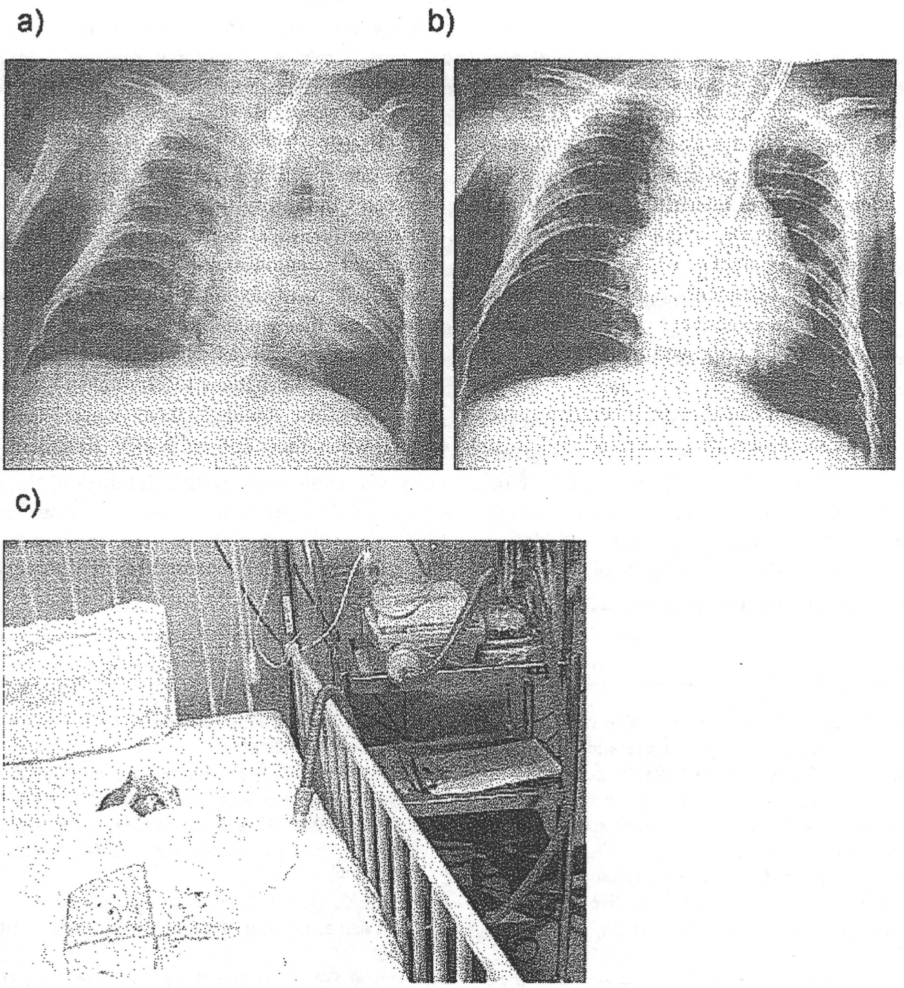

Figure 2. Chest X-ray showing change in the left upper lobar atelectasis on a) postoperative day (POD) 15 and b) POD 27. Photo of patient on ventilator is shown in c). Notice that atelectasis existed during mechanical ventilation on POD 15 (Fig. 2a) but was not present during NPPV treatment on POD 27 (Fig. 2b).

could easily open the vocal cords and assist ventilation. As described in our previous report, when NPPV is given to children, especially infants, this age group of patients generally refuses it initially, but will eventually come to accept the treatment once they see how it alleviates their symptoms such as dyspnea (1, 2). However, in the present case, the patient had never accepted NPPV treatment for his severe dyspnea as this could not be alleviated by NPPV. It is important to choose treatment carefully when deciding if a patient should receive NPPV under sedation or conventional mechanical ventilation via thoracostomy. In recently published original research papers and reviews, both intubation and tracheostomy were said to be associated with a number of adverse effects and, particularly in the pediatric population, complication rates of mechanical ventilation were as high as 40% (9), and those of tracheostomy as high as 51% (10). In addition, in our considerable and successful experience of NPPV treatment in pediatric patients (1-4), we generally use NPPV initially while we monitor and fully prepare for the conversion to endotracheal ventilation. In addition to NPPV treatment, however, sedation proved helpful for the current patient as mentioned above, and his symptoms and extent of lung collapse improved, as shown on the chest X-ray. During NPPV treatment of pediatric patients, including this case, it is important to watch for abdominal distension, which could induce vomiting and aspiration. To protect against these problems developing, we regularly check abdominal X-rays, in addition to careful physical inspection. We usually use a nasal mask and insert a gastric tube if necessary. Such cases may also occur in adults. At the start of treatment with NPPV, patients sometimes hesitate to use it because of discomfort. In such situations, we should intubate these patients, and use a ventilator if required (11). However, if the patient does not want to be intubated, it might be necessary to continue NPPV treatment (12). In these situations, NPPV treatment with sedation

