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LEAKAGE FROM NON-INVASIVE POSITIVE PRESSURE VENTILATION THERAPY MASKS AFFECTS FRACTION OF INSPIRED OXYGEN: COMPARISON OF HOME- AND INSTITUTION-DELIVERED OXYGEN THERAPY ON SIMULATED PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Abstract. *At-home non-invasive positive pressure ventilation (NPPV) has been shown to be effective in patients with chronic obstructive pulmonary disease (COPD). Especially in COPD patients with reduced ventilation capacity, NPPV can improve patients' symptoms and quality of life in combination with home oxygen therapy (HOT). Nevertheless, if the mask is not attached properly, airway leakage would occur to decrease the fraction of inspired oxygen (FiO_2) supplied to the alveoli. While the effectiveness of oxygen therapy is dependent upon the FiO_2, there is a lack of basis data to establish guidelines regarding the standard FiO_2 level required for the combined use of NPPV and HOT. In the present study, we simulated patients with COPD to determine whether leaks from the mask affect the supply of FiO_2 to the alveoli during NPPV oxygen therapy. Comparing FiO_2 values from simulated medical institution care (oxygen piping + NPPV) and home medical care (HOT + NPPV), while no decrease in FiO_2 levels was observed in cases at medical institutions, a statistically significant decrease in FiO_2 levels (with increasing leakage) was found in cases in at-home care. These results are clinically relevant, as they suggest that FiO_2 levels should be carefully monitored during at-home mechanical ventilation.*

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Keywords: Non-invasive positive pressure ventilation (NPPV), Chronic obstructive pulmonary disease (COPD), Fraction of inspired oxygen (FiO_2), Home mechanical ventilation (HMV), Home oxygen therapy (HOT)

1. Introduction.

More than 250 million people worldwide live with chronic obstructive pulmonary disease (COPD) [1], and deaths due to COPD have increased in recent years. The World Health Organization announced in 2012 that COPD will likely be the third leading cause of death in 2030 [2]. COPD has significant impacts on health and the medical economy [3]. For example, it has been reported that coronavirus disease (COVID-19) patients with COPD have a 5.9-fold higher risk of disease progression than do patients without COPD [4].

As the symptoms of COPD progress, breathing weakens and alveolar hypoventilation occurs. Not only does the body become oxygen-deficient, but carbon dioxide accumulates due to insufficient exhalation [5,6]. In this case, it is not adequate to supplement oxygen with home oxygen therapy (HOT) and it becomes necessary to discharge excess carbon dioxide [7]. HOT augments breathing with a ventilator, expelling excess carbon dioxide and promoting oxygen uptake.

At-home non-invasive positive pressure ventilation (NPPV) has shown utility in patients with COPD [8,9]. However, the fraction of inspired oxygen (FiO_2) supplied to the alveoli may also decrease with this method if the mask is not fitted correctly, as this may result in air leakage [10,11]. A decrease in the FiO_2 supplied to the alveoli due to mask leaks has been noted previously in COPD patients treated at home [11]. Specifically, an oxygen flow rate of 1-5 L and leak rate of 0-10 L/min lead to an approximately 6% reduction in FiO_2. Leakage is an unavoidable disadvantage of NPPV, and decreased FiO_2 due to these leaks is a major risk in the combined use of HOT and home mechanical ventilation (HMV). This may be because the partial pressure of oxygen supplied via HOT is insufficient to compensate for decreased FiO_2 due to leakage. Currently, there is no guideline for maintaining standard FiO_2 values when using a ventilator and HOT together.

In order to develop guidelines, it is necessary to conduct clinical research, but there is a lack of basic data for this purpose. The ventilation volume also varies depending on factors such as the patient's lung condition, disease progression, and body weight. Therefore, it is crucial to establish a baseline oxygen concentration when choosing oxygen therapy. There are various types of oxygen therapy, and devices such as nasal cannulas or oxygen masks have clinically recognized reference values for FiO_2 provided by manufacturers. However, information on FiO_2 delivered from oxygen concentrators, except for reports by Doi et al. [11,12], is not widely known in clinical settings. Furthermore, there is scarce research on its concurrent use with home ventilators. Therefore, we conducted a machine-based study that could serve as basic data. In the present study, we assessed we evaluated the effect of leakage on FiO_2 values in oxygen therapy using oxygen piping in a medical institution and compared the results with those of a previous study using HMV + HOT. This study can serve as a basis for all future studies on home therapy for COPD patients.

