten die werden behandeld door de cardioloog. Dit is een belangrijk verschil ten opzichte van andere praktijkstudies die het beleid bij hartfalen tussen huisartsen en cardiologen vergeleken. In deze onderzoeken, welke werden verricht in dezelfde tijdsperiode, werden veel 'huisarts-hartfalenpatiënten' medebehandeld door een cardioloog.

'Huisarts-hartfalenpatiënten' in ons onderzoek waren veel ouder en vaker vrouw dan 'cardiologische hartfalenpatiënten'. De huisarts stelde de diagnose hartfalen hoofdzakelijk op basis van klachten en symptomen en maakte slechts bij 12% van de patiënten gebruik van echocardiografie, terwijl bijna alle (97%) 'cardiologische hartfalenpatiënten' echocardiografie ondergingen. Bij 'huisarts-hartfalenpatiënten' werden minder vaak angiotensine converting enzym remmers (ACE-remmers) en β-blokkers voorgeschreven dan bij 'cardiologische hartfalenpatiënten' (40 versus 76%, 9 versus 30%, respectievelijk). Angst voor bijwerkingen van ACE-remmers en moeite met het titreren van de dosering van β-blokkers waren de belangrijkste redenen voor het minder voorschrijven van deze prognostisch gunstige medicatie door huisartsen.

In **Hoofdstuk 3** beschrijven we de verschillen tussen huisartsen en cardiologen betreffende hun opvattingen over de diagnostiek en behandeling van hartfalen. In het algemeen zijn er geen grote verschillen wat betreft anamnese en lichamelijk onderzoek, al vinden cardiologen auscultatie van het hart zinvoller bij de diagnostiek van hartfalen dan huisartsen. Longfoto en elektrocardiografie worden door beide clinici als zinvol ervaren. Als aanvullend diagnostisch onderzoek geven huisartsen de voorkeur aan een proefbehandeling met diuretica en cardiologen aan echocardiografie. Natriuretische peptiden bleken nog niet in het 'diagnostisch blikveld' te liggen van beide clinici op het moment dat het onderzoek werd verricht (in het jaar 2000). Wat betreft medicatie blijken huisartsen de voorkeur te geven aan mono-therapie met diuretica als startmedicatie en zijn ze huiverig om β-blokkers voor te schrijven.Cardiologen daarentegen geven de voorkeur aan een combinatie van ACE-remmers met diuretica als startmedicatie en zij schrijven vaker dan huisartsen β-blokkers voor.

Zoals reeds vermeld in hoofdstuk 1 is co-morbiditeit van cruciaal belang bij de diagnostiek en behandeling van de grote groep oudere patiënten met hartfalen. Vooral COPD is een belangrijke comorbiditeit omdat het de diagnostiek van hartfalen bemoeilijkt en omdat de aanwezigheid ervan de prognose van en de therapiekeuze bij hartfalen kan beïnvloeden. Daarbij zijn er aanwijzingen in de literatuur dat hartfalen en COPD vaak tegelijkertijd voorkomen.

We besloten daarom een literatuurstudie te verrichten om meer gedetailleerde gegevens te verkrijgen betreffende de prevalentie van hartfalen bij COPD patiënten of visa versa, alsmede de diagnostische en therapeutische consequenties van het tegelijkertijd voorkomen van hartfalen en COPD. In **Hoofdstuk 4** rapporteren we de resultaten van deze literatuurstudie. We vonden slechts één studie die de prevalentie bepaalde van (voorheen onbekend) hartfalen bij patiënten met (anamnestisch) COPD of astma. Deze prevalentie bleek 21% te zijn. Van belang hierbij is, dat het patiënten betrof met acute dyspnoe die hen noodzaakte de eerste hulp te bezoeken. Bij slechts 29% van de deelnemers werd een echocardiogram gemaakt. Of er werkelijk sprake was van COPD of astma werd niet nagegaan in deze studie. Verschillende andere studies doen wel verslag van de prevalentie van linker ventrikel systolische disfunctie (en dus niet 'hartfalen') bij COPD patiënten. De gerapporteerde prevalenties varieerden behoorlijk, met de hoogste prevalentie (10-46%) bij COPD patiënten die op dat moment een exacerbatie (acute dyspnoe) hadden. We konden geen onderzoeken in de literatuur vinden die de prevalentie onderzochten van COPD bij patiënten met hartfalen.