may be helpful.

Monitoring sedation is an important issue. We used sedation to decrease the patient's excessive effort of breathing, which was thought to be worsening his stridor. Thus, we monitor our patients by the clinical assessment of the effort of breathing and stridor. It has been reported that most physicians monitor patients who are sedated during NPPV treatment by the clinical end points rather than by using a sedation scale widely used in ICU practice (8, 13). In the future, a sedation scale for NPPV treatment should be developed according to the accumulated experience. In addition, morbidity with symptoms might be improved by NPPV (12), as indeed was observed in this case.

UVCP is not an uncommon cause of perioperative postextubation failure, and its incidence after pediatric cardiac surgery ranges between 0.7% and 8.8% (14). One-third of patients with iatrogenic UVCP recover vocal function within 1.5 to 6.6 months (15). In the present patient, NPPV with sedation was effective not only in postextubation management of UVCP, but also in improving atelectasis, which is contrary to previous no-sedation strategies. Postoperative vocal cord paralysis occurs not only in infants, but also in adults. Therefore, we may encounter similar cases in adults as what we have described here in a 3-month-old infant (16-19).

Despite the limited clinical experience, this case clearly illustrates the utility of sedation in NPPV for a patient with postoperative vocal cord paralysis. In addition, NPPV with the proper sedation may be given to adult patients, including the elderly, who do not wish to be intubated. Proper sedation means that which appears to lead to a decrease in several symptoms such as dyspnea, discomfort, and anxiety and would allow the patient to continue to receive NPPV treatment. Because patients have worse outcomes, including death, when they fail on NPPV treatment, compared with those who avoid endotracheal intubation, the maintenance of a patient's comfort in the absence of insufficient respiratory drive is an important goal of the therapy in order to optimize the chances of successful NPPV treatment (5-8).