2. Materials and Methods.

2.1. COPD patient simulation.

We used simulated COPD patients and spontaneous respiration, as based on a previous study [10]. The left lung of the TTL model (Training and Test Lung®, Michigan Instruments, Kentwood, MI, USA) was used for mandatory ventilation. The right lung provided an inspiratory effort. Spontaneous respiration was produced by attaching a lift bar between the left and right lungs. For spontaneous breathing and ventilation (right lung), the Hamilton-C1 (Hamilton Medical AG, Bonaduz, Switzerland) was used to model care in a medical institution. The EVT-4000 (Drägel Medical AG & Co. KGaA, Lübeck, Germany) was used to model home care. For treatment (left lung), the Hamilton-C1 was used for both lungs. Table 1 shows all ventilator settings used in the modelling of institutional and home medical care.

TABLE 1. Ventilator settings

	Right lung [normal]	Left lung [COPD]
Mode	[home] CMV [hospital] SIMV	[home] NIV-ST [hospital] NIV-ST
Respiratory rate [b/min]	12	5
Inspiratory pressure [cmH_2O]	15	15
Inspiratory time [s]	1	1
PEEP/CPAP [cmH_2O]	5	5
Flow trigger [L/min]	5	2
Airway resistance [cmH_2O]	20	50
Lung compliance [L/cmH_2O]	0.05	0.04
Height [cm]	170	170

Abbreviations: CMV, controlled mechanical ventilation; NIV-ST, non-invasive ventilation-spontaneous/timed; SIMV, synchronized intermittent mandatory ventilation; COPD, chronic obstructive pulmonary disease; PEEP, positive end-expiratory pressure; CPAP, continuous positive airway pressure

Left lung airway resistance was set to 50 cmH_2O, and compliance was 0.04 L/cmH_2O. Right lung airway resistance was set to 20 cmH_2O, and compliance was 0.05 L/cmH_2O. To simulate NPPV leaks in home medical care, an adapter with both an oxygen supply port and a leak port was created and attached to the inspiration side circuit of the Hamilton-C1. Oxygen was supplied to the TTL model lung through this adapter, and mixed air leaked from the leak port. For NPPV leaks in a medical institution setting, the oxygen piping and Hamilton-C1 were connected, and the oxygen supply port at the adapter was closed. The leak port was used to model leaking as it would occur in a home medical care setting.

2.2. **FiO_2 measurement and oxygen therapy simulation in a medical institution setting.** To measure FiO_2, we used oxygen piping from the outpatient clinic of Oita University Hospital (Figure 1).

Unlike in-home medical care, oxygen was added directly to the Hamilton-C1 via oxygen piping, without an oxygen concentrator, to achieve an FiO_2 range of 23%-100%. Oxygen was then leaked artificially at 0 L/min, 5 L/min and 10 L/min from the adapter. The amount of leakage was measured using a flow analyser (PF-300, Fukuda Denshi, Tokyo, Japan) and adjusted for accuracy. FiO_2 was measured for 5 min in the TTL model lung. FiO_2 was also measured at the simulated patient's mouth for each given oxygen flow and leak rate. Measurements were repeated 10 times at each setting.

2.3. **FiO_2 measurement and simulation of HOT + NPPV in a home medical care setting.** To simulate NPPV by HMV, oxygen was added to the TTL model lungs at seven O_2 flow rates (0.5, 1, 2, 3, 4, 5 and 6 L/min) through the adapter using two oxygen concentrators (KM5 5touch, Nippon Special Ceramics Co., Ltd.) (Figure 2(A)).

FiO_2 supplied to the lung was measured with an oxygen concentration meter (My Sign® O_2, iVision, Tokyo, Japan), and the value obtained reflected the actual FiO_2 level in the

