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ORIGINAL ARTICLE

The use of non-invasive ventilation for life-threatening asthma attacks: Changes in the need for intubation

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ABSTRACT

Background and objective: **Although non-invasive ventilation (NIV) has been shown to be effective in a wide variety of respiratory diseases, its role in severe asthma attacks remains uncertain. The aim of this study was to clarify the effectiveness of NIV in patients experiencing severe attacks of asthma.**

Methods: **A retrospective cohort study was performed, comparing the periods November 1999–October 2003 (pre-introduction of NIV) and November 2004–October 2008 (post-introduction of NIV). The data and clinical outcomes for patients who experienced severe attacks of asthma, and who fulfilled the inclusion criteria, were retrieved and compared.**

Results: **Fifty events (48 patients) from the pre-NIV period and 57 events (54 patients) from the post-NIV period, which required hospitalization, were included in the analysis. Nine of the 50 pre-NIV events (mean PaO_2/fraction of inspired O_2 (FiO_2) 241 ± 161; $PaCO_2$ 79 ± 40) were treated primarily by endotracheal intubation (ETI), while 17 of the 57 post-NIV events (PaO_2/FiO_2 197 ± 132, $P = 0.39$; $PaCO_2$ 77 ± 30, $P = 0.95$) were treated primarily by NIV. The rate of ETI decreased in the post-NIV period (2/57 (3.5%) vs 9/50 (18%), $P = 0.01$). NIV was started earlier than mechanical ventilation (MV) with ETI (mean time interval between arrival and start of MV 171.7 ± 217.9 min vs 38.5 ± 113.8 min for NIV, $P < 0.05$). In the post-NIV cohort, there was a trend towards a reduction in the duration of MV with ETI or NIV (36.9 ± 38.4 h vs 20.3 ± 35.8 h, $P = 0.09$), and hospital stay was shortened (12.6 ± 4.2 vs 8.4 ± 2.8 days, $P < 0.01$). No deaths occurred during this period as a consequence of asthma attacks.**

Conclusions: **The need for ETI in patients with severe attacks of asthma was decreased after introduction of NIV. The ready availability of NIV enabled the rapid commencement of MV and may decrease the need for ETI. NIV is an acceptable and useful method of stabilizing patients experiencing severe attacks of asthma.**

SUMMARY AT A GLANCE

The effectiveness of non-invasive ventilation (NIV) in patients with severe attacks of asthma was assessed in a retrospective cohort study comparing data from before and after the introduction of NIV. Introduction of NIV was associated with a reduction in the need for intubation in patients with severe attacks of asthma.

Key words: asthma, asthma attack, intubation, mechanical ventilation, non-invasive ventilation.

INTRODUCTION

Over the past 20 years, probably the most important advance in the field of mechanical ventilation (MV) has been the development of non-invasive ventilation (NIV) as a tool for the management of respiratory failure. NIV has been shown to be effective in a wide variety of clinical settings, including acute exacerbations of COPD (AE-COPD) and cardiogenic pulmonary oedema.[1–4] However, the role of NIV in patients experiencing asthma attacks remains controversial due to insufficient evidence.[5,6] In particular, no clinical trials have been carried out in severe and life-threatening asthma attacks. The use of NIV for severe asthma attacks appears to be promising, as NIV reduces dyspnoea by decreasing the workload of fatigued respiratory muscles, and improves gas exchange by enhancing ventilation.[7–9]

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Since the full introduction of NIV at our hospital in 2004, we have been evaluating the use of NIV, not only for AE-COPD, but also for other conditions involving acute respiratory failure, including asthma attacks.[10] Although nine patients who underwent treatment with NIV were included in that previous report, the overall management of patients experiencing asthma attacks has not been well described. We hypothesized that a trial of NIV in patients experiencing severe attacks of asthma would be associated with a decrease in endotracheal intubation (ETI). To test this hypothesis, we retrospectively analysed the records of more than 100 patients admitted with severe attacks of asthma, before and after the introduction of NIV.

METHODS

Introduction of non-invasive ventilation to the hospital

Non-invasive ventilation was introduced in this 900-bed urban tertiary teaching hospital at the end of 2003, and has been fully utilized since mid-2004. Bilevel positive airway pressure or CPAP is administered by NIV (BiPap Vision; Respironics, Oakland, CA, USA), using a high-flow oxygen blender that allows oxygen concentrations up to 100%. Before the introduction of NIV, there was no choice other than to perform ETI when MV was required. In contrast, NIV can now be started at any time, unless there are contraindications to its use in particular patients.

Subjects

We screened all medical records of patients admitted to the hospital for treatment of an asthma attack over two 4-year periods: November 1999–October 2003 (pre-introduction of NIV) and November 2004–October 2008 (post-introduction of NIV). The inclusion criteria were as follows: (i) patients diagnosed with bronchial asthma in accordance with the Global Initiative for Asthma guidelines;[11] (ii) at least 16 and <80 years of age; and (iii) duration of asthma attack <7 days. To exclude patients with concomitant diseases and/or those who were not suitable for NIV treatment, the following exclusion criteria were applied: (i) smoking history >10 years or history of COPD; (ii) known chronic pulmonary disease other than asthma; (iii) ETI for cardiopulmonary arrest; (iv) ETI of comatose patients (Glasgow coma scale <8); (v) haemodynamic instability defined as heart rate >150 beats/min, or systolic blood pressure > 90 mm Hg; (vi) history of heart failure; (vii) pneumonia; (viii) lung cancer; (ix) pneumothorax or mediastinal emphysema; and (x) pregnancy. Finally, only patients who fulfilled at least two of the following criteria on arrival were included in the analysis: (i) required supplemental oxygen to maintain $SaO_2 > 90\%$ or $PaO_2 > 60$ mm Hg; (ii) $PaCO_2 > 45$ mm Hg; (iii) respiratory rate >30 breaths/min; and (iv) use of respiratory accessory muscles. If the same patient was admitted more than twice with an asthma attack within 3 months, only the first event was included in the analysis. Data analysis was performed only by the co-authors, and the use of all data was approved by the institutional review board.

Management of patients

All patients underwent initial assessments that included a history, physical examination and CXR. Conventional medical treatments, such as inhaled β_2 agonists, intravenous corticosteroids and subcutaneous adrenaline were administered as required. If MV had already been applied or would be applied soon, patients were transferred to the intensive care unit (ICU) or the intermediate care unit in the emergency department. In all cases, a physician and other medical staff monitored patients closely, so that ETI could be performed promptly at any time.

Mechanical ventilation with endotracheal intubation prior to the introduction of non-invasive ventilation

Although the decisions regarding ETI were based on clinical judgements, the following factors were considered to be indications for ETI: (i) unable to maintain $SaO_2 > 90\%$ even with maximal supplementary oxygen (10–15 L/min); (ii) hypercapnia and/or respiratory acidosis ($PaCO_2 > 55$ mm Hg and/or pH < 7.25); (iii) altered level of consciousness; and (iv) progressive exhaustion and fatigue. During MV, pressure support ventilation was adjusted so that expired tidal volume was 6–8 mL/kg, and fraction of inspired O_2 (FiO_2) was titrated so that $SaO_2 > 90\%$. Expiratory positive airway pressure was also adjusted so as to improve patient–ventilator interaction by attenuating the inspiratory muscle effort required to trigger inspiration. If there were no signs of spontaneous failure of breathing or desaturation ($SaO_2 < 90\%$), the patient was extubated after a 30- to 120-min trial of a T-piece. Sedatives, such as midazolam or propofol, were used if necessary.

Patient management following the introduction of non-invasive ventilation

Patients fulfilling the indications for MV with ETI were candidates for a trial of NIV, unless there were contraindications to its use. NIV was discontinued and ETI was performed when patients presented with any of the following: (i) deterioration of SaO_2 and/or arterial blood gases (ABG) while on NIV; (ii) haemodynamic instability; (iii) deterioration in the level of consciousness; (iv) intolerance of a face mask; or (v) at the request of the patient. During NIV, pressure support ventilation was delivered through a full face mask (Comfort Full 2; Respironics Inc., Murrysville, PA, USA). During the weaning process, NIV was stopped and administration of oxygen through a Venturi mask was commenced when the patient was able to maintain $SaO_2 > 90\%$ with a FiO_2 of 0.21–0.3.

