Home oxygen therapy in COPD patients

Results from the Danish Oxygen Register 1994-2000

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INTRODUCTION

Oxygen has been used systematic in the treatment of lung disease since 1922 (9) Treatment with oxygen in the home of the patient is called "home oxygen therapy" or "domiciliary oxygen". Two randomized studies some 25 years ago showed that continuous oxygen therapy under certain circumstances improved survival in COPD patients (10, 11). Since then, home oxygen therapy has become widely spread. Today, in the western part of the world, the prevalence of home oxygen therapy varies from 15 to 241 per 100,000 inhabitants (12, 13) Home oxygen therapy is prescribed for various reasons (Figure 1).

Guidelines for COT are based on three controlled studies (10, 11, 14). The best overall information on adherence to the guidelines comes from Sweden and France (15, 16). In addition there are regional surveys from Poland, United Kingdom, Spain, Italy and the Netherlands (17-26). In most studies, less than 50% of the patients adhered to the criteria for COT. Our knowledge on factors related to compliance with criteria for COT is limited.

Despite correction of hypoxaemia, COPD patients on COT have poor survival with a large reduction in life expectancy (27) and a significant number of days spent in hospital (28). Advanced age and male gender increases risk of dying, but other possible predictors of survival have either been addressed with conflicting results or have been studied sparsely. Predictors of hospitalization have only been addressed in one study (28).

Besides improving survival, COT may have a positive effect on other outcomes e.g. quality of life and risk of hospitalization, but the evidence is not firm. Today, it is considered unethical to undertake randomized placebo controlled studies in hypoxaemic COPD patients. Therefore, in order to examine these outcomes, studies include non-hypoxaemic patients as controls.

Whereas the criteria for COT are well established, the criteria for non-continuous oxygen therapy (NCOT) are less clear (29-38). Nevertheless, many patients are prescribed NCOT in the hope that it will alleviate or diminish pulmonary symptoms.

In order to monitor the patients' characteristics, outcomes and quality of COT, national and regional oxygen registers have been established (15, 39). Through enhanced educational efforts and monitoring of compliance with guidelines on COT, The Danish Oxygen Register aimed at improving the quality of COT.

AIM OF THIS REVIEW

The main purposes of the present review is to:

A. Investigate different types of home oxygen therapy in Denmark in year 1994, when The Danish Oxygen Register was established, and during the following six years.
B. Investigate adherence to guidelines for COT, factors associated with good compliance (predictors), and the impact of a national register on adherence to guidelines for COT in COPD patients.
C. Examine effect of COT on hospitalization in COPD patients.
D. Investigate predictors of survival and hospitalization in COPD patients on COT.
E. Examine effect of NCOT on symptoms related to hypoxaemia.

GUIDELINES ON HOME OXYGEN THERAPY

The Danish guidelines for prescribing COT are in line with the international guidelines (30, 40-48) (Table 1). These guidelines are mainly based on three randomized studies: the British Medical Research Council (MRC) study, the Nocturnal Oxygen Therapy Trial (NOTT), and the Polish study of moderate hypoxaemic COPD patients (10, 11, 14). There are no Danish guidelines for prescribing NCOT. However, it is most likely that Danish doctors are adopting guidelines from US, UK and Australia, recommending NCOT to patients with symptoms related to exercise induced or nocturnal hypoxaemia and to patients with symptomatic terminal cardio-pulmonary disease without continuous hypoxaemia (30, 43, 45). Documentation of a beneficial effect of oxygen exceeding a placebo effect is not a routine in Denmark before starting the NCOT.

Level of hypoxaemia and number of hours spent on oxygen according to the guidelines on COT: Documentation of hypoxaemia (P_aO_2 < 8 kPa) and administration of oxygen at least 15 hours daily are essential (30, 41-48). Including patients with P_aO_2 < 7.3-8.0 kPa, the MRC and NOTT studies demonstrated a relationship between

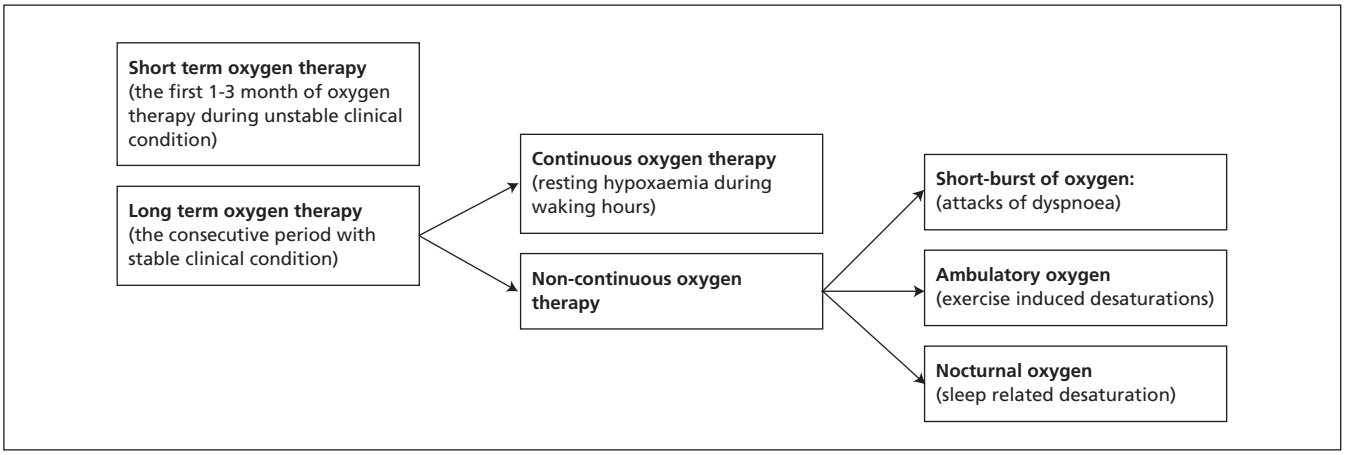

Figure 1. Terminology of home oxygen therapy. In the literature, long term oxygen therapy (LTOT) is often used as a synonym of continuous oxygen therapy (COT) and home oxygen therapy (HOT).

Table 1. Adherence to the criteria for Continuous Oxygen Therapy (COT).

Criteria for COT	Country	Year of examination	Number of patients	Adherence %	Comments	Reference
P_aO_2 <7.3 kP_a or 7.3-8.0 kP_a plus signs of tissue hypoxia[a]	Spain	Before 1985	263	44	P_aO_2 <8.0 kP_a	44
	USA (Atlanta)	Before 1985	77	30		50
	France	1984-1985	7.700	55-80	20%>8.0 kP_a and 45% >7.3 kP_a	16, 51
	England	1986-1987	61	54	Poor compliance when GPs prescribe COT	22
	England	1987	64	33	Had P_aO_2 <7.3 kP_a at reassessment	52
	Sweden	1987	560	91	P_aO_2 <8.0 kPa	15
	Sweden	1987-1989	777	appr. 85		53
	Scotland	1989-1991	519	66	34% either P_aO_2 >7.3 kP_a or not measured	24
	England	1990-1991	477	66	S_aO_2 <91%	21
	Poland	Before 1991	407	100	All prescribed by chest physicians	54
	England	1991	176	61	S_aO_2 <91%	23
	Spain	1991	62	58		17
	Denmark	1995	822	56		5
	Australia	1977-1999	505	87	P_aO_2 <8.0 kP_a	55
Oxygen prescribed and administered for at least 15 hours daily	Spain	Before 1985	263	31	Of those with P_aO_2 <7.3 kP_a	49
	England	1986-1987	61	46	Only concentrators. GPs: ↓ compliance	22
	England	1987	64	53	Number of patients with ambulatory oxygen not specified	52
	Sweden	1987-1989	777	70	Number of patients with ambulatory oxygen not specified	53
	Scotland	1989-1991	519	56	Number of patients with ambulatory oxygen not specified	24
	Switzerland	Before 1991	64	51	Related to education	56
	England	1991	176	50	21% had ambulatory oxygen	23
	Spain	1991		66	Of those who had hypoxaemia corrected	17
	England	1992-1994	86	64	Related to education program. Not randomized	57
	Denmark	1994	937	59	31% had ambulatory oxygen	2
	Denmark	1994-1995	182	65	35% had ambulatory oxygen	1
	France	Before 1996	930	55	33% had ambulatory oxygen	51
	Nederlands	Before 1998	175	48	64% had ambulatory oxygen	18
	Turkey	1995-1999	379	28	Only concentrators. Related to education and follow-up	58
	Australia	1977-1999	505	76	Of those prescribed 15-24 hours daily	55
	Greece	1998-1999	267	27		60
	New Zealand	Before 2003	43	60		59
No smoking	England	1986-1987	61	78		22
	Sweden	1987	560	92		15
	England	1987	64	74	Carboxyhemoglobin >2.5%	52
	Scotland	1989-1991	519	86		24
	England	1990-1991	477	87		21
	Poland	Before 1991	407	87		54
	England	1991	176	81		23
	England	1992-1994	86	92	Related to education program	57
	Denmark	1994	1.290	79		2
	UK	1993-1998	34	71	At prescription. No follow-up	61
	Canada	1995-1997	237	90		62
	Nederlands	Before 1998	175	84		18
	Turkey	1995-1999	379	93		58
	Australia	1977-1999	505	86		27
	Greece	Before 1998	79	71		63
	US	1996-1998	57	49	Patients on continuous oxygen therapy	64
	Greece	1998-1999	267	74		60
Increase in P_aO_2 after oxygen supply >0.7 kPa (aiming at 8.0-8.7 kPa) without a substantial increase in P_aO_2	Sweden	1987	560	80	Mean flow = 1.4 L/min	15
	England	1987	64	74	At reassessment. Flow appr. 1.8 L/min	52
	Scotland	1989-1991	519	45	Mean flow not specified	24
	England	1990-1991	477	86	>30% of the predicted max. improvement. Flow = 2.2 L/min	21
	England	1991	176	71	$S_aO_2 \geq 92\%$; Median flow = 2.0 L/min	23
	Spain	1991	62	81	Of those with hypoxaemia on air. Flow not specified	17
	England	1993-1998	34	53		61
	Denmark	1995	890	80	Of those 53% of the pts. who were checked. Flow 1.3 L/min	3
	Australia	1977-1999	505	90	Related to higher P_aO_2 at baseline	27
Follow-up after 1-3 months to assure clinical stability and then every 6-12 months	England	1986-1987	61	61	Of those 18 patients fulfilling the DHSS criteria	22
	Scotland	1989-1991	519	97	Only 56% of these had blood gases measured	24
	Poland	Before 1991	407	87	Followed up at 1 year	54
	England	1993-1998	34	0		61
	Denmark	1995	890	39	Follow up within 10 months – only 18% "sufficiently"	3
	US	1996-1998	57	35	Appropriately re-evaluation	64
	Greece	Before 1998	79	80		63
	Turkey	1995-1999	379	35	"Checked regularly"	58

a) Cor pulmonale, congestive heart failure, or packed cell volume >55%.

number of hours spent on oxygen and survival, and found significantly improved survival when oxygen was administered at least 15 hours daily (10, 11, 65). In a study of 43 hypoxaemic COPD patients on COT, the number of hours spent on oxygen therapy was positively associated with the improvement in health related quality of life (59).

