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Long-term oxygen therapy in Japan: history, present status, and current problems

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Abstract

Historically, the progress of long term-oxygen therapy (LTOT) in Japan has been characterized by collaboration among academic groups, policy makers, and industrial companies. The public health insurance program has covered the cost of LTOT since 1985. Thomas Petty's group in Denver enthusiastically carried out the public implementation of LTOT and conveyed the concept of pulmonary rehabilitation for the processing with LTOT. Although the target diseases of LTOT in Japan tended to be chronic obstructive pulmonary disease or sequelae of primary lung tuberculosis, it was soon applied for cardiac diseases as well as other pulmonary diseases. Together with increasing medical costs for geriatric patients, the political conversion from hospital based care of a traditional style to home care system has been performed, with two background reasons: the improvement of quality of life of patients and the reduction of the medical expense. Presently, LTOT plays a pivotal role in the successful implementation of home respiratory care for elderly patients. In addition, this promotes comprehensive pulmonary rehabilitation, a team approach, and close liaisons between primary care and hospitals. Currently, the total number of patients using LTOT exceeds 150,000. In Japan, LTOT resulted in an advancement in the medical care as well as in administrative decision to introduce it as a nationwide system after analyzing the results of opinion polls of patients with respiratory failure. However, the recent great earthquake in East Japan revealed that many unresolved problems remain for these patients, and these issues are of great concern.

Key words: home respiratory care, chronic respiratory failure, home oxygen therapy, elderly patients

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Introduction

It is no exaggeration to say that the recent respiratory care system in Japan has been developed in parallel with the progress of long-term oxygen therapy (LTOT), which is widely referred to as home oxygen therapy in this country. Home treatment has expanded rapidly in Japan since the 1980s. This can be attributed to the increase in the elderly population, the resulting rise in the number of chronically ill patients, and the sharp increase in medical expenditure for the nation. By mid-century, the chance of surpassing thresholds of individuals aged over 60 was 98% in Japan/Oceania, 82% in Western Europe, and 69%

in China [1]. The focus of medical treatment has been shifting away from hospital-based medical care, especially the acute care that became the norm after World War II, and has moved toward quality of life. This achievement has had many spill-over effects, including the development of medical equipment that can be used at home for treating the elderly, encouragement for the development of the medical care system by a team of multi-disciplinary specialists and health care professionals, intensification of the debate over the quality of respiratory care, and the advancement of comprehensive pulmonary rehabilitation. In addition, developments in the related area of LTOT continuously raise the awareness of pa-

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tients against traditional and unsociable medicine for chronic respiratory diseases, particularly for patients with pulmonary tuberculosis. This review will discuss aspects of LTOT that are unique to its historical development, present status, and perspective in Japan.

Historical aspects of long-term oxygen therapy in Japan

In 1798, Thomas Beddise established the Pneumatic Institute in Bristol, England, by applying the oxygen originally discovered by Priestly. He began to use oxygen to treat heart disease, asthma, and opium poisoning. The scientific studies of John Scott Haldane and Joseph Barcroft on oxygen deficiency in humans defined the benefits of oxygen therapy. Alvan Barach in New York, and Albert Andrews, Edwin Levine, and Max Sadove in Chicago are credited with providing education to those who were assigned to learn about oxygen therapy. Alvan Barach and Thomas Petty in Denver were friends during the time that Petty and his colleagues began their study on LTOT with liquid portable oxygen in the mid-1960s [2]. Later, Petty described a memento he received from Barach in 1958, in which a cartoon depicting oxygen-supported exercise by using a small portable cylinder had been enclosed [3]. This suggestion, which promoted suitable exercise under oxygen use, subsequently came to fruition with the development of LTOT-based pulmonary rehabilitation for patients by the Denver group. These promising achievements, subsequently have materialized later for LTOT in connection with two major findings in Japan. First, during the late 1970s and early 1980s, Clark and Severinghaus electrodes were adapted for transcutaneous clinical application. Further, Takuo Aoyagi accidentally discovered pulse oximetry in Tokyo while he was attempting to measure dye indicator cardiac output with an ear probe [2]. Sapporo, Kawakami et al. [4] performed cardiac catheterization on patients with stable chronic obstructive pulmonary disease (COPD) with or without pulmonary hypertension, and the outcomes were compared after 4 years. Their observations with oxygen inhalation have provided physiological evidence for improved diffusion limitation and prolonged life expectancy.

The history of LTOT in Japan has been influenced by academic groups in collaboration with policy makers and industrial companies [5, 6]. The academic groups were mostly led by the Res-