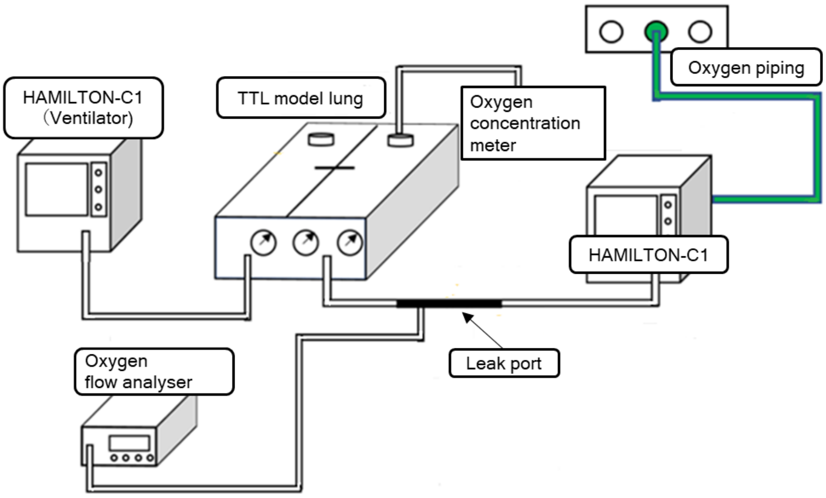

FIGURE 1. Circuit diagram (medical institution). This circuit diagram displays a method of supplying oxygen from an oxygen pipe in a medical institution. In order to simulate a leak from a non-invasive positive pressure ventilation therapy mask, a leak port was attached to the intake side circuit of the Hamilton-C1. The oxygen supply was provided by connecting the oxygen piping in the hospital directly to the ventilator. The left side of the TTL model lung represents the left lung; the right side represents the right lung.

alveoli. FiO_2 measurements were taken 10 times at each setting, over a 5-min period. A portion of the Y piece was also used to simulate the patient's mouth. Measurements were then taken using an oxygen concentration meter. However, in this case, if 10 measurements were taken continuously, oxygen would accumulate in the model lungs, rendering an inaccurate measurement of oxygen flow rate. Thus, room air from Hamilton-C1 was used in the TTL model lung to return the FiO_2 to 21% prior to the next measurement. Furthermore, leak rates of 0, 5 and 10 L/min were artificially induced using the adapter. Leak amounts were adjusted and measured using a flow analyser. FiO_2 was measured for 5 min in the model lung and at the simulated patient's mouth at each given oxygen flow rate. The leak rate setting and the measurement was repeated 10 times at each setting.

2.4. **Controlled experiments from a previous study.** As previously reported [11], oxygen was supplied to the TTL model lung at each oxygen flow rate (from 0.5 to 5 L/min) using an oxygen concentrator (state of HOT). FiO_2 was measured in the model lung. Two oxygen concentrators were used to moderate oxygen flow from 0.5 to 5 L/min (Figure 2(B)). Oxygen was added to the adapter at each oxygen flow rate, and FiO_2 was supplied to the model lung and measured with an oxygen concentration meter to obtain actual FiO_2 levels in the alveoli. Measurements were taken for 5 min, and each measurement was performed 10 times. FiO_2 in the model lung was returned to 21% between measurements, as described in the previous section. Next, a ventilator circuit was connected to the adapter, and the Hamilton-C1 was operated without leaking. The measurement for the Hamilton-C1 was performed in the same manner (Figure 2(C)).

2.5. **Statistical analyses.** FiO_2 values for simulated medical institution care (oxygen piping + NPPV) and home medical care (HOT + NPPV) settings were compared. FiO_2 values at each leak amount were also assessed. A Shapiro-Wilk test was performed to

