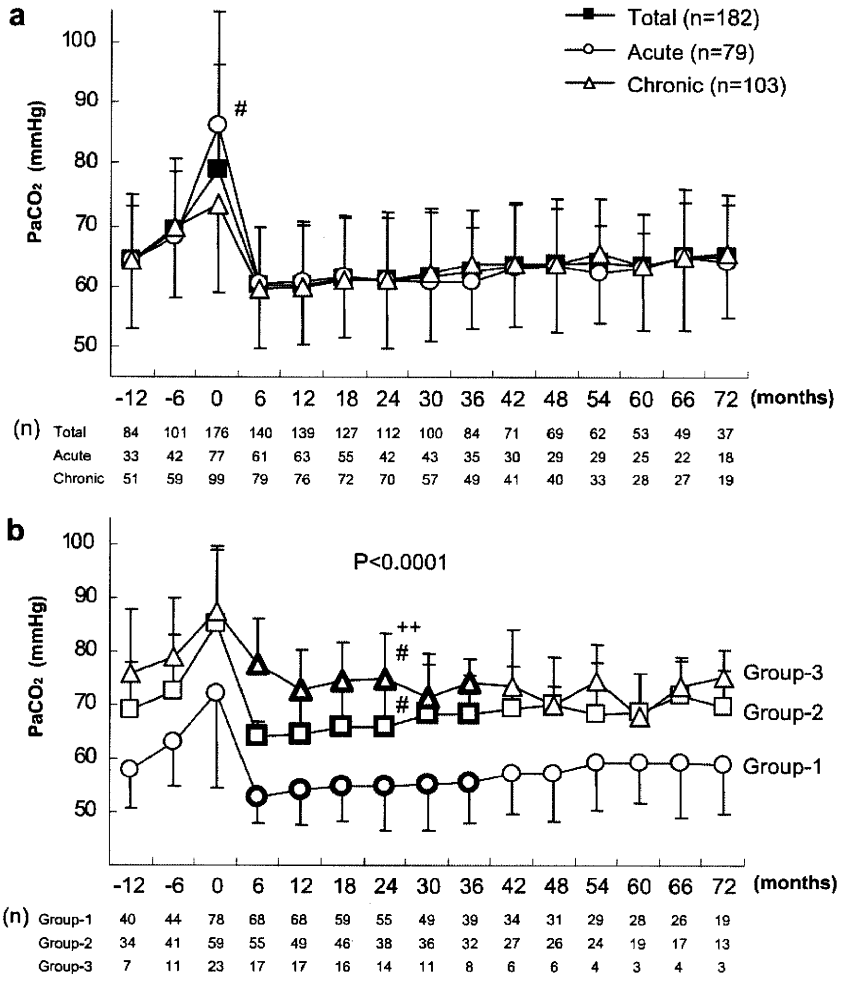

Figure 1 a. Time course of $PaCO_2$ values before and after NPPV. Comparison between patients with initiation of NPPV in either an acute or chronic state. Data are presented as mean (SD). No significant difference was noted except for values at the start of NPPV. #$p < 0.05$ (compared with patients starting NPPV while in a chronic state). b. Time course of $PaCO_2$ values before and after NPPV. Comparison among patients grouped according to the average $PaCO_2$ 3–6 months after introduction of long-term NPPV (3- to 6-mo $PaCO_2$) (Group-1, 60 mmHg>; Group-2, 60–70 mmHg; Group-3, >70 mmHg). Data are presented as mean (SD). From 6 to 36 months after initiation of NPPV, patients with relatively high 3- to 6-mo $PaCO_2$ values had significantly higher $PaCO_2$ than those with relatively low 3- to 6-mo $PaCO_2$ ($p = 0.0004$). #$p < 0.0001$ (compared to group-1), ++$p = 0.02$ (compared to group-2) by post-hoc analysis.

deterioration than those with relatively high 3- to 6-mo $PaCO_2$ levels. Mean (SD) of hospitalization rates in Group-1 to -3 were 0.23 (0.60), 0.31 (0.62), and 0.82 (1.53), respectively, in the 1st year, 0.21 (0.53), 0.41 (0.63), and 0.53 (0.62), respectively, in the 2nd year, and 0.18 (0.43), 0.49 (0.68), and 0.50 (0.52), respectively, in the 3rd year of long-term NPPV. There was no significant difference in hospitalization rates for the year preceding NPPV in Group-1 to -3 1.27 (0.96), 1.61 (1.07), and 1.43 (0.99), respectively.

Discussion

In the present study, patients that had relatively low daytime $PaCO_2$ levels a few months after NPPV had significantly higher continuation rates of NPPV and significantly lower hospitalization rates due to respiratory deterioration from the first to the third years of NPPV. Such patients had also maintained relatively low $PaCO_2$ levels from 6 to 36 months after NPPV. Neither the $PaCO_2$ level at the start of NPPV nor improvement in $PaCO_2$ after use of NPPV was a significant predictive variable.

In general, patients with hypercapnic respiratory failure started long-term NPPV during either an acute or chronic state.[1,2] The patients in the chronic state might not have been completely stable while receiving only LTOT. Actually, most of our patients who were considered to have a chronic status had experienced gradual deterioration of their symptoms over a long period even though their respiratory condition was not acutely aggravated. Their $PaCO_2$ had increased slowly during the pre-NPPV period as shown in

Table 2 Univariate modality model.

Variable	Category	(n)	HR (95%CI)	p Value
Gender	Female	85	0.53 (0.34–0.83)	0.005
	Male	97	Reference	
Age (y)	<69	89	0.92 (0.60–1.42)	0.70
	69≦	93	Reference	
BMI (kg/m^2)	18.6≦	83	0.58 (0.37–0.91)	0.02
	<18.6	79	Reference	
% predicted VC (%)	<31.4	81	0.89 (0.56–1.41)	0.62
	31.4≦	81	Reference	
FEV_1/FVC (%)	<70	68	0.87 (0.55–1.39)	0.56
	70≦	95	Reference	
Pulmonary lesions	(−)	14	0.25 (0.08–0.81)	0.02
	(+)	168	Reference	
Patients' status	Acute	79	0.78 (0.51–1.21)	0.27
	Chronic	103	Reference	
Hospitalization rate due to acute respiratory episodes before NPPV	0–1	118	0.65 (0.42–0.99)	0.04
	2≦	64	Reference	
Duration of LTOT before NPPV (y)	4.5≦	91	0.70 (0.46–1.08)	0.11
	<4.5	91	Reference	
Use of LTOT after NPPV	(+)	170	0.79 (0.32–1.96)	0.62
	(−)	12	Reference	
Ventilator mode	Controlled	106	0.54 (0.35–0.83)	0.01
	Assisted	76	Reference	
Ventilator settings				
IPAP (cmH_2O)	Continuous variable	162	0.99 (0.94–1.05)	0.82
EPAP (cmH_2O)	Continuous variable	162	0.92 (0.78–1.09)	0.33
Respiratory rate (/min.)	Continuous variable	182	0.96 (0.91–1.01)	0.14
3- to 6-mo $PaCO_2$ (mmHg)				0.0006
	<60	79	0.29 (0.16–0.54)	0.0001
	60–70	61	0.47 (0.26–0.87)	0.02
	70<	23	Reference	–

Fig. 1-a. Midgren had reported the same findings concerning $PaCO_2$ during the pre-NPPV period in post-polio patients.[15] Therefore, even in patients for whom non-invasive ventilation was initiated during the chronic state, the ABG level before NPPV might be inappropriate as a predictive variable. Furthermore, since the elevated $PaCO_2$ is effectively corrected within a few months of NPPV, it is unlikely to have any lasting predictive value for latter outcome.

The persistent CO_2 retention in patients with chronic ventilatory failure might reflect an adaptive mechanism that permits a lower level of alveolar ventilation, thus resulting in unloading of the overburdened respiratory

Table 3 Multivariate modality model.

Variable		n	HR (95%CI)	p Value
Ventilator mode	Controlled	106	0.41 (0.25–0.68)	0.0005
	Assisted	76	Reference	
BMI (kg/m^2)	18.6≦	83	0.54 (0.32–0.92)	0.02
	<18.6	79	Reference	
3- to 6-mo $PaCO_2$ (mmHg)				0.03
	<60	79	0.37 (0.18–0.77)	0.01
	60–70	61	0.44 (0.21–0.89)	0.02
	70<	23	Reference	–
Gender	Female	85	0.59 (0.36–0.97)	0.04
	Male	97	Reference	
Pulmonary lesions	–	14	0.30 (0.09–1.05)	0.06
	+	168	Reference	
Hospitalization rate due to acute respiratory episodes before NPPV	0–1	118	0.81 (0.49–1.34)	0.41
	2≦	64	Reference	

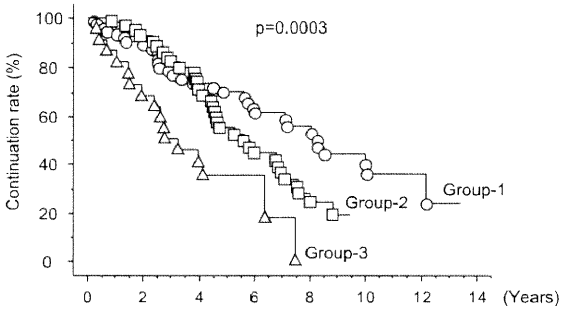

Figure 2 Kaplan–Meier curves of continuation rates of long-term NPPV in all patients. Patients were divided into 3 groups according to the average $PaCO_2$ 3–6 months after introduction of long-term NPPV (3- to 6-mo $PaCO_2$) (Group-1, 60 mmHg>; Group-2, 60–70 mmHg; Group-3, >70 mmHg). Patients with relatively low 3- to 6-mo $PaCO_2$ values had a significantly better prognosis (log-rank test, $p = 0.0003$).