piratory Failure Research Group from the Ministry of Health, Labour, and Welfare, Japan. According to Kawakami, one of the oxygen pioneers in Japan [7], the historical course toward LTOT in Japan is divided into three phases. The first phase comprises accomplishments in basic research (from 1978 to 1986), in which defining the respiratory failure, its criteria, and both pathophysiology and treatments subsequently clarified the validity of LTOT. The second phase (from 1987 to 1995) comprises the period during which many questions were raised. Specifically, this phase involved questions regarding monitoring methods for pathophysiological aspects, proposing LTOT guidelines, related examinations and treatments, and the construction of a concept for a home-care system. The third phase (from 1996 to the present) comprises the settlement of these scientific achievements, which includes the development of a home-care system including comprehensive pulmonary rehabilitation, monitoring methods for home care, strategies for severe dyspnoea and pulmonary hypertension, technological developments for ambulatory oxygen, revision of LTOT criteria, and the benefits from the view of medical expenditures. In parallel with these movements, industrial entities have made efforts to develop concentrators and ambulatory oxygen systems with demand valves, which make saving oxygen during walk or exercise possible. The Fire Prevention Law, which previously did not allow the use of oxygen at home or on public transportation, has been changed accordingly, providing an example of cooperation by policy makers. Thus, all barriers or surrounding problems for LTOT were properly addressed in order to move toward subsequent coverage by public health care insurance for LTOT. Concomitant with these movements by policy makers and companies, the Japan Respiratory Society (JRS) determined criteria for LTOT in 1984, and LTOT was thereafter covered by public health insurance in 1985. The initial criteria were based on data from two milestone clinical trials in the USA [8] and the UK [9]. These studies demonstrated that LTOT used in COPD patients prolonged survival, reduced secondary polycythaemia, and improved pulmonary haemodynamics and neuropsychological function. In 2004, chronic congestive heart failure with Cheyne-Stokes breathing during sleep was added as a new criterion, which emphasizes the role of nocturnal and intermittent hypoxaemia in the pathophysiology of chronic respiratory failure. However, two above mentioned studies

[8, 9] are based on data in COPD patients less than 70 years of age, whereas most of the patients using LTOT in Japan are over 70 years of age, suggesting lack of data for these elderly patients. A distinguishing feature of the Japanese criteria that they cover patients with COPD in addition to patients with other lung diseases and cardiac diseases, the latter of which comprises cyanotic congenital heart disease or chronic congestive heart disease. In addition to adult patients, the

number of paediatric patients with chronic respiratory failure caused by various lung diseases or cardiac diseases has reached approximately 4,000 (personal communication from Professor Saji, Toho University School of Medicine, Tokyo). Thus, a characteristic of LTOT in Japan is that it includes all generations, from children to elderly patients, and all patients are equally covered under public health insurance; however, the criteria for children have not been established yet.

Despite the contributions of the academic groups, the pace at which LTOT was being introduced to physicians throughout Japan was too slow. Thomas Petty (1932–2009), who played a pivotal role in the development of LTOT in the 1960s, greatly contributed to introducing LTOT to Japan. His most important and far-reaching accomplishment was the introduction of LTOT for the treatment of chronic lung disease, particularly COPD. He also is one of the first to demonstrate the beneficial effects of pulmonary rehabilitation programs for patients recently discharged from the intensive care unit and for those with COPD. The combined concept of LTOT and pulmonary rehabilitation was conveyed by Petty and many of his colleagues; this began in 1985 in Japan and continues until this day [10].

From the late 1980s through the 1990s, the environment surrounding LTOT in Japan

Table 1. Eligibility standards for public health insurance coverage of LTOT in Japan

1. Cyanotic congenital heart disease
2. Cases of advanced chronic respiratory failure
Patients with arterial oxygen tension of 55 mm Hg or less while using LTOT or patients with arterial oxygen tension of 60mmHg who experience severe hypoxaemia when sleeping or exercising whose doctors determine that LTOT is necessary
3. Pulmonary hypertension
4. Chronic heart failure
Based on a doctor's diagnosis, patients that are classified as NYHA III or higher, exhibit Cheyne-Stokes respiration when sleeping, and an apnoea/hypopnoea index (an index of the number of complete cessations and partial obstructions of breathing occurring per hour of sleep) of 20 or higher confirmed by using polysomnography

Extracted from the Ministry of Health, Labour and Welfare, Japan (2008) [7]