References

1. Chin K, Uemoto S, Takahashi K, et al. Noninvasive ventilation for pediatric patients including those under 1-year-old undergoing liver transplantation. Liver Transpl **11**: 188-195, 2005.
2. Chin K, Takahashi K, Ohmori K, et al. Noninvasive ventilation for pediatric patients under 1 year of age after cardiac surgery. J Thorac Cardiovasc Surg **134**: 260-261, 2007.
3. Narita M, Hatano E, Nagata H, et al. Prophylactic respiratory management after liver resection with bilevel positive airway pressure ventilation: Report of three cases. Surg Today **39**: 172-174, 2009.
4. Takahashi K, Chin K, Ogawa K, et al. Living donor liver transplantation with noninvasive ventilation for exertional heat stroke and severe rhabdomyolysis. Liver Transpl **11**: 570-572, 2005.
5. Teague WG. Non-invasive positive pressure ventilation: current status in paediatric patients. Paediatr Respir Rev **6**: 52-60, 2005.
6. Teague WG. Noninvasive ventilation in the pediatric intensive care unit for children with acute respiratory failure. Pediatr Pulmonol **35**: 418-426, 2003.
7. Essouri S, Nicot F, Clement A, et al. Noninvasive positive pressure ventilation in infants with upper airway obstruction: comparison of continuous and bilevel positive pressure. Intensive Care Med **31**: 574-580, 2005.
8. Devlin JW, Nava S, Fong JJ, Bahhady I, Hill NS. Survey of sedation practices during noninvasive positive-pressure ventilation to treat acute respiratory failure. Crit Care Med **35**: 2298-2302, 2007.
9. Norregaard O. NIV: indication in case of acute respiratory failure in children. In: Noninvasive Ventilation. European Respiratory Monographs. Vol. 41. Krister L, Muir J, Simonds A, Ambrosino N, Eds. ERS Journals Ltd, 2008: 110-132.
10. Mahadevan M, Barber C, Salkeld L, Douglas G, Mills N. Pediatric tracheotomy: 17 year review. Int J Pediatr Otorhinolaryngol **71**: 1829-1835, 2007.
11. Fauroux B, Lofaso F. Non-invasive mechanical ventilation: when to start for what benefit? Thorax **60**: 979-980, 2005.
12. Kacmarek RM. Should noninvasive ventilation be used with the do-not-intubate patient? Respir Care **54**: 223-229; discussion 229-231, 2009.
13. Sessler C, Grap MJ, Ramsay M. Evaluating and monitoring analgesia and sedation in the intensive care unit. Critical Care **12**: S2, 2008.
14. Clement WA, El-Hakim H, Phillipos EZ, Cote JJ. Unilateral vocal cord paralysis following patent ductus arteriosus ligation in extremely low-birth-weight infants. Arch Otolaryngol Head Neck Surg **134**: 28-33, 2008.
15. Truong MT, Messner AH, Kerschner JE, et al. Pediatric vocal fold paralysis after cardiac surgery: Rate of recovery and sequelae. Otolaryngol Head Neck Surg **137**: 780-784, 2007.
16. Hamdan AL, Moukarbel RV, Farhat F, Obeid M. Vocal cord paralysis after open-heart surgery. Eur J Cardiothorac Surg **21**: 671-674, 2002.
17. Itagaki T, Kikura M, Sato S. Incidence and risk factors of postoperative vocal cord paralysis in 987 patients after cardiovascular surgery. Ann Thorac Surg **83**: 2147-2152, 2007.
18. Wason R, Gupta P, Gogia AR. Bilateral adductor vocal cord paresis following endotracheal intubation for general anaesthesia. Anaesth Intensive Care **32**: 417-418, 2004.
19. Tesei F, Poveda LM, Strali W, Tosi L, Magnani G, Farneti G. Unilateral laryngeal and hypoglossal paralysis (Tapia's syndrome) following rhinoplasty in general anaesthesia: case report and review of the literature. Acta Otorhinolaryngol Ital **26**: 219-221, 2006.

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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

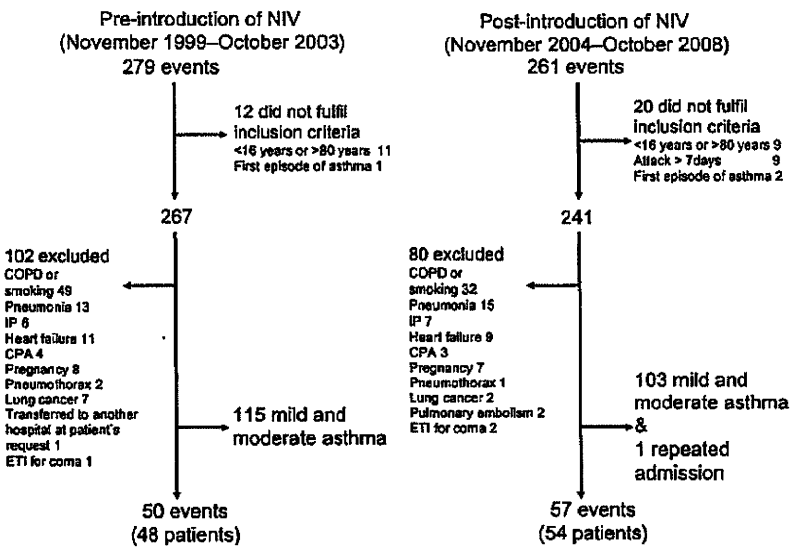

Figure 1 Diagram showing selection of patients experiencing severe attacks of asthma. CPA, cardiopulmonary arrest; ETI, endotracheal intubation; IP, interstitial pneumonitis; NIV, non-invasive ventilation.