muscles leading to decreased dyspnea, particularly while LTOT is administered.[16,17] It is presumed by some that this compensatory mechanism reveals the wisdom of nature.[17] However, ventilatory support such as NPPV should be implemented if hypercapnic ventilatory failure progresses over limits of this compensation.[8–10,18–21] An improvement in daytime $PaCO_2$ after initiation of NPPV was shown to be correlated with the change in $PaCO_2$ while receiving nocturnal NPPV[18,22] and the principal mechanism underlying the long-term improvement in daytime $PaCO_2$ was demonstrated to be an increased ventilatory response to CO_2.[8–10]

The present study showed that patients with relatively low 3- to 6-mo $PaCO_2$ values were able to maintain relatively low daytime $PaCO_2$ levels for several years and that the continuation rate of NPPV was higher and the hospitalization rate due to respiratory deterioration was lower in these patients than in those with relatively high 3- to 6-mo $PaCO_2$ values. Elliott emphasized that hypercapnia is a poor prognostic sign and that more aggressive

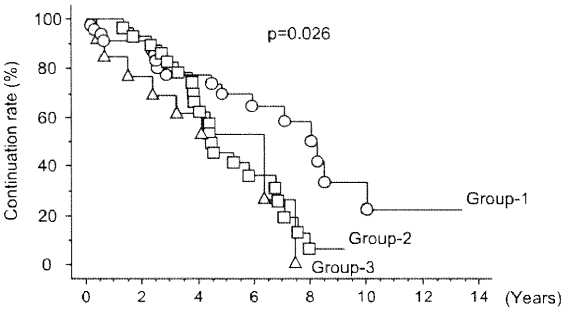

Figure 3 Kaplan–Meier curves for continuation rates of long-term NPPV in patients who began NPPV during a chronic state. Comparisons were made among patients who were divided into 3 groups according to the average $PaCO_2$ at 3–6 months after introduction of long-term NPPV (3- to 6-mo $PaCO_2$) (Group-1, 60 mmHg>; Group-2, 60–70 mmHg; Group-3, >70 mmHg). Relatively low 3- to 6-mo $PaCO_2$ was significantly associated with higher continuation rates (log-rank test, $p = 0.026$).

ventilation might have resulted in a larger decrease in daytime $PaCO_2$.[21] Tuggey et al. showed that greater minute ventilation can be achieved by using higher IPAP or larger V_T during controlled NPPV.[20] Reduction in daytime $PaCO_2$ within the first 3 months of NPPV was reported to be positively correlated with support pressure.[11] Windisch et al. found that the $PaCO_2$ value during controlled NPPV using high f_R and high inspiratory pressure decreased to a normocapnic level.[18] They also suggested that nocturnal NPPV with ventilator settings aimed at maximally decreasing $PaCO_2$ could decrease daytime $PaCO_2$ sufficiently and provide additional clinical benefits such as prolongation of life.[17,19] Dellborg et al. showed that improvements in morning $PaCO_2$ during NPPV correlated significantly with improvements in symptoms and sleep quality after 9 months of NPPV, which indicates the importance of lowering $PaCO_2$ during nocturnal NPPV.[23] These reports support the beneficial effect of nocturnal high intensity NPPV in reducing nocturnal and, therefore, daytime $PaCO_2$ values.

The present study also showed that patients with relatively high 3- to 6-mo $PaCO_2$ values retained relatively high $PaCO_2$ levels throughout their clinical course, although long-term NPPV decreased the $PaCO_2$ level in all 3 groups (Fig. 1-b). Patients with relatively high 3- to 6-mo $PaCO_2$ levels had longer periods of LTOT before the initiation of NPPV and more severe ventilatory defects at the start of NPPV. These results indicate the possibility that patients with more advanced disease tend to have higher daytime $PaCO_2$ than those with less advanced disease, with and without application of long-term NPPV. Therefore, it remains unclear whether reducing the nocturnal $PaCO_2$ to a nearly normocapnic level in every patient is possible. Besides, whether a greater reduction in daytime $PaCO_2$ is beneficial in every patient has not been clarified. The excessive resetting of $PaCO_2$ might theoretically augment patients' dyspnea in spontaneous breathing because there is a possibility that, to keep $PaCO_2$ at the set low level, patients have to increase and maintain ventilation exceeding the capacity of their respiratory muscles.

Our study has several limitations. Beginning of the use of and prevalence of the use of NPPV were delayed for more than five years in Japan compared to European countries.[24] Therefore, in many post-tuberculosis patients with hypercapnic respiratory failure, LTOT had been the only available treatment and their $PaCO_2$ values had already risen to extremely high levels before the start of long-term NPPV.[7] For this reason, in some of our patients, the daytime $PaCO_2$ value could not be reduced below 60 mmHg with long-term NPPV although both IPAP levels and improvement in daytime $PaCO_2$ values were almost equivalent to those of previous studies.[1,2,4,9–11,25,26] The patients in those previous studies had lower $PaCO_2$ values at the start of NPPV than our patients and it was not unexpected that their $PaCO_2$ values after NPPV was lower than those of our patients.[1,2,4,9–11,25,26] In such patients, the target values of $PaCO_2$ after NPPV can be supposed to be much lower than for our patients.

In 92% of our patients LTOT was concomitantly used immediately after the initiation of NPPV. This percentage appears to be high, but we think that the difference in percentage of LTOT usage between a previous study[12] and

our study might be attributed to higher $PaCO_2$ and lower PaO_2 of our patients after initiation of long-term NPPV.

In conclusion, we first found that patients with a relatively low $PaCO_2$ a few months after NPPV maintained relatively low $PaCO_2$ levels for several years and that $PaCO_2$ a few months after the initiation of NPPV is a significant predictive variable for rates of continuation of NPPV and hospitalization rates due to respiratory deterioration. The target level of daytime $PaCO_2$ after NPPV should be less than 60 mmHg in patients with extremely severe hypercapnia like ours, although more studies are needed to clarify to what extent the daytime $PaCO_2$ value should be reduced in individual patients with moderate to severe hypercapnia.

Conflicts of interest

All authors have no conflicts of interest to disclose.

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ORIGINAL ARTICLE

Long-term nasal continuous positive airway pressure treatment lowers blood pressure in patients with obstructive sleep apnea regardless of age

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Effective treatment with nasal continuous positive airway pressure (nCPAP) lowers blood pressure (BP) in patients with obstructive sleep apnea (OSA). It was reported that OSA might influence BP in middle-aged but not in elderly patients. However, effects of nCPAP treatment in elderly hypertensive OSA patients are not well known. We investigated long-term compliance with nCPAP and its effects on BP in elderly and middle-aged OSA patients. This observational study involved 92 OSA patients (81 men, 11 women; 46 middle-aged, 46 elderly; body mass index (BMI), 27.7 (27.0–28.7) kg m^{-2}; apnea hypopnea index, 43.0 (39.4–46.6) per h; 95% confidence intervals). BP and BMI were measured before the study and at two checkpoints after usage of nCPAP (616 (553–679) and 1048 (985–1114) days). Diastolic BP decreased by 5.69 (3.09–8.29) mm Hg after 600 days of nCPAP treatment and by 4.50 (1.80–7.19) mm Hg after 1000 days (P=0.003). There were no significant changes in systolic BP, BMI or usage time of nCPAP. With a daily average of 3 h or more of nCPAP treatment, diastolic BP decreased significantly in subject groups ⩾60 and <60 years of age. Even in the elderly, a daily average use of nCPAP for 3 h would lower diastolic BP in OSA patients.
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Keywords: compliance; diastolic blood pressure; elderly

INTRODUCTION

Obstructive sleep apnea (OSA) is strongly associated with hypertension. In the seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure Education Program, OSA was defined as an identifiable cause of hypertension from numerous epidemiological data.[1–3] Effects of nasal continuous positive airway pressure (nCPAP) on blood pressure (BP) in patients with OSA were variable in previous studies, but the net reduction in BP was significant compared with that in controls.[4–6] In addition, the long-term effect of nCPAP treatment on BP has been shown.[7,8] Recently published meta-analyses[9,10] suggested that effective nCPAP treatment indeed lowers BP in patients with OSA, but age-related differences in the effects of nCPAP treatment on BP remain to be elucidated.

The combination of systolic and diastolic hypertension is common in middle-aged hypertensive patients, whereas isolated systolic hypertension is predominantly a disease of elderly hypertensive patients.[11] Systolic/diastolic hypertension represents multiple etiologic factors, with evidence to suggest that the sympathetic nervous system is an important mediator.[12] Meanwhile, isolated systolic hypertension results from the age-dependent loss of arterial compliance.[13] Because it is known that nCPAP attenuates the increase in sympathetic activity in OSA,[14] the effectiveness of nCPAP treatment may differ between elderly and middle-aged persons with OSA. Haas *et al.*[15] showed that sleep-disordered breathing (SDB) was associated with systolic/diastolic hypertension in persons aged 40–59 years, but there was neither a significant nor consistent relationship between hypertension and SDB among those more than 60 years of age. This age-related difference may reflect different underlying pathophysiological processes. However, a relatively low proportion (20.7%) of participants aged ⩾60 years had study results showing at least moderate SDB (apnea hypopnea index (AHI) ⩾15) but the effects of nCPAP treatment were not investigated. Therefore, it is important to evaluate age-related differences in the effects of nCPAP treatment on BP in patients with OSA.

We hypothesized that long-term nCPAP treatment with sufficient usage time lowers BP in elderly as well as in middle-aged hypertensive OSA patients. Thus, we investigated long-term compliance with nCPAP and its effects on BP in elderly and middle-aged OSA patients.