In COPD patients with less severe hypoxaemia (P_aO_2 >7.3 kPa), COT provided no survival benefit according to the Polish study by Górecka et al (14). Despite weak evidence, those patients with moderate hypoxaemia combined with signs of tissue hypoxia are also recommended for COT.

Correction of hypoxaemia: The treatment group in the MRC study received oxygen at a flow rate of 2 L/min, or at higher flow rate if this was necessary to achieve a P_aO_2 >8.0 kPa (11). In the NOTT study, the oxygen flow was titrated to a level that maintained a P_aO_2 >8.0 kPa during rest, and further increased by 1 L/min for sleep and exercise (10). While the ATS, Canadian, and Australia/New Zealand guidelines have adapted these criteria (30, 45, 46), most European guidelines recommend a fixed oxygen flow that is sufficient to rise P_aO_2 at least 0.7 kPa and above 8.0 kPa, or S_aO_2 above 90% (41-43, 47). The increase in P_aO_2 should be achieved without an unacceptable rise in P_aCO_2.

Level of hypercapnia and airflow obstruction: In the early British guidelines for COT, P_aCO_2 >6.0 kPa and FEV_1 <1.5 L was a part of the inclusion criteria (66). In accordance with this criteria, all patients in the MRC study had FEV_1 <1.4 L. The effect of COT was most favourable in those patients with hypercapnia (10, 11). However, in the most recent British guidelines, no threshold level of airflow obstruction has been included, and P_aCO_2 is no longer considered in the qualification process (43).

Smoking: Although tobacco smoking was not allowed in the MRC study, about one third of the patients admitted smoking (11). Today, it is still unknown whether smokers differ from non-smokers regarding the effect of COT (65). Due to risk of fires and to difficulties in administration oxygen at least 15 hours daily in smokers, most guidelines still exclude smokers. Yet, smoking is not a contraindication in Austria (48), and numerous guidelines have not stated their attitude to smoking (43, 44, 47).

Clinical stability at the time of start of home oxygen therapy: The guidelines often state that before considering COT the patient should be clinically stable and on optimal medical treatment. In practice, stable hypoxaemia should be assessed at least twice, 3 weeks apart, and within 90 days of discharge from hospital (30, 41-43, 45, 67). The provision of domiciliary oxygen to patients hypoxic at hospital discharge has been termed short-term oxygen therapy (STOT). Although there are no evidence-based guidelines, this practice is widespread (24, 61, 64, 68-70).

In the selection of candidates for COT, the NOTT study and a study by Levi-Valensi et al evaluated the spontaneous evolution of blood gases (71, 72). They found that about 30-50% of patients initially classified as clinically stable didn't fulfil the hypoxaemia criteria at re-evaluation at 2-3 months, and Levi-Valensi et al demonstrated that 20% of those who still met the hypoxaemia criteria at 1 month were no longer hypoxaemic after 3 months. Due to the lack of randomized controlled trials, it is difficult to decide whether hypoxic patients at discharge should be provided STOT or observed without oxygen therapy. In the study by Levi-Valensi et al, low P_aO_2 at discharge predicted hypoxaemia level of P_aO_2 at re-evaluation, but it was not possible to select candidates for COT: for example if P_aO_2 was below 6.7 kPa at discharge one of 23 patients improved enough to allow suspension of oxygen therapy, but in 36 of 54 patients the probationary period would have been unnecessary and possibly harmful for the patients (71). Two recent studies have focused on STOT (69, 73). Eaton et al showed that 30% of the initially hypoxaemic patients didn't meet the hypoxaemia criteria at 2-month follow-up, and despite oxygen therapy, 17% of the patients died in the follow-up period (69). Correspondingly, Andersson et al found that 14 of 20 patients (70%) didn't need LTOT after one month (73). Although many patients don't fulfil the hypoxaemia criteria at 3-months reevaluation, symptoms of hypoxaemia and high mortality in the follow-up period justifies initiation of STOT. In general, when clinical stability is assured, P_aO_2 (at room air) declines after initiation of COT (74). However, it appears that some patients may have a temporary increase in P_aO_2, but very few remain normoxemic (25). Therefore, if hypoxaemia is measured during clinical stability, spontaneous improvement of P_aO_2 should not lead to an interruption of the treatment (25, 75).

Follow-up setting: In order to select candidates for COT, and to assure proper use of oxygen and optimal medical treatment, follow-up was very close in both the NOTT and MRC studies (11, 72). As the majority of the patients starts STOT immediately after a hospitalization, reassessment is recommended after 1-3 months treatment (30, 41-43, 45, 67). When the patient fulfils the criteria for COT, follow-up is necessary in order to ensure optimal flow rate necessary to correct hypoxaemia, to check the compliance of oxygen administration, to ensure non-smoking status, and to assess needs of oxygen equipment and proper service from the oxygen supplier. The question of exactly how often patients who qualify for COT should be re-evaluated has only been addressed in a study by Cottrell et al (76). Studying 50 patients for one year, they found that a 6-month re-evaluation interval was more cost-effective in comparison with a 2-months interval. Most guidelines recommend follow-up once or twice annually (41-43, 45). In Denmark, reassessment is recommended four times annually (40). According to a recent study by Chaney et al a respiratory therapist-managed oxygen therapy clinic seems able to decrease inappropriate oxygen therapy with significant cost savings (70). The British Thoracic Society recommends follow-up by a respiratory health worker visiting the patient's home (42). In various countries, the follow-up in the clinic is combined with home visits by a respiratory nurse (77-80). This practice may improve compliance of COT and optimize medical treatment, and the randomized study by Farrero et al found it cost-effective with a decrease in hospital resources used (79).

Affiliation of prescribing doctor: According to the most recent British guidelines, prescription and monitoring of COT to patients with severe respiratory failure is a task that is best managed by a respiratory physician (43). In other guidelines, e.g. ATS and GOLD, this issue has not been addressed (30, 44).

Hypoxaemia in non-COPD patients: In most countries other chronic hypoxaemic conditions than COPD are treated with COT (2, 39, 68, 81, 82). This use of oxygen therapy rests on extrapolation of data from the COPD patients in the NOTT and MRC studies. In a randomized, unpublished study of 62 patients with lung fibrosis COT failed to improve survival (83). Similarly, studying moderate hypoxaemia in patients with cystic fibrosis, Zinman et al found that 8 hours nocturnal oxygen therapy had no effect on survival, hospitalization, or disease progression during a 3-years period (84). In general, due to ethical reasons and the relative small number of patients with other hypoxaemic conditions than COPD, it is difficult to undertake large randomized placebo-controlled studies in these patients.

ORGANIZATION OF HOME OXYGEN THERAPY IN DENMARK

In 1994, Denmark consisted of 16 counties with 45, 000 to 614, 000 inhabitants. Each county has its own organization of HOT. In eight counties the general practitioners (GPs) took part in prescribing home oxygen. However, as GPs in Denmark are not able to test blood gases, they either must rely on previous tests at the hospital or just assume that the patient had hypoxaemia on basis of severe symptoms and poor lung function. Liquid oxygen became available in July 1995. In general, the suppliers were able to choose between a concentrator and gas cylinders on economic grounds. In cases of a large consumption of oxygen it was more favourable for the suppliers to deliver a concentrator. All costs of HOT, including consumption of electricity by oxygen concentrators, are covered by the local hospital. This is also the case if a GP prescribes HOT.

METHODS

IDENTIFICATION OF PATIENTS ON HOT

The Danish Oxygen Register was established in November 1994. The patients were identified through the oxygen suppliers. The register covered 98-100% of the Danish population (Figure 2). Identification and vital status of patients on HOT were confirmed by The National Board of Health, and until August 1995 by the patient hospital or GP files.

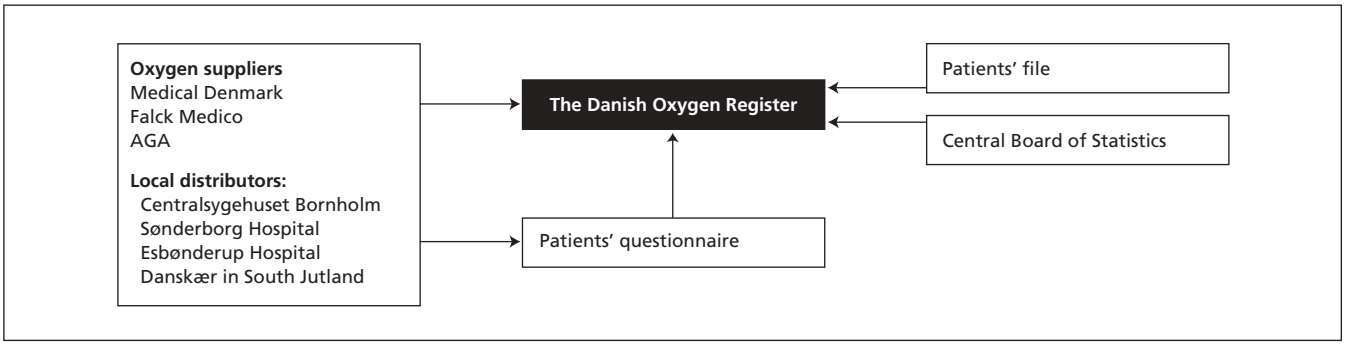

Figure 2. Collection of data to The Danish Oxygen Register.

