Effects of physical activity in mild to moderate COPD: a systematic review

Niels Chavannes, J J H Vollenberg, C P van Schayck and E F M Wouters

SUMMARY

Pulmonary rehabilitation has become an evidence-based treatment for patients with severe chronic obstructive pulmonary disease (COPD). However, large numbers of patients who suffer from mild to moderate COPD receive treatment from their general practitioners (GPs). To encourage compliance, advice given to patients in general practice should be clear, practical, and acceptable. This is particularly true of the advice that is given by GPs to improve their patients' physical condition by walking, cycling or swimming, as recommended by the Dutch College of General Practitioners in their guideline for the treatment of COPD. We performed a literature search on the effects of physical activity in patients with mild to moderate COPD on exercise tolerance, dyspnoea and quality of life (QOL). We also looked at the numbers of hospitalisation days and exacerbations, expressed as oral prednisolone courses.

The literature search included Medline (1983 to 1999), EMBASE (1984 to 2000), and the Cochrane Library (2000). All hits were screened for subject and language and abstracts were selected on the basis of a protocol that included disease severity, hypothesis, outcome parameters, and control group. Review articles on physical exercise and COPD were examined and reference lists of selected articles were screened for relevant studies.

The broad literature search generated 4968 articles and, after exclusion according to title and abstract, 35 original studies and 27 review articles were analysed. Of these, five original studies fitted the criteria and none of the review articles was selected. A positive influence of physical activity on exercise tolerance in mild to moderate COPD was reported in four out of five studies. There was no clear effect on dyspnoea or QOL, probably because of the low numbers of subjects. No studies that addressed the number of hospitalisation days or prednisolone courses as outcomes were included.

Physical exercise training (usually as part of a package of rehabilitation) can improve the fitness of patients with mild or moderate COPD, but it has not been shown to benefit QOL or dyspnoea significantly, or indeed long-term disease progression.

Keywords: *physical exercise; chronic obstructive pulmonary disease; COPD.*

N Chavannes, MD, **GP** registrar; J J H Vollenberg, general practitoner; and C P van Schayck, MSc, PhD, professor of preventive medicine; Department of General Practice, University of Maastricht. E F M Wouters, MD, PhD, professor of pulmonology, Department of Pulmonology, Academic Hospital Maastricht, The Netherlands.

Address for correspondence

Dr Niels Chavannes, Department of General Practice, University of Maastricht, PO Box 616, 6200 MD Maastricht, The Netherlands. E-mail: niels.chavannes@hag.unimaas.nl

Submitted: 24 April 2001; Editor's response: 17 July 2001; final acceptance: 11 March 2002.

Introduction

THE Dutch College of General Practitioners' guideline for the treatment of chronic obstructive pulmonary disease (COPD) encourages general practitioners (GPs) to take a proactive approach.[1] In The Netherlands, patients with COPD are advised by their GPs to improve their physical condition; for example, by walking, cycling or swimming. In patients with severe COPD, however, a pulmonary rehabilitation programme is considered.[1] While the efficacy of pulmonary rehabilitation programmes has been proven extensively, the advice that is recommended to GPs is not evidence-based at present.[2,3,4] Pulmonary rehabilitation usually consists of a prolonged period of inpatient or outpatient revalidation, including intensive specific exercises, breathing techniques and education, supervised by specialised rehabilitation staff. Exercise tolerance, dyspnoea and quality of life (QOL) usually improve, while the number of inpatient days in hospital decrease.[4,5] The effects on lung function parameters are not consistent. The true prevalence of COPD is hard to determine; estimates range from between 5% to 15% in the mature population, but it is acknowledged that GPs treat most patients with mild to moderate COPD.[1,6] In general practice it is important that the advice given is clear, practical, and acceptable to patients; characteristics that are not applicable to the complex, intensive, and exhaustive nature of pulmonary rehabilitation programmes. We questioned what evidence is available in literature regarding the efficacy of physical activity on functional status and prognosis in patients with mild to moderate COPD.