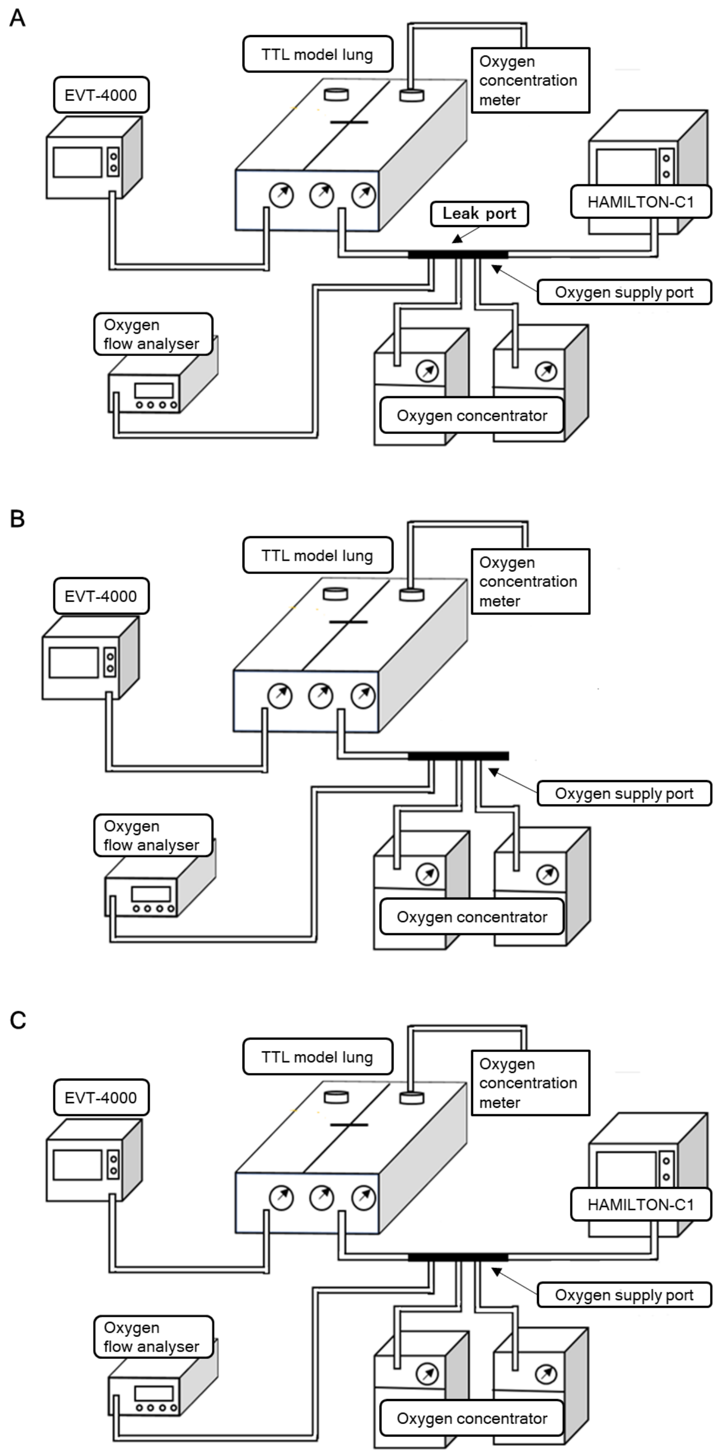

FIGURE 2. Circuit diagram (Home Oxygen Therapy). These circuit diagrams depict oxygen therapy using a ventilator and oxygen concentrator for in-home medical care. Oxygen was supplied from the oxygen concentrator through oxygen supply ports on the intake side circuit. (A) Simulation of non-invasive positive pressure ventilation. In order to simulate a leak from a non-invasive positive pressure ventilation therapy mask, a leak port was attached to the intake side circuit of the Hamilton-C1: (B) without leakage; (C) with a ventilator and without leakage.

confirm normal distribution of the data. Comparisons between the two groups were conducted by t-test. Multiple comparisons between groups and all variables were conducted via the Holm method. Statistical analyses were performed with R Statistical Software (Version 3.5.0, The R Foundation for Statistical Computing, Vienna, Austria). $P < 0.05$ was considered statistically significant.

3. **Results.** FiO_2 measurements from the simulated oxygen therapy in a medical institution setting (FiO_2 set at 23% to 100%; 0, 5 and 10 L/min leaks induced) remained above set FiO_2 levels (Table 2, Figure 3).

TABLE 2. FiO_2 measurements with simulated oxygen therapy in a medical institution setting

Leak [0 L/min]		Leak [5 L/min]		Leak [10 L/min]	
Set value [%]	FiO_2[a] [%]	Set value [%]	FiO_2[a] [%]	Set value [%]	FiO_2[a] [%]
23	23.1 ± 0.2	23	23.6 ± 0.3	23	23.4 ± 0.2
25	25.5 ± 0.2	25	25.7 ± 0.4	25	25.5 ± 0.2
30	30.9 ± 0.1	30	31.1 ± 0.2	30	31.2 ± 0.4
40	42.2 ± 0.2	40	41.4 ± 0.2	40	41.7 ± 0.4
50	51.5 ± 0.7	50	52.7 ± 0.7	50	52.0 ± 0.3
60	62.7 ± 0.5	60	63.6 ± 0.5	60	62.7 ± 0.4
70	73.2 ± 0.7	70	74.1 ± 0.9	70	74.2 ± 0.7
80	84.2 ± 0.4	80	84.0 ± 0.5	80	83.6 ± 0.7
90	94.1 ± 0.7	90	95.3 ± 0.6	90	95.4 ± 1.3
100	103.0 ± 0	100	103.0 ± 0	100	103.0 ± 0