PRESCRIBED OXYGEN
AND DELIVERED OXYGEN EQUIPMENT

The oxygen suppliers provided information on delivered oxygen equipment, usage of oxygen, prescribed oxygen flow and number of hours per day. In general, the suppliers were able to choose between a concentrator and gas cylinders. In cases of a large consumption of oxygen it was more favourable for the suppliers to deliver a concentrator (85). Liquid oxygen became available August 1995. Mobile oxygen (cylinders of two to five litres) and liquid oxygen were preferably prescribed if the patient spent a lot of time outside. Although a portable lightweight concentrator has been developed, it has not yet been introduced in Denmark. The actual usage of oxygen was calculated from the oxygen concentrator meter readings and from delivered oxygen cylinders.

MEDICAL DATA

From the patient hospital or GP files, we achieved information on cause of hypoxaemia, medical treatment, smoking habits, carboxyhaemoglobin (CO-Hgb) level, carbon monoxide in expired air, height, weight, electrocardiogram, forced expiratory volume after one second, forced ventilatory capacity, and arterial blood gas tensions. Regarding patients who were on HOT at establishment of the register, the highest P_aO_2 values (on room air) between May 1993 and November 1994 were registered. In new patients, the highest P_aO_2 values without supplemental oxygen and obtained within the period of one month before to three months after initiation of HOT was registered.

A CO-Hgb >2.0% (>3.0% (8)) or CO in expired air >10 ppm were considered as active smoking.

QUESTIONNAIRE BY MAIL

In November 1994 all patients on HOT received a questionnaire by mail. The questionnaire provided information on daily use of oxygen (number of hours daily) according to the patient; outdoor activity (yes/no); WHO performance status scale; smoking habits (current smoking/ex-smoker/never smoker); height; weight; and subjective effect of oxygen therapy on various symptoms (See appendix A). It was answered by 72% of the COPD patients (responders). The most pronounced differences between responders and non-responders were the 3-months mortality rate (6.5% versus 24.4%) and prevalence of current smokers (17.2% versus 32.8%). All patients who started home oxygen therapy between 01.11.1994 and 31.07. 1995 received the same questionnaire 1-4 weeks after initiation of therapy. In case of non-response, 1-2 reminders were sent after 3-5 months. Among hypoxaemic COPD patients, the response rate was 54.8% (253/462). Again, responders had a much lower 3-months mortality rate compared to non-responders (2.4% versus 37.8%).

MORTALITY, HOSPITALIZATION, AND OUTPATIENT VISIT

The National Board of Health provided information on hospital admissions, contacts with outpatient clinics, vital status, and cause of death. Patients were followed up to 31.12.2000.

DEFINITION OF "FOLLOW-UP", "SUFFICIENT FOLLOW-UP",
AND "ADHERENCE TO GUIDELINES FOR COT"

"Follow-up": at least one contact to an outpatient clinic or a home visit within a 10-months period.

"Sufficient follow-up": 1) follow-up, 2) measured arterial blood gases or oximetry with oxygen supply, 3) oxygen at least 15 hours daily, and 4) non-smoking status.

"Adherence to guidelines for COT": 1) objective verified hypoxaemia, 2) blood gases measured with oxygen supply, 3) non-smoking, and 4) use of oxygen at least 15 hours daily.

GROUPS OF PATIENTS STUDIED

The patient studied comprises data from 8 different samples of patients:

A. A sample of 1,835 patients on HOT due to cardio-pulmonary disease on the 1st of November 1994, including 1,354 (73.8%) due to COPD (2). A cross-sectional study and analysis of a nation-wide database (Danish Oxygen Register).
B. A sample of 182 patients, who were started on home oxygen therapy at the pulmonary Department, Bispebjerg Hospital in the period 01.11.94 to 31.07.95. Data on outdoor activity, usage of oxygen according to the patients and actual consumption were obtained from 125 patients (1).
C. A subgroup of the 1,354 COPD patients (n=890) who had HOT at least 10 months in the period 01.11.94 to 31.08.95 (3).
D. A sample of 154 patients who started NCOT between November 1994 and July 1995 and answered a questionnaire on symptomatic effect of oxygen therapy (4).
E. A sample of 246 hypoxaemic COPD patients who started HOT between November 1994 and July 1995 with data on usage of oxygen according to the patient (5).
F. A sample of 221 hypoxaemic COPD patients who started HOT between November 1994 and July 1995 with data on body mass index and oral corticosteroid treatment (6).
G. A sample of 170 moderate hypoxaemic COPD patients (P_aO_2 on room air and rest: 7.3-9.5 kPa) who started HOT between November 1994 and July 1995 and were treated with HOT for at least one month (7).
H. A sample of 17, 558 patients who received HOT from November 1994 to December 2000 with focus on 8, 492 COPD patients (8).

STATISTICAL METHODS

A chi-squared, two sample t-tests and Mann-Whitney U tests were used as appropriate to compare differences between groups.

Linear regression analysis, using Spearman correlation coefficients, were applied to relate the actual usage of oxygen to usage according to the patient (1) and to relate the prescribed number of hours according to the oxygen suppliers with used number of hours according to the patient (2). Multiple logistic regression analyses were used to estimate the impact of various variables (predictors) on "adherence to guidelines" (2), follow-up (3), "sufficient follow-up"

(3) (see definition section 6.6), and administration of oxygen 15-24 hours daily (Table 2) (2).

The Kaplan-Meier estimate was used to produce survival and admission rates (time until first admission), and the log rank test to test differences between COPD and cancer patients (4), and difference between patients who started HOT in 1995 and 1999 (8).

Cox regression model was used to determine individual predictors of survival and hospitalization (6, 8). The hazard ratios were adjusted for those covariates (confounders), which were related to outcome (time to death or 1. hospitalization, separately) and to the independent variable (BMI, treatment with oral steroids, outdoor activity, WHO performance status, or year of start on HOT). Age and gender were forced into the model. The results of regression analyses are given in terms of estimated relative risks (RRs) (hazard ratios), with corresponding 95% confidence intervals (CIs). P-value <0.05 was accepted as significant. Analyses were performed with the statistical package for the social sciences (SPSS) version 8.0-11.0 (SPSS Inc., Chicago, USA).

HOME OXYGEN THERAPY IN DENMARK IN YEAR 1994 AND THE FOLLOWING SIX YEARS

BACKGROUND

In the early 1980s two randomized studies showed that continuous oxygen therapy under certain circumstances improved survival in COPD patients (10, 11). Since then, home oxygen therapy has become widely accepted. However, only Sweden and France have provided data on a national basis, and other information on HOT stem from regional studies or questionnaire surveys. Furthermore, data on HOT in Denmark is very sparse, and there is no data from other countries after mid 1990s. Thus, it was considered worthwhile to establish a national register in order to get data on the quality of COT in Denmark.

INCIDENCE AND PREVALENCE OF HOT

Own results

At establishment of The Danish Oxygen Register, 01.11.1994, a total of 1,835 patients received home oxygen therapy due to cardio-pulmonary disease, including 1,354 (73.8%) due to COPD (26.8 per 100,000 inhabitants). In our 16 counties, the prevalence of COPD patients on HOT varied from 14 to 53 per 100,000. The prevalence of HOT was significantly higher in those eight counties where GPs took part in HOT prescribing compared with the rest of the counties: 34.4 versus 19.2 per 100.000 ($p<0.001$). Adherence to criteria for COT was 5.3 (95% CI: 2.9-9.1) times as likely if the oxygen was prescribed by a pulmonary department compared to oxygen therapy initiated by a GP (2).

From 1995 to 2000, the annual incidence of oxygen therapy increased from 20.5 to 25.2 per 100, 000 (Figure 3). Correspondingly, the prevalence of COPD patients on HOT increased to 42.1 per 100,000 (Figure 4). On 31.12.2000, the prevalence of COPD patients on HOT varied from 20.1 to 94.4 per 100.000 in the 16 counties.

Among new COPD patients on HOT, only 15.4% of those alive at 6 months had treatment stopped (8). This interruption of therapy was often permanent and only 7.9% of these patients restarted oxygen therapy within a 6-months period (8).

Discussion

In early 1990s, the prevalence of home oxygen therapy varied from 10 to 241 per 100.000 individuals in the western part of the world (13, 86). As stated by Viskum, the prevalence depends on various conditions: e.g. frequency of obstructive lung disease in the terminal phase, the strictness with which the criteria for oxygen therapy are met, the possibilities for financing the treatment, the demand and acceptance in the population for the treatment. In accordance with the questionnaire survey by Viskum, we found that the prevalence of HOT was lower in areas where the treatment was prescribed by a chest physician (86). We found that this relationship was explained by a better compliance with guidelines for COT. Similarly, low prevalence and good compliance has been recorded in Poland and Sweden, where chest physicians are responsible for all or nearly all patients on home oxygen treatment (86). Concerning prescription of HOT in Denmark during 1994 to 2000, there have been no legal changes, but most hospitals are now re-evaluating the patients if HOT is initiated by a general practitioner.

Previous studies from Sweden and France demonstrated increasing prevalence of domiciliary oxygen therapy up to mid 90's (15, 39, 87, 88). In France, according to ANTADIR register, which comprises some 70% of all patients on HOT, the prevalence increased from about 6 to 37 per 100.000 from 1983 to 1992 (39, 88). In Sweden, the prevalence doubled to 15 per 100,000 between 1987 and 1993 (15, 87). In these countries about 60-75% of the patients on HOT had COPD (15, 39, 87). In the same period, the prevalence of HOT increased from approximately 15 to 36 per 100,000 in Denmark. In the following six years, we found that the prevalence of HOT in COPD patients increased by 57%, and the increase in incidence was slightly smaller (23%). From 1994 to 1999, the age-standardized mortality rate for COPD mortality in Denmark has increased from 70 to 82 per 100.000 (data from the National Health Services Central Register in Denmark). In the same period, the age-standardized hospitalization rate for COPD in Denmark has increased from 300 to 450 per 100,000 (data from the National Board of Health). It appears that the increased incidence and prevalence of COPD patients on HOT was at least partly explained by an increased number of patients with severe COPD applying for oxygen therapy. An increasing number of clinically unstable COPD patients who had oxygen therapy prescribed immediately after a hospitalization without proper

Table 2. Characteristics of patients with and without mobile oxygen, and with and without outdoor activity (1).