Statistical analysis

Evaluation of outcomes was based on the following factors: type and duration of MV; length of stay in hospital and ICU or intermediate care unit; requirement for sedation; timing of ETI and NIV; reasons for discontinuation of NIV; initial ventilator settings; and survival. Sequential ABG data for patients receiving MV were recorded at baseline and at 2- to 6-h intervals. In addition to the cohort analysis, subset analysis was also performed, comparing patients who were primarily managed by NIV with those who were primarily managed by MV with ETI.

In the cohort analysis, unpaired *t*-tests were used to assess differences in continuous variables and chi-square tests were used for categorical variables. The Mann–Whitney *U*-test was used for continuous variables in the subset analysis because of the small number of cases. Changes in ABG from baseline were assessed by repeated measures analysis of variance (ANOVA). Two-tailed *P*-values < 0.05 were considered statistically significant. All statistical analyses were performed using JMP 7.0.2 statistical software (SAS Institute Inc., Cary, NC, USA).

RESULTS

In the periods pre- and post-introduction of NIV, 279 and 261 admissions related to asthma attacks, respectively, were screened. Fifty events (48 patients) from the pre-NIV period and 57 events (54 patients) from the post-NIV period fulfilled the criteria for severe asthma attacks and were included in the analysis (Fig. 1). Two patients were admitted on one occasion each, in both the pre- and post-introduction periods. In total, the two cohorts included nine patients managed by MV, who were also included in our previous study investigating the efficacy of NIV for acute respiratory failure due to any cause.[10] In the previous study, a tentative diagnosis was made on arrival and the screening period was shorter; therefore, the number of patients receiving MV in this study is not consistent with the numbers in the previous study.

The patient characteristics, vital signs, PaO_2/FiO_2 ratio and $PaCO_2$ at baseline were similar for both groups. However, in the post-introduction period more patients were regularly taking inhaled corticosteroids and long-acting β_2 agonists than in the pre-introduction period (Table 1). The medications used during asthma attacks were not significantly different between the two groups (Table 2).

In the pre-introduction period, ETI was the primary treatment for eight patients. For the other 42 events, manual respiratory support with a bag valve mask was used for three patients, with one of these patients requesting ETI after 30 min due to respiratory muscle fatigue. A total of nine patients were intubated. In contrast, ETI was not used at all as a primary treatment, during the post-introduction period. Instead, NIV was used for 17 patients. NIV failed in two of these patients and they required ETI. One patient was intubated after 20 min due to intolerance of the mask and extreme agitation. The other patient was intubated due to deterioration in ABG 75 h into NIV and recurrence of asthma during weaning from NIV. Only these two patients were intubated (Fig. 2). Over the 8-year study period, no patient received MV more than twice. The rate of ETI was significantly lower in the post-introduction period than in the pre-introduction period (Table 3).

The length of hospital stay was significantly shorter in the post-introduction than the pre-introduction period (10.8 ± 6.4 days vs 7.9 ± 4.1 days, $P < 0.01$), whereas the lengths of stay in the ICU or intermediate care unit were similar (32.1 ± 29.0 h vs 26.3 ± 29.4 h, $P = 0.3$).

In the subset analysis for those who received MV, there were no significant differences in severity

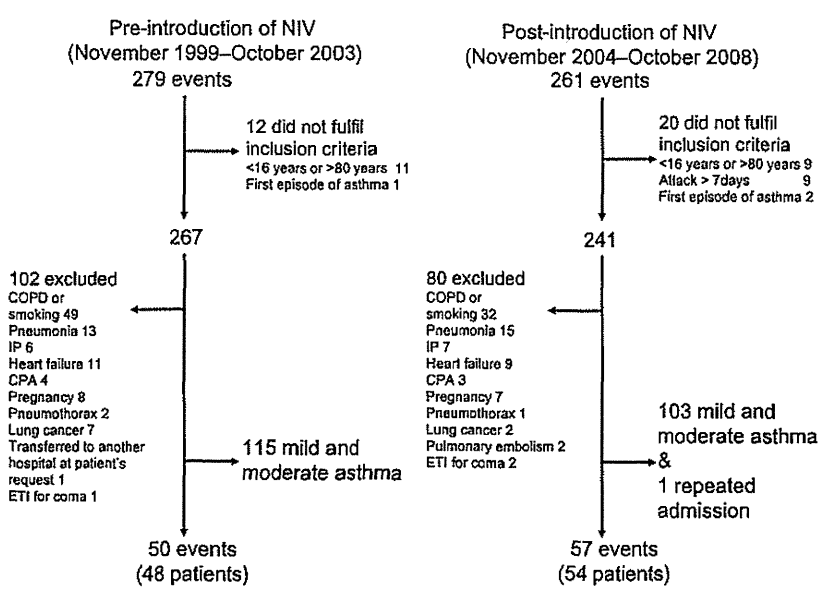

Figure 1 Diagram showing selection of patients experiencing severe attacks of asthma. CPA, cardiopulmonary arrest; ETI, endotracheal intubation; IP, interstitial pneumonitis; NIV, non-invasive ventilation.

Table 1 Baseline characteristics of patients experiencing severe attacks of asthma, pre- and post-introduction of NIV

	Pre-introduction of NIV ($n = 50$)	Post-introduction of NIV ($n = 57$)	*P*-value
Age, years	45.6 ± 20.0	52.0 ± 17.9	0.08
Women, *n* (%)	32 (64)	42 (74)	0.28
Duration of asthma, years	13.1 ± 11.7	12.1 ± 10.7	0.65
Duration of attack, days	2.38 ± 1.71	1.84 ± 1.08	0.05
Systolic arterial blood pressure, mm Hg	135.1 ± 27.9	139.6 ± 28.0	0.43
Heart rate, beats/min	109.3 ± 19.8	111.4 ± 19.0	0.58
Respiratory rate, breaths/min	30.2 ± 6.18	27.9 ± 8.69	0.39
PaO_2/FiO_2 ratio	218.8 ± 111.0	204.7 ± 99.1	0.49
$PaCO_2$, mm Hg	57.6 ± 27.4	56.5 ± 25.5	0.84
pH	7.29 ± 0.16	7.30 ± 0.15	0.92
Use of accessory muscles, *n* (%)	27 (54)	38 (67)	0.18
GCS	14.7 ± 0.9	14.7 ± 1.0	0.93
Long-term use of inhaled corticosteroids, *n* (%)	14 (28)	28 (49)	0.02
Long-term use of inhaled LABA, *n* (%)	2 (4)	19 (33)	<0.0001
Long-term use of systemic corticosteroids, *n* (%)	4 (8%)	3 (5%)	0.57

Data are mean ± SD, unless otherwise indicated.

FiO_2, fraction of inspired oxygen; GCS, Glasgow coma scale; LABA, long-acting β_2 agonist; NIV, non-invasive ventilation.

Table 2 Medications administered to patients experiencing severe attacks of asthma, pre- and post-introduction of NIV

	Pre-introduction of NIV ($n = 50$)	Post-introduction of NIV ($n = 57$)	*P*-value
Inhaled bronchodilator, *n* (%)	50 (100)	57 (100)	1.00
Methylprednisolone (i.v.), mg†	128.4 ± 96.9	149.1 ± 80.3	0.23
Adrenaline (subcutaneous), *n* (%)	18 (36)	18 (32)	0.63

†Maximum dose per day through the hospital stay (mean ± SD). If corticosteroids other than methylprednisolone were used, the dose was converted to methylprednisolone equivalents.

NIV, non-invasive ventilation.

(Table 4). NIV was started significantly earlier than MV with ETI (mean time interval between patient arrival and start of MV 171.7 ± 217.9 min vs 38.5 ± 113.8 min for NIV, $P < 0.05$). In the NIV cohort, there was a trend towards a reduction in the duration of MV with ETI or NIV (36.9 ± 38.4 h vs 20.3 ± 35.8 h, $P = 0.09$), and hospital stay was shortened (12.6 ± 4.2 days vs 8.4 ± 2.8 days, $P < 0.01$) (Table 4). In both groups ABG improved rapidly 2–6 h after the initiation of MV. The levels of consciousness of all confused patients in the NIV cohort returned to normal within 2–6 h, except for one patient in whom NIV failed (Fig. 3). NIV was well tolerated and caused no complications. None of the 17 patients required sedation while receiving NIV. In contrast, all 11 patients who were intubated, including the two patients in whom NIV failed, received continuous sedation (Table 4). No complications occurred as a result of delaying intubation in the two patients who failed to respond to NIV. Retention of secretions was not a problem. All patients included in this study survived and were discharged.