Notes: [a]mean ± standard deviation

Abbreviations: FiO_2, fraction of inspired oxygen

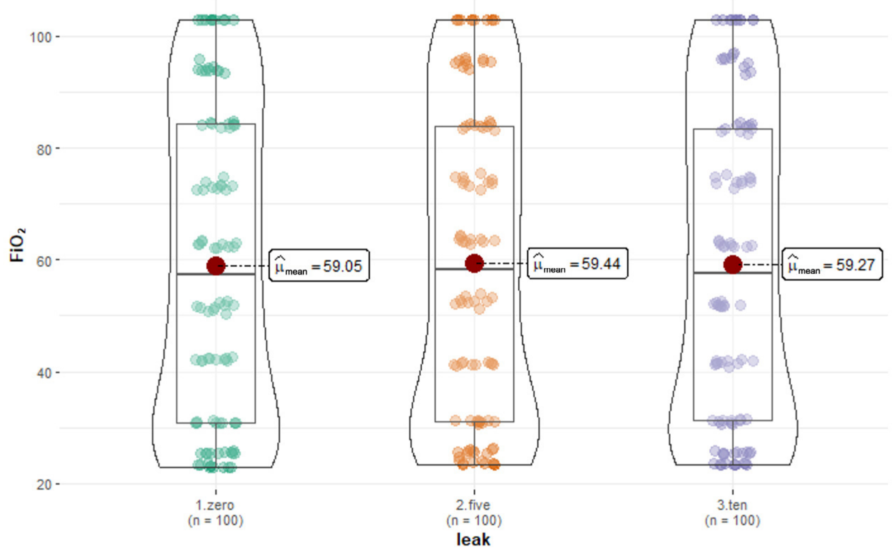

FIGURE 3. Institutional oxygen therapy. Oxygen therapy was performed by directly connecting the oxygen piping to a ventilator at a medical institution. Decreased FiO_2 was measured with a 5 L/min and 10 L/min leak, but no measurements fell below the specified FiO_2 value. Red dot is mean value.

However, in the home medical care setting, FiO_2 values decreased by 3.5% at the 0.5 L/min O_2 flow rate with 10 L/min leak rate. The maximum FiO_2 reduction was 10.9% at the 6 L/min O_2 flow rate (Table 3). According to the results of this study, even though oxygen can be supplied to patients through home oxygen therapy, the FiO_2 is approximately 48.6% with a leak-free oxygen flow rate of 6 L/min, and it is about 25.6% at 0.5 L/min. If leakage is present, considering a decrease in FiO_2 values of around 3% to 11%, it is necessary to administer oxygen therapy.

Table 3. FiO_2 measurements with simulated oxygen therapy in a home medical care setting

Leak [0 L/min]		Leak [5 L/min]		Leak [10 L/min]	
O_2 flow [L/min]	FiO_2[a] [%]	O_2 flow [L/min]	FiO_2[a] [%]	O_2 flow [L/min]	FiO_2[a] [%]
0.5	25.6 ± 1.0	0.5	23.6 ± 0.1	0.5	22.1 ± 0.1
1	30.2 ± 0.3	1	25.7 ± 0.2	1	23.3 ± 0.1
2	35.9 ± 0.3	2	30.6 ± 0.2	2	26.1 ± 0.1
3	38.9 ± 0.3	3	34.7 ± 0.4	3	28.9 ± 0.2
4	42.6 ± 0.5	4	38.7 ± 0.2	4	32.7 ± 0.2
5	44.6 ± 0.6	5	40.9 ± 0.2	5	35.1 ± 0.4
6	48.6 ± 0.7	6	43.3 ± 0.8	6	37.7 ± 0.5

Notes: [a]mean ± standard deviation

Abbreviations: FiO_2, fraction of inspired oxygen

There was also a significant difference in FiO_2 at each of the three leak amounts across all conditions ($P < 0.01$) (Figure 4).