Behalve gelijkenis in klachten en verschijnselen bij lichamelijk onderzoek, wordt het herkennen van hartfalen bij COPD patiënten of visa versa gecompliceerd door de verminderde diagnostische waarde van de longfoto en het elektrocardiogram. Ook precieze metingen met echocardiografie kunnen hinder ondervinden van de verhoogde luchthoudendheid van de longen bij COPD patiënten. Wat betreft de medicamenteuze behandeling van gelijktijdig voorkomen van hartfalen en COPD kunnen 'long- en hartfalen cocktails' over het algemeen veilig worden toegediend, maar (kortwerkende) β2-adrenoreceptor agonisten en digitalis hebben respectievelijk een potentieel ongunstig cardiaal en pulmonaal effect.

In **Hoofdstuk 5** beschrijven we wat er in de literatuur bekend is over etiologische en pathofysiologische mechanismen die een rol (kunnen) spelen bij het ontstaan van hartfalen bij COPD of visa versa. De relatie tussen COPD en hartfalen lijkt multifactorieel bepaald, met roken als gemeenschappelijke etiologische factor. Lokale en systemische inflammatie en mogelijk ook lokale en systemische atherosclerose zijn eveneens gemeenschappelijke etiologische factoren. Een belangrijk startpunt voor beide aandoeningen lijkt disfunctie van de alveolaire-capillaire membraan te zijn, resulterend in verminderde zuurstofdiffusie en (bij ernstigere gevallen) ook sympathische en structurele veranderingen in hart en longen, die op hun beurt weer een verdere ontwikkeling van COPD of hartfalen kunnen veroorzaken.

In verder gevorderde stadia van COPD of hartfalen kunnen verschillende mechanische, sympathische, hypox(em)ische en ook metabole mechanismen zorgen voor verdere verergering of ontwikkeling van het andere syndroom. Momenteel is er nog veel onbekend omtrent de relatie tussen beide aandoeningen. Met name de rol die pulmonale atherosclerose zou kunnen spelen dient verder onderzocht te worden.

In **Hoofdstuk 6** beschrijven we de resultaten van ons onderzoek naar de prevalentie van voorheen onbekend hartfalen bij oudere patiënten die door de huisarts geclassificeerd waren als COPD-er. Alle 405 deelnemers ondergingen in een stabiele fase van hun 'COPD' een uitgebreid diagnostisch onderzoek en uiteindelijk bepaalde een expert panel of hartfalen en/of COPD aanwezig was. Het panel gebruikte alle beschikbare resultaten van de diagnostische onderzoeken, behalve het natriuretisch peptide NT-proBNP. Van de 405 deelnemers met de huisarts-diagnose COPD hadden er 83 (20,5%, 95% B.I. 16,7-24,8) voorheen onbekend hartfalen (42 patiënten systolisch, 41 'geïsoleerd' diastolisch en niemand 'geïsoleerd' rechtszijdig hartfalen). In totaal 244 (60,2%) patiënten hadden COPD

volgens de GOLD criteria; 50 (20,5%, 95% B.I. 15,6-26,1) patiënten gecombineerd met voorheen onbekend hartfalen. Zover wij weten is dit het eerste onderzoek dat aantoont dat voorheen onbekend hartfalen vaak (20,5%) voorkomt bij COPD patiënten in een stabiele fase van hun aandoening. Indien patiënten met vastgesteld hartfalen (die niet uitgenodigd werden om deel te nemen) meegeteld zouden worden, zou de prevalentie van hartfalen 26% zijn in deze populatie van 'ongeselecteerde' eerstelijns COPD patiënten. De prevalentie van hartfalen in stabiele COPD patiënten is daarmee ongeveer 4 keer zo hoog als bij mensen van 65 jaar en ouder in de algemene populatie.

In **Hoofdstuk 7** wordt de diagnostische waarde nagegaan van klachten, symptomen en enkele aanvullende testen (longfoto, elektrocardiografie en natriuretisch peptide (NT-proBNP)) voor het stellen of uitsluiten van de diagnose hartfalen bij COPD patiënten. De diagnostische waarde van deze testen werd bij de 405 deelnemers vastgesteld door gebruik te maken van multivariabele logistische regressie analyse in combinatie met berekening van de oppervlakte onder de 'receiver operating characteristic' curves (ROC-oppervlakte).