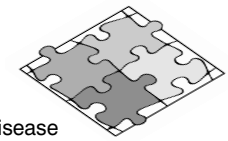
In this study, physical activity was defined as 'general physical condition enhancement; for example, walking, cycling or swimming, and/or training of (most) large muscle groups'. We performed a literature search to find out whether physical activity has an influence on exercise tolerance, QOL and dyspnoea in patients with mild to moderate COPD and whether it influences the number of hospitalisation days and number of exacerbations, expressed as oral courses of prednisolone.

Method

The literature search was performed using Medline® Advanced (version WinSPIRS 4.0, from 1983 to November 1999), EMBASE Excerpta Medica (version WinSPIRS 4.0, from 1984 to 1989, 1990 edition; and 1989 until April 2000, 2000 edition), and the Cochrane Library (2000, issue 1). It included the search terms 'COPD', 'chronic obstructive pulmonary disease', 'chronic bronchitis', and 'emphysema', combined with 'physical activity', 'exercise', 'sports', and 'training'.

The 4968 electronically-generated titles were selected on the basis of English or Dutch language and then screened

HOW THIS FITS IN



What do we know?

Chronic obstructive pulmonary disease (COPD) is a chronic and progressive disease with a heavy burden on daily life and is a major cause of death. Pulmonaryrehabilitation has become an evidence-based treatment for patients with severe COPD, while large numbers of patients with mild to moderate COPD primarily receive treatment from their GPs.

What does this paper add?

GPs can recommend physical exercise training to patients with mild to moderate CPOD to improve their fitness, but it has not yet been shown to benefit quality of life or dyspnoea. More research into long-term effectiveness in these patients is justified and desirable.

for relevance to the research questions. Articles were excluded if they did not deal with the relationship between physical activity and COPD, or if they only dealt with the training of highly specific muscle groups, or if they only included severe COPD, or if they were studies comparing two training programmes without control.

The next step was to look at the abstract. Articles were excluded if they did not include at least one of the relevant parameters (exercise tolerance, dyspnoea, QOL, number of exacerbations or prednisolone courses), or if they only included severe COPD or intensive care patients, or if they did not include an abstract, or if the language used was not English or Dutch, or if they clearly did not cover any of the hypotheses. The remaining studies, including one or more of the relevant outcome parameters in mild to moderately severe COPD, or COPD of indeterminate severity, were examined in full text after removing double hits. If there was any doubt, consultation between two researchers took place until full consensus was reached. The results had to be reported separately if severe COPD was included in the population as well, whether mild, moderate or severe. The patients classified as having severe COPD were consequently excluded. If severity was not reported in these terms, a forced expiratory volume (FEV_1) of 50% lower than predicted was determined as the lower threshold for inclusion, in accordance with the Dutch definition of patients with mild to moderate COPD.[1] If FEV_1 could not be elucidated then the study was excluded. Finally, a control group without intervention of physical activity had to be present, allowing inclusion for RCTs and cluster controlled trials (CCTs) only.

Review articles on the relationship between physical activity and COPD in non-severe COPD (or which did not mention severity), and covering one or more of the outcome parameters, were also examined. These had to fulfill the following criteria: they had to be reviews on the influence of physical activity (as described before) of patients with mild to moderate COPD (these patients could be described separately); at least one of the outcome parameters had to be examined; there had to be a systematic approach of the literature search; and they had to be written in Dutch or English.