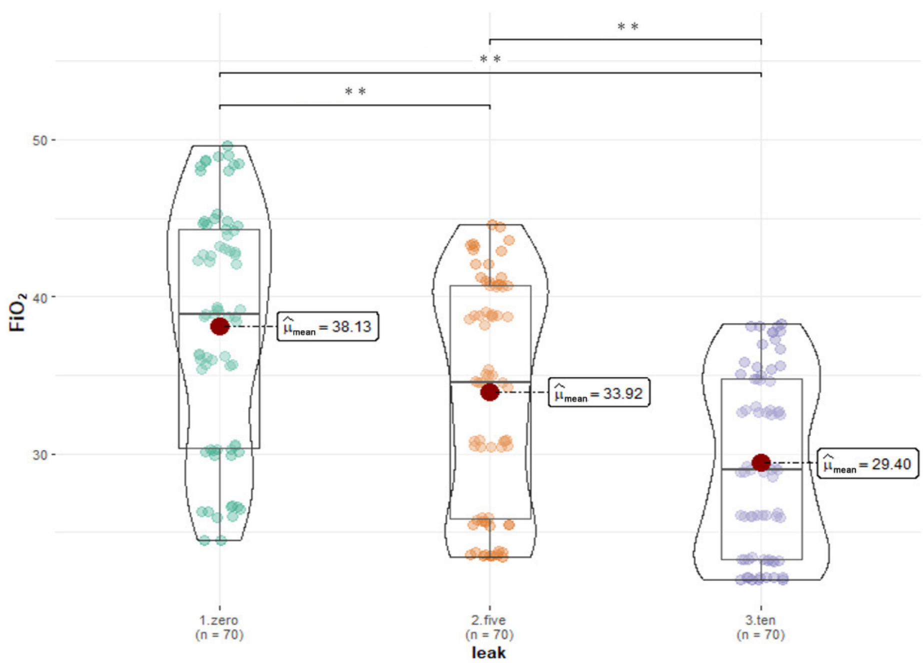

Figure 4. At-home oxygen therapy. In the home oxygen therapy setting, an adapter was attached to the middle of the ventilator circuit, and oxygen was added. When the leak rate increased from 0 to 10 L/min, FiO_2 values decreased significantly. Red dot is mean value.

These results were compared with those of our previous study utilizing HOT alone [11]. Supplying oxygen to the model lung with only an oxygen concentrator yielded an FiO_2 level of over 90% at 4 and 5 L/min O_2 flow rates (Table 4).

Table 4. Comparisons between flow rates in the present study and those in a prior study

Pure oxygen concentration		With 0 [L/min] ventilator leak Previous study (Doi et al. [11])		With 0 [L/min] ventilator leak Present study	
O_2 flow [L/min]	FiO_2[a] [%]	O_2 flow [L/min]	FiO_2[a] [%]	O_2 flow [L/min]	FiO_2[a] [%]
0.5	33.9 ± 0.3	0.5	23.0 ± 0.2	0.5	25.6 ± 1.0
1	59.8 ± 0.8	1	25.0 ± 0.3	1	30.2 ± 0.3
2	80.1 ± 0.9	2	28.5 ± 0.3	2	35.9 ± 0.3
3	87.4 ± 0.8	3	33.4 ± 0.4	3	38.9 ± 0.3
4	90.8 ± 0.4	4	37.8 ± 0.6	4	42.6 ± 0.5
5	92.5 ± 0.8	5	41.5 ± 0.8	5	44.6 ± 0.6

Notes: [a]mean ± standard deviation

Abbreviations: FiO_2, fraction of inspired oxygen

Similarly, at lower flow rates, an FiO_2 of over 90% was not obtained (at 3 L/min: 87.4%; at 2 L/min: 80.1%; at 1 L/min: 59.8%; at 0.5 L/min: 33.9%). In addition, when the O_2 flow rate was set below 3 L/min, FiO_2 values decreased markedly, as seen previously [11]. When using a ventilator with an oxygen concentrator, the highest reduction in FiO_2 was 54.0% at an O_2 flow rate of 3 L/min.

Unlike the previously reported 5 L/min O_2 flow rate, measurements of up to 6 L/min O_2 were possible when a ventilator was added. Furthermore, the FiO_2 value obtained with the addition of a ventilator was higher in this study than that in a previous study conducted by our research group [11], in which we reported a lower maximum FiO_2 reduction of 48.5%.

4. **Discussion.** There is scarce research on the concurrent use of ventilators and oxygen therapy. In hospital settings, it is unnecessary to consider the combination of these two as, when connected to oxygen piping, the supply of a predetermined level of oxygen can be adjusted. However, the situation changes significantly when considering home use. Unlike hospitals, homes lack oxygen piping, and for stable oxygen supply, options are limited to low-pressure membrane-type oxygen concentrators or high-concentration, low-pressure adsorption-type oxygen concentrators. Alternatively, one may resort to oxygen cylinders, which have higher pressure but may be challenging for prolonged use. The findings of this study contribute to future advancements in oxygen therapy.