Onafhankelijke klinische determinanten voor de aanwezigheid van hartfalen bij COPD patiënten waren: ischemische hartziekte in de voorgeschiedenis, Queteletindex, een naar lateraal verplaatste hartpunt en de polsfrequentie. De ROC-oppervlakte van dit multivariabele 'klinische model' met deze vier voorspellers was 0,70 (95% BI 0,64-0,76). De ROC-oppervlakte van NT-proBNP als enige diagnostische test was 0,72 (95% BI 0,66-0,79). Toevoeging van NT-proBNP aan het 'klinische model' gaf de hoogste toegevoegde waarde met een significante toename van de ROC-oppervlakte tot 0,77 (95% BI 0,71-0,83). De op een na beste combinatie was elektrocardiografie toegevoegd aan het 'klinische model' (ROC-oppervlakte 0,75; 95% BI 0,69-0,81). Het blijkt dus dat een beperkt aantal makkelijk te bepalen items uit anamnese (met voorgeschiedenis) en lichamelijk onderzoek, aangevuld met natriuretisch peptide (NT-proBNP) en/of elektrocardiografie de diagnostische zekerheid van de clinicus betreffende aan- of afwezigheid van hartfalen bij de individuele patiënt in de huisartspraktijk met stabiele COPD flink kan verhogen.

Zover bekend is dit het eerste onderzoek waarbij de collectieve waarde van items uit anamnese, lichamelijk onderzoek en aanvullende diagnostisch onderzoek voor het vaststellen van hartfalen bij patiënten met COPD in de eerste lijn werd nagegaan. De diagnostische waarde van het natriuretisch peptide voor het detecteren van hartfalen was in ons onderzoek overigens lager dan bij voorgaande

onderzoeken waarbij patiënten met verdenking op hartfalen werden ingesloten, of waaraan patiënten met acute dyspnoe op een eerste hulp deelnamen. Verschillen tussen de onderzochte populaties zijn waarschijnlijk verantwoordelijk voor deze discrepantie.

In **Hoofdstuk 8** vergeleken we de diagnostische waarde van verschillende bepalingen van natriuretische peptiden bij 200 COPD patiënten (een willekeurige steekproef van de oorspronkelijke 405 deelnemers). De waarde van NT-proBNP, BNP Centaur en BNP AxSYM werd vergeleken bij het aantonen of uitsluiten van voorheen onbekend hartfalen bij oudere COPD patiënten. Over het geheel genomen waren de verschillende bepalingen vergelijkbaar wat betreft het aantonen of uitsluiten van hartfalen bij deze patiënten. Het diagnostisch onderscheidingsvermogen van alle geteste natriuretische peptiden bleek significant groter te zijn voor systolisch dan voor 'geïsoleerd' diastolisch hartfalen. Bij patiënten met 'geïsoleerd' diastolisch hartfalen die in een stabiele fase verkeren en onderzocht worden in rust, kan men geen overvulling (volume overbelasting van het hart) of verhoogde ventriculaire vullingsdrukken verwachten. Dit lijkt dan ook de belangrijkste reden voor een lagere diagnostische waarde van (NT-pro)BNP in onze stabiele COPD populatie, omdat (NT-pro)BNP positief is gecorreleerd met het volume en de druk in de ventrikels.

De ernst van het COPD had geen invloed op de (NT-pro)BNP bloedspiegels, maar een slechtere linker ventrikel functie duidelijk wel.

In **Hoofdstuk 9** werd de (toegevoegde) diagnostische waarde van cardiovasculaire magnetische resonantie (CMR) beeldvorming voor het vaststellen van hartfalen onderzocht. Daartoe werd een 'nested-case control' onderzoek uitgevoerd binnen de grotere diagnostische studie van 405 patiënten. Bij 37 COPD patiënten met hartfalen volgens het panel (cases) en 41 COPD patiënten zonder hartfalen (controle personen) werd een CMR verricht. Van de CMR metingen bleek de linker ventrikel ejectiefractie (LVEF) < 45% de beste test karakteristieken te hebben voor het aantonen of uitsluiten van hartfalen, met een positief voorspellende waarde van 1,0 (95% BI 0,92-1,0) en een negatief voorspellende waarde van 0,87 (95% BI 0,83-0,90). CMR bleek de test met de hoogste diagnostische waarde voor het detecteren van hartfalen bij COPD patiënten, met een ROC-oppervlakte van 0,88 (0,80-0,97). Indien toegevoegd aan de informatie uit anamnese (met voorgeschiedenis) en lichamelijk onderzoek bleek de aanvullende diagnostische waarden van CMR hoger te zijn dan die van elektrocardiografie of het natriuretisch peptide. CMR is daarmee een krachtig

diagnostisch instrument voor het vaststellen of uitsluiten van hartfalen. Indien echocardiografie oninterpreteerbaar is, kan CMR zeker als diagnostisch alternatief dienen.