Reference lists of selected studies were screened for relevant articles using the same methodology that was used in the broad literature search. Effect and standard error of the effect were calculated from the means and standard deviations of each group. Pooling of the different outcomes used to describe exercise tolerance, such as walking distance and endurance, was impossible. Therefore, a standardised effect was calculated for each study by dividing the effect by the pooled standard deviation. These standardised effect values were summarised using a random effects meta-analysis according to a method which has been described in detail by DerSimonian *et al.*[7]

Results

Literature

The broad literature search generated 4968 hits. After subsequent selection according to title and abstract, 35 original studies and 27 review articles were examined. No review article fitted the criteria, while seven original studies did. One Dutch study turned out to be a double publication and was excluded.[8] As a result of poor compliance, one study contained a control group of one subject and was not discussed further.[9] The key aspects and results of the remaining five studies[10-14] are summarised in Table 1.

Patients

The most important characteristics of the population and interventions are presented in Table 2. Only Ringbaek[14] mentions the number of smokers. Only Grosbois[13] gives information on symptom patterns, and concludes that all patients experienced dyspnoea on exertion and were less active. This is the only CCT included, and patients could choose the programme in which they participated. In the study by Ringbaek[14] there were significant differences between the control and intervention groups at the beginning of the study. Grosbois[13] reported non-significant worse test results at baseline in the control group. Dropouts were reported by Cambach,[10] but the number is unclear, Grosbois[13] reported 13 and Ringbaek[14] seven. No differences were found between participants and dropouts. The study aim was to exclude any patients suffering from severe COPD, to ensure that only data on mild to moderate disease were described. Applying the term 'mild to moderate COPD' resulted in patients with a FEV_1 of between 47% and 77% of that predicted, in line with the original study aim.

Method

Only Clark (1996)[11] chose physical activity alone as the study intervention, as part of a physiotherapist-supervised programme which could be carried out at home. The other studies also used specific training, education, and recreation. Cambach[10] applied a crossover design in which each group experienced an intervention period and a control period. This study included both asthma and COPD patients, but the results were specified; only the data on COPD are presented. Furthermore, only the first arm data were included in the meta-analysis to avoid any risk of carry-over owing to the design. Grosbois[13] studied the period during follow-up after a rehabilitation programme. During an 18-month period, one group received no maintenance exercises and

Table 1. Characteristics and results of studies fitting criteria.

Author	Study design	*n*	Studied parameters	Significant results
Cambach *et al*[10] (Netherlands)	RCT	23	Exercise tolerance (CE, 6MWT), QOL (CRQ), dyspnoea (CRQ)	Improved exercise tolerance (CE, not 6MWT), QOL and dyspnoea after three months, and again three months later (CE and 6MWT), QOL and dyspnoea
Clark *et al*[11] (UK)	RCT	48	Exercise tolerance (CE, WT)	Improved exercise tolerance after three months (WT, not CE)
Clark *et al*[12] (UK)	RCT	43	Exercise tolerance (WT)	Improved exercise tolerance after three months (WT)
Grosbois *et al*[13] (France)	CCT	58	Exercise tolerance (CE), dyspnoea (VAS)	Improved exercise tolerance in subgroups after 18 months (CE); no difference in dyspnoea
Ringbaek *et al*[14] (Denmark)	RCT	38	Exercise tolerance (6MWT), dyspnoea (BS), QOL (SGRQ, PWBI)	No effects on exercise tolerance, dyspnoea or QOL after two months

CE = cycle ergometry (physiological parameters, maximal exertion in watts); 6MWT = six-minute walking test (distance in metres); WT = walking test (endurance in joules); CRQ = chronic respiratory disease questionnaire (including dyspnoea score); SGRQ = St George's respiratory questionnaire; PWBI = psychological wellbeing index; VAS = visual analogue scale; BS = Borg scale.

Table 2. Characteristics of study populations and interventions.