DISCUSSION

This study showed that the rate of ETI for patients with severe attacks of asthma was significantly reduced after the introduction of NIV, without worsening the prognosis for the patient. Based on the absence of major progression of treatment during the screening period, introduction of NIV appears to be strongly associated with a reduction in the number of patients requiring intubation.

In the present study, NIV was started significantly earlier than MV with ETI. Because ETI is difficult and risky in patients experiencing an attack of asthma, much time is often wasted in trying to decide whether or not it should be performed. Indeed, it has been suggested that intubation of patients with severe attacks of asthma should be performed in a controlled setting by a physician with extensive experience in airway management.[7] The easy and more rapid availability of NIV enabled the implementation of MV early in the course of the asthma attacks and may have led to a reduction in the rate of ETI and low

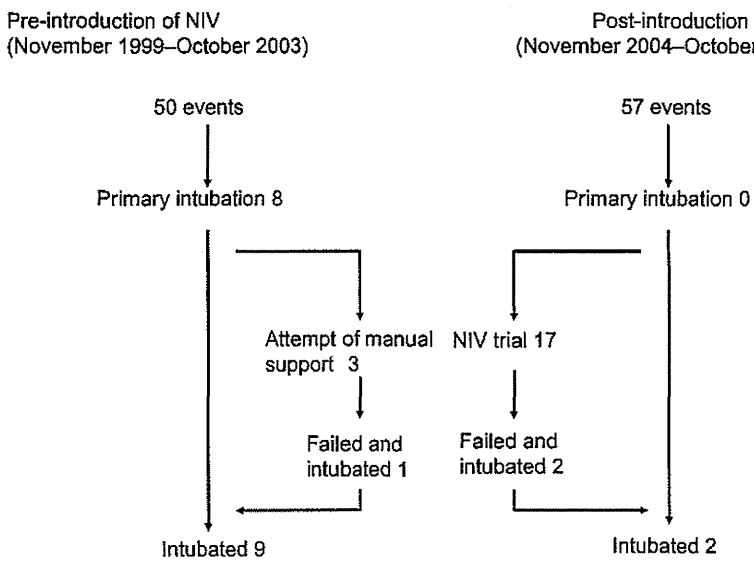

Figure 2 Diagram showing management of patients experiencing severe attacks of asthma. NIV, non-invasive ventilation.

Table 3 Clinical outcomes in patients experiencing severe attacks of asthma, pre- and post-introduction of NIV

	Pre-introduction of NIV ($n = 50$)	Post-introduction of NIV ($n = 57$)	*P*-value
MV (NIV and/or MV with ETI), *n* (%)	9 (18)	17 (30)	0.15
ETI, *n* (%)	9 (18)	2 (2)† (4)	0.01
NIV, *n* (%)	0 (0)	17 (30)	<0.0001
Hospital stay, days	10.8 ± 6.4	7.9 ± 4.1	<0.01
Stay in ICU or intermediate care unit, h	32.1 ± 29.0	26.3 ± 29.4	0.30

†() denotes the number of patients for whom NIV failed. Data are mean ± SD unless otherwise indicated.
ETI, endotracheal intubation; ICU, intensive care unit; MV, mechanical ventilation; NIV, non-invasive ventilation.

mortality by preventing deterioration in the condition of the patients. Moreover, most patients in the present study began to improve relatively quickly and did not require MV for a long period. The use of NIV may also be a good strategy for giving patients time to respond to other conventional medical treatments. It is possible that NIV may be overused because of its ready availability. However, in the manner in which it was utilized in this study, when indicated and under supervision, NIV did not appear to lead to serious adverse events.

Mortality among patients experiencing severe attacks of asthma varies considerably between studies.[12–16] Afessa *et al.* reported that mortality among patients who required MV was as high as 21%. However, this may have been partly a consequence of cardiopulmonary arrest, which was excluded from the present analysis.[15,17] Although none of the patients included in the present study died, the severity of their asthma attacks did not seem to differ significantly from that of the patients in other studies, as judged by the results of ABG analyses and the definition of severe asthma attacks in the consensus guidelines,[12,18–20]

Some previous trials have reported on the benefits of NIV in asthma attacks.[21–25] However, based on the results of ABG analyses, the asthma attacks were more severe in the present study than in the two previous studies focusing on severe asthma[22,24] (Tables 1,4). It is difficult to conduct a randomized controlled trial of MV for patients with severe asthma, because this could potentially deny access to a promising treatment modality. Holley *et al.* initiated a trial to determine whether NIV would reduce the need for ETI, but the trial was terminated prematurely because of this ethical problem.[26] Because prospective evaluation of the role of NIV in life-threatening asthma attacks is quite difficult, the present retrospective study may be of clinical significance.

Non-invasive ventilation was used even in seven confused patients. Altered consciousness may be considered a relative contraindication to NIV because of poor cooperation and the risk of pulmonary aspiration. However, successful application of NIV in confused patients has been reported previously.[27–30] In the present study, almost all the patients who received NIV showed rapid improvement in cognitive function, as well as respiratory status. However, NIV cannot always replace MV with ETI. As patients with severe attacks of asthma may deteriorate rapidly, it seems sensible to use NIV in settings where close monitoring and prompt intubation are possible.[31]

Table 4 Subset analysis comparing data for patients who were managed primarily by NIV, including those for whom NIV failed and those who were managed primarily by MV with ETI

	MV with ETI ($n = 9$)	NIV ($n = 17$)	*P*-value
Women, *n* (%)	7 (78)	14 (82)	0.94
Age, years	47.6 ± 16.3	54.6 ± 17.8	0.31
PaO_2/FiO_2 ratio	241.8 ± 160.9	197.1 ± 132.3	0.39
$PaCO_2$, mm Hg	79.0 ± 39.7	76.8 ± 29.9	0.95
pH	7.18 ± 0.18	7.18 ± 0.17	0.8
GCS	13.3 ± 1.8	13.8 ± 1.6	0.39
Time from arrival to start of MV <30 min, *n* (%)	4 (44)	16 (94)	<0.01
Time between arrival and start of MV, min	171.7 ± 217.9	38.5 ± 113.8	<0.05
Intubated, *n* (%)	9 (100)	2† (12)	<0.0001
IPAP, cm H_2O	14.4 ± 6.4	12.4 ± 4.3	0.34
EPAP, cm H_2O	5.1 ± 1.5	5.6 ± 1.8	0.46
FiO_2	0.39 ± 0.03	0.67 ± 0.29	0.08
Hospital stay, days	12.6 ± 4.2	8.4 ± 2.8	0.01
Stay in ICU or intermediate care unit, h	60.3 ± 40.3	48.9 ± 45.7	0.3
Duration of MV, h	36.9 ± 38.4	20.3 ± 35.8	0.09
Use of sedation, *n* (%)	9 (100)	2† (12)	<0.0001

Data are mean ± SD unless otherwise indicated.

†Both these patients were intubated after failure of NIV. Patients were sedated only during MV with ETI.

EPAP, expiratory positive airway pressure; ETI, endotracheal intubation; FiO_2, fraction of inspired oxygen; GCS, Glasgow coma scale; ICU, intensive care unit; IPAP, inspiratory positive airway pressure; MV, mechanical ventilation; NIV, non-invasive ventilation.