	Number of patients				P-level for differences between two groups	
	39	9	42	34		
Groups	O & M	H & M	O & S	H & S	O vs H	M vs S
Age, years	67.7	64.1	67.2	72.9	*	ns
Concentrator, %	75	89	68	83	ns	ns
Use of oxygen, hours/day	17.8	20.8	15.5	18.1	ns	*
Use >15 hrs/day, %	74	89	48	74	ns	*
Use of mobile oxygen, hours/day	1.32	1.13	0	0	ns	ns
Use of mobile unit >2, hours/week, %	49	22	0	0	ns	ns
Stationary oxygen, hours/day	16.5	19.6	15.5	18.1	*	ns
Activity score (WHO), median	2.47	2.75	2.32	2.82	**	ns

Continuous and ordinal values are stated as mean.
O = Outdoor activity; H = Home bound; M = Mobile oxygen; S = Stationary source without mobile oxygen.
ns = non-significant; * = $p < 0.05$; ** = $p < 0.01$.

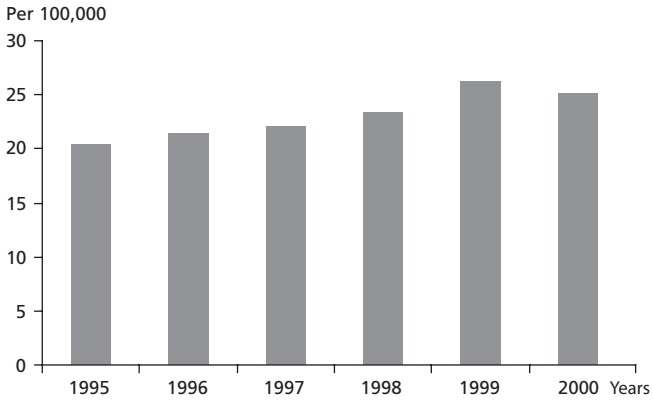

Figure 3. Changes in the incidence of home oxygen therapy from 1995 to 2000 by COPD.

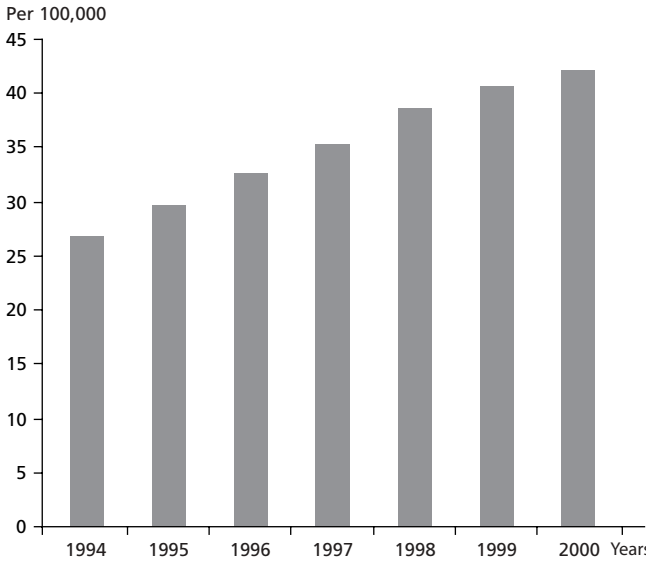

Figure 4. Changes in the prevalence of home oxygen therapy from 1994 to 2000 by COPD.

re-evaluation of the adherence criteria may also explain some of the increase in the incidence and prevalence. Moreover, an increased survival, although it was small, may explain some of the increase in prevalence (see section 7.4.).

PATIENTS CHARACTERISTICS, AFFILIATION OF PRESCRIBING DOCTOR, AND PRESCRIBED OXYGEN FLOW IN THE PERIOD FROM 1994 TO 2000

Own results

The majority of the COPD patients were females (Table 3). Among new patients, the mean age increased from 70.6 to 72.4 years ($p<0.001$) (Table 3). About 77% of the COPD patients were prescribed oxygen therapy by a hospital doctor immediately after a hospitalization for an acute exacerbation, and the number of prescriptions from general practitioners was declining (Table 3). Among new patients on HOT, the average oxygen flow during the study period increased from 1.30 L/minute to 1.42 L/minute ($p<0.001$).

Discussion

In contrast to most other countries, more women than men (about 60%) were on HOT in Denmark. In Sweden, Australia, and US approximately half of the COPD patients were women (15, 55, 68, 89). Since 1993, females are responsible for approximately 60% of all hospital admissions due to exacerbation in COPD in Denmark (Data from The National Health Services Central Register in Denmark). In addition, women seem to be more willing to use oxygen the correct number of hours than men (15-24 daily). In accordance with a Dutch study we found that being female was an independent predictor of adequate administration of oxygen (See section 8.1) (2, 18).

Compared to the MRC and NOTT studies where patients aged above 70 years were excluded, the mean age of patients on HOT in Denmark, Sweden, Japan, France, Australia, and USA was 5-10 years higher and between 67-75 years (39, 53, 55, 68, 90). According to preliminary data from Sweden, age of the new patients on HOT seemed to have increased from 1987 to 1993 (87). In the period 1994 to 2000 the age of our new patients has also increased in average by 1.8 years (8).

As recommended by the most recent British guidelines, a decreasing number of Danish patients had oxygen therapy prescribed by general practitioners, who are unable to measure blood gases and to obtain sufficient experience in this special therapy (43). Most of the data on affiliation of the prescribing doctor is either old or comes from small studies, and there was a great variation in number of patients initiated by a general practitioner. A recommendation on centralized organization may be difficult to implement in countries with long distances between respiratory physicians. In this situation, at least initial evaluation in a respiratory department should be mandatory with coordinated follow-up afterwards at either internists or general practitioners capable of measuring blood gases or at least oxygen saturation.

Although the oxygen flow used in Danish patients has increased to 1.42 L/minute and is similar to prescribed flows in Sweden (15), it is significantly lower than in Italy, England, and the randomized clinical trials (MRC & NOTT) where 1.5-2.5 L/minute was used (10, 11, 21, 23, 91, 92).

OXYGEN EQUIPMENT

Own results

According to the oxygen suppliers, an increasing number of the COPD patients had delivered oxygen concentrator or liquid oxygen, and had mobile oxygen (Table 3). In 2000, 211 (9.3%) patients had liquid oxygen systems.

Mobile oxygen is prescribed to patients in order to make them mobile and to ensure administration of oxygen at least 15 hours daily. However, patients who received mobile oxygen had a limited usage of mobile oxygen, as only 39% of the patients had a usage >2 hours/week, and 27% had used less than one cylinder (regarded as nought) (1). In 1995, 65% of the patients reported outdoor activity, and a little less than half of these patients received mobile oxygen, while 25% of the home bounded patients had a mobile unit (Table 2). Recent data from Copenhagen, comprising approx. 15% of all patients in Denmark, showed that this relationship between delivered mobile oxygen and reported outdoor activity has not improved (unpublished data). Those patients with outdoor activity had a higher usage of mobile oxygen compared with patients bound to their home ($p=0.036$).

Discussion

Similar to Sweden, an increasing number of patients is delivered oxygen concentrators (53). Despite severe COPD a little more than half of the patients reported outdoor activity and should thus be considered as suitable candidates for additional mobile oxygen (1, 6, 23). Patients with outdoor activities should have mobile oxygen in order to increase the number of hours spent with oxygen and in order to make the patient even more mobile. The administration of mobile oxygen varies between 20 and 67% between countries (23, 53, 93, 94), and may depend on the following factors: mobility of patients prescribed HOT; weight, feasibility, and costs of mobile oxygen systems; patients and doctors' demand on and expectations to usage. Since the early 90's, the number of patients with mobile oxygen has increased from 5% to 58% (8, 86). Development of lighter and more convenient mobile systems is probably not the

Table 3. Changes between patients' characteristics, treatment modalities, and survival in COPD patients who started LTOT for the first time during 1995, 1999, and 2000, and COPD patients who received LTOT on the 1st of November 1994 and on the 31st of December 2000, respectively.

	Years			P-level for difference between 1995 and 2000	1st of November 1994	31st of December 2000
	1995	1999	2000			
Number of patients	1031	1306	1268		1354	2265
Prescribed oxygen at least 15 hours/day, %	66.2	85.3	85.5	<0.001	49.3	84.2
Oxygen concentrator or liquid oxygen, %	77.8	96.0	96.9	<0.001	55.6	96.1
Followed up in the outpatient clinic 1-6 months after start[1], %	62.9	67.4	60.5	0.43	NA	NA
Prescribed LTOT by a general practitioner, %	16.4	7.7	6.9	<0.001	26.5	8.8
Started LTOT within one week after discharge from hospital, %	74.4	82.2	82.6	<0.001	NA	NA
Females, %	55.9	58.9	57.8	0.42	57.0	60.5
Age, years, mean (SD)	70.6 (8.6)	72.1 (9.0)	72.4 (9.3)	<0.001	69.6 (8.7)	71.4 (9.1)
Oxygen flow, L/minute, mean (SD)	1.30 (0.70)	1.36 (0.73)	1.42 (0.73)	<0.001	1.26 (0.71)	1.46 (0.82)
Mobile oxygen, %	29.9	41.1	42.8	<0.001	28.1	58.0
Survival, years, median (95% CI)	1.07 (0.92-1.23)	1.40 (1.25-1.55)	Not applied	0.032[2]	Not applied	Not applied

CI: Confidence interval.
1) Of those alive after 6 months. 2) 1995 compared to 1999 (Log rank).

whole explanation. The attitude of the doctors combined with the demand by the patients have changed in favour of prescribing mobile oxygen systems to more patients. In our study from 1995 (1), only 39% of the patients with mobile oxygen had used it for more than two hours/week. In addition, many of these patients were not leaving their homes. One explanation for this rather low number could be that although small cylinders often are mounted on a stroller, they are difficult to handle for weak patients. When the patients had outdoor activity, the usage of stationary oxygen fell by a couple of hours, resulting in a lower overall consumption. This indicates that some patients were spending a considerable time outside home without using their mobile unit. This is in accordance with previous studies reporting low usage of mobile oxygen (94, 95). It is possible that transtracheal oxygen therapy improves the overall compliance and the use of mobile oxygen, but this therapy has very restricted criteria, which only very few patients fulfil (96). It seems that liquid oxygen had not solved the problem with low use of mobile oxygen, and small cylinders are still the most distributed mobile system (8, 95, 97, 98). The weight of the mobile unit was often stated as the most important factor preventing sufficient use. Therefore, development of more handy units is urgent.