Study	Male/ female (*n*)	Mean age in years	Reasons for exclusion	FEV_1 % predicted	Intervention	Frequency	Duration
Cambach[10]	13/10	62	Heart complaints, locomotor disabilities	59	Primary care physiotherapist, giving both general and specific muscle training, education and recreation	3 times/week	12 weeks
Clark 1996[11]	-	57	-	61	Home training of large muscle groups at low intensity	7 times/week	12 weeks
Clark 2000[12]	25/18	49	Heart complaints, arthritis, daily oral steroids	77	Hospital-based general and specific muscle training	2 times/week	12 weeks
Grosbois[13]	47/11	62	Heart complaints, locomotor disabilities	49	Outpatient clinic together with home-based general and specific muscle training and education	7 times/week	18 months
Ringbaek[14]	7/38	63	Other pathology, domiciliary oxygen, psychiatric disorders	47	Hospital-based general and specific muscle training, education and muscle stretching	2 times/week	8 weeks

three groups received different types of exercise. The measurements carried out in the separate studies are summarised in Table 1.

Results

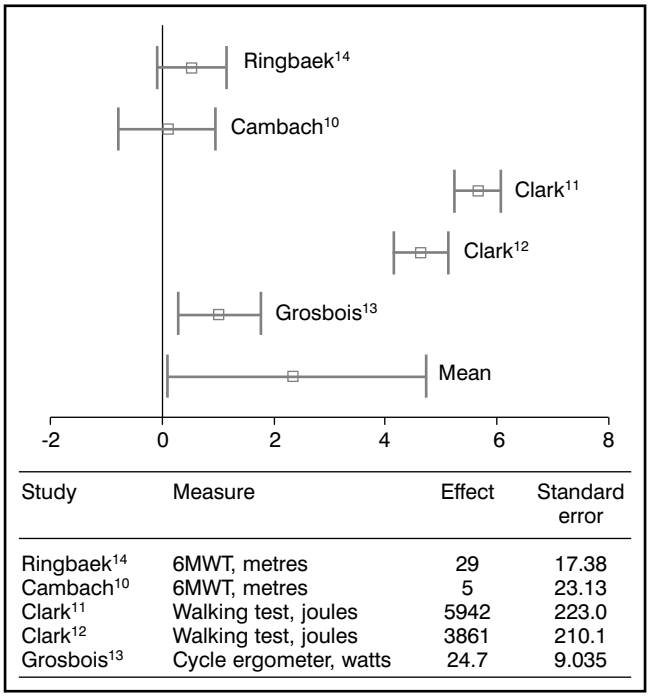
Most of the studies showed significant differences between intervention and control groups with regard to exercise tolerance. In Figure 1, a random effects meta-analysis aims to summarise the effects on exercise tolerance. However, numbers were small and different outcomes had to be integrated to produce the figure. The effects of physical activity on QOL in patients with mild to moderate COPD were inconclusive. The two studies involved used different instruments to assess QOL. Cambach found a significant positive effect during intervention and three months later, in concordance with other studies.[15,16] Ringbaek found no significant effects, possibly because of a shorter intervention period and less frequent training. Although there are indirect signs for positive effects of physical activity on QOL in mild to moderate COPD, data are inconclusive at present.

No consistent effect was found on dyspnoea, either. Only Cambach found a significant improvement during the intervention and after three months. The instrument used to measure dyspnoea was part of the QOL questionnaire. Dyspnoea was also measured using a visual analogue scale and the Borg scale, which reflected the subjective nature of dyspnoea.

None of the studies used numbers of hospitalisation days or prednisolone courses as outcome measurements.

Discussion

An attempt was made to summarise the results in a randomised effects meta-analysis, after calculation of a standardised effect per study. Although interpretation is ham-



Study	Measure	Effect	Standard error
Ringbaek[14]	6MWT, metres	29	17.38
Cambach[10]	6MWT, metres	5	23.13
Clark[11]	Walking test, joules	5942	223.0
Clark[12]	Walking test, joules	3861	210.1
Grosbois[13]	Cycle ergometer, watts	24.7	9.035

Figure 1. Random effects meta-analysis of physical activity on exercise tolerance.