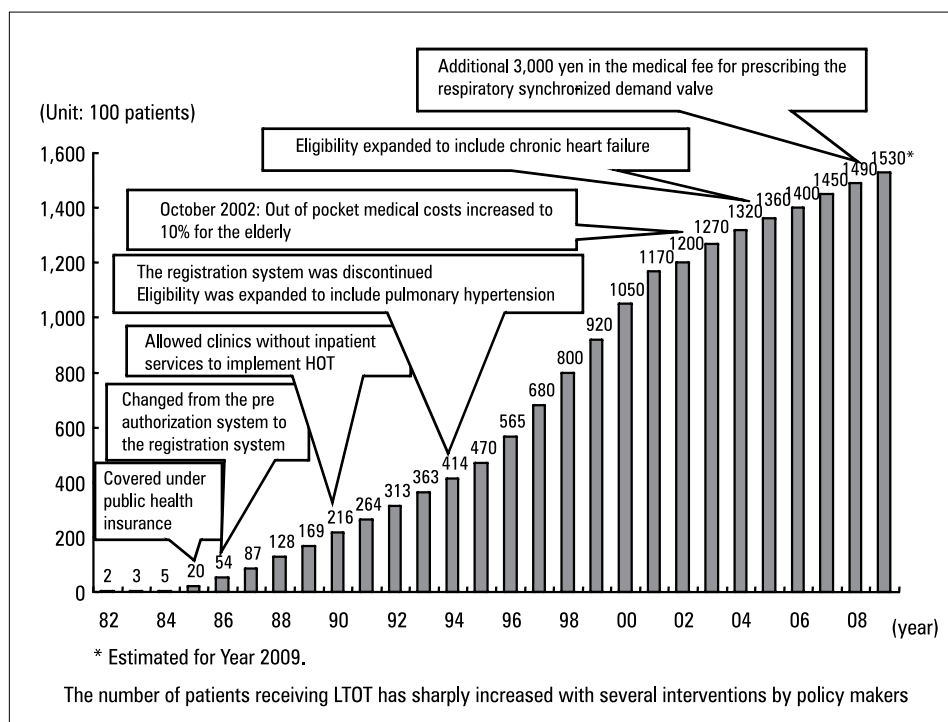


Figure 1. Annual changes in the number of patients receiving long-term oxygen therapy in Japan

dramatically improved. The implementation of LTOT changed from the pre-authorization system to the registration system by the authorities, although the latter remained a barrier to expansion to general physicians. The registration system was abolished after the prescription and management of LTOT were extended to clinics without inpatient services. Relaxing the regulations resulted in the expansion of LTOT from chest physician specialists to general physicians. This solved the issue of disproportionate medical management with regard to urban areas versus rural areas, the latter of which has a more limited number of chest physician specialists. Furthermore, an indication for pulmonary hypertension was added to the criteria. The current criteria for eligibility for LTOT in Japan are shown in Table 1. These changes contributed to the steady increase in the number of LTOT patients in Japan. According to data of the Medical Gas Association in Japan, it is assumed that approximately 150,000 people used home oxygen therapy (HOT) as of 2009; although estimating the precise number of patients with LTOT is difficult, a speculative number can be obtained from industrial sources. The annual changes in the number of LTOT patients and related topics are shown in Figure 1, which reveals that the number of patients increased because of several interventions by policy makers.

Comprehensive pulmonary rehabilitation combined with the use of LTOT

In 1994, a research group supported by the Ministry of the Environment started a project to study the benefit of LTOT for pulmonary rehabilitation, as advocated by Petty and colleagues. This project, led by the author of this article, has continued for a total of 16 years and has contributed to the initial development of pulmonary rehabilitation in Japan. Until this period, pulmonary rehabilitation in Japan was mainly realized by physiotherapists. Further, the physiotherapists merely guided the patients, most of whom had sequelae of lung tuberculosis (Tbsq), in postural drainage or breathing techniques through diaphragm training, but this was not a comprehensive program for patients with COPD. Our working hypothesis, combined with both LTOT and comprehensive pulmonary rehabilitation, was proposed in 1995 [11], after an inspection of modern pulmonary rehabilitation in the USA. Subsequently, this concept was adopted with respect to the clinical guidelines of both the Japan Society for Respiratory Care (2003) and the JRS (2003, 2009, and 2013). The hypothesis is mainly an instruction for patients with LTOT and comprises 7 different components, as shown in Figure 2. In this concept, the combined roles of nutrition and exercise as basic education for patients with LTOT and his/her family members

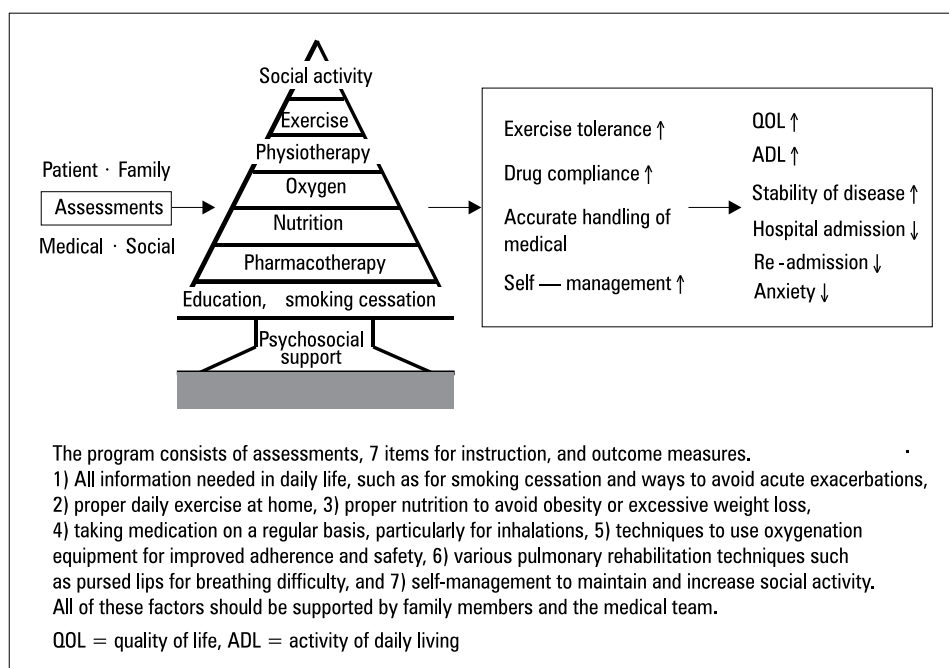


Figure 2. Framework of comprehensive pulmonary rehabilitation for patients with LTOT