SURVIVAL OF COPD PATIENTS ON HOT

Own results

The median survival time of all COPD patients who started HOT between 1995 and 1999 was 1.27 years (95% CI: 1.20-1.34) (Figure 5) (8). Compared to patients who started HOT in 1995, the median survival time was increased by 0.33 year in patients who started HOT in 1999 (Table 3) (8). Patients who started HOT in an unstable clinical condition right after a hospital admission had a higher RR of dying compared to patients who started therapy in the outpatient clinic (RR = 1.16 (95%-CI: 1.08-1.25; $p < 0.001$ (Figure 6)). Adjustment for gender and age does not change this association between mortality rate and clinical condition at start of HOT.

Discussion

The survival of our COPD patients was substantially lower than in other countries. After one year, only 55.5% of the patients were still alive compared to 70-88% in other studies (10, 53, 55, 90, 99, 100) (Figure 5). Best survival has been reported in the NOTT study where patients were younger and had no concomitant diseases (10), and in a Japanese study (90). Although the mean age of the patients in the French and Australian study was comparable with our patients, the one-year survival rates in these studies were markedly better than in our patients, 81% and 75%, respectively (55, 100). This difference in mortality is mainly due to a much higher 3-months mortality in our study. Most of our patients started HOT in an unstable clinical condition right after a hospital admission, which is related to high morality. In line with Hjarmarsen et al, we found that HOT started in the outpatient clinic was independently associated with better survival compared with treatment started in connection with discharge from hospital (101). High mortality rates in COPD patients with hospitalization due to acute exacerbation have also been reported in other studies (69, 102, 103). Conners et al reported, regardless of prescribed LTOT, a 2-months mortality of 20% – half of them died at the hospital before discharge (102). In a similar Danish study, the 3-months mortality was 19% (5.5% at the hospital) (103). In their study, however, patients with hypoxaemia and cor pulmonale had even higher mortality rate. In a study of 126 hypoxaemic patients who started short term oxygen therapy at hospital discharge, 17% had deceased after 2 months (69).

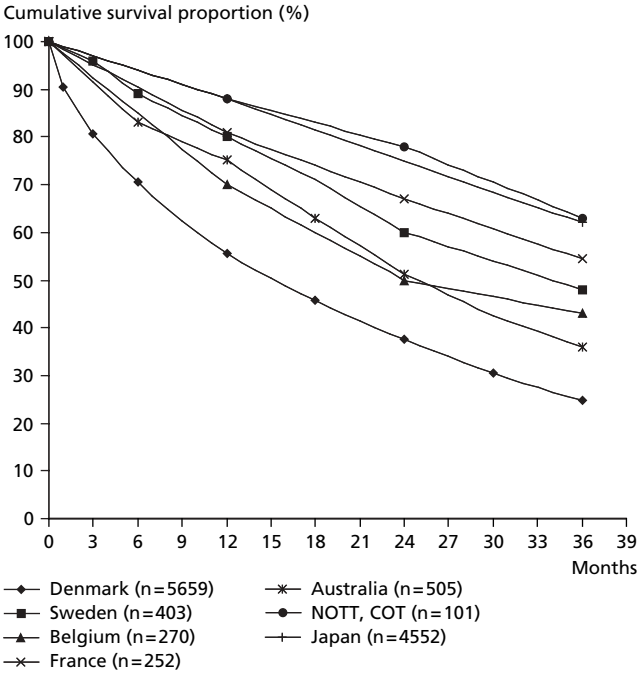

Figure 5. Survival of COPD patients on home oxygen therapy in different countries.

In the NOTT and MRC studies, a period of 3 months with clinically stable condition was ensured (10, 11). In Belgium, Sweden, and Japan, a minimum period of 3-4 weeks assessing the stability of hypoxaemia was recommended (53, 90, 99). Whether this was actually practiced was not reported. However, it seems that most of the Swedish patients started in a clinically stable condition, because only 4% had LTOT stopped with two years due to normalization of blood gases (53). Therefore, we believe that different practice in initiating HOT (stable or unstable condition) may explain the higher mortality in our patients compared to patients in the other studies (53, 55, 90, 99, 100). In addition, our patients may have started LTOT with a more advanced disease. We have shown that our patients were frequently hospitalized before LTOT, were often on systemic corticosteroids, and were often unable to undertake outdoor activities – all suggesting severe disease (5, 6). Finally, exclusion of patients with poor compliance and expected short-term survival in the Belgian study, may be another explanation for the better survival in their study (99).

ADHERENCE TO GUIDELINES FOR CONTINUOUS OXYGEN THERAPY

BACKGROUND

In order to improve the quality of COT, it is important to identify factors (predictors) of good adherence to criteria for COT. Through enhanced educational efforts and monitoring of compliance with guidelines on COT, The Danish Oxygen Register aimed at improving the quality of COT.

ADHERENCE TO GUIDELINES FOR COT 1994-95 AND FACTORS ASSOCIATED WITH GOOD COMPLIANCE (PREDICTORS)

Own results

Hypoxaemia: In our study of COPD patients on HOT 01.11.1994 (2), 57.5% of 807 patients and 69.4% of those 669 patients with measured P_aO_2 (on room air) met the hypoxaemia criteria. Among new patients (5), 462 of all 822 (56%) or (70.6%) of those 653 patients with data on P_aO_2 (on room air) adhered to the hypoxaemia criteria. Patients without hypoxaemia consisted of three groups: 1) normoxaemic patients using NCOT for episodic desaturation (approximately 25% in Denmark) 2) patients who became normoxaemic during clinical stabilization (approximately 72%) 3) patients who improved in arterial oxygen gas tension attributable to COT (approximately 3%).

Post-P_aO_2 above 8 kPa: Although the goal of oxygen therapy is to raise the resting P_aO_2 to above 8.0 kPa, this was not achieved in 21% of our COPD patients (3) and 40% of patients with mixed diagnoses, predominately COPD (1).

Administration of oxygen 15-24 hours daily: Among our COPD patients, 59% used oxygen 15-24 hours daily (2). An explanation of this poor compliance could be prescribed NCOT in patients with episodic hypoxaemia. However, in a subgroup of 246 COPD patients with hypoxaemia at rest, only 65.8% used oxygen more than 15 hours daily (5). Adequate treatment was especially prevalent when HOT was initiated by a Chest physician and when the patient was a female, was prescribed oxygen 15-24 hours daily, was younger than 66 years, had no outdoor activity, had P_aO_2 (room air) <6.3 kPa, and was a non-smoker (ORs 1.84; 1.87; 3.48; 2.02; 1.72; 1.95; and 1.69, respectively; Table 4) (2).

Self reported administration of oxygen matched the prescription of hours/day (number of hours/day: $R=0.46$; $p<0.001$) (2) and matched the actual consumption of oxygen ($R=0.50$; $p<0.001$; Figure 7) (1). Patients overestimated the administration time by 0.55 hours/day. Among patients who reported to use oxygen more than 15 hours/day, the actual usage was less than 15 hours/day in 29% of the patients (1).

Check on tobacco smoking: On November 1994, only 295 (21.8%) of all COPD patients had CO measured in blood or expired air (2). According to the file or questionnaire, which contains data on nearly all COPD patients, 21.1% admitted that they were still smoking (2). Among 246 hypoxaemic COPD patients who started HOT between 01.11.94 and 31.07.95, 17.5% were current smokers, and only 71 (22.6%) had CO-level measured (5). In a regional survey where pulmonary physicians where responsible for all patients on HOT, 56.7% of the COPD patients in 1995 had CO measured in the blood or expired air (8).

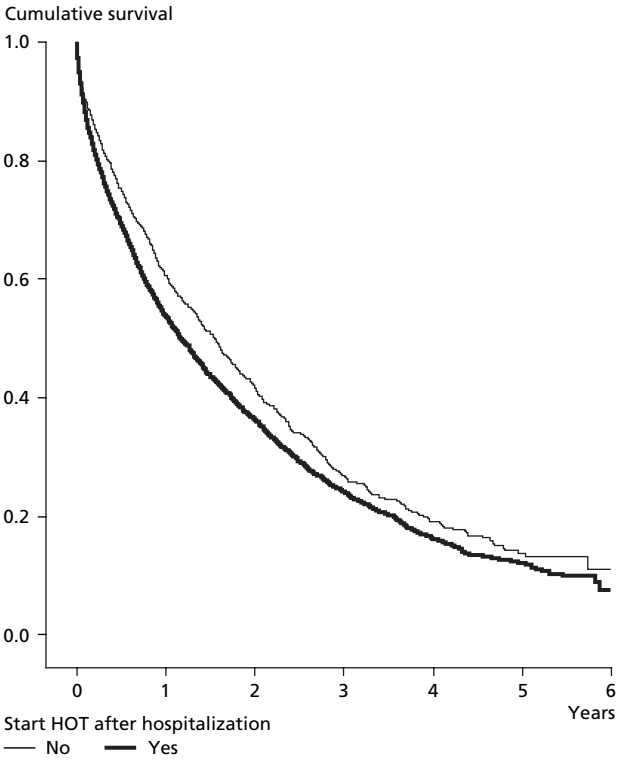

Figure 6. Survival of COPD patients who started home oxygen therapy (HOT) between 01.01.1995 and 31.12.1999 either in connection with discharge from hospital (n = 4,362) or from the outpatient clinic (n = 1,295). The median survival time was 1,17 years and 1,56 years in the two groups, respectively ($p < 0.001$).