pered by the fact that pooling is impossible, an overall positive effect of physical activity seems to perpetuate. A positive influence of physical activity on exercise tolerance in patients with mild to moderate COPD is described by four out of five researchers. However, in the study by Cambach, improvement in the six-minute walking test at three months was only 5 m compared with the control group. Although this difference increased up to 47 m at six months, we have chosen to include the initial figure only, so as not to overestimate the effect and to avoid any carry-over effect owing to the cross-over design. Ringbaek only found a non-significant improvement of the walking test. However, the duration of intervention was only two months and the frequency of training activity was just twice weekly. This brought Ringbaek to the conclusion that the low frequency is the cause of absence of effects in his study. However, Clark (2000) did find effects at the same training frequency but applied the intervention for three months. In addition, it is noteworthy that, in Ringbaek's study, there were significant differences between the intervention and control groups at baseline, the control group consisting of more women, more smokers, and a better six-minute walking test. It is not inconceivable that this, especially the last difference, has contributed to the observed absence of effects in this study. It seems possible that a twice-weekly frequency may be effective in enhancing exercise tolerance if applied for at least three months. Effects on both dyspnoea and QOL were inconclusive. This may partly be as a result of the subjective nature of these outcome measures, in contrast with objective measures of exercise tolerance.

Interestingly, Grosbois found a significant improvement in dyspnoea lasting 18 months in all patients during the intervention, but observed no difference between the intervention and control groups. He points out the motivation to perform exercises as a possible important factor for the effect on dyspnoea. No effect on dyspnoea was found by Ringbaek, either. As in other studies,[17,18] the long-term effects of physical activity on dyspnoea remain controversial.

None of the studies that were included examined the effects of physical activity on the number of hospitalisation days or number of exacerbations, expressed as courses of prednisolone. Because few studies have evaluated the long-term effects of pulmonary rehabilitation, information on this topic is scarce. Ries[18] did not find pulmonary rehabilitation to have a significant effect on hospitalisation days, while other investigators reported improvements in different patient categories.[19-22] However, none of these studies fitted the criteria of this review.

One of the most important drawbacks of this review is the small number of articles and patients included, especially with regard to the parameters of dyspnoea and QOL. This is partly a result of the choice of definition of physical activity and the exclusion criteria. All studies were designed as rehabilitation programmes. Only Clark[11] applied the intervention in the home setting, with it being supervised weekly by a hospital physiotherapist. To our knowledge, physical activity with little or no guidance, after recommendation from the GP, has not been studied. Furthermore, few studies have been aimed at the patient with mild to moderate COPD. Ries described that patients in the early stages of COPD do not recognise the disease or do not consider it as disabling enough to necessitate rehabilitation.[4] This may be a reason why dyspnoea and QOL did not appear to improve. Therefore, it is important for the GP to advise a method of physical activity that is acceptable enough to be maintained for longer periods and clear enough to be performed independently.

Different interventions and measurements have been applied, a fact which frustrates direct comparison in the random effects meta-analysis. Most programmes offered specific exercises, education, and sometimes psychosocial support, in addition to physical activity. The controls usually received no programme. This makes it difficult to determine what part of the intervention has contributed most to the effect. On the other hand, education and support are usually an integral part of the package the GP offers.

The duration of interventions varied from eight weeks to 18 months. Only Cambach followed up for 12 weeks after the intervention. There is no consensus on the optimal duration of pulmonary rehabilitation. Effects have been described starting from two weeks,[23] while others recommend several months.[24-26]

Respiratory rehabilitation in the early stages of COPD could become a treatment of preference in the future.[4,5,27,28] Rehabilitation in primary care or at home appears to be appropriate and effective.[9,10,12,29] However, too little research has been done in this patient group to draw firm conclusions on this matter. We conclude that physical exercise training (usually as part of a package of rehabilitation) can improve the fitness of patients with mild or moderate COPD, but that it has not been shown to significantly benefit QOL or dyspnoea, or long-term disease progression.