In het laatste hoofdstuk (**Hoofdstuk 10**) gaan we dieper in op de klinische consequenties van onze bevindingen en bespreken we de mogelijkheden voor toekomstig onderzoek. We gaan in detail in op de therapeutische consequenties van het beschouwen van COPD als een 'vasculaire ziekte'. Intensivering van de samenwerking tussen huisartsen, cardiologen en longartsen, zowel in de praktijk als in onderzoek, is zeker nodig om verder de gezamenlijke pathofysiologische routes te exploreren en behandelopties te onderzoeken om zodoende de prognose van COPD en hartfalenpatiënten te verbeteren.

Other publications by the author

Other publications by the author

1. Rutten FH, Bohnen AM, Hufman P, Bruinsma M, Leerink HJG, Strootman FA, Brussen AJSH, Dijkstra RH, van der Laan JR. NHG-standaard Angina pectoris. Huisarts Wet 1994;37:398-406.

2. Rutten FH, Willems FF. Huisarts en pijn op de borst. Practicum huisartsgeneeskunde een serie voor opleiding en nascholing. Maarssen: Elsevier/Bunge, 1999.

3. Rutten FH, Kessels AGH, Willems FF, Hoes AW. Electrocardiography in primary care; is it useful? Int J Cardiol 2000;74:199-205.

4. Rutten FH, Hak E, Hoes AW. Using anticoagulation or aspirin to prevent stroke. Results of the study cannot be generalised to the general practice population. [letter] BMJ 2000;320:1009-1010.

5. Rutten FH, Hoes AW. Behandeling hartfalen.[Ingezonden brief] Huisarts Wet 2000;43:396.

6. Rutten FH. Atriumfibrilleren in de huisartspraktijk. In: Van den Bosch WJHM, Treffers PE, eds. Bijblijven. Houten: Bohn, Stafleu, Van Lochum, 2000;60-67.

7. Rutten FH, Kessels AGH, Willems FF, Hoes AW. Is elektrocardiografie in de huisartspraktijk nuttig? (dubbelpublicatie) Huisarts Wet 2001;44:477-81.

8. Rutten FH. Diagnostiek van ischemische hartziekten in de huisartspraktijk. In Van den Bosch WJHM, Treffers PE, eds. Bijblijven. Houten: Bohn, Stafleu, Van Lochum, 2002;19-28.

9. Mede-auteur Multidisciplinaire richtlijn Chronisch hartfalen. Mosterd WL, Rosier PFWM, eds. Alphen aan den Rijn: Van Zuiden, 2003.

10. Rutten FH, Hak E, Stalman WAB, Verheij TJM, Hoes AW. Is treatment of atrial fibrillation in primary care based on thromboembolic risk assessment? Fam Pract 2003;20:16-21.

11. Boode BSP, Frijling BD, Heeringa J, Rutten FH, Van den Berg PJ, Zwietering PJ, Romeijnders ACM, Van Lieshout J. NHG-Standaard Atriumfibrilleren. Huisarts Wet 2003;46:819-830.

12. Rutten FH, Grundmeijer HGLM, Grijseels EWM, Van Bentum STB, Hendrick JMA, Bouma M, Eijzenga W, Van Pinxteren B. NHG-Standaard Acuut coronair syndroom (Acuut myocardinfarct en instabiele angina pectoris). Huisarts Wet 2003;46:831-843.

13. Vermeer GJ, De Boer MJ, Bouma M, Bär FWHM, Van Bentum STB, Lamfers EJP, Rutten FH, Kapteijn BAE. Landelijke Transmurale Afspraak Acuut coronair syndroom. Huisarts Wet 2003;46:844-847.

14. Rutten FH, Bohnen AM, Schreuder BP, Pupping MDA, Bouma M. NHG-Standaard Stabiele angina pectoris (tweede herziening). Huisarts Wet 2004;47:83-95.