Set FiO_2 values did not decrease with artificially induced leak rates of 0, 5, and 10 L/min, even in the medical institution oxygen therapy setting. This was attributed to the supply of oxygen via oxygen piping, which provided adequate pressure. The Hamilton-C1 was initially set to compensate for a ventilation volume leak rate of 2 L/min; therefore, it reacted to 5 and 10 L/min artificial leaks with increased compensatory ventilation. Under normal conditions, it is thought that the Hamilton-C1 air valve opens to compensate for shortages in the leaked ventilation volume. However, in the present study, FiO_2 values were set individually. The oxygen valve also opened and compensated for ventilation volume changes while maintaining the default FiO_2 value. Therefore, when using the Hamilton-C1 in a hospital setting, FiO_2 values with leaks of up to 10 L/min might be sufficiently stabilized. In addition, the Hamilton-C1 is equipped with a function to compensate for leaks of up to 30 L/min.

We observed similar results to those of prior studies for the home medical care setting (HMV + NPPV + HOT), but not for the medical institution oxygen therapy setting. Doi et al. [11] reported that the minimum FiO_2 level was 1.4% (at 0.5 L/min O_2 flow) and the maximum level was 6.3% (at 5 L/min O_2 flow) for a 0 to 10 L/min leak. However, in the present study, the minimum FiO_2 level was 3.5% (at 0.5 L/min O_2 flow), and the maximum FiO_2 level was 10.9% (at 6 L/min O_2 flow) (Table 3). While Doi et al. [11] observed a maximum oxygen flow rate of 5 L/min via one HOT device, we documented a maximum of 6 L/min via two HOT devices. Goutorbe et al. [10] reported O_2 flow rates of up to 8 L/min under 0 L/min to 10 L/min leak conditions.

In the present study, we were only able to measure leak rates of 0 L/min to 10 L/min at a maximum O_2 flow of 6 L/min. This was because when O_2 flow rates were set to 7 L/min or higher, an HMV flow sensor abnormality was detected, and no further measurements were recorded. In the HMV approach used in this study, an alarm occurred when the sensor detected a 1 L/min difference between the air supply ventilation and the expiration rate. This discrepancy from previous studies may have occurred owing to performance differences between the Hamilton-C1 used in this study and the HMV (VELA) that was previously used [11].

Studies by Doi et al. [11] and Goutorbe et al. [10] offer clues for solving the problem of leakage. First, NPPV therapy with oxygen piping in medical institutions may be less susceptible to leaks, since the oxygen piping used is directly connected to a ventilator; therefore, even if a leak occurs in NPPV, it supplements the set FiO_2 and ventilation volume. Second, compensation for default FiO_2 and ventilation volume losses due to leaks depends on the particular ventilator used. For instance, the Hamilton-C1 has a capacity of up to 30 L/min, even when set to 100% FiO_2. Therefore, the ventilator used by Doi et al. [11] is expected to have the same capability, because it is a comparable model to the one used in the present study. Goutorbe et al. [10] used Legendair® (Airox™, Pau, France). However, the use of oxygen piping in medical institutions means leakage is less likely in such settings, thus preventing a decrease in FiO_2.

Goutorbe et al. conducted a leak test with an oxygen cylinder directly connected to a ventilator, and the slight increase in FiO_2 was thought to be due to small leaks. The observed increase in FiO_2 was less than the oxygen compensation provided by the piping in this study design. In the present study, as well as the study conducted by Doi et al. [11], FiO_2 was supplied by connecting an HOT between the model lung and the HMV. This was insufficient to prevent decreases in FiO_2 against the leakage. FiO_2 was further reduced by the increased ventilation, which compensated for the leaks in the HMV circuit. We concluded that the cause of the FiO_2 decrease was the mixture of FiO_2 supplied from HOT, which increased ventilation.