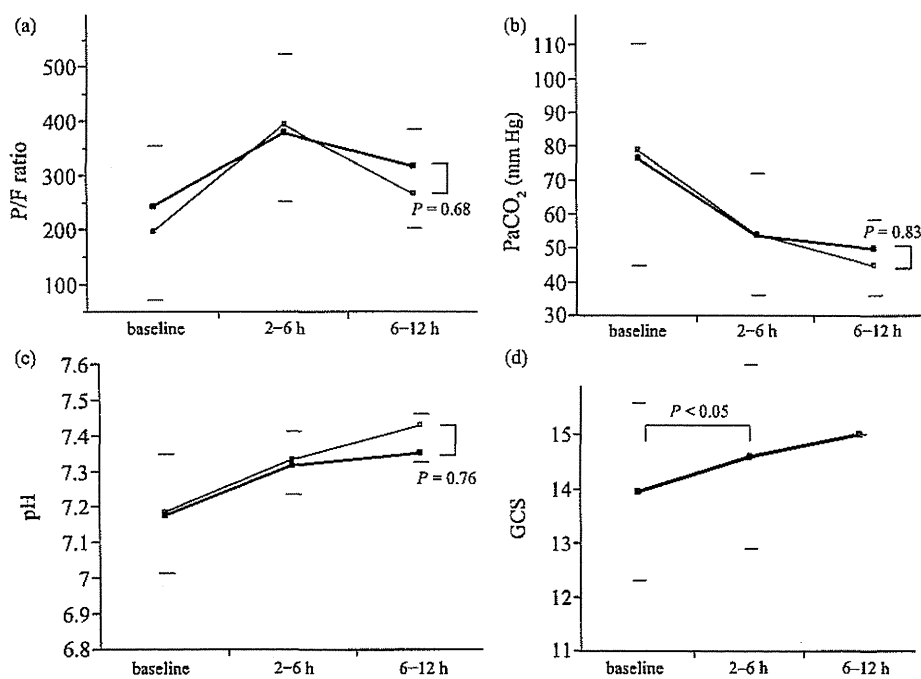

Figure 3 Changes over time in (a) PaO_2/FiO_2 (P/F) ratio, (b) $PaCO_2$, (c) pH and (d) Glasgow coma score (GCS), in patients experiencing severe attacks of asthma who were managed by mechanical ventilation (MV) with endotracheal intubation (ETI) or by non-invasive ventilation (NIV). Values were compared by repeated measures analysis of variance. There were no significant differences between patients receiving MV with ETI or NIV. GCS improved after 2–6 h in all patients except for one patient in whom NIV failed. Levels of consciousness could not be evaluated precisely in patients receiving MV with ETI because of continuous sedation. (—) NIV; (—) MV with ETI. FiO_2, fraction of inspired oxygen.

This study has some limitations. First, because of the retrospective design, it was not possible to elucidate the possible effects of confounding factors, such as increased frequency of use of long-acting β_2 agonists and inhaled corticosteroids use, as well as utilization of beds. Second, some patients with undiagnosed COPD may have been included, because asthma and COPD may have similar physiological features.[32–34] Third, it was not possible to perform pulmonary function tests during the asthma attacks because the results would not have been reliable.

In conclusion, NIV is an acceptable and useful method of stabilizing respiratory status in patients with severe attacks of asthma. The ease of application and more immediate availability of NIV enables the earlier commencement of MV, and may decrease the need for ETI. Prospective randomized studies, although ethically difficult to perform, would help to confirm these results.

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Mouse Models of Apnea: Strain Differences in Apnea Expression and its Pharmacologic and Genetic Modification

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Abstract Mouse strain differences exist in post-hypoxic ventilatory behavior, specifically, the C57BL/6J (B6) mouse exhibits irregular breathing including apnea during re-oxygenation after acute hypoxic exposure, while A/J mouse does not. This phenomenon of the B6 mouse responding to the hypoxia-reoxygenation cycle which is a mimic of human sleep apnea syndrome let us consider the B6 mouse as an animal model of sleep apnea. Moreover, the B6 mouse tends to show spontaneous apnea and post-sigh apnea compared to the A/J mouse. In this brief review, we present evidence that pharmacologic approaches as well as genetic modification can improve irregular breathing including apnea in the B6, suggesting that these pharmacologic treatment might be effective for the patients with sleep apnea who cannot tolerate nCPAP. Moreover our findings regarding genetic difference and modification should be helpful to explore the pathogenesis of sleep apnea.

1 Introduction

There is a close relationship among the types of sleep apnea (central, obstructive, and mixed) in regard to both the pathogenesis and in the clinical management of sleep apnea syndromes. One feature of particular interest will be the dynamic responses of the respiratory control system, specifically the instability over time that could operate to produce repetitive apneas. The recurrent nature of clinically significant sleep apnea can be understood in terms of feedback control, or "loop gain" (Strohl et al. 2007). We discuss the findings in a mouse model for recurrent apneas and propose that there exist genetic mechanisms that could determine loop gain in the respiratory control system, in addition, pharmacologic treatment can modify the ventilatory behavior as well as loop gain.

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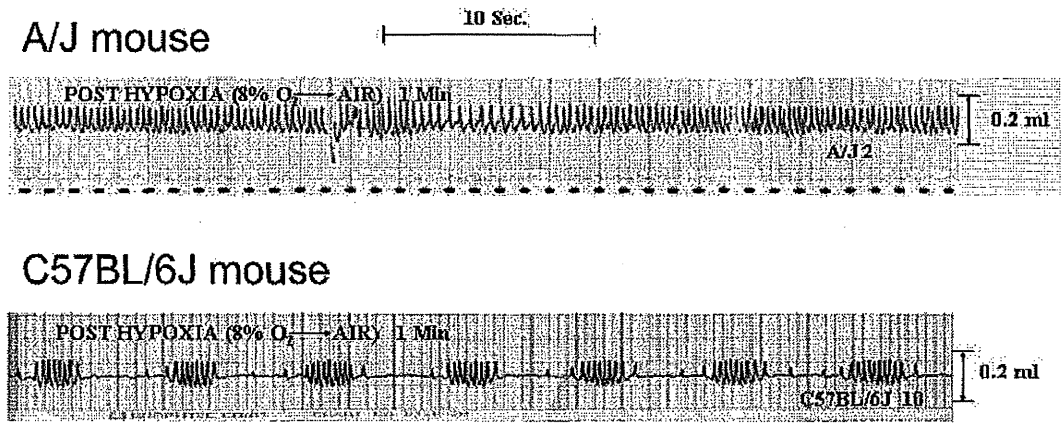

Fig. 1 Tracings indicating the pattern of breathing over time upon reoxygenation in the B6 or A/J mouse. The B6 pattern resembles periodic breathing

2 Mouse Strain Differences in Ventilatory Behavior

The measurement of ventilatory behavior was made by plethysmography. We used a round Lucite chamber (600-ml volume) containing an inlet port for the administration of test gases, in which plethysmographic chamber mouse can move freely. With this chamber, we evaluated ventilatory behavior under unanaesthetized and unrestricted condition during awake. When the gas inside this chamber was exchanged to mimic the arterial oxygen level in human sleep apnea patients, C57BL/6J (B6) mouse exhibited the periodic breathing including apnea during reoxygenation after acute hypoxic exposure, while A/J mouse shows regular breathing during same phase (Han et al. 2002) (Fig. 1). For the another mouse strain differences in ventilatory behavior, the B6 mouse shows the post-sigh irregular breathing including apnea and spontaneous apnea compared to the A/J mouse during room air resting breathing (Yamauchi et al. 2008) (Fig. 2). Thus these findings let us consider the B6 mouse as an animal model of recurrent apnea.

3 Genetic Modification for the Ventilatory Behavior

For exploring the responsible genes for the irregular breathing in the B6 mouse mentioned above, we employed the chromosome substitution strain, B6a1 mouse. B6a1 mouse is the B6 mouse of which only difference is that chromosome 1 is replaced with A/J's chromosome 1. Interestingly, we found that B6a1 mouse behaved like the A/J mouse not showing post-hypoxic irregular breathing and post-sigh apnea or spontaneous apnea (Strohl et al. 2007; Yamauchi et al. 2008). These findings imply that some genes on the chromosome 1 might be responsible for the irregular breathing in the B6 mouse.