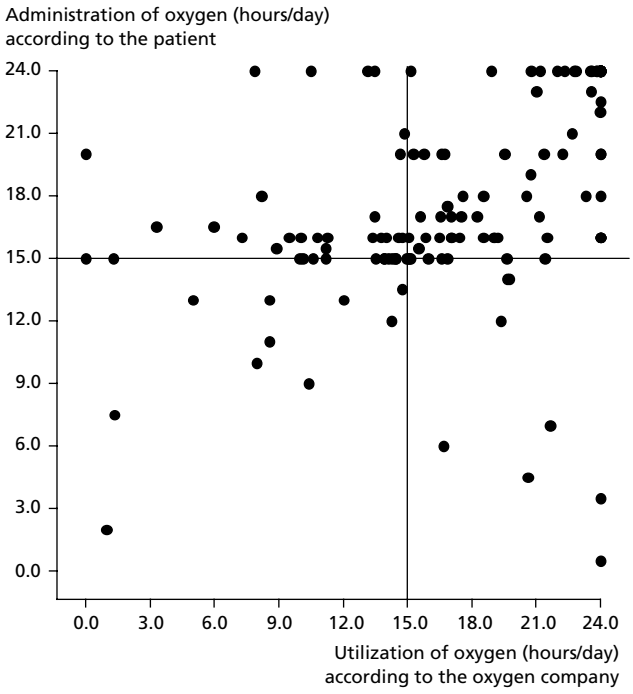

Figure 7. The relationship between utilization of oxygen (hours/day) according to the oxygen company and according to the patient.

Table 4. Predictors of correct administration of oxygen 15-24 hours daily according to the patient. The odds ratios (OR) calculated from a multiple logistic regression analysis. 95% confidence interval in parentheses. Data from (2).

		Odds ratios
Gender, male = 1		1.87 (1.26-2.78)
Long-term oxygen therapy started by		
Chest physician at pulmonary department		1.84 (1.05-3.23)
Chest physician at medical department		1.08 (0.61-1.91)
Internist		1.02 (0.57-1.83)
General practitioner		1
Prescribed 15-24 hours per day, no=1		3.48 (2.27-5.35)
Age, years	<66	2.02 (1.23-3.32)
	66-72.9	1.54 (0.95-2.49)
	≥73	1
Had outdoor activity, no=1		0.58 (0.37-0.91)
P_aO_2 (room air), kPa	<6.3	1.95 (1.17-3.25)
	6.3-7.19	1.72 (1.06-2.79)
	≥7.2	1
Current smoker, no=1		0.59 (0.35-0.98)

P_aCO_2, (room air) and duration of HOT were not associated with correct administration of oxygen. Only statistically significant factors are shown. Data from 600 of 1354 COPD who had HOT the 1st of November 1994 and information on the listed variables.

The frequency and quality of follow-up: Of 890 COPD patients, only 38.5% had a follow up, and only 17, 5% of all patients had a "sufficient follow-up", which included check on tobacco, compliance with treatment, and oxygen flow necessary to rise P_aO_2 above 8.0 kPa or S_aO_2 above 90% (3). Female gender, HOT initiated 3-12 months ago, HOT started by a chest physician at pulmonary department and LTOT prescribed ≥15 hrs/day were found to be significant predictors of "sufficient follow-up" (OR: 1.7, 2.0, 3.7 and 1.9, respectively).

Overall adherence to guidelines: Among 535 patients with sufficient information, only 34.4% fulfilled the following criteria: objective verified hypoxaemia, blood gases measured with oxygen supply, non-smoking, and use of oxygen at least 15 hours daily (compliance with guidelines) (2). Compliance with guidelines for COT was 5.3 (95% CI: 2.9-9.1) times as likely if the oxygen was prescribed by a pulmonary department compared to oxygen therapy initiated by a GP (2). Moreover, the rate of appropriate re-evaluation was significantly higher among pulmonary physicians than among primary care physicians (3). There was a tendency towards better adherence to guidelines when the patient was a female (OR= 1.4 (95-% confidence interval 1.0-2.1)) (2), and female gender was an independent predictor of "sufficient follow-up" (OR= 1.70 (95%-confidence interval 1.06-2.74)) (3).

Discussion

In the late 80's and early 90's, several studies have shown poor adherence to the guidelines for COT in all countries studied (Table 1). Some centres prescribe NCOT for palliation, however, none of the above mentioned studies have included patients with cancer. In the listed studies, some of the patients may be prescribed NCOT for other reasons than palliation, for example nocturnal desaturations, exercise induced desaturations, and attacks of dyspnoea.

Adherence to the hypoxaemia criteria

Several small and large surveys have confirmed our findings that about 50-70% of the patients on HOT didn't meet the hypoxaemia criteria (Table 1). This is either due to normalization of blood gases after recovery from an exacerbation in COPD without stopping HOT or initiation of HOT without hypoxaemia. Countries with lower frequency of STOT do not have the same practical problem of re-evaluating arterial blood gases and stopping STOT in patients who claim subjective benefits despite normalization of blood gases (25, 53).

Adherence to appropriate correction of hypoxaemia

Several studies have confirmed our results that a resting P_aO_2 above 8.0 kPa was not achieved in 15-25% of the patients (Table 1). Whether these patients were prescribed a too low oxygen flow or had to accept a lower flow due to side effects e.g. CO_2 retention, is unknown. Compared with the MRC and NOTT studies, the prescribed oxygen flows in the Nordic studies were substantial lower, suggesting that in some of these patients the set of oxygen flow may not be optimal (3, 10, 11, 15). However, although the prescribed flows in the British studies were higher, this did not increase the proportion of patients with corrected hypoxaemia (21, 23). In 5 of 42 patients from the MRC study, it proved impossible to raise the P_aO_2 >8.0 kPa when breathing 2 L/minute of oxygen.

It is uncommon to check the post-P_aO_2 on patients own oxygen equipment, and because oxygen concentrators may provide insufficient flow or concentration of oxygen in comparison with hospital setting, the number of patients with too low post-P_aO_2 may be underestimated (104-106).

The goal of supplemental oxygen is to achieve a P_aO_2 >8.0 kPa without an unacceptable rise in P_aCO_2. Most authors agree that this complication is not common in low-flow oxygen therapy, but the number of hypoxaemic patients who are denied sufficient oxygen on this account is only sparsely reported in the literature. In the NOTT study, no patients had to be discontinued on the oxygen therapy (10). In a review of the organization of respiratory home care in Italy, it was reported that in 5 of 70 patients (7.1%), COT had to be suspended due to CO_2 retention (97).

Adherence to correct administration of oxygen (at least 15 hours daily)

In line with our studies (1, 2, 5), most studies fund that approximately 60% of the patients used oxygen 15 hours daily or more, and that ineffective usage has been caused by inadequate prescription, and lack of instruction in use of oxygen (16, 18, 56-58) (Table 1), and this occurs more often when GPs are responsible for the treatment (Table 4) (18, 22, 63). There is mounting evidence that in mobile patients, ambulatory oxygen increases the number of hours on oxygen (1, 16, 95). Moreover, good compliance is seen in home bound patients with severe disease (Table 2) (16, 107). Furthermore, non-smoking and low P_aO_2 are associated with good compliance (Table 4) (16, 18, 58, 60). According to the Turkish study by Atis et al, regular follow-up increased the likelihood of correct use 3.8-fold (58). Conversely, there is less consistence concerning the influence of age, sex, lung function, and side effects due to COT on compliance with treatment (Table 4) (1, 16, 18, 23, 55, 56, 58, 60, 62).

Figures for compliance with treatment are often obtained from a patient questionnaire. According to several studies, patients overestimate the number of hours with oxygen (1, 10, 11, 17, 22, 58). Moreover, the measured oxygen consumption represents the maximum possible use rather than the actual amount of oxygen breathed by the patient. In the study by Restrick et al, 27% of the patients acknowledged that for a median time of 2 hours they did not wear the cannulae when the concentrator was switched on (23). Thus, the actual number of hours spent with oxygen is probably less than reported in the papers.

Check on tobacco smoking

Continued smoking in patients on HOT results in fire hazard and may attenuate the effect of the treatment. A non-significant part of the patients (5-29%) on HOT were still smoking (Table 1). As patients were not checked for tobacco smoking routinely, these figures may even be underestimated. Only two studies have focused on characteristics of smoking in HOT patients. In the non-randomized study of 86 patients, Pecham et al found significantly fewer smokers among instructed patients (57). According to our and Walshaw's

studies, affiliation of the prescribing doctors was not related to the smoking status of the patient (2 "data not shown", 22).

The frequency and quality of follow-up

While the quality of the entry criteria for COT are well-exposed, only a few studies have focused on the follow-up (3, 22, 24, 54, 64, 68). In line with our results, similar poor follow-up was found in other countries (22, 24, 58, 64, 68). Silverman et al found that only 27% of their patients, who started oxygen therapy 1992, had at least one claim for either oximetry or arterial blood gas measurement during the same year (68). In another American study, Oba et al found that among patients who started oxygen treatment immediately after discharge from hospitalization, only 35% were appropriately re-evaluated within the recommended 3-month interval (64). In a Scottish study, blood gas measurements were repeated within one year in 56% patients – half of these during a clinically unstable condition (24). Walshaw et al examined 61 patients on COT and found that 18 fulfilled the criteria for prescribing COT, however, only 11 were regularly attending a respiratory outpatient department (22). In a selected group of 379 Turkish patients, regular follow-up was reported by only 35% of the patients (58). In accordance with the study by Oba et al, we found that the rate of appropriate reevaluation was significantly higher among pulmonary physicians than among primary care physicians (3, 64).

Overall adherence to guidelines

In general, the quality of surveillance of COT is poor. In our study of 1354 COPD patients, good compliance with guidelines was 5.3 (95% CI: 2.9-9.1) times as likely when the oxygen was prescribed by a pulmonary department compared to COT initiated by a GP (2). This is in accordance with a study by Sivakumaran & Garrett who found that patients treated by chest physicians met the prescription criteria for COT more frequently than those started by GPs (99% versus 33%) (108). The best compliance with the hypoxaemia criteria has been recorded in Poland and Sweden, where chest physicians are responsible for all or nearly all patients on HOT (25, 53).

THE IMPACT OF A NATIONAL REGISTER ON ADHERENCE TO GUIDELINES FOR COT IN COPD PATIENTS

In order to monitor the quality of COT, national and regional oxygen registers have been established (15, 39). Through enhanced educational efforts and monitoring of compliance with guidelines on COT, the Danish Oxygen Register aimed at improving the quality of COT.

Own results

According to the oxygen suppliers, an increasing number of the COPD patients were prescribed oxygen at least 15 hours daily, had delivered oxygen concentrator or liquid oxygen, and had mobile oxygen (Table 3).