15. Bouma M, Rutten FH, Bohnen AM, Wiersma TJ. Samenvatting van de standaard 'Stabiele angina pectoris' (tweede herziening) van het Nederlands Huisartsen Genootschap. Ned Tijdschr Geneeskd 2004;45;2221-2225.

16. Rutten FH. Diagnostiek van chronisch hartfalen. In: Van Veldhuisen DJ, Jaarsma T, eds. Zorg rondom hartfalen. Houten: Bohn, Stafleu, Van Lochem, 2004;46-71.

17. Walma EP, Rutten FH, Mosterd A. Hartfalen. In Prins A, Verheugt FWA, eds. Cardiologie. Reeks praktische huisartsgeneeskunde. Houten; Bohn, Stafleu, Van Lochem, 2004;167-190.

18. Rutten FH, Walma EP, Kruizinga GI, Bakx HCA, Van Lieshout J. NHG-standaard Hartfalen, eerste herziening. Huisarts Wet 2005;48:64-76.

19. Grundmeijer HGLM, Van Bentum STB, Rutten FH, Bakx JC, Hendrick JMA, Bouma M, Eizenga WH, Verduijn MM. NHG-standaard Beleid na een doorgemaakt myocardinfarct. Huisarts Wet 2005;48:220-31.

20. Boomsma LJ, De Boer MJ, Bouma M, Bär FWHM, Van Bentum STB, Lamfers E, Rutten FH, Vermeer GJ. Landelijke Transmurale Afspraak Beleid na een doorgemaakt myocardinfarct. Huisarts Wet 2005;48:232-35.

Dankwoord

Dankwoord

Het liefst zou ik het schrijven van een proefschrift vergelijken met een hardloopwedstrijd. Doordat er bij het schrijven van een proefschrift echter vele personen betrokken zijn die een belangrijke bijdrage leveren, gaat een vergelijking mank. Hardlopen is daar toch een te individuele sport voor.

Bij de onderzoeken die tot dit proefschrift leidden waren vele mensen betrokken die ik allen allerhartelijkst wil bedanken voor hun steun, enthousiasme en begeleiding. Dit geldt zeker ook voor degenen die ik niet bij naam ga noemen.
Verschillende afdelingen van het UMC Utrecht waren bij de onderzoeken betrokken die tot dit proefschrift hebben geleid. Naast het Julius Centrum waren dit de afdelingen cardiologie, longziekten en radiologie. Alle medewerkers van deze afdelingen die hebben meegewerkt wil ik hartelijk danken.

Allereerst wil ik mijn promotor Prof. Dr. AW Hoes bedanken. Beste Arno, jij was de initiator van de onderzoeken. Je was er vanaf het begin met hart en ziel bij betrokken. Je was promotor en co-promotor in een. Ik kon met alle problemen bij jou terecht, op gezette tijden, maar ook buiten de afspraken om. Jouw deur stond dan altijd open en jij wist snel en adequaat mijn vragen te beantwoorden. Jouw vakkennis, ideeën en schrijfvaardigheid zijn van A tot Z in dit proefschrift terug te vinden.
Prof. Dr. DE Grobbee, beste Rick, jij was als promotor wat meer op de achtergrond, echter jouw aanwezigheid was altijd tastbaar. In de eindfase heb je cruciale sturing en adviezen gegeven welke er toe geleid hebben dat de presentatie van de resultaten werd "opgekrikt".
Prof. Dr. J-WJ Lammers, beste Jan-Willem, jij droeg als promotor zorg voor het "longgedeelte" van het onderzoek. Een vlotte organisatie op de longfunctie-afdeling vormde de spil in het onderzoek. Ik ben blij dat ik gebruik mocht maken van de werkruimte, kennis en kunde van deze afdeling. Daarnaast was jij bij alle panelbesprekingen aanwezig. Deze besprekingen waren gezellig en leerzaam en vormden een platvorm voor het ontwikkelen van nieuwe ideeën zoals het opzetten van een dyspnoe-poli. Deze panelbesprekingen toonden hoe vruchtbaar huisartsen, cardiologen en longartsen kunnen samenwerken.
Dr. M-JM Cramer, beste Maarten-Jan, jij was van de cardiologen het meest betrokken bij het onderzoek. Naast het participeren in de panelbesprekingen heb je ook nog eens alle echo- en elektrocardiogrammen beoordeeld. Daarbij was je altijd erg betrokken, zeer stimulerend en enthousiasmerend.
Dr. HJ Kirkels en Dr. R Rienks, beste Hans en Rienk, jullie hebben er voor gezorgd dat het onderzoek kon starten en ik een werkkamer kreeg in het Centraal