is emphasized. Instruction regarding smoking cessation for these patients is another important option, because sporadic fire accidents due to smoking were reported in the early stage of LTOT. It is considered that LTOT in Japan has produced secondary progress or awareness in all areas of respiratory care, which includes a wide spectrum of health care professionals. Because it is interesting to view these effects from an academic viewpoint by utilizing published data, a systematic review of the literature was conducted to identify data related to LTOT published from 1983 to March, 2013. The PubMed database was searched by using the following defined search terms: “long-term oxygen therapy” or “home oxygen therapy”. The total number of hits for manuscripts written in English language was 744 and, among them, 47 were from Japan as of March 2013. However, when the same term was used for searching the literature for reports written in Japanese and published in this country, the amount reached approximately 2,500. Most reports regarding LTOT are described as original research (n=1,528) or as an educational review (n=1,081) and were conducted by academic physicians and chest specialists or health care professionals. Thus, the progression of LTOT has resulted in a parallel increase in medical staff in the entire area related to chronic respiratory care or pulmonary rehabilitation. These movements also result in greater recognition that patients with disability due to chronic respiratory failure are increasing in number and emphasize their right to receive equal or better treatments. In 2006, a monograph of clinical guidelines for oxygen therapy was published in collaboration with the Japanese Respiratory Society and the Japanese Society for Respiratory Care & Rehabilitation. Furthermore, two textbooks on pulmonary rehabilitation for health care professionals were published in 2003 and 2007, respectively, by the same societies. The first book, which was released in 2012, is a manual for exercise therapy, and the second one is for patient education on various respiratory diseases, particularly for patients with COPD. Further, the total number of respiratory physiotherapists who received training and passed examinations reached approximately 30,000 in 2012. A new system for qualified nurses for respiratory care has started in 2011 with the support of the Japan Nursing Association, and these trainees will have a central role in respiratory care in the future, particularly for patients with COPD. These effects are all derived from the establishment of LTOT in Japan.

Survey of LTOT in Japan

In 2005, the JRS first published the *Japanese White Paper on Home Respiratory Care* [12], which is a summary of surveys from patients with chronic respiratory failure, general physicians, and qualified chest physicians. This is the first report to consider the responses of both physicians and patients on LTOT.

This report included a total of 4,341 medical institutes, which comprised institutions accredited by the JRS (n = 534), randomly selected general hospitals (n = 2,307), and institutions related to the Japan Physicians Association (n = 1,500). The breakdown of reported LTOT patients (Fig. 3A) is similar to that in the aforementioned report by the former Ministry of Health and Welfare [13]. The most common disease was COPD, which was reported for approximately half of the patients, followed by TBsq. Although LTOT can be provided through clinics that have no inpatient services, these clinics accounted for only a few percentage points, whereas the majority of the patients received treatment by chest physician specialists. Survey data on those patients, which belonged to the Japan Federation of Patient Organization for Respiratory Diseases, is also of interest. Of the 2,237 people who returned a response, 55% were receiving LTOT and/or home mechanical ventilation. The mean flow rate of oxygen was less than 1 l/min and between 1 l and 2 l in 45% and 34%, respectively. Although 70% of the patients were prescribed oxygen for 24 hours, the precise hours of use (adherence) were not determined. Moreover, 28% of the patients showed $\text{PaO}_2 > 60$ mmHg, suggesting that they did not fulfil the eligibility criteria for LTOT; however, an improvement in breathlessness (91%), better activity of daily living (73%), and improved exercise capacity (55%) were observed after initiation of LTOT. The doctors mainly had an interest in the improvement of arterial blood gas or pulse oxymetry, whereas the matter of concern for patients was the improvement of breathlessness; in fact, 16% of these patients had their own pulse oximeter and many other wished to have one, suggesting that patients felt better regarding breathlessness and were also concerned about oxygen saturation values. The matter of greatest concern or dissatisfaction after beginning LTOT was related to electric blackouts or natural disasters (57%). Indeed, these occurred during the Great Earthquakes in East Japan on March 11, 2011.

Approximately 20,000 people were killed and 66% of these individuals were over 60 years of