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METHODS

Study subjects

The medical ethics committee at our institution reviewed and approved the study. All participants provided informed consent. In Japan, according to health insurance rules, patients with OSA who use nCPAP under the health insurance system must come to the hospital every month and pay a medical fee at each visit. We enrolled 101 outpatients with OSA who were consecutively seen in our hospital and who had been using nCPAP continuously for more than 3 years and who came to our hospital every month. Nine patients were excluded from analysis because of change in medication during the observation period. A total of 92 patients who received the same medical regimen (including antihypertensive medications) beginning 1 month before the start of this study and throughout the study were investigated. Tobacco and alcohol consumption did not change during the study. Because these participants included 66 patients who had been enrolled in a previous study[7] that investigated compliance with long-term nCPAP treatment and its effect on BP, polysomnography for all the OSA patients was performed by the same methods as in our previous studies.[7,16,17] The amplitude of airflow was monitored by thermistors (Nihon Kohden, Tokyo, Japan) that were placed at the nose and the mouth. Apnea was defined as the complete cessation of airflow and hypopnea as a clear reduction in airflow or abdominal excursion lasting for 10 s or more, accompanied by a decrease in oxygen saturation of at least 3%.[7,16,17,18] The number of episodes of apnea and hypopnea per hour was defined as the AHI. Each of the OSA patients had an AHI of 20 or more, because the health insurance system in Japan covers nCPAP only if the AHI is 20 or more. Following a diagnostic sleep study the patients underwent CPAP titration via standard polysomnography with manual control. To investigate smoking history, we calculated the Brinkman index by the following formula:

$$\text{Brinkman index} = \text{number of cigarettes smoked per day} \times \text{number of smoking years}$$

Study design

We performed a retrospective study of a cohort of patients with OSA who had used nCPAP continuously for more than 3 years to investigate the long-term effects of nCPAP treatment on BP in elderly and middle-aged OSA patients. In this study, to compare the results with that of Haas *et al.*,[15] 'elderly' was defined as the age 60 or over. After OSA patients had undergone 3 years of nCPAP treatment, we examined their medical charts. We obtained information about each patient's nCPAP treatment almost every month in the outpatient department of our hospital, and also obtained other data such as for body weight and BP.[7] This information was gathered at two time points as close as possible to a yearly interval (616 (553–679) and 1048 (985–1114) days).

Epworth Sleepiness Scale

The Epworth Sleepiness Scale[19] was administered before nCPAP treatment in 92 patients with OSA. With the Epworth Sleepiness Scale, individuals score themselves on a scale of 0 (not at all likely to fall asleep) to 3 (very likely to fall asleep) according to how easily they would fall asleep in eight situations, with possible overall scores of 0–24. The higher the score is, the sleepier the individual is.

Blood pressure and body weight

Patients' BP and body weight were measured before the study and every month after treatment had begun. The resting BP was measured in the right arm after a 5-min rest using a conventional mercury sphygmomanometer.[20] The first and last Korotkoff sounds were used to determine systolic and diastolic BP, respectively. The average of the second and third of three consecutive measurements was used as the BP value for the month. Weight was measured on a portable scale with the subject wearing light clothes. These BP and weight measurements are standard practice at our respiratory medicine clinic. Each parameter at two checkpoints was calculated by the mean value over 3 months.

Hypertension was defined as a systolic pressure above 140 mm Hg or a diastolic pressure above 90 mm Hg. Patients taking any antihypertensive medication were classified hypertensive.

Compliance with nCPAP treatment

We checked compliance using the nCPAP machine, based on data that were taken from the regular examination of the machine every 1 or 2 years. Compliance data on the daily average time (h per day) of usage of the nCPAP apparatus were acquired by reading the time counter in each nCPAP machine. To determine the average daily usage that was sufficient to lower BP of the OSA patients, we compared baseline diastolic BP values with those at the second checkpoint according to various intervals of usage. Usage was evaluated according to 30-min increments as follows: <30 min, 30 min, 1 h, 90 min, 2 h, 150 min, 3 h and so on. After identifying the minimum number of hours that were needed to lower BP significantly, we assigned patients to a 'good compliance group' if they used nCPAP an average of that minimum time or more; those who used nCPAP less were assigned to the 'poor compliance group'.

Statistical analysis

All statistical analyses were performed using nonparametric tests with statistical software (StatView version 5.0 for Windows; Abacus Concepts, Berkeley, CA, USA). Differences between the two groups were compared with the Mann–Whitney *U*-test. Differences between any two conditions in OSA patients were compared with the Wilcoxon signed-rank test. When more than two conditions were compared, a significant difference was tested among all of the conditions by the Friedman test. Correlations between variables were analyzed by the Spearman's rank correlation test. A *P*-value <0.05 was considered statistically significant. The data are expressed as the mean (95% confidence interval).

RESULTS

Effects on blood pressure

Table 1 shows the characteristics of patients according to age group before nCPAP. When both groups are considered together, these patients had a mean AHI of 43.0 (39.4–46.6). All received nCPAP with an adequate pressure of 9.3 (8.8–9.8) cm H_2O. nCPAP treatment reduced the patients' AHI to a mean of 2.1 (1.6–2.6) ($P<0.0001$). The mean Epworth score for the 92 subjects was 9.5 (8.4–10.6). Among the 92 patients with OSA, 68 had hypertension and 19 had diabetes mellitus. Forty-seven of the patients with hypertension took medication. Thirty-six patients were receiving a calcium inhibitor, twenty-four an angiotensin II receptor antagonist, six an α-blocker, seven a β-blocker, eight a diuretic drug and seven a nitrous drug. Thirteen patients were taking three or more antihypertensive drugs. In the older group, six patients had a history of stroke and two patients had a history of myocardial infarction before nCPAP treatment. After long-term nCPAP treatment, the diastolic BP in OSA patients significantly decreased whereas the systolic BP did not (Table 2). Diastolic BP decreased by 5.69 (3.09–8.29) mm Hg after 600 days of nCPAP treatment and by 4.50 (1.80–7.19) mm Hg after 1000 days of nCPAP treatment ($P=0.003$). The body mass index (BMI) did not change significantly during the treatment period nor did usage time of nCPAP. The diastolic BP decreased in 59 out of the 92 patients. However, the degree of decrease in diastolic BP did not significantly correlate with age, BMI or the Brinkman index. Moreover, the degree of improvement in AHI, the lowest arterial oxygen saturation during sleep and the percentage of time spent at less than 90% arterial saturation also did not significantly correlate with the degree of decrease in diastolic BP.

Age-related differences

In accordance with a previously reported procedure,[15] we divided OSA patients into two age groups: those ≥ 60 years of age and those <60 years of age (Table 1). There were 81 men and 11 women with a mean age of 55.6 (53.0–58.0) years and BMI of 27.9 (27.0–28.7) kg m^{-2}. The number in each group was the same ($n=46$). There were no differences in sex, nCPAP usage time, heart rate and BP between

Table 1 Comparison of characteristics of patients with OSA before usage of nCPAP grouped according to age

	<60 years old (n=46)	*≥60 years old* (n=46)	P-value
Sex (female/male)	6/40	5/41	0.86
Compliance (good/poor)	32/14	29/17	0.59
Age (years)	44.6 (42–47)	66.7 (65–68)	<0.0001
BMI (kg m^{-2})	29.2 (27.9–30.4)	26.5 (25.6–27.5)	0.003
AHI (events per h)	47.5 (42.0–52.9)	38.5 (33.8–43.2)	0.02
Epworth Sleepiness Scale score	9.98 (8.7–11.3)	8.84 (6.9–10.8)	0.19
Smoking history	19	30	0.02
Brinkman index	294.1 (219.3–368.9)	551.2 (467.4–635.0)	0.009
Hypertension	30	38	0.06
Diabetes mellitus	11	8	0.44
Heart failure[a]	1	2	0.56
History of cardiovascular events			
Myocardial infarction	0	2	0.15
Stroke	0	6	0.01
BP medication			
Calcium Inhibitor	8	28	<0.0001
Angiotensin II receptor antagonist	6	18	0.005
α-Blocker	4	2	0.40
β-Blocker	3	4	0.70
Diuretic drug	1	7	0.03
Nitrous drug	0	7	0.006
Any BP medication	12	35	<0.0001
Three or more drugs	3	10	0.04
Usage time 600 days (h per day)	4.42 (3.77–5.06)	4.04 (3.36–4.72)	0.54
Usage time 1000 days (h per day)	4.15 (3.51–4.80)	4.13 (3.44–4.82)	0.997
Heart rate (beats per min)	78.7 (77.1–80.3)	75.8 (74.2–77.4)	0.12
Systolic blood pressure (mm Hg)	135.8 (132.2–139.4)	138.0 (133.0–143.1)	0.65
Diastolic blood pressure (mm Hg)	87.3 (83.8–90.9)	82.2 (78.4–86.1)	0.09

Abbreviations: AHI, apnea hypopnea index; BMI, body mass index; BP, blood pressure.
Data presented as mean (95% confidence interval).
[a]Diagnosis was based on information from medical charts.

Table 2 Selected characteristics in 92 patients with OSA before and after nCPAP treatment

	Before nCPAP	*After 600 days of nCPAP*	*After 1000 days of nCPAP*	P-value
BMI (kg m^{-2})	27.9 (27.0–28.7)	27.5 (26.5–28.4)	27.3 (26.3–28.2)	0.08
Usage time (h per day)		4.23 (3.77–4.69)	4.14 (3.68–4.60)	0.11
Systolic blood pressure (mm Hg)	136.9 (133.8–140.0)	133.0 (130.9–134.9)	133.3 (130.9–135.7)	0.3
Diastolic blood pressure (mm Hg)	84.8 (82.2–87.4)	78.8 (76.5–81.1)	80.5 (78.7–82.4)	0.003

Abbreviations: BMI, body mass index; nCPAP, nasal continuous positive airway pressure.
Data presented as mean (95% confidence interval).

groups. The percentage of smokers was greater in the older group than in the younger group. The majority (82.6%) of the older participants were classified as being hypertensive compared with 65.2% of the younger group. Approximately three quarters (76.1%) of the older participants were taking antihypertensive medications compared with 26.1% of the younger participants. There were also more patients taking three or more antihypertensive drugs in the older group than in the younger group (P=0.04). BMI and AHI were significantly lower in the older group than in the younger group.