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

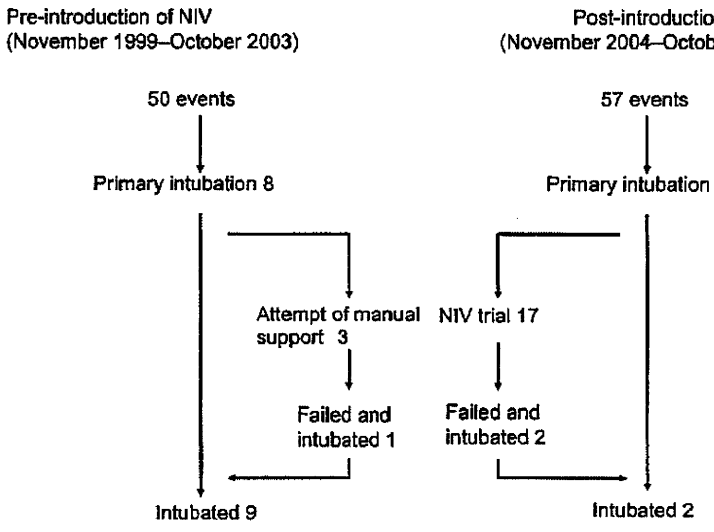

Figure 2 Diagram showing management of patients experiencing severe attacks of asthma. NIV, non-invasive ventilation.

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.

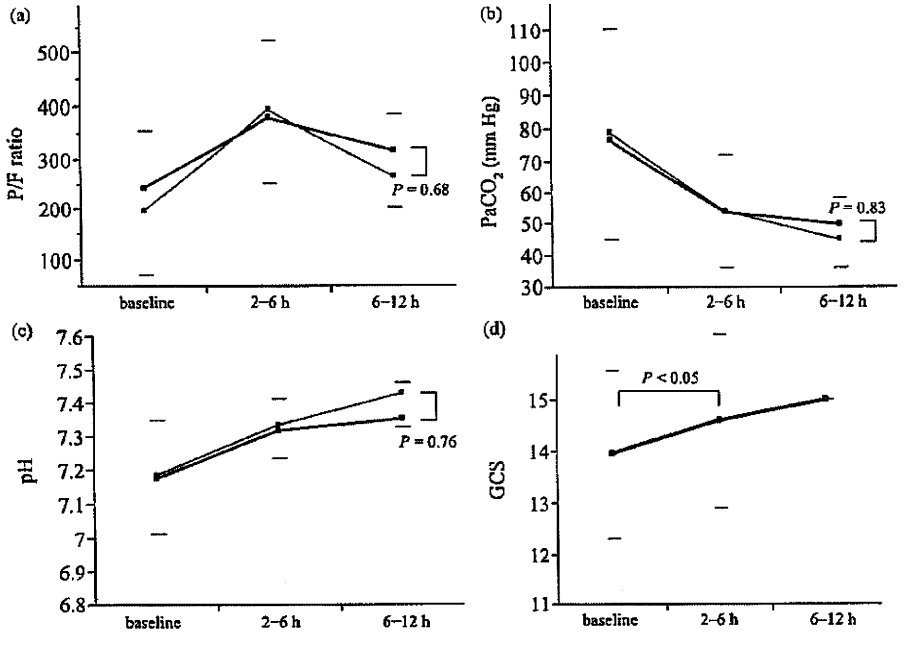

Figure 3 Changes over time in (a) PaO_2/FiO_2 (P/F) ratio, (b) $PaCO_2$, (c) pH and (d) Glasgow coma score (GCS), in patients experiencing severe attacks of asthma who were managed by mechanical ventilation (MV) with endotracheal intubation (ETI) or by non-invasive ventilation (NIV). Values were compared 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.