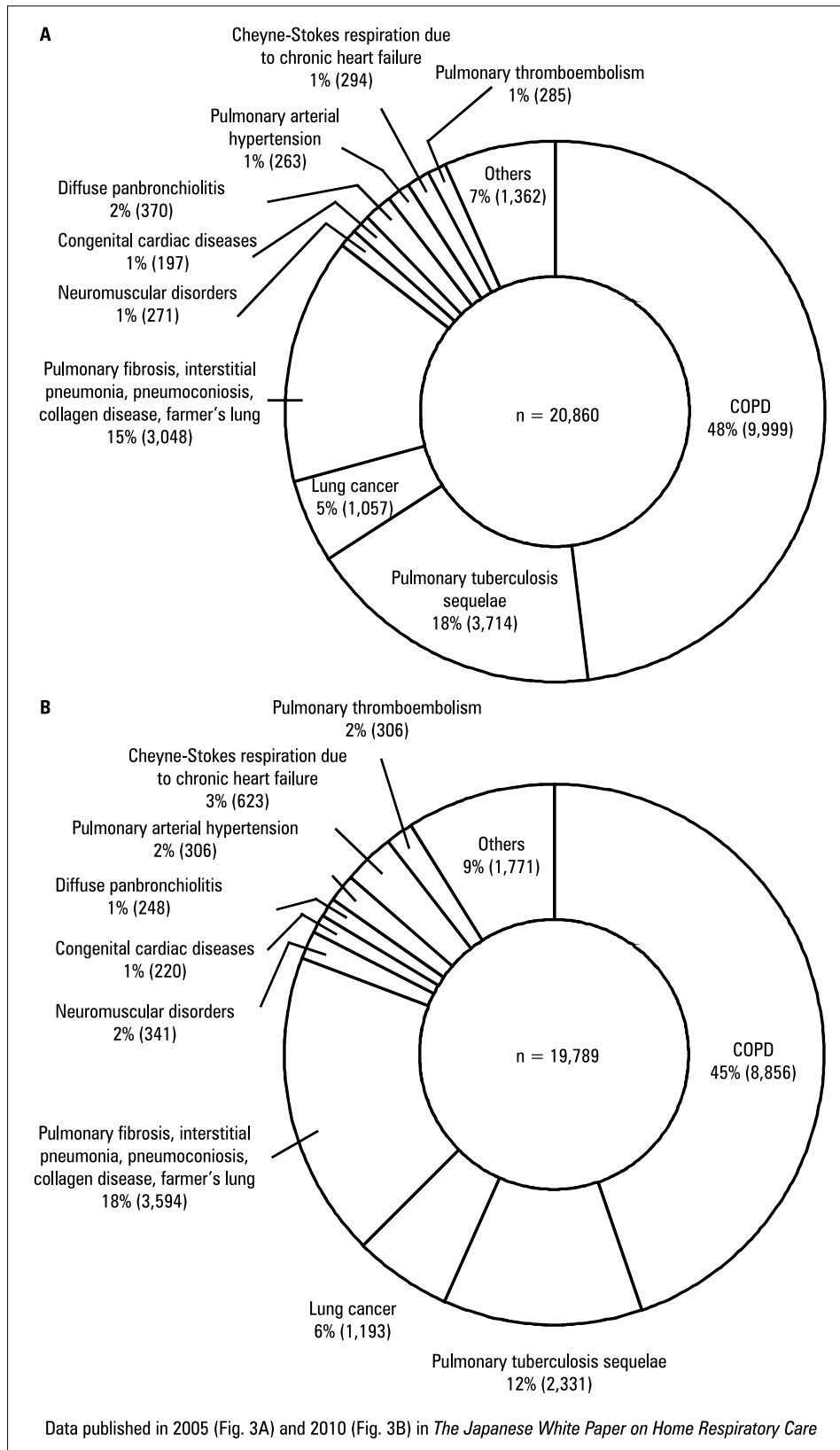


Figure 3. The breakdown of patients who received LTOT (long-term oxygen therapy) in Japan

age. In the aftermath of this natural disaster, the problems occurring among elderly patients were poor access to medication, medical equipment,

and medical supplies. A retrospective cohort study [14] was conducted at a regional medical centre, the Ishinomaki Red Cross Hospital, Mi-

yagi, Japan, in the area affected most severely. The study was performed 6 months after the disaster. The characteristics, clinical courses, and outcomes of COPD patients hospitalized after emergency visits during the study period were investigated and compared. One hundred patients (112 episodes) were identified. Within a few days after the disaster, patients undergoing oxygen therapy at home came to the hospital to receive oxygen. In the sub-acute phase (from the third to the fifth week), the number of hospitalizations due to COPD exacerbations was significantly higher than the numbers observed before the earthquake ($p < 0.05$). On admission, COPD patients reported significantly reduced participation in the activities of daily living after, as compared to before the disaster. The incidence of cases of exacerbated COPD normalized 6 weeks after the earthquake. Many patients with LTOT felt victims and became refugees. For instance, at least 100 people gathered to seek a power source for a concentrator and had to stay at least several days at the centre hospital (personal communication, Professor Yanai of the Ishinomaki Red Cross Hospital, Miyagi) because of electric blackouts at their homes.

The survey data indicate that 94% of patients used a concentrator and portable oxygen, whereas only 6% of the patients used liquid oxygen. More than 60% of the institutions replied that they provided comprehensive patient education at the time of LTOT initiation. Further, 83% of the patients had obtained physical disability certification in order to receive support for part of the expense of LTOT because each patient must pay out-of-pocket money ranging from approximately 5,000 to 12,000 yen (39–94 €) per month, even though the procedure is covered by public medical insurance. Only 45% of the patients received pulmonary rehabilitation. A summary of the data in the first survey of the *Japanese White Paper on Home Respiratory Care* indicates that LTOT in Japan is still prospering, but studies on the following aspects are required: (1) patient education and pulmonary rehabilitation, (2) the possibility of an early intervention, such as LTOT use for patients with $\text{PaO}_2 > 60$ mm Hg, and (3) patients' societies and the JRS should work in cooperation to improve social welfare and the social environment for patients with severe disability. Furthermore, improving the social environment and proper maintenance and service for equipment used for LTOT are required, the latter of which is addressed to providers and includes a safety net for the equipment, tele-monitoring, and

a strategy in the case of a great disaster. In order to arrange the new system, nurses specially trained in the care of patients with chronic respiratory disability are requested from the Japan Nursing association, the JRS, and the Ministry of Health and Welfare in Japan. All of these information indicates a growing tendency towards improvement of the situation among patients with respiratory disability, who occasionally committed suicide at pre-LTOT era, because of too long hospitalization for oxygen treatment [5].