Figure 1 shows the changes in BP according to age group after long-term nCPAP treatment. Diastolic BP decreased significantly in both age groups after 1000 days of nCPAP treatment (P=0.01, <60 years of age; P=0.02, ≥60 years of age). The degrees of decrease in diastolic BP did not differ significantly between the older and the younger groups (P=0.43, before 600 days; P=0.69, before 1000 days). There were no differences in body weight (P=0.23, <60 years of age; P=0.16, ≥60 years of age) and nCPAP usage time (p=0.58, <60 years of age; P=0.98, ≥60 years of age) in both age groups during the study period.

Blood pressure and compliance

When usage times were checked according to 30-min intervals to determine the minimum number of hours that were needed to lower BP significantly, a significant decrease in diastolic BP (7.7 (4.5–10.8) mm Hg, P<0.0001, n=61) was achieved by a daily average of at least 3 h of nCPAP treatment. However, nCPAP usage time *per se* was not

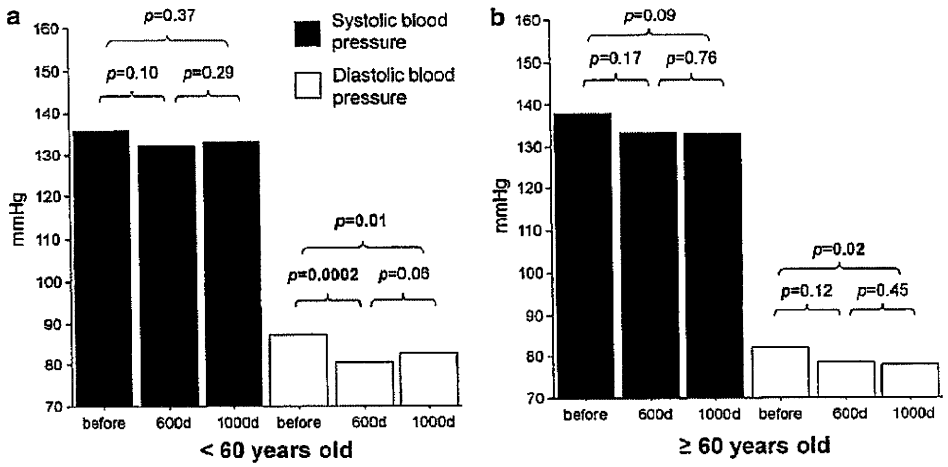

Figure 1 Mean systolic and diastolic blood pressure values in patients aged <60 years (n=46, (a)) and patients aged ⩾60 years (n=46, (b)) before nasal continuous positive airway pressure (nCPAP) treatment and after 600 and 1000 days of nCPAP treatment.

Table 3 Baseline characteristics of patients with OSA with either good or poor compliance with nCPAP

<60 years old (n=46)	*Good compliance* (n=32)	*Poor compliance* (n=14)	*P-value*
Sex (female/male)	5/27	1/13	0.65
Age (years)	46.3 (43–49)	40.7 (34.7–46.7)	0.09
BMI (kg m^{-2})	29.1 (27.7–30.6)	29.3 (26.6–32.0)	0.82
AHI (events per h)	47.7 (41.2–54.2)	47.0 (35.8–58.2)	0.83
Epworth Sleepiness Scale score	9.61 (7.9–11.3)	10.8 (8.6–13.0)	0.45
Smoking history	10	9	0.04
Brinkman index	275.2 (174.4–376.3)	336.1 (242.7–429.5)	0.15
Hypertension	23	7	0.16
Antihypertensive drug	9	3	0.63
Heart rate (beats per min)	77.7 (75.8–79.6)	81.0 (78.1–83.9)	0.30
Systolic blood pressure (mm Hg)	136.6 (132.0–141.1)	134.0 (127.5–140.4)	0.59
Diastolic blood pressure (mm Hg)	90.0 (85.7–94.3)	81.3 (75.8–86.8)	0.03
Usage time 600 days (h per day)	5.50 (5.23–5.77)	1.93 (1.67–2.19)	<0.0001
Usage time 1000 days (h per day)	5.25 (4.98–5.52)	1.63 (1.37–1.89)	<0.0001
⩾60 years old (n=46)	*Good compliance* (n=29)	*Poor compliance* (n=17)	*P-value*
Sex (female/male)	3/26	2/15	0.94
Age (years)	67.6 (65.7–69.4)	65.2 (63.2–67.3)	0.11
BMI (kg m^{-2})	26.5 (25.3–27.8)	26.5 (24.9–28.1)	0.7
AHI (events per h)	38.5 (32.1–44.9)	38.6 (31.2–46.0)	0.9
Epworth Sleepiness Scale score	9.85 (7.5–12.2)	6.46 (3.1–9.9)	0.11
Smoking history	19	11	0.96
Brinkman index	605.7 (488.1–723.3)	449.3 (351.6–547.0)	0.69
Hypertension	25	13	0.41
Antihypertensive drug	23	12	0.5
Heart rate (beats per min)	75.4 (73.4–77.4)	76.5 (73.9–79.1)	0.65
Systolic blood pressure (mm Hg)	139.8 (134.0–145.6)	135.1 (124.9–145.2)	0.32
Diastolic blood pressure (mm Hg)	83.6 (78.9–88.3)	79.9 (72.6–67.3)	0.57
Usage time 600 days (h per day)	5.53 (5.29–5.77)	1.49 (1.24–1.74)	<0.0001
Usage time 1000 days (h per day)	5.56 (5.32–5.80)	1.69 (1.33–2.05)	<0.0001

Abbreviations: AHI, apnea hypopnea index; BMI, body mass index.
Data presented as mean (95% confidence interval).

significantly correlated with the degree of decrease in diastolic BP. A total of 61 patients used nCPAP for a daily average of 3 h or more (good compliance group) and 31 patients used nCPAP <3 h daily (poor compliance group). We further divided the age groups into those with good compliance and poor compliance (Table 3). Differences in sex, age, BMI or AHI between the good and poor compliance groups were not significant. Diastolic BP decreased significantly in both age groups with good compliance, but not in either age group

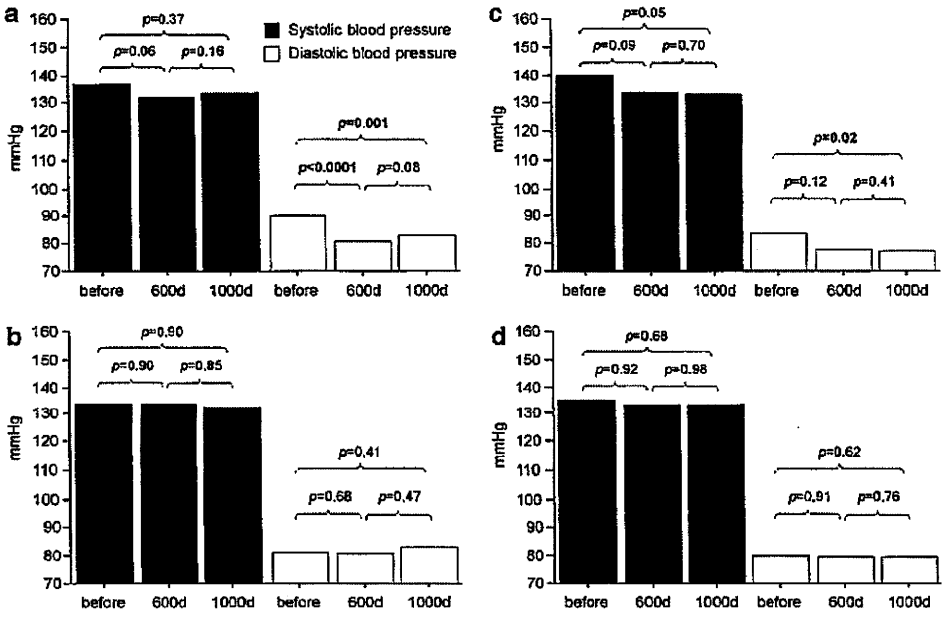

Figure 2 Mean systolic and diastolic blood pressure values in patients aged <60 years with good compliance (n=32, (a)), aged <60 years with poor compliance (n=14, (b)), aged ≥60 years with good compliance (n=29, (c)) and aged ≥60 years with poor compliance (n=17, (d)) before nasal continuous positive airway pressure (nCPAP) treatment and after 600 and 1000 days of nCPAP treatment.

having poor compliance. Systolic BP did not change in any group (Figure 2). The degree of decrease in diastolic BP did not differ significantly between the older and younger groups with good compliance (P=0.27, before 600 days; P=0.87, before 1000 days).

DISCUSSION

This study showed that long-term nCPAP treatment lowered diastolic BP not only in middle-aged OSA patients but also in elderly OSA patients. To achieve a significant effect on diastolic BP, we required an average daily usage of nCPAP for 3 h, which was consistent with our previous report.[7] With that level of compliance, diastolic BP in elderly hypertensive OSA patients decreased significantly. However, as noted above, nCPAP usage time *per se* did not significantly correlate with the degree of decrease in diastolic BP. It has been reported that mean usage time of nCPAP was positively but not significantly correlated with mean net change in BP (P=0.13).[10] Thus, the effects of nCPAP treatment would be affected by not only usage time but also other factors such as the arousal index or daily sleep time. Several studies have explored the impact of nCPAP treatment on BP.[4–6] These studies included older adults, but uncertainty has remained regarding long-term effects of nCPAP treatment in elderly hypertensive OSA patients, likely attributable to the level of severity of OSA, sample size and duration of intervention. Although it was reported that OSA might not influence BP in elderly patients,[15] the present study clearly showed for the first time that long-term nCPAP treatment with good compliance lowered diastolic BP in elderly OSA patients.