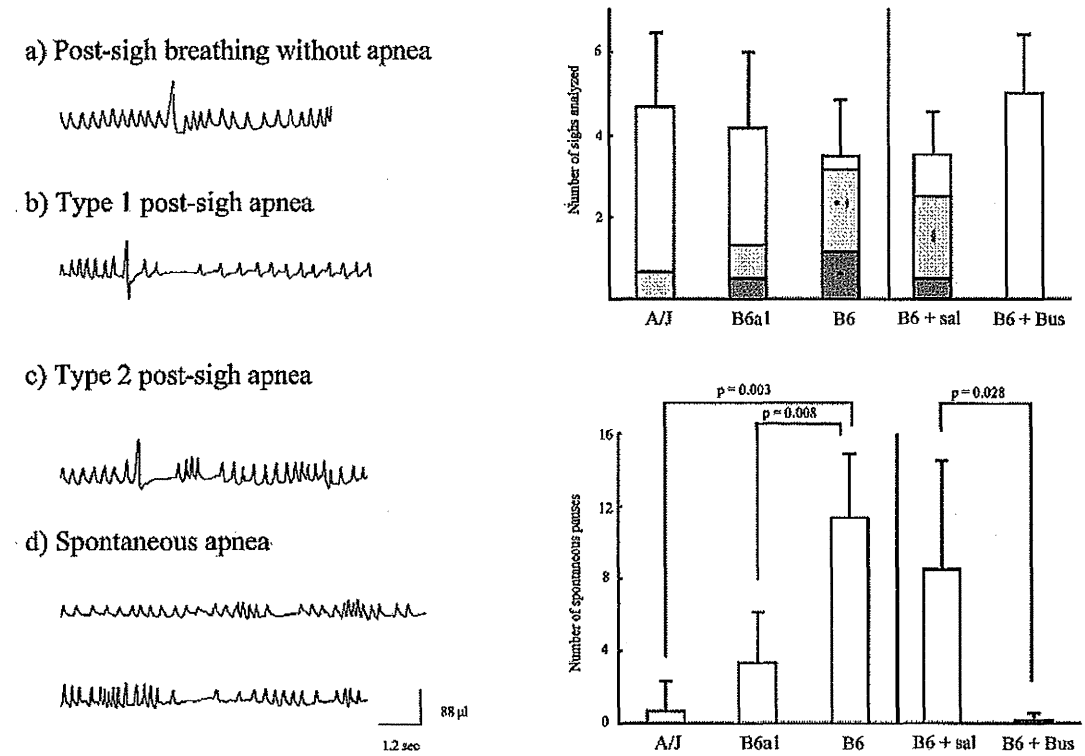

Fig. 2 Left panel shows examples of post-sigh breathing behavior and spontaneous apnea. Right upper panel shows the number of analyzed sighs and a type of post-sigh breathing. The sections inside each bar indicate the mean value for post-sigh breathing without apnea (*white*), Type 1 post-sigh apnea (*gray*), and Type 2 post-sigh apnea (*dark*). B6 + Sal: saline-treated B6 mice, B6 + Bus: buspirone-treated B6 mice. *Significant difference from A/J ($p < 0.05$), †significant difference from B6a1 ($p < 0.05$), §significant difference from B6 + Bus ($p < 0.05$). Right lower panel shows the number of spontaneous apnea for each stain and each condition. Reproduced with permission from Yamauchi et al. 2008

4 Pharmacologic Treatment for the Irregular Breathing in the B6 Mouse

4.1 Acetazolamide

One drug used to modify respiratory drive is the carbonic anhydrase inhibitor, acetazolamide (ACZ). ACZ is used to treat periodic breathing associated with altitude and heart failure, and is believed to work by increasing respiratory drive. Thus we hypothesized that ACZ can modify the post-hypoxic ventilatory behavior in the B6 mouse. Intraperitoneal injection of ACZ (40 mg/kg) improved the post-hypoxic periodic breathing. In addition, ACZ significantly decreased hypercapnic ventilatory

responsiveness without producing a significant difference in hypoxic responsiveness (Yamauchi et al. 2007).

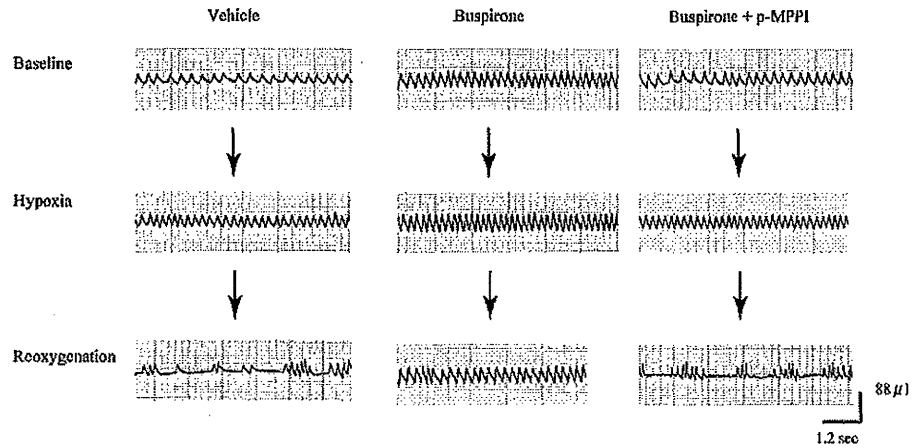

Fig. 3 Typical examples for breathing in the B6 during each phase; Baseline, resting breathing in room air; hypoxia, breathing during the hypoxic exposure; reoxygenation, breathing during the first minute after reoxygenation. Left: vehicle. Middle: 5 mg/kg buspirone. Right: 5 mg/kg of both buspirone and p-MPPI. Reproduced with permission from Yamauchi et al. 2008

4.2 Buspirone

Serotonin (5-HT) containing neurons of the central nervous system are involved in respiratory control. Buspirone, a partial agonist of the 5-HT1A receptor, has been reported to reverse apneustic breathing in a pediatric patient after an operation to remove an astrocytoma located in the pons and medulla (Wilken et al. 1997), and to improve respiratory dysfunction in a patient with Rett Syndrome (Andaku et al. 2005). Thus we hypothesized that Buspirone improves irregular breathing in the B6 mouse. Intraperitoneal injection of Buspirone improved the post-hypoxic periodic breathing, post-sigh apnea, and spontaneous apnea (Figs. 2 and 3.). Moreover, in the B6 mouse, buspirone decreased hypercapnic ventilatory responsiveness while hypoxic ventilatory responsiveness was not affected. Pretreatment with p-MPPI, which is a 5-HT1A receptor antagonist, reversed the effects of buspirone in the B6. Buspirone did not affect neither hypercapnic nor hypoxic ventilatory responsiveness in the A/J mouse (Yamauchi et al. 2008; Yamauchi et al. 2008). These findings imply that 5-HT1A receptor activation may play a critical role for the irregular breathing in the B6 mouse.

5 Loop Gain in the Respiratory System

A high loop gain promotes recurrent apnea as the response to the initial disturbance is overcompensated, while a low loop gain dampens subsequent oscillations in breathing (Khoo 2001). B6 mouse we proposed as an animal model of recurrent apnea in this chapter has higher loop gain than A/J mouse. ACZ and Buspirone lowered the loop gain decreasing the hypercapnic ventilatory responsiveness and

apneic threshold, and then stabilized the irregular breathing in the B6 mouse (Yamauchi et al. 2007; Yamauchi et al. 2008).

6 Conclusions

B6 mouse is a recurrent apnea model and has relatively higher loop gain. ACZ and Buspirone improve irregular breathing in the B6 mouse by modifying the high loop gain. Thus these drugs might be effective for the sleep apnea patients who refuse or cannot tolerate nCPAP, especially those with respiratory system with high loop gain. Genetic manipulation also can improve the breathing irregularity as shown with B6a1 mouse. Chromosome substitution strain is very useful for exploring the responsible genes for the irregular breathing, which may clarify the pathogenesis of sleep apnea.

Acknowledgments

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Current Situations and Issues in Respiratory Medicine in Japan

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Current Situations and Issues in Respiratory Medicine in Japan

JMAJ 53(3): 178–184, 2010

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Abstract

The essence of the current shortage of physicians in Japan is not just a shortage in the absolute number. It is also a shortage of physicians in particular fields of medicine, as well as an uneven geographic distribution of hospital-employed physicians. The Future Planning Committee of Japanese Respiratory Society conducted a survey to determine the actual status and issues pertaining to the practice of respiratory medicine in 2007–2008, as part of an effort to seek appropriate measures to increase the number of respiratory physicians. For this survey, 3,000 hospitals were randomly sampled from nationwide that had a department of internal medicine, then, 1,232 (41.1%) hospitals that returned the questionnaire were subjected to analysis.

The national average number of physicians per 10 beds was 0.83 for internists, 0.50 for respiratory physicians, and 0.21 for physicians specialized in respiratory diseases. Among all prefectures of Japan, there were 3.9-fold and 6.1-fold differences for internists and respiratory specialists, respectively. Even amongst large hospitals with 300 beds or more, the self-containment level, which indicates the extent to which the diagnosis and treatment of diseases can be completed within a particular hospital, was low for the treatment of acute respiratory failure, chemotherapy of lung cancer, and diagnosis and treatment of intractable diseases such as pulmonary circulatory disease in rural areas with a population of less than 50,000. This suggests a qualitative disparity in the practice of respiratory medicine among different areas of Japan. On the other hand, the survey also indicated that physicians not specialized in respiratory diseases have to deal with intractable respiratory diseases like acute respiratory failure or interstitial pneumonia in rural areas, suggesting possible disadvantages to patients in rural areas who are in need of respiratory medicine. In order to promote equality in medical practice in Japan, it is urgent to foster respiratory physicians and specialists and distribute them appropriately.