Accordingly, a second survey was performed in 2009 and the data were published in 2010 [15] in *The Japanese White Paper on Home Respiratory Care*. This study, which was performed on the same scale as the first one but used a different patient group, comprised a total of 5,043 medical institutes, including institutions accredited by the JRS ($n = 804$), randomly selected general hospitals ($n = 2,739$), and institutions related to the Japan Physicians Association ($n = 1,500$). A total of 824 responses were obtained from patients with LTOT and the mean age of the patients was 69.0 years. In the second survey, COPD was a leading disease (45%), followed by interstitial lung diseases (18%) and chronic congestive heart failure (CHF) with Cheyne-Stokes breathing (3%) (Fig. 3B). A comparison of the breakdown of the LTOT patients between the first and second surveys revealed that the percentages of COPD and TBsq had decreased [(48% → 45%) and (18% → 12%), respectively], whereas diffuse lung diseases and congestive heart failure with Cheyne-Stokes breathing had increased [(15% → 18%) and (1% → 3%), respectively]. The prevalence of COPD in Japan (2001) is reportedly 8.6% of the general population over age 40, and approximately 1% of them receive LTOT [16]. Current data indicate that the number of patients with COPD is increasing in parallel to the increase in the geriatric population. Presumably, such patients are managed by primary care physicians or at general hospitals; however, a precise number of patients was not provided in the second survey. The overall data of the second survey was similar to the data of the first survey. Both revealed that LTOT strongly increased the awareness of patients and stimulated the activity of health care professionals.

Research topics on LTOT

Despite the importance of LTOT in the management of COPD or other diseases in Japan, many deficits remain, according to our knowledge, regarding its mechanisms of action, indications for

prescription, and effects on patients' outcomes. Both clinical decision-making and insurance coverage policies today are based mostly on research performed in the 1970s. Little has been done in the past 20 years and remarkably little research is currently being conducted in this area.

Gender difference in outcomes

After medical insurance was applied to LTOT in 1985, the Respiratory Failure Research Group, supported by the Ministry of Health and Welfare, have continued the initiative in evaluating the usefulness and safety of LTOT. The International Symposium on Domiciliary Respiratory Care was held in Tokyo (1993) and the proceedings of the Conference were published later [13, 17]. Separately, Miyamoto and associates [18] analysed sex-related differences in survival based on a very large population that had received LTOT from 1986 to 1993. A total of 9,759 patients with COPD, TBsq, and chronic interstitial pneumonia were selected in 1,212 medical institutions for analysis of survival rates. The mean survival periods of the women who died during the follow-up periods were significantly longer than those of the men, the difference was: 0.41 years for COPD, 1.84 years for TBsq, and 0.78 years for chronic interstitial pneumonia. They concluded that women have a better prognosis compared to men when they begin receiving LTOT, regardless of the cause of respiratory failure. However, this study was the beginning of a dispute [19–21]. Machado and co-workers [22] reported that survival was significantly worse in females and in those with a lower body mass index and lower PaO₂ in patients with COPD receiving LTOT. The reasons for these different conclusions are still not known. Survival is considered "fraught with complexities" and multiple comorbidities are likely to affect the complex clinical course in patients using LTOT. Ekström and associates also reported [23] that survival was significantly better in women. They performed a prospective study of patients aged 50 years or older who were starting long-term LTOT for COPD in Sweden between 1992 and 2008. In total, 8,712 patients (55% women) were included and 6,729 patients died during the study period. Compared with women, men had significantly more arrhythmia, cancer, ischemic heart disease, and renal failure, and less hypertension, mental disorders, osteoporosis, and rheumatoid arthritis ($p < 0.05$ for all odds ratios). Comorbidity was an independent predictor of mortality, and the effect was similar for the sexes. Women had lower mortality which remained unchanged even after

adjusting for comorbidity: hazard ratio (HR), 0.73 [95% confidence interval (CI), 0.68–0.77; $p < 0.001$]. Although the comorbidities were different in men and women, this does not explain the sex-related difference in mortality in oxygen-dependent COPD. More recently, two interesting studies have been published on this topic [24, 25]. A total of 213 patients with COPD (FEV₁, $51 \pm 17\%$ predicted; men, 59%; age, 64 ± 7 years) were included prospectively and studied by cluster analysis [24]. Multimorbidity is common in patients with COPD, and different comorbidity clusters can be identified. Low-grade systemic inflammation is mostly comparable among comorbidity clusters. An increasing knowledge of the interactions between comorbidities enhances the understanding of their development and contributes to strategies for prevention or improved treatment. It is estimated that the time-dependent effects of cardiovascular drugs on survival in oxygen-dependent COPD account for the perpetual and immeasurable time bias [25]. Furthermore, a group from Sweden studied 2,249 COPD patients using LTOT [25], and 1,129 (50%) patients died during observation. The adjusted time-dependent model was compatible with reduced mortality for antiplatelet drugs (HR, 0.86; 95%CI, 0.75–0.99; $p < 0.030$) and a trend for reduced mortality for angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (HR, 0.90; 95%CI, 0.79–1.04; $p < 0.166$) and statins (HR, 0.86; 95% CI, 0.72–1.03; $p < 0.105$), whereas β -blockers increased mortality (HR, 1.19; 95% CI, 1.04–1.37; $p < 0.010$). They concluded that anti-platelet drugs improve survival and β -blockers decrease survival in oxygen-dependent COPD. Thus, the controversy on the gender difference in the survival rate of COPD with LTOT is moving in the direction of the role of medications or multimorbidities. The gender difference in the outcomes of COPD provoked controversy, which has continued to a more recent period [25]. An initial study compared patients with LTOT due to various lung diseases in terms of gender difference [18], however, a more recent study revealed a gender difference in COPD patients alone.