Comparing COPD patients from the inner city of Copenhagen who were on HOT in 1995 with patients on HOT in year 2000, registration of smoking habits and measurement of CO-level were unaltered (Table 5).

Despite the fact that a high number of COPD patients initiated oxygen therapy during an unstable clinical condition, only 3,944 (46.4%) of the patients were followed-up in an outpatient clinic with the possibility of re-evaluation of the criteria for COT (Table 3).

Discussion

This is the first study that systematically evaluated adherence to guidelines before and after the establishing an oxygen register. After the establishing of the Danish Oxygen Register significantly more COPD patients are treated according to the guidelines on administration of oxygen (prescribed at least 15 hours daily), and therefore it is most likely that patients are using oxygen that many hours. Previously, we have shown a significant correlation between prescribed and used oxygen (1). Furthermore, an increasing number of COPD patients were equipped with an oxygen concentrator, which is the preferable oxygen system when patients use oxygen continuously.

Table 5. Smoking status of COPD patients, residing in the central part of Copenhagen, and on LTOT in 1995 and 2000, respectively.

	Years		P-level for difference
	1995 n=240 (%)	2000 n=279 (%)	
Asked about smoking	180 (75.0)	216 (77.4)	0.52
Admitted smoking (% of asked patients)	34 (20.4)[1]	32 (15.5)[2]	0.23
Measured CO	136 (56.7)	141 (50.5)	0.16
Abnormal value (% of checked patients)	21 (15.4)	19 (15.8)	0.64
Asked about smoking or measured CO-level	187 (77.1)	222 (79.6)	0.65
Indication of smoking (% of asked or checked patients)	47 (25.1)	47 (21.2)	0.34

1) 13 cases of "don't know".
2) 10 cases of "don't know".

The number of smokers seems not to go down. As the CO-level in blood or expired air is not checked in many of the patients, the number of patients who smoke may be even higher than the approximate 20% we estimated in the subgroup of the Copenhagen patients. Follow-up in the outpatient clinic or at home by a respiratory nurse was poor and have not improved.

So far, the utilization of data from this oxygen register has not been optimal. Direct access to own data and current feedback on adherence to guidelines for COT may improve the quality. This has been practiced in patients with hernia surgery. Two and an half year after implementation of the Danish Hernia Database, the quality of operation improved significantly (109). From this database, feedback was provided to participants twice yearly, with the results for the specific participant compared with the entire database.

EFFECT OF HOT ON HOSPITALIZATION IN COPD PATIENTS

Studies with historical controls may be biased by the fact that frequent hospitalizations and the decision of prescribing HOT are interrelated: physicians may be more likely to initiate HOT in patients with frequent hospitalizations rather than in patients with a stable condition. A reduction in hospitalizations after initiation of HOT could therefore simply reflect a "regression to the mean phenomenon". The effect of HOT are studied on COPD patients with severe hypoxaemia (P_aO_2 <7.3 kPa) and moderate hypoxaemia (P_aO_2: 7.3-9.5 kPa), separately.

OWN RESULTS

Taking the "regression to the mean phenomenon" into account, we investigated the effect of HOT on hospitalizations in a larger study with 162 severe hypoxaemic patients acting as their own controls. In a selected group of patients (n=37) who started HOT in the outpatient clinic and therefore considered more clinical stable, the beneficial effect on bed days was still present (5). We found that the first months of LTOT were associated with a significant reduction of days spent in hospital, as compared to the pre-oxygen period (5).

A similar study with 170 moderate hypoxaemic patients revealed that the hospital admission rates, number of days spent in hospital, and number of patients with at least one hospitalization were not reduced (pre-oxygen period versus post-oxygen period) (7). We had statistical power to detect a difference of 7.8 bed-days between the two periods at 5% significance level, so we may have overlooked a difference in bed-days less than 7.8 days. In addition, as this was not a randomized study, we can not exclude that oxygen therapy had prevented progression of the disease, and that without this therapy, the hospitalization could have been even higher. Supporting this hypothesis, our patients with moderate hypoxaemia had a very pro-

gressive disease with high one year mortality (33.5%) – even higher than those with severe hypoxaemia (21.6%).

DISCUSSION

An early study from the 1970s and three recent studies, all including patients acting as their own controls, indicate that COT reduces hospitalizations by 30-50% (110-112). However, the MRC study, which had a randomized control group, failed to confirm this possible advantage of COT (11). Our results are comparable with findings of previous studies where reductions of 40-50% were observed (110-112).

PREDICTORS OF SURVIVAL AND HOSPITALIZATION IN COPD PATIENTS ON HOT

The MRC study showed that oxygen therapy given for approximately 15 hours per day significantly prolonged life compared with no oxygen (11, 65). The survival difference between the treated and the control group became apparent at 500 days and was statistically significant at 3, 4, and 5 years. The NOTT study, which used ambulatory oxygen for as many hours as possible (median 19.4 hours, mean 17.8 hours), compared with nocturnal oxygen given for approximately 12 hours per day from a stationary source, showed a better survival from the start in patients on continuous oxygen (113). So, it seems that the more continuous the therapy, the greater the benefit in terms of survival. Whereas the positive effect of COT on survival is well established, the mechanism behind this is still uncertain. Yet, stabilization or slightly decrement in pulmonary arterial pressure seems partly responsible for the beneficial effect on survival (11, 114-116). Re-examining The Nocturnal Oxygen Trial, Petty & Bliss suggested that the improved survival on COT might at least partially be caused by increased mobility (117). However, the effect of COT on the ability to exercise was not evaluated, and the association between "high level of mobility" and better survival was independent of the duration of oxygen administration. Whereas predictors of survival and hospitalization in normoxaemic COPD patients without HOT are well-studied, it is less clear for hypoxaemic COPD patients on HOT (118-122).

OWN RESULTS

Survival: Low BMI was strongly associated with high mortality ($p < 0.001$). Maintained treatment with oral steroids was only associated with higher mortality in overweight patients (BMI ≥ 25 kg/m^2), RR = 3.8 (1.4-10.5), p = 0.011.

In multivariate analyses body mass index, gender, age, and poor performance status were significantly associated with poor survival (Table 6). Lack of outdoor activity was related to increased mortality (RR of dying was 1.42 (0.97-2.08)).

Hospitalization: Whereas BMI had no influence on risk of hospitalization in patients using oral steroids, high BMI was independently associated with reduced risk of hospitalization in patients without oral steroids (the RR of hospitalization for each 1-kg/m^2 increase in BMI was 0.94 (CI: 0.90-0.99), p = 0.009). Overall, the use of oral steroids was associated with increased risk of hospitalization, RR = 1.7 (1.2-2.4), p = 0.002. This increase was especially pronounced in the group with BMI above 25 kg/m^2, where steroid treatment increased the risk of hospitalization with RR = 3.6 (1.5-8.7), p = 0.005.

OTHERS RESULTS

In agreement with previous studies, we found that male gender, increasing age, decreasing BMI, and poor performance status were independent predictors of mortality (Table 7). Although BMI has only been assessed in a few studies, it has become clear that patients with low BMI have a very poor survival (6, 39, 55). Pulmonary hypertension is also considered to be an independent predictor of increased mortality (114, 123, 124, 127, 128). In accordance with Ström et al, we found a significant relationship between performance status and risk of mortality (6, 89). The role of blood gases and lung function, in respect to predict survival, are less consistent – some have identified high P_aCO_2, low P_aO_2, FEV_1, FVC, and FEV_1/FVC as predictors of poor survival, while this is not supported by other studies (Table 7). It appears that outdoor activity, oral corticosteroids, and diffusion capacity may play a role in predicting risk of mortality. In previous studies of COPD patients without HOT, maintained treatment with oral steroid is clearly associated with increased mortality (130-133). In patients on COT, this association has only been studied by Ström et al and us, and unfortunately with ambiguous results (6, 89). While we found that mortality was higher in steroid treated patients with BMI above 25 kg/m^2, Ström et al found that oral steroids were associated with increase mortality only in females.

Diffusion capacity has been assessed in only one study, where low values were associated with reduced survival (99). We were unable to confirm the result of Hjalmersen et al, that HOT started by an university hospital compared to a general hospital was associated with less risk of mortality, RR = 0.48 (p = 0.03) (data not shown) (101).

In keeping with Chailleux et al, we found that low BMI was an independent risk factor of hospitalization, although the relationship was only significant among patients without oral steroids (28). In contrast to the ANTADIR study, we evaluated time until first hospitalization in all patients, while they studied duration and rate of hospitalization only in those patients who survived at least one year. When we undertake the same analyses, we find that the rate of hospitalization and days spent in hospital are less than 50% in those with BMI above 25 kg/m^2 compared with those with BMI less than

Table 6. Relative risks of mortality with (95% confidence intervals) in COPD patients on home oxygen therapy. Results of a univariate and multivariate analysis with Cox regression model, after adjustment for age, BMI & oral steroid class, outdoor activity, performance status, and gender.

	Univariate	P-value	Multivariate	P-value
Age, per 1 year	1.02 (1.00-1.04)	0.035	1.02 (1.00-1.04)	0.037
Gender (female = 1)	1.34 (1.01-1.78)	0.040	1.60 (1.15-2.21)	0.005
BMI & oral steroid (OS) class		0.001		0.001
BMI <20 kg/m^2 & no OS	1.33 (0.87-2.04)		1.23 (0.79-1.92)	
BMI 20-24.9 kg/m^2 & no OS	1		1	
BMI ≥25 kg/m^2 & no OS	0.35 (0.19-0.67)		0.33 (0.17-0.63)	
BMI <20 kg/m^2 & OS	1.79 (1.01-3.16)		1.62 (0.90-2.90)	
BMI 20-24.9 kg/m^2 & OS	1.10 (0.70-1.76		0.95 (0.59-1.53)	
BMI ≥25 kg/m^2 & OS	0.75 (0.38-1.50)		0.79 (0.39-1.59)	
Outdoor activity (yes = 1)	1.76(1.31-2.37)	<0.001	1.42(0.97-2.08)	0.07
WHO performance score[a]		<0.001		0.039
0	0.46 (0.04-2.22)		0.27 (0.04-1.96)	
1	1		1	
2	1.39 (0.98-1.96)		0.99 (0.65-1.49)	
3	1.62 (0.93-2.82)		0.98 (0.51-1.88)	
4	4.14 (2.23-7.70)		2.46 (1.30-4.67)	

a) As performance score of "1" is the most frequent observation, this score is assigned the value of "1".