Key words Shortage of physicians, Respiratory specialists, Regional disparity, Equalization of healthcare

Introduction

In recent years, Japan has been facing a serious shortage of physicians. In essence, it is not just a shortage in absolute numbers of physicians; it is also a shortage of physicians in particular fields of medicine such as obstetrics, pediatrics, and emergency medicine, uneven geographic distribution of physicians, and a worsening work environment for hospital-employed physicians. On the other hand, as the ageing of Japanese population progresses, the number of patients with pneumonia, respiratory failure, lung cancer, chronic obstructive pulmonary disease (COPD), or asthma continues to increase, enhancing the role of respiratory physicians in the practice of general internal medicine and further emphasizing the importance of respiratory medicine. And

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Table 1 Numbers of internists, respiratory physicians, and respiratory specialists per 10 departmental beds ($n_{I/10}$, $n_{R/10}$, and $n_{S/10}$, respectively) and the ratios of respiratory specialists to respiratory physicians and respiratory physicians to internists ($ratio_{S/R}$ and $ratio_{R/I}$) among 47 prefectures in Japan

Code	Prefecture	n [a]	$n_{I/10}$ [b]	$n_{R/10}$ [c]	$n_{S/10}$ [d]	$Ratio_{S/R}$ [e]	$Ratio_{R/I}$ [f]
0	Nationwide	1,232	0.83	0.50	0.21	0.43	0.14
1	Hokkaido	80	0.73	0.52	0.18	0.35	0.15
2	Aomori	28	0.51	0.33	0.14	0.42	0.13
3	Iwate	21	0.57	0.43	0.16	0.37	0.19
4	Miyagi	35	0.81	0.78	0.32	0.41	0.15
5	Akita	14	0.53	0.54	0.18	0.33	0.15
6	Yamagata	12	0.62	0.56	0.37	0.67	0.15
7	Fukushima	25	0.60	0.29	0.13	0.45	0.080
8	Ibaraki	24	0.89	0.34	0.12	0.36	0.063
9	Tochigi	13	0.58	0.51	0.30	0.60	0.17
10	Gumna	31	0.65	0.44	0.17	0.38	0.16
11	Saitama	52	1.18	0.49	0.17	0.35	0.094
12	Chiba	58	0.74	0.31	0.11	0.34	0.095
13	Tokyo	92	1.02	0.58	0.24	0.42	0.14
14	Kanagawa	47	0.95	0.51	0.22	0.43	0.13
15	Yamanashi	20	0.79	0.52	0.28	0.53	0.18
16	Nagano	8	0.47	0.50	0.17	0.33	0.24
17	Niigata	17	0.82	0.45	0.14	0.31	0.10
18	Toyama	9	0.80	0.36	0.31	0.86	0.11
19	Ishikawa	9	0.81	0.67	0.34	0.50	0.15
20	Fukui	27	0.92	0.45	0.21	0.47	0.12
21	Gifu	27	0.66	0.31	0.13	0.42	0.12
22	Shizuoka	22	1.34	0.71	0.23	0.32	0.17
23	Aichi	34	1.08	0.56	0.25	0.44	0.18
24	Mie	7	0.88	0.40	0.16	0.40	0.12
25	Shiga	19	0.81	0.40	0.19	0.47	0.10
26	Kyoto	25	1.09	0.50	0.22	0.45	0.12
27	Osaka	67	0.87	0.56	0.25	0.45	0.16
28	Hyogo	40	0.89	0.46	0.21	0.46	0.13
29	Nara	25	0.77	0.64	0.12	0.19	0.18
30	Wakayama	16	0.76	0.44	0.24	0.59	0.12
31	Tottori	6	0.85	0.61	0.27	0.44	0.14
32	Shimane	15	0.60	0.48	0.21	0.44	0.13
33	Okayama	26	0.78	0.45	0.22	0.49	0.17
34	Hiroshima	24	0.61	0.44	0.21	0.48	0.14
35	Yamaguchi	12	0.73	0.33	0.19	0.57	0.049
36	Tokushima	14	0.91	0.54	0.24	0.45	0.098
37	Kagawa	17	0.94	0.53	0.19	0.35	0.16
38	Ehime	17	1.15	0.60	0.37	0.62	0.13
39	Kochi	14	0.80	0.53	0.23	0.43	0.10
40	Fukuoka	50	0.85	0.45	0.21	0.46	0.16
41	Saga	5	0.82	0.66	0.094	0.14	0.15
42	Nagasaki	25	0.92	0.67	0.27	0.41	0.19
43	Kumamoto	29	0.82	0.69	0.30	0.44	0.24
44	Oita	33	0.72	0.36	0.18	0.50	0.11
45	Miyazaki	12	0.59	0.21	0.070	0.33	0.13
46	Kagoshima	19	0.89	0.63	0.43	0.69	0.12
47	Okinawa	10	0.72	0.81	0.13	0.15	0.18

a) Number of hospitals analyzed (n).
b) Number of internists per 10 beds in the department of internal medicine ($n_{I/10}$).
c) Number of respiratory physicians per 10 beds in the department of internal medicine ($n_{R/10}$).
d) Number of respiratory specialists per 10 beds in the department of respiratory medicine ($n_{S/10}$).
e) Ratio of respiratory specialists to respiratory physicians ($ratio_{S/R}$).
f) Ratio of respiratory physicians to internists ($ratio_{R/I}$).

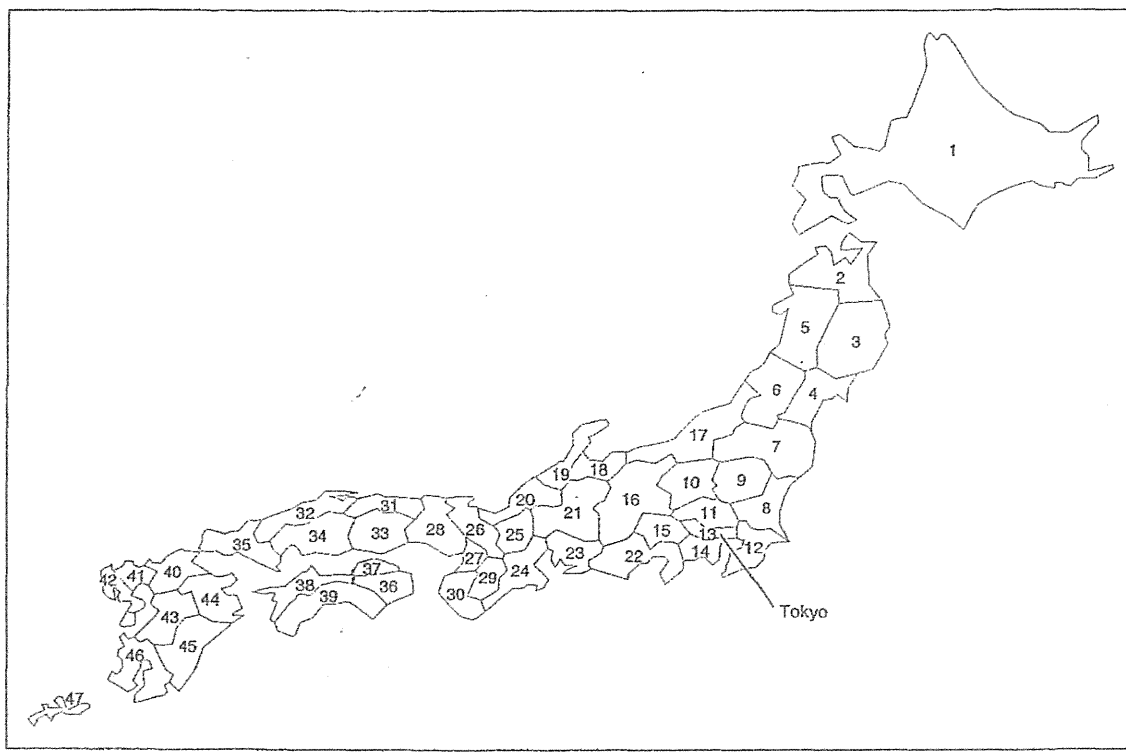

Fig. 1 A map of Japan, showing the locations of its 47 prefectures
The numbers shown correspond with the prefecture code in Table 1.

of course, there remains the significant issue that the number of physicians engaged in respiratory medicine in the front-line of medical practice is not enough.[1]

The Future Planning Committee of Japanese Respiratory Society conducted a survey on the actual status and issues pertaining to the practice of respiratory medicine in 2007–2008, as part of an effort to seek appropriate measures to increase the number of respiratory physicians in Japan.