Hypercapnia in patients with LTOT

Another study from Japan [26] suggested that the hypercapnia observed in patients with chronic respiratory failure is not an ominous sign for prognosis when they are receiving LTOT. Aida and associates selected 4,552 patients with COPD and 3,028 with TBsq receiving LTOT from 1985 to 1993 throughout Japan, and prospectively analysed their prognoses. The hypercap-

nic patients ($\text{PaCO}_2 > 45$ mm Hg) had a better prognosis than did the normocapnic patients ($35 < \text{PaCO}_2, 45$ mm Hg) for TBsq, but no difference was found between the 2 groups with COPD. Furthermore, Cox's proportional hazards model revealed that in TBsq, hypercapnia was an independent factor for a favourable prognosis, and that the relative risk for mortality was 0.76 in patients with $45 < \text{PaCO}_2 < 55$ mm Hg, 0.64 for those with $55 < \text{PaCO}_2 < 65$ mm Hg, and 0.49 for patients with $\text{PaCO}_2 > 65$ mm Hg, against normocapnic patients. This favourable effect of hypercapnia in TBsq was particularly apparent in the patients without severe airway obstruction. Even a rise of 5 mm Hg or more in PaCO_2 over the initial 6- to 18-month follow-up period was not associated with a poor prognosis in TBsq, although it was in COPD. From these findings, they concluded that hypercapnia should not generally be considered an ominous sign for prognosis in patients who receive LTOT [26]. The effects of hypercapnia on survival in COPD patients with LTOT are not discussed even in the recent research recommendation by the NIH [27]. However, because nasal positive-pressure ventilation may be a useful addition to LTOT in stable hypercapnic patients with COPD in terms of quality of life [28], this treatment option for patients with LTOT and hypercapnia should be also discussed in terms of better quality of life.

Moderate hypoxaemia or severe breathlessness

Among these proposals, the efficacy of LTOT in moderate hypoxaemia is important, although it was previously concluded that LTOT had no effect on prolonged survival among such patients [29]. However, the majority of patients with severe COPD wish to be eligible for LTOT in order to improve severe breathlessness in daily life, as shown in the survey data [12].

Presently, this option is the greatest issue in research on LTOT. Breathlessness or dyspnoea is a term used to characterize a subjective experience of breathing discomfort that is comprised of qualitatively distinct sensations that vary in intensity. It encompasses multiple somatic perceptions that are variously described as air hunger, increased breathing effort, chest tightness, rapid breathing, incomplete exhalation, or a feeling of suffocation. Thus, it is known that dyspnoea is a major detriment to quality of life [30–32]. Dyspnoea is the perception that the respiratory muscle response is inadequate or unsustainable. This perception arises from the sensory cortex, which integrates information from multiple sources, including the peripheral and cen-

tral chemoreceptors, mechanoreceptors (arising from the large airways, lung parenchyma, and the chest wall), and respiratory motor centres (in the medulla as well as the motor cortex). A multidisciplinary approach to dyspnoea that addresses various pathophysiological factors from symptom production to perception is required. Regarding the clinical aspects, nurses (education), physiotherapists (exercise therapy), respiratory therapists, occupational therapists (ergonomics and accommodation strategies), dieticians (to optimize nutrition), and psychologists/chaplains (to address symptom meaning) all have important roles to play [33, 34].

Studies of supplemental oxygen for relief of dyspnoea have shown mixed results in hypoxaemic patients with cancer and severe lung disease; however, no study has suggested a benefit for non-hypoxaemic patients [35]. Studies of supplemental oxygen for dyspnoea in advanced cancer, which included many cases in the Japanese cohort, are more complex. Based upon evidence of moderate quality, evidence-based guidelines from the American College of Physicians (ACP) recommend oxygen for the short-term relief of hypoxaemia in adults with dyspnoea and serious illness at the end of life [36, 37]. However, the presence of hypoxaemia does not reliably predict the symptomatic response from oxygen therapy [38, 39]. Studies of supplemental oxygen for relief of dyspnoea for palliative care have shown mixed results in hypoxaemic patients with cancer and severe lung disease. Alternative therapies such as acupuncture have been examined as potential therapies to reduce dyspnoea, and a retrospective series and a small randomized trial have shown mixed results [40, 41]. More recently, Suzuki et al. demonstrated [42] that acupuncture is a useful adjunctive therapy in reducing breathlessness in patients with COPD.