Table 7. Literature presenting data on predictors of survival in COPD patients on COT.

Potential predictors	Related to survival	Not related to survival
Age	6, 28, 39, 55[1], 89[2], 90, 99, 123-125	101,127-129
Gender	6, 28, 39, 89[2], 90, 126	99, 101, 124, 128, 129
P_aO_2 (on room air)	28, 39, 90, 128	6, 55, 89, 99, 101, 123-125[3], 127,129
P_aO_2 (on room air)	11[4], 39[5], 127[6]	6, 28, 55[1], 89, 90[7], 99, 101, 123-125[3], 128, 129
% FEV_1 or FEV_1	28, 39, 89[8], 55[1], 124, 128[9], 129	6, 99, 101, 123, 125[3], 127
FEV_1/FVC	99, 128	39, 90, 101, 123
% FVC or VC	90, 129	39, 89, 99, 101
Diffusion capacity	99	
Pulmonal hypertension	114[10], 123, 124, 127, 128	99[11], 125, 129
Performance status	6, 89	
Oral corticosteroids	6[12], 89[1]	
BMI	6, 28, 39, 55	99, 101, 124

1. Only females.
2. Only patients without maintained systemic corticosteroids.
3. Only 22 patients included.
4. P_aCO_2 (mmHg) + 1.18 Red Cell Mass (%) <100.
5. Low P_aCO_2 related to high risk of dying.
6. High P_aCO_2 related to high risk of dying.
7. Increasing P_aCO_2 over time was associated with increased risk of dying.
8. Only males.
9. In those with P_aCO_2 <8.0 kPa.
10. Only in the nocturnal oxygen therapy group.
11. "Right heart failure" – not further specified.
12. Only BMI >25 kg/m^2.

25 kg/m^2. Again, this association between lower hospitalization and high BMI was only significant among patients without oral steroids (data not shown). Furthermore, in the ANTADIR study, use of oral corticosteroids was not taken into account. Two studies of non-hypoxaemic COPD patients have shown an association between malnutrition and hospitalization. In a study of 39 COPD patients, poor nutritional status expressed as reduced triceps skin fold was associated with hospitalization (134), and in another study, lean mass depletion and weight loss were associated with early readmission (135).

EFFECT OF NON-CONTINUOUS OXYGEN THERAPY ON SYMPTOMS RELATED TO HYPOXAEMIA

Although the criteria for NCOT are not clear (10, 11, 14), about half of all patients on home oxygen therapy in UK receive NCOT, and this figure is probably even higher in USA (136, 137). NCOT is not aimed at improving survival, but prescribed in order to decrease dyspnoea, increase exercise capacity and tolerance, prevent nocturnal desaturations, and improve quality of sleep and life (29, 30, 32-38). In contrast to most other studies, we investigated the effect of NCOT on different symptoms during domestic activities. We examined whether patients with beneficial effect differed from those without subjective effect in terms of patients' characteristics, utilisation of oxygen, hospitalization and survival. Furthermore, we examined the relationship between the reported beneficial effect of NCOT on dyspnoea and physical activity during domestic activities.

OWN RESULTS

While on oxygen, 76.3% of 142 patients reported improved dyspnoea score (0-10) more than 0.5 point, 78.3% had improved quality of life, 59.5% improved sleep, 48.5% increased physical activity, 49.3% felt less tired, and 40.0% reported improved thinking (4). Only 11 (7.7%) patients reported no subjective improvement on oxygen. Fifty-seven of 132 (43.2%) patients with complete data (43.2%) reported both improvements in dyspnoea and physical activity, whereas 43 (32.6%) patients reported beneficial effect on dyspnoea without an improvement in physical activity. Only 7 (5.3%) patients reported improved physical activity without any beneficial effect on breathlessness.

The subjective effect of NCOT was not significantly associated to hours spent with oxygen, the underlying disease, gender, hospitalization, or survival.

OTHERS RESULTS

The reported beneficial effect of NCOT on dyspnoea and exercise performance in many of our patients, and our observation that these effects were unrelated, are in line with studies where patients are tested during controlled circumstances, for example during treadmill test (4, 32-34, 36, 38).

Only one small study has evaluated the effect of NCOT during normal daily activity (26). In this study, patients on average used 3 cylinders each month (that means less than $^1/_2$ hour per day with a flow of 1 L/minute). Benefit from NCOT was reported by 43 of 45 patients (96%), however, this beneficial effect was not specified (26).

Eaton et al compared ambulatory oxygen as needed with compressed air in a 12-week double blinded randomized cross over study of 41 COPD patients with resting P_aO_2 >7.3 kPa, but with exertional arterial oxygen saturation ≤ 88% and dyspnoea (138). They found that oxygen therapy delivered by light weight cylinders (2 kg) improved disease specific health related quality of life (Chronic Respiratory Questionnaire), albeit being statistically significant, the improvement was modest in terms of clinical relevance, and there was no improvement in generic health related quality of life (138). Interestingly, at study completion, 14 of 34 "responders" (41%) did not want to continue oxygen therapy due to poor acceptability.

According to non-randomized studies, it appears that COT improves disease specific quality of life modestly in hypoxaemic COPD patients (59, 139, 140).

CONCLUSION

Since establishment of The Danish Oxygen Register, the incidence and prevalence of COPD patients on HOT has increased whereas the incidence seems to level off. The prevalence of HOT was significantly higher in those counties where GPs took part in HOT prescribing compared with the rest of the counties.

Most of the COPD patients were prescribed oxygen therapy by a hospital doctor immediately after a hospitalization for an acute exacerbation, and the number of prescriptions from general practitioners has declined. The number of patients with mobile oxygen has increased, but most of them used it rarely.

In general, the compliance with guidelines for COT was poor. Good compliance from the patient and appropriate re-evaluation from the doctor were more frequent when HOT was prescribed by a pulmonary department compared to oxygen therapy initiated by a GP. Six years after establishment of the oxygen register, adherence to

guidelines for oxygen therapy has improved concerning administration of oxygen, but has remained poor concerning re-evaluation of treatment and smoking cessation.

Compared to other countries, survival of our COPD patients on HOT was inferior but it has increased slightly during the observation period. Different practice in starting HOT (stable or unstable condition) may explain the higher mortality of our patients compared to patients in other studies. Independent predictors of increased mortality were low BMI, advanced age, male gender, poor performance status, and maintained oral corticosteroid therapy in patients with overweight.

Risk of hospitalization and number of days spent in hospital was high. Overall, the use of oral steroids was associated with increased risk of any hospitalization, and this risk was especially pronounced in the group with BMI above 25 kg/m^2.

High BMI was independently associated with reduced risk of any hospitalization in patients without oral steroids.

We found evidence suggesting that COT reduces hospitalization in severe hypoxaemic COPD patients. Most patients on NCOT reported symptomatic benefits by the therapy, especially less dyspnoea, better sleep, and health related quality of life.

PERSPECTIVES

Although much has been learned on the effect of STOT and COT since the MRC and NOTT study, there are substantial lacks in our knowledge on home oxygen therapy. Due to an ethical dilemma, some of the unanswered questions are difficult to address in randomized clinical trials e.g. effect of COT on health status, exacerbations, hospitalization, and effect of COT in non-COPD patients with chronic hypoxaemia. In order to increase the evidence of the guidelines for COT, prospective studies are required in order to determine the effect of: 1) STOT in patients with borderline hypoxaemia, 2) COT in smokers who accept administration of oxygen at least 15 hours daily and refrain from smoking during this period, 3) increasing the oxygen flow during sleep and exercise, 4) COT in patients with moderate hypoxaemia combined with signs of tissue hypoxia.

Secondly, in order to improve the quality of surveillance of COT, more effort has to be put into education of the patients and staff responsible for COT, centralization of the domiciliary organizations, better equipment for ambulation and travelling, regular follow up preferably with home visits. The role of an oxygen register with feedback on adherence to guidelines for COT has to be determined.

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APPENDIX A
QUESTIONS TO THE PATIENTS ON HOT

1. How many hours per day do you spend with oxygen?
2. Performance status (WHO)
   0. able to carry out normal activity
   1. restricted in activity, but ambulatory
   2. confined to bed part of, up and about for more than 50% of waking hours
   3. confined to bed for more than 50% of waking hours
   4. totally confined to bed
3. Outdoor activity – "Yes or No"?
4. Live alone – "Yes or No"?
5. Do you smoke tobacco – "Yes or No"?
6. Do you have less dyspnoea with oxygen therapy – "Yes, No or Don't know"?
7. Does oxygen therapy improve physical activities – "Yes, No or Don't know"?
8. Does oxygen therapy help you to think clear – "Yes, No or Don't know"?
9. Does oxygen therapy make you less tired – "Yes, No or Don't know"?
10. Does oxygen therapy improve your sleep – "Yes, No or Don't know"?
11. Does oxygen therapy improve your quality of life – "Yes, No or Don't know"?
12. Mark on the vertical line (10 cm) the degree of breathlessness *without* oxygen therapy

Extreme breathlessness	No breathlessness
10	0

13. Mark on the vertical line (10 cm) the degree of breathlessness *with* oxygen therapy

Extreme breathlessness	No breathlessness
10	0

ABBREVIATIONS

ANTADIR: Association Nationale pour le Traitement a Domicile de l'Insuffisance Respiratoire Chronique
CI: Confidence interval
CO: Carbon monoxide
CO-Hgb: Carboxyhaemoglobin
COPD: Chronic obstructive pulmonary disease
COT: Continuous oxygen therapy
FEV_1: Forced expiratory volume in the first second
FVC: Forced vital capacity
HOT: Home oxygen therapy
LTOT: Long term oxygen therapy
MRC: Medical Research Council
NCOT: Non-continuous oxygen therapy
NOTT: Nocturnal Oxygen Therapy Trial
OR: Odds ratio
P_aO_2: Arterial oxygen tension
P_aCO_2: Arterial carbon dioxide tension
RR: Relative risk
S_aO_2: Arterial oxygen saturation
STOT: Short term oxygen therapy

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