Militair Hospitaal. Dit alles in een periode dat er personele onderbezetting en ruimtegebrek was binnen de afdeling cardiologie. Rienk, jij stond zelfs je eigen werkkamer aan mij af indien dit nodig was. Hans, jij was daarnaast belangrijk voor de noodzakelijke "kritische overwegingen" bij de cardiologische aspecten van het onderzoek.
Prof. Dr. WPThM Mali, beste Willem, jij hebt een belangrijke bijdrage geleverd door er voor te zorgen dat cardiovasculaire magnetische resonantie beeldvorming mogelijk werd voor deelnemers aan het onderzoek.
Prof. Dr. KGM Moons, beste Carl, jij hebt me enthousiast gemaakt voor diagnostisch onderzoek en me op weg geholpen bij het beschrijven van de resultaten ervan.
Prof. Dr. ThJM Verheij, beste Theo, jij hebt de ruimte gegeven om dit onderzoek vanuit de afdeling huisartsgeneeskunde van het Julius Centrum te laten uitwaaieren over het UMCU. Je was altijd geïnteresseerd in de voortgang en daarnaast bereidwillig om in de leescommissie plaats te nemen.

De leden van de beoordelingscommissie wil ik hartelijk danken dat ze tijdens de warme zomermaanden de tijd namen om mijn proefschrift te beoordelen: Prof. Dr. PAFM Doevendans, Prof. Dr. K Swedberg, Prof. Dr. M Prokop, Prof. Dr. PNR Dekhuijzen en Prof. Dr. ThJM Verheij.

Elly Lutgert-Hagman en Ineke Kasteleijn, jullie wil ik bedanken voor het maken van alle echocardiogrammen. Soms moesten de deelnemers met kunst en vliegwerk tussen de bedrijven door gezien worden. Door jullie flexibiliteit konden de deelnemers toch nog voor het donker weer naar huis. Elly, ik ben onder de indruk van je volhardendheid en nauwgezetheid waarmee je te werk gaat. Je hebt de meeste echocardiogrammen gemaakt en beoordeeld en alsof dat niet genoeg was, fungeerde je ook nog als een ware gids voor de deelnemers door ze in het "UMCU-doolhof" te vergezellen.
De andere echolaborantes bedank ik voor het "bijspringen" als er weer eens een deelnemer voor mijn onderzoek tussendoor moest.
Paul Munnik en alle longfunctie-laborantes wil ik hartelijk danken voor het uitvoeren van de longfunctiemetingen. Jullie vormen een hecht team en alle metingen verliepen dan ook ogenschijnlijk moeiteloos. Het geduld waarmee jullie het gepuf en gesteun van alle longpatiënten aanhoren is bewonderenswaardig.
Dr. Pieter Zanen, jij hebt mij het een en ander geleerd over longfunctiemetingen en zorgde voor "longstof " om over na te denken. Jij hebt er ook voor gezorgd dat uiteindelijk alle longfunctiedata van de deelnemers in mijn databestand kwamen. Dat was wel een Talisker waard.

Zelfs in het weekend ging de onderzoeken door. Op zaterdagen werden bereidwillige deelnemers vakkundig gescand door Niels Blanken, Greet Bouwman, and Marianne Nagtegaal. Gelukkig kon ik jullie een aantal van deze zaterdagen van drop voorzien. Evert-Jan Vonken, jij hebt alle technische problemen rond de cardiovasculaire magnetische resonantie glad gestreken en voor het uitvoeringsprotocol gezorgd. Ik ben onder de indruk van jullie werk en de prachtige beelden die dit oplevert. Anneke Hamersma zorgde voor een gesmeerde planning en Lennart Bongartz voor het "tracen" van alle scans.
Dr. Brigitta Veldhuis, Dr. Prins en Dr. Fernández, jullie hebben vakkundig alle thoraxfoto's beoordeeld en samen met Hansje Person er voor gezorgd dat het maken van de longfoto's vlot verliep in het Centraal Militair Hospitaal. Brigitta, jij hebt daarnaast geholpen bij het van de grond krijgen van de cardiovasculaire MRI.
Het Saltro laboratorium wil ik bedanken voor het analyseren, maar ook voor het ophalen van alle bloedmonsters. Mieke van de Geest was het aanspreekpunt en zorgde dat alles logistiek vlot verliep en René van Oers zorgde er voor dat uiteindelijk alle laboratoriumbepalingen volgens plan verliepen.