Our results in the medical institution therapy setting match those of Goutorbe et al. [10], revealing an upward trend in FiO_2 values even when a leak occurs. Goutorbe et al. [10] reported that at an O_2 flow rate of 1 to 4 L/min, FiO_2 is higher with a 10 L/min leak than with a 5 L/min leak. Conversely, Goutorbe et al. [10] did not find similar results with a 10 L/min leak and 8 L/min O_2 flow rate. This was mainly because of different methods for FiO_2 and oxygen delivery (i.e., piping versus oxygen cylinder). O_2 was supplied at a pressure of 400 ± 40 kPa and a flow rate of 60 L/min or more in the oxygen supply line. The oxygen cylinder was set to the hospital oxygen delivery standard (an average of approximately 200 kPa). Oxygen piping can supply a large amount of FiO_2

at any time at an average pressure of 400 kPa. As a result, there is a dramatic pressure difference of 200 kPa between the oxygen pipe and the oxygen cylinder, and a difference in oxygen supply capacity. In the case of a high FiO_2 value that requires a large amount of oxygen, differences in pressure between cylinder-supplied and pipe-supplied oxygen may account for this decrease. The amount of oxygen supplied from the oxygen pipe in the hospital is constant, while the amount of oxygen supplied from the oxygen cylinder is limited. The cylinder is not only restricted in terms of the duration of oxygen supply, but also the available pressure that it can provide as the level of oxygen decreases.

HOT can be used for up to 5,000 continuous hours, whereas oxygen cylinders can only be used for a short period of time, depending on the oxygen flow rate. Adsorption-type oxygen concentrators use an adsorbent (zeolite), which can absorb air and separate its oxygen and nitrogen components. Pressurized air is directed through the zeolite to absorb nitrogen and extract pure oxygen [13]; depressurized air is subsequently directed through the zeolite to release nitrogen and yield oxygen at a concentration of 90% or more. However, a major drawback of HOT is that its maximum pressure is only approximately 40 kPa. Therefore, oxygen therapy may be performed using this approach without a decrease in prescribed FiO_2 values (accommodating up to a 30 L/min leak), if performed with oxygen piping connected to a hospital- or medical-grade ventilator. If this is performed as done by Goutorbe et al. [10], it is possible to maintain the specified FiO_2 value with a 10 L/min leak rate if the O_2 flow rate is up to 4 L/min. The findings reported in our previous study [11], and those of Goutorbe et al. [10], agree with the results observed in the present study, and collectively provide critical information required for the optimisation of institutional and home-based medical care.

Some limitations are acknowledged in the present study. First, COPD patients were simulated with TTL model lungs; future studies should be conducted in humans to evaluate the efficacy of home-care medical equipment. Second, an error may have occurred in the FiO_2 value assessments due to HMV performance. At present, there are many types of home ventilators. The performance of this specialized equipment, in terms of flow compensation and maximum value of FiO_2 supplied, varies with the manufacturer. There is currently no guideline for measuring FiO_2 values with the combined use of HOT and HMV. Therefore, in the future, true FiO_2 values should be requested from manufacturers for experimental verification. Furthermore, it is crucial to carefully monitor FiO_2 levels when using a ventilator at home, and the development of a remote patient health monitoring system [14] capable of real-time FiO_2 monitoring in a home environment is also anticipated. The present study provides a scientific and methodological basis for future, valid assessments of FiO_2 reductions caused by leaks during HMV and HOT use in NPPV. Furthermore, basic scientific studies should be performed to investigate the regulatory mechanisms underlying these effects.

This study was a machine-based study without human subjects, and we were able to clarify the behavior of the machine and build evidence. In future studies, we will collect basic data through animal experiments, and measure actual FiO_2 levels in patients with COPD and evaluate the impact of these levels on patient prognosis, so that we can formulate guidelines. This study marks the first step toward the goal of developing oxygen concentrators that allow for equivalent treatment at home as in medical facilities.

5. **Conclusions.** The use of oxygen piping at medical institutions was found to guarantee default FiO_2 values, even with leaks up to 30 L/min with NPPV. In addition, we found that a combination of HOT and HMV in a home medical care setting resulted in decreased FiO_2 across multiple leak rates, and the decrease in FiO_2 values was greater with HOT than with oxygen cylinder use. The results suggest that FiO_2 values decrease

due to differences in oxygen supply methods between home medical care and institutional medical care. Therefore, it is pertinent that FiO_2 levels are carefully monitored during in-home mechanical ventilation. Future studies should assess actual FiO_2 values in human populations, and how these values affect patient prognosis, especially in hospital and home care settings. This study has provided evidence that will serve as a basis for future research.

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