Methods

The purposes of the survey were to determine (1) the location of hospitals, number of physicians in relation to the hospital scale, and the actual status of clinical practice, and (2) to what extent the diagnosis and treatment of diseases can be completed in a particular hospital (the self-containment level).

Of the approximately 9,000 hospitals in Japan, there are 5,620 hospitals with a department of internal medicine, after excluding dedicated sanatorium types and medical school affiliated hospitals. Questionnaires were sent to the 3,000 hospitals that were randomly sampled from these 5,620 hospitals. Medical school affiliated hospitals were excluded from the sampling because, although they generally have a greater number of physicians than other hospitals, some are working for the purpose of education and research rather than clinical practice.

Questionnaires were recovered from 1,251 hospitals (41.7%), and eventually 1,232 hospitals (41.1%) were analyzed ($n=1,251$). With regard to the hospital size (number of beds), 28.7% were large-sized hospitals (300 or more beds), 42.4% were middle-sized (100 or more and fewer than 300 beds), and 28.9% were small-sized (fewer than 100 beds). In terms of the location, 22.6% were located in metropolitan areas (population 500,000 or greater), 22.6% in urban areas (population 200,000 or more and fewer than 500,000), 32.3% in provincial areas (population 50,000 or

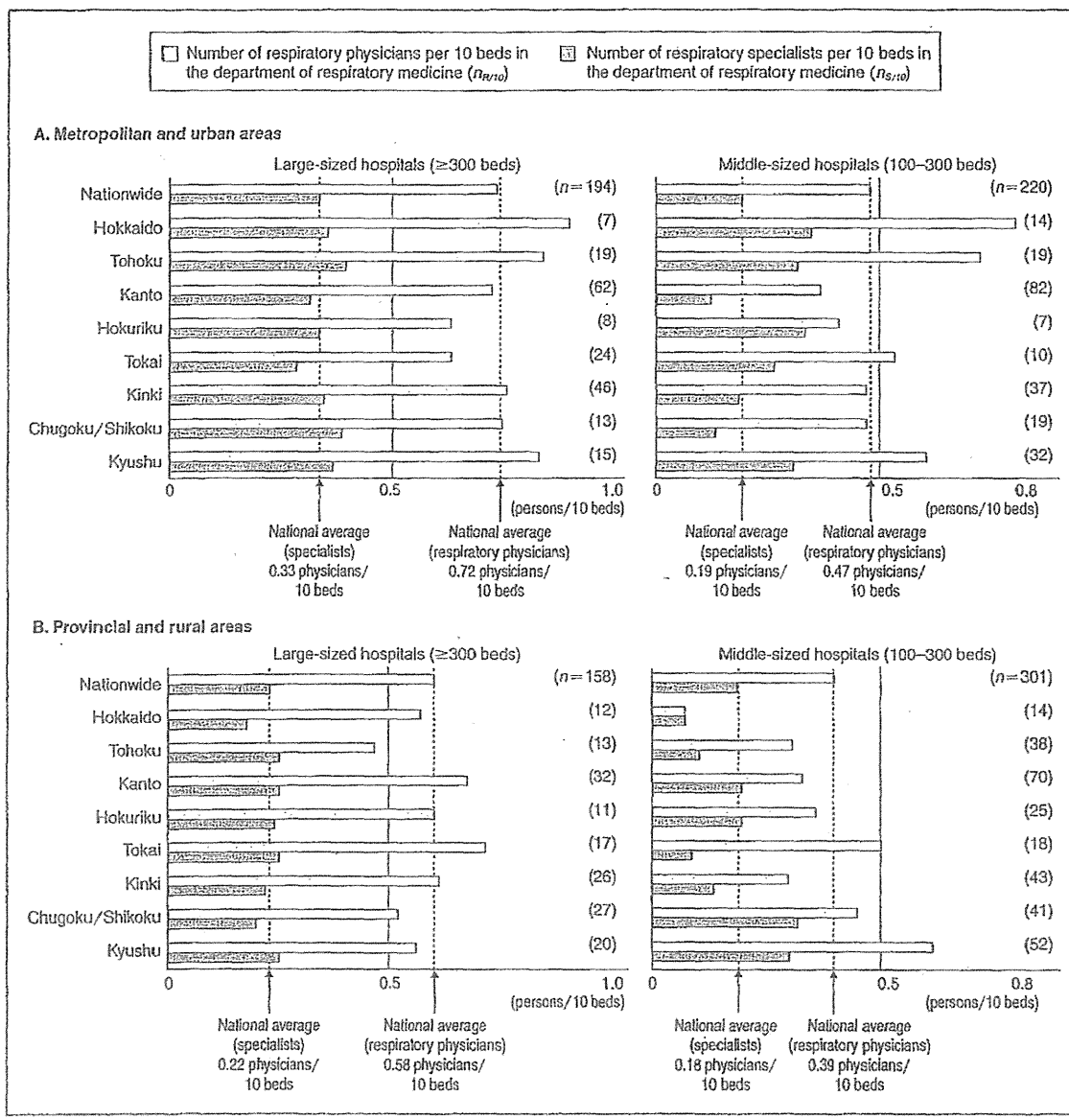

Fig. 2 Numbers of respiratory physicians and specialists: Comparison among eight branch areas of Japanese Respiratory Society

more and fewer than 200,000), and 22.5% in rural areas (fewer than 50,000 population). The numbers of beds per hospital were 224.8 on average; 97.6 for the department of internal medicine and 22.7 for the department of respiratory medicine. The mean numbers of physicians per hospital were 8.1 for full-time internists, 1.1 for full-time respiratory physicians, and 0.5 for respiratory specialists.

Results

Number of physicians by prefecture

Table 1 shows the number of hospitals subjected to analysis (n), the numbers of internists, respiratory physicians, and respiratory specialists per 10 departmental beds ($n_{I/10}$, $n_{R/10}$, and $n_{S/10}$, respectively), the ratio of respiratory specialists to respiratory physicians ($ratio_{S/R}$), and the ratio

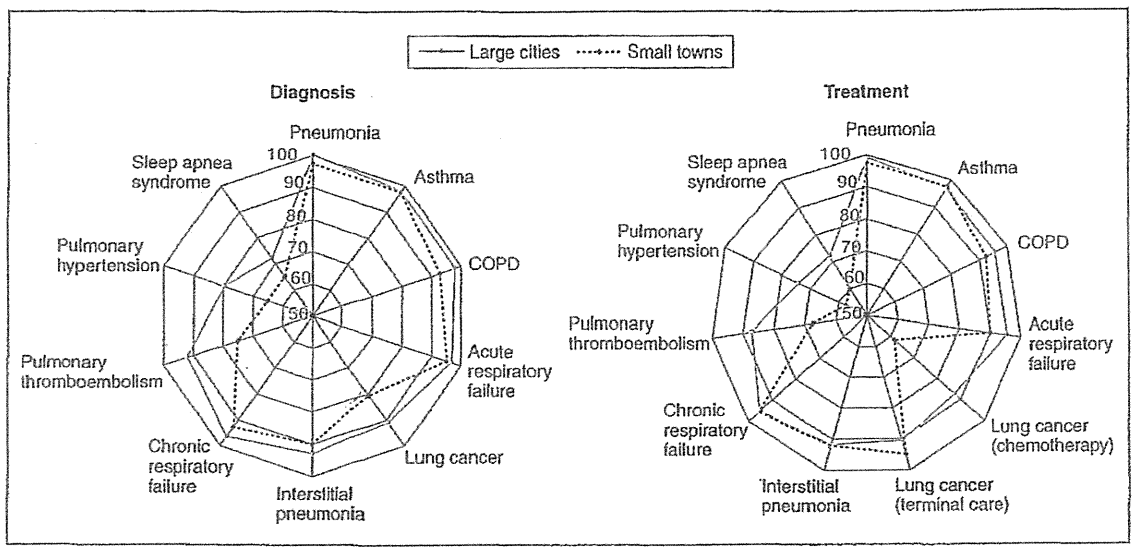

Fig. 3 The self-containment level for diagnosis and treatment among large-sized hospitals (300 or more beds): Large cities vs. small towns

of respiratory physicians to internists ($ratio_{R/I}$), among 47 prefectures in Japan (see **Fig. 1** for the location map). The national averages per 10 departmental beds were: 0.83 for internists ($n_{I/10}$), 0.50 for respiratory physicians ($n_{R/10}$), and 0.21 for respiratory specialists ($n_{S/10}$). There were considerable deviations in the results among prefectures. The greatest differences was a 2.9-hold difference for the number of internists ($n_{I/10}$) between Shizuoka and Nagano, a 3.9-fold difference in the number of respiratory physicians ($n_{R/10}$) between Okinawa and Miyazaki, and a 6.1-fold difference in the number of respiratory specialists ($n_{S/10}$) between Kagoshima and Miyazaki. As for the national averages for the ratios, the respiratory specialists to respiratory physicians ($ratio_{S/R}$) and the respiratory physicians to internists ($ratio_{R/I}$) were 0.43 and 0.14, respectively.