The combination of systolic/diastolic hypertension is common in middle-aged hypertensive patients, whereas isolated systolic hypertension is predominately a disease of elderly hypertensive patients.[11] Systolic/diastolic hypertension represents multiple etiologic factors, with evidence to suggest that the sympathetic nervous system is an important mediator.[12] Meanwhile, isolated systolic hypertension results from age-dependent arterial wall thickening and stiffness and endothelial dysfunction.[13] Activation of the sympathetic nervous system is an important mechanism linking OSA to hypertension,[21,22] and nCPAP attenuates the increase in sympathetic activity in OSA.[14] Therefore, the potential mechanisms linking OSA to hypertension and the effectiveness of nCPAP treatment may be different in elderly patients than in middle-aged patients.

In this study, long-term nCPAP treatment lowered diastolic BP but not systolic BP. Although some studies have reported a decrease in systolic and diastolic BP, most of the trials in those meta-analyses were composed of mainly normotensive patients.[9,10] In the present study, approximately three quarters (73.9%) of the participants had hypertension and nearly half of the participants were taking antihypertensive medication. From our previous study,[7] both systolic and diastolic BP were lowered by a daily average of 3 h of nCPAP treatment in hypertensive OSA patients who were not taking any antihypertensive medication, while nCPAP treatment lowered diastolic BP alone in such patients being administered antihypertensive medications. This difference in study population might affect the results. In addition, Davies *et al*.[23] reported that, compared with closely matched control subjects, patients with OSA had increased ambulatory diastolic BP during both day and night but had increased systolic BP only at night. Because we did not perform ambulatory BP monitoring, we might have overlooked a decrease in systolic BP at night. Therefore, OSA may predominantly raise diastolic BP in hypertensive OSA patients.

This study also showed that long-term sufficient nCPAP usage, that is, 3 h or longer daily, is effective in lowering BP in both middle-aged and elderly hypertensive OSA patients and that the degree of decrease in diastolic BP did not differ significantly between age groups. Therefore, differences in etiologies of hypertension between middle-aged and elderly OSA patients might not be great enough to create obvious differences in effectiveness of nCPAP. However, statistical significance in the drop in diastolic BP was not observed at 600 days but was seen at 1000 days of nCPAP treatment in elderly patients. Although we cannot rule out the possibility that the sample size was insufficient to confirm a significant decrease in diastolic BP at 600

days, diastolic BP of the elderly OSA patients might have gradually decreased through nCPAP treatment and, due to age-related differences in the mechanisms linking OSA to hypertension, an additional investment of time might be required to see significant decreases in BP in elderly patients. Although we did not evaluate sympathetic nerve activity or arterial compliance in the participants in this study, some reversible factors may have been present that could be gradually improved by nCPAP even in elderly hypertensive OSA patients. For instance, some studies[24,25] have shown that BP decreased after nCPAP treatment in patients with heart failure and OSA, suggesting that decreased cardiac load may also contribute to the decrease in BP observed in elderly patients. Although we did not monitor cardiac function of the participants using echocardiography before and during the study, there might be more patients with heart failure among the older participants because a significantly greater number of the older participants were taking diuretics than were the younger participants (Table 1).

There is a higher prevalence of SDB in the elderly than in middle-aged adults.[26,27] But elderly individuals with OSA experience less daytime sleepiness than younger patients with this disorder,[28,29] and partially as a result they are less motivated to be adherent to nCPAP treatment.[28] Moreover, a randomized sham-placebo-controlled, crossover study[30] showed no significant fall in 24-h mean BP in patients with nonhypersomnolent hypertensive OSA after 1 month of nCPAP treatment. Also in the present study, the mean score on the Epworth Sleepiness Scale in the elderly OSA patients was 8.84 (6.9–10.8), which was lower than that of middle-aged patients although it was not significant. However, long-term nCPAP treatment lowered diastolic BP in elderly OSA patients with good compliance despite a lack of hypersomnolence. In addition, a prospective cohort study showed a significantly high mortality risk from untreated SDB, irrespective of symptoms of sleepiness.[31] Therefore, it is important to find occult OSA in the elderly and to treat it with nCPAP.

Haas *et al.*[15] showed that SDB was associated with systolic/diastolic hypertension in persons aged 40–59 years, but that there was neither a significant nor consistent relationship between hypertension and SDB among those more than 60 years of age. But results of the present study showed a significant diastolic BP decrease in both those who were $\geqslant 60$ and <60 years of age, and the degrees of decrease in diastolic BP were not significantly different between the two groups. It might be thought that the difference in severity of OSA in the participants between the two studies affected the results. The AHI of each OSA patient was 20 or more and the mean AHI of the patients aged $\geqslant 60$ years was 38.5 (33.8–43.2) in this study, whereas a relatively low proportion (20.7%) of participants aged $\geqslant 60$ years had at least moderate SDB (AHI $\geqslant 15$) in the study by Haas *et al.*

The main limitation of this study was its retrospective uncontrolled design. However, conducting a prospective controlled study over such a long time period presents an ethical dilemma, because long-standing uncontrolled hypertension could affect the patients' prognosis through possible cardiovascular events. The second point was the difference in BMI and AHI between OSA patients $\geqslant 60$ and <60 years of age. The degree of response to nCPAP treatment may depend on the severity of OSA. However, the degree of decrease in diastolic BP did not significantly correlate with BMI or the degree of improvement in AHI. Third, although the number of participants classified as hypertensive was not statistically different between the two age groups, a significantly greater number of the older participants were taking three or more antihypertensive medications than the younger participants. Therefore, there might be more patients with difficult-to-control hypertension that responded to nCPAP treatment among the older patients. The role of nCPAP in patients with difficult-to-control hypertension has been analyzed.[32,33] Both studies found a significant decrease in systolic BP, particularly at night after several months of nCPAP treatment, whereas the decrease in diastolic BP was not statistically significant either at night or during the day. However, we found a significant decrease in diastolic but not in systolic BP during daytime. Although differences in the mechanisms whereby nCPAP treatment lowered BP of the participants between these studies and our study are unclear, the decrease in diastolic BP in our present study may not be related to difficult-to-control hypertension. Fourth, we did not use the latest American Academy of Sleep Medicine manual for the scoring of sleep and associated events and hypopnea was measured by thermistors because all the participants of this study had undergone diagnostic polysomnography before 2006. Therefore, if the latest criteria and an airflow pressure sensor were used, the hypopnea index might have differed from that shown presently. However, although these differences could affect the data on the AHI of the participants they would not have influenced the effectiveness of sufficient nCPAP treatment for BP. Finally, we did not perform ambulatory BP monitoring. It is well known that ambulatory BP monitoring is a better predictor of cardiovascular events than office BP measurements.[34,35] Therefore, to estimate usual BP and minimize the difference in clinical implications between the office BP and ambulatory BP, we averaged the second and third of three consecutive measurements as the BP value for each of the 3 monthly visits that are usual for nCPAP patients. Then the BP values for the two checkpoints (600 and 1000 days) were derived from the mean value of 3 monthly clinic visits closest to each of the two checkpoint periods. Although randomized controlled trials have examined the effect of nCPAP treatment for OSA on BP using office BP measurements,[36,37] further study is needed to confirm our findings by ambulatory BP monitoring.

Treatment of hypertension is critically important for the care of older adults who are particularly vulnerable to cardiovascular events. From large prospective studies, a BP fall of 3.3 mm Hg would be expected to be associated with a 20% stroke and 15% coronary heart disease event risk reduction.[38] Thus, the BP falls observed with nCPAP treatment represent the potential for significant reductions in vascular risk. The current study results showed that long-term nCPAP treatment lowered diastolic BP in not only middle-aged subjects with OSA but also in elderly patients with OSA. To achieve a significant effect on diastolic BP, daily average usage of nCPAP for 3 h is needed. It is noteworthy that elderly OSA patients used nCPAP treatment over the long-term with good compliance.

Hypertension has numerous etiologies, especially in the elderly. In addition, elderly OSA patients often lack typical clinical symptoms. Even in elderly hypertensive patients, we should consider the possibility of underlying OSA, which is treatable with sufficient nCPAP treatment.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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INTERNAL MEDICINE

ORIGINAL ARTICLE

Noninvasive Ventilation Improves the Outcome of Pulmonary Complications after Liver Resection

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Abstract

Background Pulmonary complications are associated with increased mortality after liver resection. Although noninvasive ventilation (NIV) has proved to be an effective treatment for respiratory failure after abdominal surgery, including organ transplantation, its efficacy for pulmonary complications following liver resection per se has not been reported. The aim of this retrospective study was to investigate the effects of NIV in patients with postoperative pulmonary complications after liver resection.

Methods A retrospective single center study. Between April 2002 and March 2005, we used NIV in 16 patients who met the criteria for NIV after liver resection: respiratory failure and/or a massive atelectasis (NIV group). We also reviewed data on 10 patients who underwent liver resection from April 1999 to March 2002, and met the criteria for NIV after the operation and received conventional treatment (non-NIV group).