Wat is een onderzoeker zonder ondersteuning door mensen van data-management? Ik had het geluk door meerdere personen ondersteund te worden. Diana Balk, Renate Siebes, Chantal van Isterdael en last but not least Frances Verheij. Frances jij was mijn steun en toeverlaat bij het belangrijkste deel van het onderzoek. Naast het invoeren van alle data zorgde jij dat de deelnemers op kwamen dagen en wisten waar ze naar toe moesten. Daarnaast zorgde jij voor de lay-out van dit proefschrift.
Peter Zuithoff, jij was onmisbaar bij het analyseren van alle gegevens. Heel wat uren hebben we samen achter de computer doorgebracht en "gestoeid" met SPSS. Gelukkig hadden we soms nog tijd om over belangrijke zaken zoals het live-optreden van Bruce Springsteen te praten.
Verder wil ik Geert van der Heijden bedanken voor zijn tips hoe je searches in Medline uitvoert en Alfred Sachs voor het "brainstormen" over het pulmonale vaatbed.

Alle deelnemende huisartsen en hun assistentes, waaronder de huisartsen van het Huisartsen Netwerk Utrecht (HNU) bedank ik voor hun enthousiaste bijdrage en het feit dat ik in de medische dossiers van hun patiënten mocht "snuffelen". Jullie waren onmisbaar bij het werven van de deelnemers, het verzamelen van medische informatie en ook nog eens het invullen van een vragenlijst over hartfalen.
Alle deelnemende cardiologen van het UMC Utrecht, Diakonessenhuis Utrecht, Mesos Medisch Centrum Utrecht, Sint Antonius Ziekenhuis Nieuwegein, Deventer Ziekenhuis Deventer, Slingeland Ziekenhuis Doetinchem, Ziekenhuis Rijnstate

Arnhem, Beatrixziekenhuis Gorinchem en het Elkerliek Ziekenhuis Helmond wil ik bedanken voor de gelegenheid die ze mij boden om hun medische dossiers in te zien en voor het invullen van de vragenlijst. Deze dank geldt ook voor Gerrit Dun, internist uit het Ziekenhuis Rivierenland Tiel. Daarnaast dank ik alle cardiologen en internisten die de enquête hebben ingevuld.

Wat is een onderzoek zonder deelnemers?
Ik wil alle deelnemers van harte bedanken voor hun bereidwilligheid tot deelname aan dit onderzoek. Jullie geduld werd vaak op de proef gesteld. Het duurde soms wel 3 uur voordat alle onderzoeken klaar waren. Daarnaast werden sommigen van jullie ook nog eens gevraagd om terug te komen om een uur stil te liggen onder de veel herrie producerende MRI scanner. De inspanningen die sommige deelnemers zich getroosten bleek wel uit het feit dat er zelfs bij waren die met zuurstoffles met toebehoren deelnamen aan dit onderzoek.

Doordat ik werkzaam ben op een van de grootste kamers van het Julius Centrum heb ik veel kamergenoten (gehad). Naast noeste arbeid was er tijd voor een geintje en werden er naast onderzoeks- en persoonlijke perikelen ook verwikkelingen in en rondom het huisartsenvak en het huisarts zijn besproken. Kamergenoten van het eerste uur waren Catherine Weijnen (how to win the publication game), Birgit van Staaij (goed in musicale stukjes), Bram Smits (loste in no-time computerproblemen op) en Ruud Oudega (drie banen tegelijk is ook best leuk). Later kwamen daarbij Wim Opstelten (bij het volgende blaasjesonderzoek sluit ik zeker 2 maal zoveel deelnemers in!), Lex Goudswaard en Paul Jansen. Rykel van Bruggen, Maarten Brinkhuijzen en Mariëlle van Avendonk zorgden er voor dat onze kamer een echt "diabetes-hol" werd. Gelukkig waren er ook niet-diabetes onderzoekers op onze kamer actief: Tjarda Scheltens, Roeland Geijer, Renee Bijkerk en de andere "hartfalenonderzoekers" Pieta Bruggink-André de la Porte en Hans Kelder. Lidewij Broekhuizen is momenteel de jongste ent aan de tak van huisartsonderzoekers. Bedankt voor de gezelligheid en veel succes en weinig stress bij het afronden van jullie proefschrift.