General practitioners treat many patients with COPD. The

extent to which these patients are inspired to undertake physical activity remains unknown. However, we expect that the dyspnoea spiral (dyspnoea leading to less exercise tolerance, leading to increased dyspnoea) is a prevalent problem, especially in rapidly worsening disease. Although it is unclear as to what measure of guidance is needed, paying more attention to the matter of physical activity could mean higher work demands on already overloaded general practices. However, COPD is a chronic and progressive disease with a heavy burden on daily life, and a major cause of death. Intensive symptomatic treatment is costly and causes numerous side effects. Recommending guided physical activity twice weekly for at least three months could be an important extension of current therapy.

Little is known about cost. We only found indirect signs that the number of hospitalisation days could be decreased by physical activity. If this could be confirmed in a formal study, it is likely that physical activity would have a positive influence on costs. Haas found that the longer rehabilitation is postponed, the more expensive it will be for the patient, the family, and for society.[30] We recommend that in general practice more attention should be paid to the patterns of physical activity in patients with mild to moderate COPD. More research into the long-term effectiveness, including the cost, in these patients is justified and desirable.

References

1. Geijer RMM, van Schayck CP, van Weel C, *et al*. Dutch College of General Practitioners guideline: treatment of COPD. *Huisarts Wet* 1997; **40(9):** 430-442.
2. Lacasse Y, Wong E, Guyatt GH, *et al.* Meta-analysis of respiratory rehabilitation in chronic obstructive pulmonary disease. *Lancet* 1996; **348:** 1115-1119.
3. Lacasse Y, Guyatt GH, Goldstein RS. The components of a respiratory rehabilitation program. A systematic overview. *Chest* 1997; **111:** 1077-1088.
4. Ries AL. Position paper of the American Association of Cardiovascular and Pulmonary Rehabilitation. Scientific basis of pulmonary rehabilitation. *J Cardiopulm Rehabil* 1990; **10:** 418-441.
5. Lertzman MM, Cherniack RM. Rehabilitation of patients with chronic obstructive pulmonary disease. *Am J Respir Dis* 1976; **114:** 1145-1165.
6. van Schayck CP, Tirimanna PRS, van den Boom G, *et al.* Actual increase of the prevalence of asthma and COPD in the Netherlands. *Neth J Med* 1998; **142(43):** 2352-2355.
7. DerSimonian R, Liaird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7:** 177-188.
8. Cambach W, Chadwick-Straver RVM, Wagenaar RC, van Keimpema ARJ. Effectiviteit van een revalidatieprogramma voor patiënten met astma en COPD uitgevoerd in de eerstelijnsgezondheidszorg. [Efficacy of a rehabilitation programmefor patients with asthma and COPD performed in primary care.] *Neth J Fys* 1998; **4:** 26-36.
9. Lin MC, Liaw MY, Huang CC, Tsai YH. A multidisciplinary pulmonary rehabilitation program for patients with moderately severe chronic obstructive pulmonary disease. *J Formos Med Assoc* 1997; **96:** 869-873.
10. Cambach W, Chadwick-Straver RVM, Wagenaar RC, *et al.* The effects of a community-based pulmonary rehabilitation programme on exercise tolerance and quality of life: a randomised controlled trial. *Eur Respir J* 1997; **10:** 104-113.
11. Clark CJ, Cochrane L, Mackay E. Low intensity peripheral muscle conditioning improves exercise tolerance and breathlessness in COPD. *Eur Respir J* 1996; **9:** 2590-2596.
12. Clark CJ, Cochrane LM, Mackay E, Paton B. Skeletal muscle strength and endurance in patients with mild COPD and the effects of weight training. *Eur Respir J* 2000; **15:** 92-97.