Results Respiratory-cause mortality was significantly lower in NIV group than in non-NIV group (0.0% vs. 40.0%, p=0.007), and all-cause mortality tended to be lower in NIV group (18.8% vs. 50.0%, p=0.100). After NIV treatment for 24 hours, the PaO_2/FiO_2 ratio and $PaCO_2$ were improved significantly but no significant improvement was noted in non-NIV group. Rate of reintubation was significantly lower in NIV group (12.5% vs. 50.0%, p=0.040). NIV was tolerated in all 16 NIV group patients, and no severe NIV-related complications were observed.

Conclusion NIV is effective in patients with respiratory failure and/or massive atelectasis after liver resection.

Key words: noninvasive ventilation, respiratory failure, massive atelectasis, liver resection

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Introduction

Abdominal surgery is most often followed by diaphragmatic dysfunction and a marked decrease in vital capacity, which often leads to respiratory failure or massive atelectasis (1). In particular, the surgical procedures involved in liver resection damage the function of the right diaphragm. Pulmonary complications occur in as many as 22.5 to 30.0% of patients undergoing liver resection and are associated with a prolonged hospital stay and increased postoperative mortality (2, 3).

Noninvasive ventilation (NIV) has proved effective in patients with acute exacerbation of chronic obstructive pulmonary disease (COPD), hypercapnic cardiogenic pulmonary edema or acute respiratory failure (4-6). NIV has been shown to be an effective treatment for postoperative respiratory failure after solid organ transplantation or abdominal surgery (7, 10). However, there have been no detailed reports on the use of NIV following liver resection.

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Since April 2002, we have used NIV in patients with respiratory failure and/or massive atelectasis after liver resection. We also have used NIV after liver transplantation and previously reported its efficacy in hepatic posttransplant pediatric recipients (11). Based on these experiences, we hypothesized that NIV improves the clinical course and outcome of patients with respiratory failure and/or massive atelectasis after liver resection compared with conventional treatment. Therefore, we retrospectively investigated the efficacy of NIV following liver resection.

Patients and Methods

Study design and populations

This retrospective study was performed in a single university hospital. Following the approval of the Ethics Committee of Kyoto University, potential subjects were identified by search of an operation database. Clinical data were abstracted by reviewing medical records.

Since April 2002, NIV has been used in patients who met one of the following criteria after liver resection: 1) respiratory failure and/or 2) massive atelectasis. Respiratory failure was defined as hypoxemia with a PaO_2/FiO_2 ratio <300 mmHg. Massive atelectasis was defined as the presence of an obstruction extending beyond one lung lobe detected by chest X-ray or computed tomography. Informed consent was obtained from all patients or their families prior to NIV treatment.

Of the 280 consecutive patients who underwent liver resection at Kyoto University Hospital between April 2002 and March 2005, 16 met the criteria for NIV after the operation and all were supported by NIV (NIV group). We also reviewed data on 10 patients who met the criteria for NIV out of the 273 consecutive patients who underwent liver resection between April 1999 and March 2002, a period during which NIV had not been used after liver resection (non-NIV group).

Preoperative patient characteristics, operative procedures, postoperative course and outcome were compared between the two groups. Primary endpoints were all-cause mortality in hospital, respiratory-cause mortality in hospital, and reintubation. Secondary endpoints were length of intensive care unit (ICU) stay and hospital stay in survivors and the PaO_2/FiO_2 ratio and $PaCO_2$ after NIV treatment for 24 hours.

Conventional treatment without NIV

Patients in non-NIV group received oxygen supplementation to achieve percutaneous oxygen saturation (SpO_2) above 90%, inhaled bronchodilators (β-adrenergic agonists), sufficient analgesia with morphine via continuous epidural injection, and pulmonary physiotherapy until oxygenation and clinical status improved.

Protocol for NIV

For NIV, bilevel positive airway pressure (bilevel PAP) devices (VPAP-II, ResMed, Bella Vista, NSW, Australia) were used. A full-face mask or a nasal mask was used (ResMed). The initial mode was the spontaneous/timed (S/T) mode in all patients. An experienced respiratory clinician first secured the mask with the help of other doctors. After the mask had been appropriately placed, the initial level of pressure support (difference between inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP): IPAP - EPAP) was given at 2 to 8 cmH_2O, and was increased gradually by 1 to 2 cmH_2O until the respiratory distress decreased. Supplementary oxygen was administered via a face mask as required. Initially, NIV was continued without interruption until oxygenation and clinical status had improved and was used as needed after the initial improvement as long as necessary. NIV was discontinued when respiratory failure occurred or massive atelectasis resolved.

FiO_2 was calculated in patients supported by NIV, using the approximation formula. For patients who received supplemental oxygen via a face mask, the assumed FiO_2 was calculated as previously described by Jeffrey and Warren, although their study was, strictly speaking, not for NIV masks but oxygen masks with and without the Venturi attachment (12).

Criteria for extubation

Criteria for postoperative extubation had been unchanged in NIV and non-NIV groups. Extubation was considered in operating room when 1) vital signs were stable; 2) spontaneous breathing was sufficient (tidal volume >200 mL and $SpO_2 \geq 95\%$ at $FiO_2 \leq 0.40$). When extubation failed, invasive mechanical ventilation was continued in ICU. In ICU, extubation was considered when 1) vital signs were stable and $SpO_2 \geq 95\%$ at $FiO_2 \leq 0.40$; 2) underlying disease and its complication were stable; 3) mechanical ventilation support was minimal (pressure support ≤ 6 cmH_2O with positive end-expiratory pressure (PEEP) ≤ 4 cmH_2O); 4) spontaneous breathing was sufficient.

Criteria for reintubation

In both groups, invasive mechanical ventilation (MV) with reintubation was required when any of the following major criteria or three or more of the minor criteria were met. Major criteria were respiratory arrest, respiratory pauses with loss of consciousness or gasping respiration, encephalopathy, and cardiovascular instability and minor criteria were an increase in the respiratory rate or $PaCO_2$ by 20% or more, a decrease in PaO_2 compared with that at the beginning of NIV, the development of conditions in which endotracheal intubation was needed (e.g., difficulty in removing airway secretions), or intolerance to NIV mask due to discomfort.

Statistical analysis

Statistical analysis was performed using SPSS version 11.0.1 (SPSS, Inc., Chicago, IL, USA). Data are expressed as means ± SD. Differences in variables between the two

Table 1. Preoperative Patient Characteristics and Operative Procedure

	NIV	non-NIV	p value
Number of subjects	16	10	
Age	66.5 ± 14.6	61.7 ± 11.5	0.15
Sex, Male/Female	13 / 3	8 / 2	0.94
BMI	23.7 ± 3.2	25.3 ± 3.2	0.41
Pulmonary function test results			
FVC (L)	2.92 ± 0.71	3.26 ± 0.51	0.17
%VC (%)	95.3 ± 17.0	106.5 ± 15.3	0.15
$FEV_{1.0}$ (L)	2.01 ± 0.66	2.44 ± 0.40	0.06
$\%FEV_{1.0}$ (%)	70.3 ± 15.7	73.9 ± 8.6	0.36
PaO_2 (room air, mmHg)	83.2 ± 8.5	79.6 ± 12.9	0.46
$PaCO_2$ (room air, mmHg)	39.7 ± 4.0	43.1 ± 3.4	0.13
Diagnosis			
HCC/CCC/metastasis or other	12/ 2/ 2	9/ 0/ 1	
Child' s score	5.7 ± 1.1	6.4 ± 1.4	0.12
Child's classification A/B/C	13/ 3/ 0	6/ 4/ 0	
MELD score	6.74 ± 3.82	9.48 ± 4.43	0.13
Surgical procedure*			
Limited resection	4	2	
Sectorectomy	3	2	
Lobectomy or more	9	6	
Operation time (min)	517.6 ± 194.1	540.5 ± 234.2	>0.99
Blood loss (mL)	2811.5 ± 2002.7	8515.1 ± 9539.9	0.07
Transfusion (mL)	2297.5 ± 2118	5038 ± 7080.2	0.60
Extubation in operating room/ICU	11 / 5	4 / 6	0.16
Postoperative intubation duration (days)	1.1 ± 3.0	1.4 ± 2.7	0.25

Data are shown as means ± SD.
* Types of surgical procedures are based on the Couinaud anatomical classification of the liver.
Abbreviations: BMI, body mass index; FVC, forced vital capacity; %VC, percent vital capacity; FEV1.0, forced expiratory volume in 1 second; HCC, hepatocellular carcinoma; CCC, cholangiocellular carcinoma; MELD score, Model for End-Stage Liver Disease score; ICU, intensive care unit.

groups were assessed using a Mann-Whitney *U* test, with $p< 0.05$ indicating statistical significance.

Results

Preoperative patient characteristics and operative procedures are shown in Table 1. These parameters did not differ significantly between NIV and non-NIV groups. Anesthetic procedures and opiate usage also were similar in both groups (data not shown).

Patient characteristics at the point when inclusion criteria for NIV were fulfilled and outcome in each group are summarized in Table 2. There were no significant differences in the APACH II score, PaO_2/FiO_2 ratio and $PaCO_2$ at the time of fulfillment of the inclusion criteria between two groups. There were also no significant differences in the prevalence of massive atelectasis or respiratory infection.

In the NIV group, mean IPAP and EPAP levels were 8.9± 2.2 cmH_2O and 4.3±0.6 cmH_2O, respectively. NIV was well tolerated by all patients. Mean NIV usage time during the initial 24 hours was 19.8±6.7 hours and ten of 16 patients (62.5%) received NIV all day long on the first day. Mean treatment period with NIV was 6.4±6.1 days (range, 1-23 days). No severe complications, including pneumothorax and aspiration pneumonia, occurred.