Regional comparison of the numbers of respiratory physicians and specialists per 10 departmental beds ($n_{R/10}$ and $n_{S/10}$) by hospital size, in metropolitan and urban areas (population 200,000 or more) (based on the branch areas of Japanese Respiratory Society) (Fig. 2A)

Among large-sized hospitals ($n=194$), the number of respiratory physicians per 10 departmental beds ($n_{R/10}$) was 0.724 on average, ranging from 0.880 (Hokkaido Area) to 0.621 (Tokai Area) and 0.623 (Hokuriku Area), in terms of the branch areas of Japanese Respiratory Society. The number of respiratory specialists per 10 beds ($n_{S/10}$) was 0.329 on average (range: 0.385 of Tohoku Area to 0.278 of Tokai Area). Among middle-sized hospitals ($n=220$), the number of respiratory physicians ($n_{R/10}$) was 0.473 on average (range: 0.790 of Hokkaido Area to 0.360 of Kanto Area), and the number for respiratory specialists ($n_{S/10}$) was 0.194 (range: 0.339 of Hokkaido Area to 0.118 of Kanto Area.

Regional comparison of the numbers of respiratory physicians and specialists per 10 departmental beds ($n_{R/10}$ and $n_{S/10}$) by hospital size, in provincial and rural areas (population less than 200,000) (based on the branch areas of Japanese Respiratory Society) (Fig. 2B)

Among large-sized hospitals ($n=158$), the number of respiratory physicians per 10 departmental beds ($n_{R/10}$) was 0.579 on average (range: 0.693 of Tokai Area to 0.447 of Tohoku Area). The number of respiratory specialists ($n_{S/10}$) was 0.223 on average (range: 0.235–0.240 of Tohoku, Kanto, Kyushu, and Tokai Areas, to 0.173 of Hokkaido Area). Among middle-sized hospitals ($n=301$),

the number of respiratory physicians ($n_{R/10}$) was 0.390 on average (range: 0.597 of Kyushu Area to 0.068 of Hokkaido Area). The number of respiratory specialists ($n_{S/10}$) was 0.181 (range: 0.308 of Chugoku/Shikoku Area to 0.068 of Hokkaido Area).

Self-containment level

When the self-containment levels for various respiratory diseases were examined among large-sized hospitals in relation to the location of the hospital, the survey found that the difference between metropolitan areas and rural areas was within 5% for the diagnosis and treatment of pneumonia, asthma, COPD, interstitial pneumonia, and chronic respiratory failure. On the other hand, the self-containment level was distinctly lower in rural areas for the treatment of acute respiratory failure, the diagnosis and treatment (chemotherapy) of lung cancer, and the diagnosis and treatment of pulmonary thromboembolism, pulmonary hypertension, and sleep apnea syndrome. However, the self-containment level for the terminal care of lung cancer was higher in rural areas (**Fig. 3**).

Personnel exchanges with university medical department offices

Analysis of the responses from 1,186 medical facilities as to the presence/absence of personnel exchanges with university medical department offices (called "ikyoku" in Japan) in relation to the size and location of the hospital revealed that the percentage of large-sized hospitals with such exchanges was highest in rural areas (82.9%), followed by metropolitan areas (82.4%), urban areas (80.4%), and provincial areas (77.4%), showing certain personnel exchanges existed in most hospitals. Among middle-sized hospitals, the percentage of such personnel exchanges was highest in rural areas (67.5%) and lowest in metropolitan areas (43.2%). Among small-sized hospitals, the percentage of the exchanges was highest (59.0%) in metropolitan areas, followed by rural areas (50.9%).

Discussion

One of the reasons for the shortage of physicians in Japan is an uneven distribution of hospital-employed physicians. According to the report of the Japanese Ministry of Health, Labour and Welfare, in 2007 there was a maximum 2.1-fold difference in the number of hospital-employed physicians per 100,000 population among prefectures.[2] On the other hand, this survey revealed a maximum 2.9-fold difference in the number of internists, 3.9-fold in respiratory physicians, and 6.1-fold in respiratory specialists among prefectures. Such disparity brings up the importance of quality equalization in respiratory medicine that transcends the borders of prefectures. Analysis of personnel exchange levels between university medical department offices and various community hospitals suggests that medical practice in rural areas is barely maintained by the personnel support from university medical department offices. This indicates that whether physicians in residency choose a university hospital or a community hospital as the site of training exerts a great influence on the status of medical practice for a region.

Geographical comparisons of the numbers of respiratory physicians and specialists per 10 departmental beds ($n_{R/10}$ and $n_{S/10}$) by hospital size revealed that, in Hokkaido and Tohoku Areas, the numbers of each type of physicians exceeded national averages in both large- and medium-sized hospitals in metropolitan and urban areas. However, for large- and middle-sized hospitals in provincial and rural areas of Hokkaido and Tohoku Areas, these figures were lower than the national averages. In particular, shortages of respiratory physicians and specialists were prominent in Hokkaido Area. These findings suggest that, in Hokkaido and Tohoku Areas, physicians are concentrated at large-sized hospitals and in urban areas, creating a depopulation of physicians among middle-sized hospitals and in rural areas. In contrast, distributions of respiratory physicians and specialists for middle-sized hospitals in provincial and rural areas showed higher densities in the western part and lower densities in the eastern part of Japan.

Among large-sized hospitals, the self-containment level was lower in rural areas than in large cities for the treatment of acute respiratory failure, chemotherapy for lung cancer, and diagnosis and treatment of intractable diseases such as pulmonary circulatory disorders, even though there was no marked difference for pneumonia, asthma, COPD, and terminal care of lung cancer. This suggests that the level of respiratory medicine is unevenly distributed in terms of the

quality. On the other hand, the difference in the self-containment level between large cities and small towns remained within 10% for intractable diseases like acute respiratory failure and interstitial pneumonia. This suggests that physicians who are not specialized in respiratory medicine have to entirely deal with respiratory diseases in regions where respiratory physicians are scarce. Middle-sized hospitals also show similar disparity. Furthermore, among small-sized hospitals, the self-containment level was even lower in large cities and small towns. In small towns where small-sized hospitals are predominant, there is the possible delay in the diagnosis and treatment before a patient arrives at a specialized hospital. Thus, patients in small towns may be at disadvantage in the field of respiratory medicine.

According to the report on the number of specialists by Subspeciality Society of Japanese Board of Medical Specialties, there were 14,657 gastrointestinal disease specialists and 10,354 circulatory disease specialists (as of March 2008).[3] On the other hand, the number of respiratory specialists was distinctly fewer, at 3,580.

The need for respiratory medicine in Japanese society is increasing, and people are asking to improve regional disparity and equalize the quality of medical practice. Therefore, it is urgent to foster more respiratory physicians and specialists in the nation to respond to those voices, including appropriate distribution of manpower.

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Supplementary note

A survey covering 168 community hospitals in Japan was conducted in 2004 to clarify the actual situation of respiratory physicians. It revealed that, in the department of respiratory medicine, the ratio of the number of full-time respiratory physicians to the number of departmental beds and that of respiratory specialists were 79% and 68%, respectively. In the department of gastrointestinal medicine, the ratio for full-time physicians was 61%, and 55% for the specialists. These differences clearly indicated the shortage of respiratory physicians.[1]