13. Grosbois JM, Lamblin C, Lemaire B, *et al.* Long-term benefits of exercise maintenance after outpatient rehabilitation program in patients with chronic obstructive pulmonary disease. *J Cardiopulm Rehabil* 1999; **19:** 216-225.
14. Ringbaek TJ, Broendum E, Hemmingsen L, *et al.* Rehabilitation of patients with chronic obstructive pulmonary disease. Exercise twice a week is not sufficient! *Respir Med* 2000; **94:** 150-154.
15. Goldstein RS, Gort EH, Stubbing D, *et al.* Randomised controlled trial of respiratory rehabilitation. *Lancet* 1994; **344:** 1394-1397.
16. Gosselink HAAM, Wagenaar RC, van Keimpema ARJ, Chadwick-Straver RYM. Het effect van een reactiveringsprogramma bij patiënten met CARA. [The effect of a reactivation programme in patients with NSCLD.] *Neth J Fys* 1990; **7/8:** 193-199.
17. Ketelaars CAJ, Abu-Saad HH, Schlösser MAG, *et al.* Long-term outcome of pulmonary rehabilitation in patients with COPD. *Chest* 1997; **112:** 363-369.
18. Ries AL, Kaplan RM, Limberg TM, Prewitt LM. Effects of pulmonary rehabilitation on physiologic and psychosocial outcomes in patients with chronic obstructive pulmonary disease. *Ann Intern Med* 1995; **122:** 823-832.
19. Cox NJM, Hendricks JC, Binkhorst RA, *et al.* A pulmonary rehabilitation program for patients with asthma and mild chronic obstructive pulmonary diseases (COPD). *Lung* 1993; **171:** 235-244.
20. Foglio K, Bianchi L, Bruletti G, *et al.* Long-term effectiveness of pulmonary rehabilitation in patients with chronic airway obstruction. *Eur Respir J* 1999; **13:** 125-132.
21. Parker L, Walker J. Effects of a pulmonary rehabilitation program on physiologic measures, quality of life, and resource utilization in a health maintenance organization setting. *Respir Care* 1998; **43(3):** 177-182.
22. Wright RW, Larsen DF, Monie RG, Aldred RA. Benefits of a community-hospital pulmonary rehabilitation program. *Respir Care* 1983; **28:** 1474-1479.
23. Carter R, Coast JR, Idell S. Exercise training in patients with chronic obstructive pulmonary disease. *Med Sci Sports Exerc* 1992; **24:** 281-291.
24. Belman MJ. Exercise in chronic obstructive pulmonary disease. *Clin Chest Med* 1986; **7:** 585-597.
25. Carter R, Nicotra B. The effect of exercise training and rehabilitation on functional status in patients with chronic obstructive pulmonary disease (COPD). *Int J Rehab Health* 1996; **2:** 143-167.
26. Geul-Klaren GA. Reactiveringsprogramma voor CARA-patiënten. Een nadere uitwerking van een integrale behandelingswijze. [Reactivation programme for NSCLD patients. A further explication of an integral treatment strategy.] *Neth J Fys* 1991; **9:** 190-195.
27. Bruinings AL, Bauer H, Mensen EAM, Willems LNA. Goede resultaten van poliklinische longrevalidatie: 2 jaar ervaring in het Rijnlands Zeehospitium te Katwijk. [Good results of outpatient pulmonary rehabilitation: two years' experience in Rijnlande Zeehospitium, Katwijk.] *Neth J Med* 1996; **140:** 1504-1508.
28. Kumar S. Pulmonary rehabilitation in chronic obstructive pulmonary disease: is someone too well or too sick to benefit from it? *Physiother Singapore* 1999; **2:** 105-109.
29. Cambach W, Chadwick-Straver RVM, Wagenaar RC, *et al.* Feasibility of a pulmonary rehabilitation programme in community-based physiotherapy practices. *J Rehab Sci* 1994; **7:** 104-112.
30. Haas A, Cardon H. Rehabilitation in chronic obstructive pulmonary disease. *Med Clin North Am* 1969; **53**: 593-606.

Acknowledgements

We are grateful to Dr Arnold Kester, statistician, and Ms Anne-Marie Korsten, management assistant for their valuable contribution in constructing Figure 1.