After treatment for 24 hours, the PaO_2/FiO_2 ratio and $PaCO_2$ had improved significantly in NIV group but not in non-NIV group (Fig. 1). In NIV group, respiratory rates did not change significantly after treatment for 24 hours (17.2± 3.3 breaths per minute vs. 16.7±3.5, p=0.4722). Respiratory-cause mortality was significantly lower (0.0% vs. 40.0%, p= 0.007) and all-cause mortality tended to be lower (18.8% vs. 50.0%, p=0.10) in the NIV group than the non-NIV group. In NIV group, three patients died: one due to hepatic infarction, one due to non-respiratory sepsis and the third due to rupture of esophageal varices. In non-NIV group, five patients died: three from acute respiratory distress syndrome and one each from cardiac shock and septic shock. Reintubation rates were significantly lower in NIV group than in non-NIV group (12.5% vs 50.0%, p=0.04). Of two reincubated patients in NIV group, one was reincubated due to pneumonia and another to non-respiratory sepsis. All seven reintubated patients died (Fig. 2). There were no significant differences in ICU or hospital stay in survivors between two

Table 2. Patient Characteristics at Point Inclusion Criteria were Met and Outcome

	NIV			non-NIV			p value
Number of subjects	16			10			
Inclusion day (POD)	5.9	±	8.7	6.5	±	11.1	0.49
Reasons for inclusion*							
Respiratory failure	14			9			0.30
Massive atelectasis	4			3			0,78
Respiratory infection	1			0			0,43
Before treatment							
APACH II	11.0	±	5.3	13.5	±	4.6	0.31
PaO_2/FiO_2 (mmHg)	187.3	±	97.8	141.6	±	75.2	0.11
$PaCO_2$ (mmHg)	44.7	±	6.1	45.6	±	8.1	0.79
After treatment for 24 hours							
PaO_2/FiO_2 (mmHg)	300.6	±	74,7	155.2	±	83.4	0.001
$PaCO_2$ (mmHg)	40.9	±	4.1	40.5	±	7.3	0.69
Outcome							
All-cause mortality in hospital (%)	18.8			50.0			0.10
Respiratory-cause mortality in hospital (%)	0.0			40.0			0.007
Reintubation (%)	12.5			50.0			0.04
ICU stay among survivors (days)	2.8	±	4.8	0.8	±	1.1	0.51
Hospital stay (days)	40.0	±	24.6	32.4	±	9.9	0.66

Data are shown as means ± SD.
* Some patients met both criteria.
Abbreviations: APACH II, Acute Physiology and Chronic Health Evaluation.

groups.

Five patients (31.3%) in NIV group were extubated in ICU, with three of these patients starting NIV immediately after extubation. In non-NIV group, six (60%) were extubated in the ICU. The duration of postoperative intubation was 3.4±4.8 days in NIV-group and 2.3±3.3 days in non-NIV group. Of those extubated in ICU, five of six (83.3%) in non-NIV group died, while only one of five (20%) in NIV group died. That death was due to a non-respiratory cause. All of three patients who were extubated in ICU and who received subsequent NIV were discharged alive.

No patient received enteral nutrition in either group and no apparent aspiration or aspiration pneumonia was observed.

Discussion

This retrospective study showed that application of NIV after liver resection rapidly improved postoperative respiratory failure, resulting in a low rate of reintubation, while results with oxygen supplementation, drug therapy or physiotherapy were not as efficacious. NIV was tolerated for a long period on the initial day and subsequently continued as required. Moreover, respiratory-cause mortality was significantly lower than that with conventional treatment. Our results indicate that NIV is an effective treatment for postoperative respiratory failure and/or a massive atelectasis after liver resection.

NIV has proved to be an effective treatment for acute respiratory failure in patients undergoing solid organ transplantation, including liver transplantation (7). It also has been shown that NIV reduces the length of ICU stays, mortality and the incidence of endotracheal intubation in patients after abdominal surgery (10). However, there has been no detailed examination of its effects on postoperative pulmonary complications and mortality after liver resection. To our knowledge, this is the first report that showed the efficacy of postoperative NIV following liver resection *per se*.

Our data analysis showed that NIV was remarkably efficacious in patients extubated in ICU in terms of decreasing respiratory-cause mortality. Patients extubated in ICU are considered to have been exposed to more severe operative stress than those extubated in operating room. Thus, NIV may have contributed to the rescue of higher-risk patients. Moreover, all of the patients who received NIV immediately after extubation survived. Early or subsequent induction of NIV should be considered after extubation, particularly in ICU.

The rate of reintubation was reduced in NIV group in comparison with that in non-NIV group. MV with endotracheal intubation has been associated with a higher risk of infection and increased mortality in patients undergoing abdominal surgery (8, 13). In patients with COPD, Girou et al found that NIV reduced the number of ventilator-related complications and the rate of nosocomial pneumonia (5). In the present study, the rate of mortality among reintubated patients was extremely high. We suppose that the avoidance of reintubation by NIV may have contributed to the lower

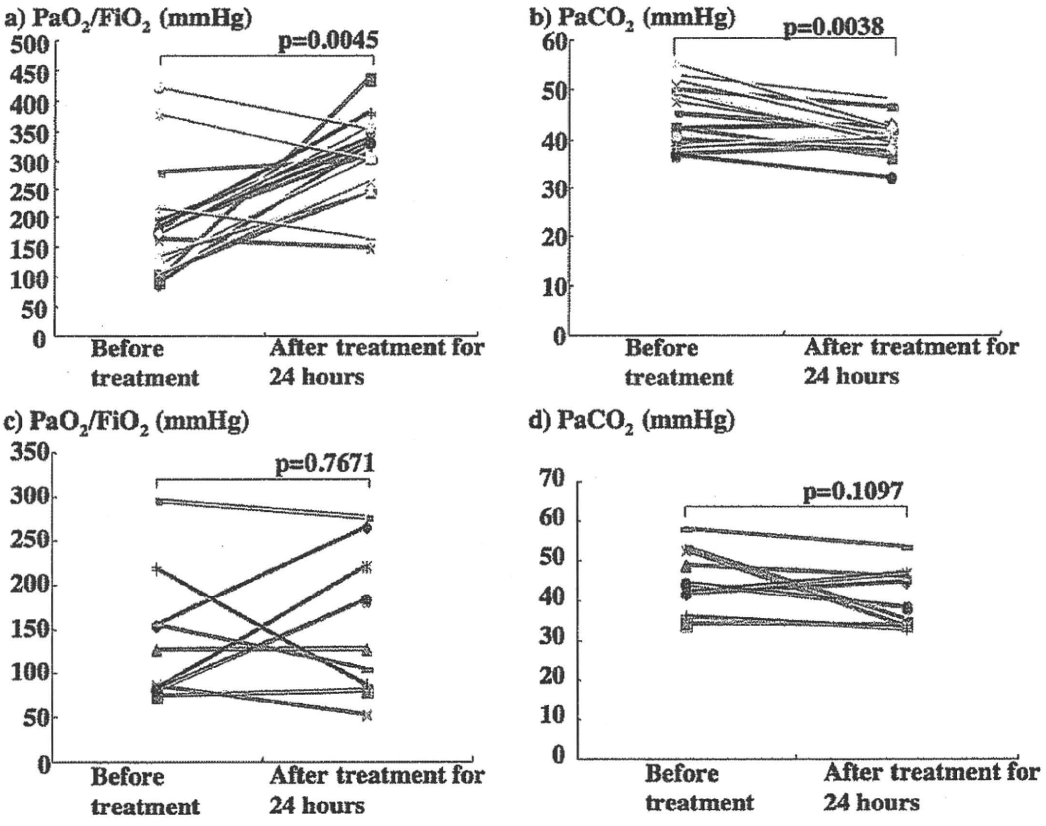

Figure 1. Changes in the PaO_2 FiO_2 ratio and $PaCO_2$ after treatment for 24 hours in the NIV (a, b) and non-NIV (c, d) groups.

mortality in NIV group.

Postoperative atelectasis induces lung injury and predisposes patients to developing pneumonia, especially when it persists longer than 72 hours (14, 15). NIV is well known to be effective in the treatment of atelectasis (11). Among the patients in the present study, it is possible that the prevention of and/or rapid resolution of atelectasis by NIV could have avoided the development of more severe complications and reduced respiratory-cause mortality. Perceived complications and discomfort following the use of NIV have limited its use in patients undergoing abdominal surgery. In the present study no severe adverse events, such as aspiration or gastric distention, were observed. Jaber et al also showed that NIV could be used after esophageal or gastrointestinal surgery without adverse events (10). We suppose that application of NIV is more favorable after liver resection than after other abdominal surgeries, as liver resection does not usually require the manipulation of the gastrointestinal tract. All patients in the NIV group tolerated well the use of NIV via a mask. Feasibility of NIV was indicated by the fact NIV usage time on the first day and treatment period with NIV were enough long. Skillful respiratory care might ensure the safe and comfortable use of NIV after surgery.

The present study has some limitations. First, it is a retrospective single-center study with a small number of subjects. Certainly a large prospective study could provide conclusive evidence of the efficacy of NIV after liver resection. However, such a randomized controlled trial may be difficult because NIV has been widely used in postoperative critical care settings. Rather, in a further multi-center randomized controlled trial, it would be more worth determining whether the combination of earlier extubation and subsequent induction of NIV can decrease postoperative complications or improve survival. Second, the present study compared treatment group with historical control. Although there were no drastic changes in surgical procedures or postoperative management except for NIV between two groups, historical control bias cannot be denied absolutely. In addition, no patient received enteral nutrition in either group. While this nutritional strategy could have contributed to the prevention of aspiration during NIV, early induction of enteral nutrition is the current standard in postoperative management. Third, FiO_2 during NIV was only assumed on the basis of a simple oxygen mask study, without direct measurement in a NIV mask.