These observations all suggest that the current situation in Japan is more complex because more than half of the patients receiving LTOT do not have COPD, which means that they are receiving LTOT for conditions for which LTOT use is not supported by scientific data, and approximately 30% of these cases are presenting with moderate hypoxaemia. Further studies regarding survival, quality of life, or other measurable outcomes are required in these patients.

Issues arising regarding LTOT for elderly patients

Although the majority of patients with LTOT are elderly, knowledge regarding the effects of or issues associated with LTOT in these patients remains scarce. Elderly COPD patients may have

specific geriatric issues, such as the presence of multiple comorbidities, including cognitive impairment, medication adherence, caregiver involvement, and the necessity for institutionalized care. COPD is particularly relevant in this context because the presence of lung disease is associated with a greater number of geriatric syndromes (e.g. low body mass index, dizziness, and falls) and the risk of associated impairments in the activities of daily living. Recent work has further demonstrated an association between COPD severity and the risk of cognitive decline, specifically in chronically hypoxic or oxygen-dependent individuals with COPD [43, 44]. Moreover, COPD and cognitive impairment have each been associated with high rates of hospitalization [45] and death [46] in older adults. We reported data on elderly COPD patients using LTOT [47] with the objective of identifying factors that determine outcome in elderly patients receiving LTOT for COPD. We followed 157 COPD patients (121 men and 36 women) from 1983 to 1994, and 96 of these patients (61.2%) died. The mean age of the patients was 79.2 years and the mean duration of LTOT was 2.81 years. The mean FEV₁ was 0.80 L and the mean FEV₁/FVC was 48%. The overall survival was poor, with a 5-year survival of 21.6% (median survival: 3.01 years). Among the variables tested by univariate analysis, the following factors were associated with outcome: %IBW < 85 (HR = 2.15, *p* < 0.001), serum albumin (g/dl) < 3.5 (HR 1.81, *p* < 0.01), haemoglobin (g/dl) < 11.0 (HR 1.86, *p* < 0.01), FEV₁/FVC > 50% (HR 0.63, *p* < 0.05), and high dyspnoea ranking (MMRC 4 or 5) (HR 1.74, *p* < 0.05). The coexistence of bronchiectasis (HR 3.96, *p* < 0.01) and malignancy (HR 1.85, *p* < 0.01) also contributed to poor outcome. Multivariate analysis showed that the independent prognostic factors influencing outcome were nutritional status (%IBW) (HR = 2.08, *p* < 0.01), dyspnoea ranking (HR 2.04, *P* < 0.01), the coexistence of malignancy (HR 2.02, *p* < 0.01), and FEV₁/FVC > 50% (HR 0.52, *p* < 0.01). We conclude that the outcome in elderly COPD patients receiving LTOT is poor, and that outcome is independently influenced by 4 major factors: malnutrition, severity of dyspnoea, the coexistence of malignancy, and airflow obstruction.

A clinical trial is required in the future

The National Heart, Lung, and Blood Institute, in collaboration with the Centres for Medicare and Medicaid Services, convened a working group to discuss research on LTOT in 2004 [27]. Although LTOT has been proven by clinical trials

to prolong life in patients with COPD and severe resting hypoxaemia [9, 10], scientific research has not provided definitive guidance regarding who should receive LTOT and how it should be delivered. Deficiencies in knowledge and in current research activity related to LTOT are especially striking in comparison to the importance of LTOT in the management of COPD and the associated costs. The NHLBI Workshop Report recommended following clinical trials in subjects with COPD [27]: (1) the efficacy of ambulatory O₂ supplementation in subjects who experience oxyhaemoglobin desaturation during physical activity but are not severely hypoxaemic at rest; (2) the efficacy of LTOT in subjects with severe COPD and only moderate hypoxaemia; (3) the efficacy of nocturnal O₂ supplementation in subjects who show episodic desaturation during sleep that is not attributable to obstructive sleep apnoea; and (4) the effectiveness of an activity-dependent prescription for the O₂ flow rate that is based on clinical tests performed at rest, during exercise, and during sleep. In addition, the efficacy and cost-effectiveness for elderly patients should be assessed at two aspects: improvement of quality of life and cost-effectiveness. Furthermore, elderly patients are prone to having problems with understanding the instructions provided by the medical staff, which may cause low adherence. Previously, Zielinski noted an association [48] between low compliance and a lack of sufficient information regarding oxygen therapy provided to patients from prescribing physicians, indicating that proper education of patients is important. However, the data from our survey also indicate that education of the patients receiving LTOT remains insufficient because only one-third of patients received proper information, and this information came mostly from the technicians who delivered the oxygen equipment.

Conclusions

A quarter of a century has passed in Japan since public health insurance began covering LTOT in 1985. Comprehensive pulmonary rehabilitation has progressed along with an increased number of patients who receive LTOT. The awareness of respiratory disability is rapidly growing among both patients and health care professionals, which supports the further progress of LTOT in our country. However, further scientific studies are required to optimize LTOT in the patients with end-stage chronic lung diseases, because sufficient scientific evidence is lacking.

Conflict of interests

The authors declare no conflict of interest.

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