Mijn collega huisartsen en assistentes van huisartsenpraktijk de Grebbe in Rhenen wil ik hartelijk danken voor het opvangen van de steekjes die ik her en der heb laten vallen. Zeker Bernard Frijling heeft als duo-maat moeten "ruimen". Daarnaast deden jullie mee met de twee onderzoeken evenals de collega's van Nieuw Rhenen en kwamen de eerste deelnemers uit Rhenen. Niek de Wit neemt een bijzondere plaats in omdat hij behalve collega ook mede-Juliaan is. Hij was belangrijk bij het "filosoferen over onderzoek" in de breedste zin. Samen treinen naar Bunnik en

fietsen door de velden naar de Uithof was en is erg gezellig en leerzaam. Ook Wim Stalman heeft als ex-collega nog zijn "onderzoekssteentje" bijgedragen.

En dan belangrijke supporters buiten mijn werkkring.
Familie en vrienden, jullie wil ik danken voor het heerlijke leven naast het proefschrift.

Speciale dank gaat uit naar mijn ma en mijn schoonouders. Jullie waren altijd bereid om bij te springen en op de kinderen te passen. Ook onmisbaar waren Ria en Sjaak. Jullie waren samen oppas voor de kinderen, coach en mededeelneemster bij hardloopwedstrijden. Jullie opgewektheid en ongebreidelde energie gaf mij steeds weer een kick. Ik vind het erg leuk dat Sjaak paranimf is.
In mijn vriendenkring neemt Fons Kessels een bijzondere plaats in omdat hij mij tijdens de jaarlijkse wandelingen in de Ardennen warm heeft gemaakt voor onderzoek en mij hielp bij mijn eerste wankele "onderzoeksschreden". Daarnaast speelde Bart Berden een rol bij mijn stap om met onderzoek te beginnen door alsmaar te vragen "wanneer ga jij nu eens promoveren?" Het is fijn dat jij samen met Sjaak mij terzijde staat bij de verdediging. Het samen eten met Vera en Yvonne moet weer worden geïntensiveerd!
Ena Rutten, mijn creatieve zus, jouw bedank ik voor de prachtige omslag van het proefschrift.

Yvonne, Karlijn en Jorn, jullie verdienen de eerste plaats, maar staan achteraan in dit dankwoord. Zonder thuis ben ik nergens. Ieder van jullie heeft op zijn eigen manier bijgedragen aan het slagen van deze exercitie. Yvonne, jij weet wat het is om te promoveren, dat gaf altijd veel steun. Karlijn en Jorn, jullie moesten regelmatig stoppen met computerspelletjes, omdat pa zonodig achter de computer moest zitten. Dit deden jullie (meestal) zonder mokken. Net als ik snakken jullie naar het "boekjesfeest".

Curriculum vitae

Frans Rutten was born on October 18, 1959 in Venlo, the Netherlands. In 1978, after graduating secondary school at the Collegium Marianum in Venlo (Atheneum-B), he started Medical School at the University of Nijmegen, the Netherlands. In 1986 he obtained his medical degree. As part of his internship, he worked in the Sumve Hospital in Tanzania in 1985 and studied vaccination rates of children. From August 1986 till December 1987 he worked as a physician in the department of internal medicine and cardiology of the St. Jozef Hospital, Kerkrade. From December 1987 till December 1988 he worked as physician in the department of cardiology in the Academic Hospital Maastricht. In January 1989 he started his 2-year vocational training in general practice at Utrecht University. In November 1991 he settled as a general practitioner in Rhenen, and from 1991 onwards he participated in Dutch general practice guidelines (NHG-standaarden). Till 1999 he worked full-time in this general practice. In July 1999 he started the work described in this thesis at the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht (supervised by Prof. Dr. AW Hoes, Prof. Dr. DE Grobbee and Prof. Dr. J-WJ Lammers). The projects were financially supported by the Netherlands Heart Foundation (NHS) and the Netherlands Organisation for Scientific Research (NWO). From October 2005, he will continue to work both at the Julius Center and as a general practitioner in Rhenen.