In conclusion, although this was a retrospective study, NIV for respiratory failure and/or massive atelectasis was found to be more useful after liver resection than conventional treatment. It was shown that NIV could improve the outcome of liver resection by reducing respiratory-cause

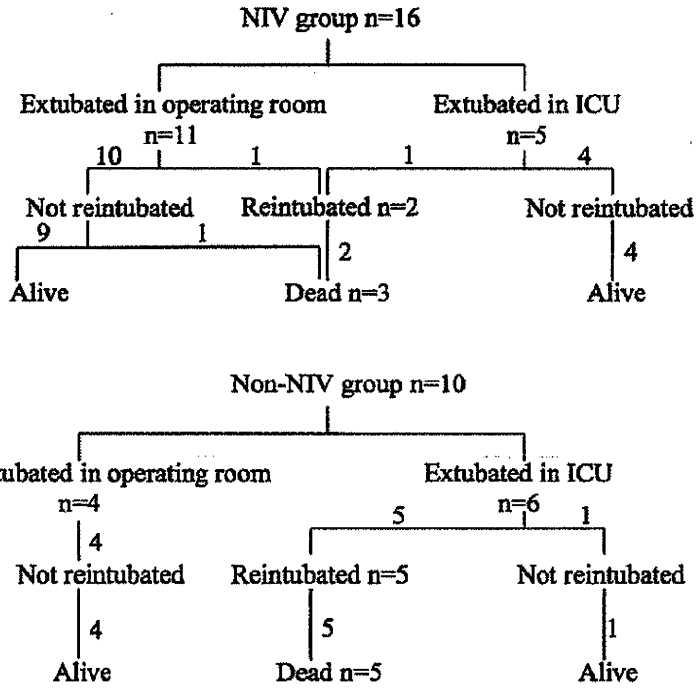

Figure 2. Results in patients who received noninvasive ventilation (NIV group) and those who did not receive noninvasive ventilation (non-NIV group) after liver resection.

mortality. A further clinical trial investigating the efficacy of subsequent NIV after extubation should be considered to establish improved criteria for application of NIV after liver resection.

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Contributions of Each Author: MN had primary responsibility for the development of the research question, performed all data analysis, and wrote the manuscript. EH provided guidance with the development of the research question and the interpretation of the research results, and made editorial comments on the manuscript. KT, TH, TO, AN, TT, IK and MN provided editorial comments on the manuscript. KC offered guidance on the interpretation of the research results and editorial comments on the manuscript.

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INTERNAL MEDICINE

CASE REPORT

Avoidance of Reintubation by Using Sedation during Noninvasive Positive Pressure Ventilation in a 3-Month-Old Infant with Postoperative Respiratory Failure

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Abstract

Maintaining alertness during noninvasive positive pressure ventilation (NPPV) is important, but there are no established guidelines for the use of sedation. We report our first experience of an infant with post-surgical vocal cord paralysis, severe stridor and breathing difficulties, who was reintubated after NPPV treatment without sedation, but who avoided a third reintubation through the use of sedation with the second NPPV treatment. NPPV treatment with the proper sedation can improve blood gas data in those patients with severe dyspnea, which can occur during respiratory care in several situations, and can affect not only infants, but also adults including elderly patients.

Key words: cardiovascular surgery, noninvasive ventilation, sedation, vocal cord paralysis

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Case Report

A 3-month-old boy with trisomy 21 and coarctation of the aorta (COA), cardiac atrial (ASD) and ventricular septal defect (VSD), patent ductus arteriosis (PDA) and severe secondary pulmonary hypertension (height, 48.4 cm [-2.8 SD]; weight, 2.9 kg [-3.0 SD]; human atrial natriuretic peptide level, 261.0 pg/mL; human brain natriuretic peptide level, 192.6 pg/mL) underwent cardiovascular repair surgery (that is, COA repair, closure of ASD and VSD, and PDA ligation) and was transferred postoperatively to the intensive care unit with conventional mechanical ventilation. Chest X-ray showed left upper lobar collapse. Flexible optical bronchoscopy (FOB) revealed extrabronchial compression causing mild obstruction in the left main bronchus, which was thought to have resulted from the aorta repair.

On postoperative day (POD) 7, the endotracheal tube was removed, followed by slight stridor and gradual arterial carbon dioxide retention (Fig. 1). On POD 10, percutaneous oxygen saturation fell to 85% while he was breathing 12 L/minute oxygen via a face mask. He exhibited respiratory distress and loud stridor and NPPV was immediately started with 12 L/minute oxygen in timed mode (30 breaths/minute, inspiratory positive airway pressure (IPAP) 11.0 cm water, expiratory positive airway pressure (EPAP) 7.0 cm water) with a nasal mask of infant size (ResMed, Bella Vista NSW, Australia). Oxygen saturation remained around 93% and otolaryngeal examination revealed unilateral vocal cord paralysis (UVCP). Tracheal intubation was repeated and conventional mechanical ventilation applied. A repeat FOB on POD 15 showed only mild stenosis in the left main bronchus; the left upper lobar collapse improved, although remained during mechanical ventilation (Fig. 2a). On POD 17

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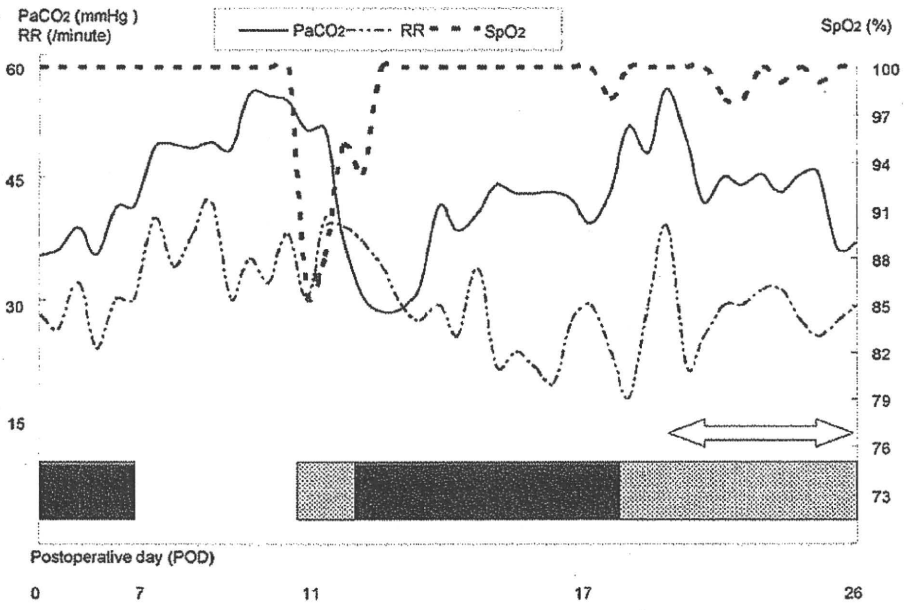

Figure 1. Time course of percutaneous oxygen saturation (SpO_2), partial pressure of arterial carbon dioxide ($PaCO_2$) and respiratory rate (RR). Note that after the second extubation, the RR rose and hypercapnea developed although NPPV without sedation was administered immediately. NPPV alone did not improve the patient's condition. However, after sedation was administered, the RR was quite stabilized but hypercapnea did not worsen (black bar, duration of mechanical ventilation; small dots bar, duration of noninvasive mechanical ventilation (NPPV); arrow, duration of sedation). Abbreviation: NPPV: noninvasive positive pressure ventilation, $PaCO_2$: partial pressure of arterial carbon dioxide, POD: post-operative day, RR: respiratory rate, SpO_2: percutaneous oxygen saturation

after endotracheal tube removal, NPPV was applied immediately to prevent postextubation failure in timed mode (the same setting as above). Within a few hours, severe respiratory distress and stridor developed. Asynchrony was apparent between NPPV and the patient when awake. As we thought that reintubation might worsen the UVCP and that the increased work of breathing was causing stridor and the worsening oxygenation, intravenous midazoram (0.18 mg/kg/h) and chlorpromazine (0.3 mg/kg/h) were administered with NPPV. The level of sedation was determined by the clinical assessment of a decrease in the excessive effort of breathing. Good synchronization with the NPPV instrument was achieved, the stridor resolved and his condition stabilized. Atelectasis disappeared on chest X-ray (Fig. 2b). NPPV was shifted toward nocturnal use on POD 28 and weaning from NPPV occurred on POD 42 (Fig. 2c). Vocal cord movement was normal on otolaryngeal examination on POD 64. The patient was discharged from hospital on POD 67.

Discussion

The safety of sedation in patients receiving NPPV treatment, who do not tolerate NPPV well, has not been established definitively. Because of this, in the past in our hospital, we have not sedated patients experiencing severe respiratory issues, including adults, the elderly, children and infants under 1 year of age (1-4). In practice, however, sedatives are occasionally administered with care to infant cases experiencing severe agitation or anxiety (5-7). However, in Asian countries (including Japan) there have been no reports of the use of sedative drugs during NPPV treatment either in children or in adult patients. Recently, the result of a survey of sedation practices during NPPV treatment for acute respiratory failure has been reported (8). In this survey, sedation during NPPV treatment was administered to patients with COPD exacerbation, cardiogenic pulmonary edema, do-not-intubate, extubation failure, neuromuscular disease, obesity, hypoventilation, and others. However, Australia/Asia accounted for only 3.3% of the total responders. In addition, we could find no report in the English abstracts of papers published from the Asian region, including Japan, on the use of sedative drugs during NPPV treatment either in pediatric or adult cases. Thus, further investigation is required worldwide, including the Asian region.

In the present case, vocal cord stenosis due to unilateral vocal cord paralysis might have generated highly negative pressure, which based on Bernoulli's principle, might have possibly exacerbated vocal cord stenosis and severely increased the work of breathing (9). The benefits of sedation were partly due to relief from excessive respiratory effort that might increase vocal cord stenosis; therefore, NPPV