REFERENCES

1 Brochard L, Mancebo J, Wysocki M *et al.* Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. *N. Engl. J. Med.* 1995; 333: 817–22.
2 Bott J, Carroll MP, Conway JH *et al.* Randomised controlled trial of nasal ventilation in acute ventilatory failure due to chronic obstructive airways disease. *Lancet* 1993; 341: 1555–7.
3 Lenique F, Habis M, Lofaso F *et al.* Ventilatory and hemodynamic effects of continuous positive airway pressure in left heart failure. *Am. J. Respir. Crit. Care Med.* 1997; 155: 500–5.
4 Naughton MT, Rahman MA, Hara K *et al.* Effect of continuous positive airway pressure on intrathoracic and left ventricular transmural pressures in patients with congestive heart failure. *Circulation* 1995; 91: 1725–31.
5 Ram FS, Wellington S, Rowe B *et al.* Non-invasive positive pressure ventilation for treatment of respiratory failure due to severe acute exacerbations of asthma. *Cochrane Database Syst. Rev.* 2005; (3): CD004360.
6 Burns KE, Sinuff T, Adhikari NK *et al.* Bilevel noninvasive positive pressure ventilation for acute respiratory failure: survey of Ontario practice. *Crit. Care Med.* 2005; 33: 1477–83.
7 Papiris S, Kotanidou A, Malagari K *et al.* Clinical review: severe asthma. *Crit. Care* 2002; 6: 30–44.
8 Cormier Y, Lecours R, Legris C. Mechanisms of hyperinflation in asthma. *Eur. Respir. J.* 1990; 3: 619–24.
9 Stather DR, Stewart TE. Clinical review: mechanical ventilation in severe asthma. *Crit. Care* 2005; 9: 581–7.
10 Tomii K, Seo R, Tachikawa R *et al.* Impact of noninvasive ventilation (NIV) trial for various types of acute respiratory failure in the emergency department; decreased mortality and use of the ICU. *Respir. Med.* 2009; 103: 67–73.
11 Global Initiative for Asthma. Global strategy for asthma management and prevention, 2008. [Accessed 30 Nov 2009.] Available from URL: http://www.ginasthma.com/
12 McFadden ER Jr. Acute severe asthma. *Am. J. Respir. Crit. Care Med.* 2003; 168: 740–59.
13 Weiss KB, Wagener DK. Changing patterns of asthma mortality. Identifying target populations at high risk. *JAMA* 1990; 264: 1683–7.
14 Braman SS, Kaemmerlen JT. Intensive care of status asthmaticus. A 10-year experience. *JAMA* 1990; 264: 366–8.
15 Afessa B, Morales I, Cury JD. Clinical course and outcome of patients admitted to an ICU for status asthmaticus. *Chest* 2001; 120: 1616–21.
16 Pendergraft TB, Stanford RH, Beasley R *et al.* Rates and characteristics of intensive care unit admissions and intubations among asthma-related hospitalizations. *Ann. Allergy Asthma Immunol.* 2004; 93: 29–35.
17 Shapiro JM. Intensive care management of status asthmaticus. *Chest* 2001; 120: 1439–41.
18 Medoff BD. Invasive and noninvasive ventilation in patients with asthma. *Respir. Care* 2008; 53: 740–8; discussion 9–50.
19 British Thoracic Society; Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma. *Thorax* 2003; 58 (Suppl. 1): i1–94.
20 American Thoracic Society. Proceedings of the ATS workshop on refractory asthma: current understanding, recommendations, and unanswered questions. *Am. J. Respir. Crit. Care Med.* 2000; 162: 2341–51.
21 Pollack CV Jr, Fleisch KB, Dowsey K. Treatment of acute bronchospasm with beta-adrenergic agonist aerosols delivered by a nasal bilevel positive airway pressure circuit. *Ann. Emerg. Med.* 1995; 26: 552–7.
22 Meduri GU, Cook TR, Turner RE *et al.* Noninvasive positive pressure ventilation in status asthmaticus. *Chest* 1996; 110: 767–74.
23 Fernandez MM, Villagra A, Blanch L *et al.* Non-invasive mechanical ventilation in status asthmaticus. *Intensive Care Med.* 2001; 27: 486–92.
24 Soroksky A, Stav D, Shpirer I. A pilot prospective, randomized, placebo-controlled trial of bilevel positive airway pressure in acute asthmatic attack. *Chest* 2003; 123: 1018–25.
25 Soma T, Hino M, Kida K *et al.* A prospective and randomized study for improvement of acute asthma by non-invasive positive pressure ventilation (NPPV). *Intern. Med.* 2008; 47: 493–501.
26 Holley MT, Morrissey TK, Seaberg DC *et al.* Ethical dilemmas in a randomized trial of asthma treatment: can Bayesian statistical analysis explain the results? *Acad. Emerg. Med.* 2001; 8: 1128–35.
27 Benhamou D, Girault C, Faure C *et al.* Nasal mask ventilation in acute respiratory failure. Experience in elderly patients. *Chest* 1992; 102: 912–17.
28 Meduri GU, Turner RE, Abou-Shala N *et al.* Noninvasive positive pressure ventilation via face mask. First-line intervention in patients with acute hypercapnic and hypoxemic respiratory failure. *Chest* 1996; 109: 179–93.
29 Adnet F, Racine SX, Lapostolle F *et al.* Full reversal of hypercapnic coma by noninvasive positive pressure ventilation. *Am. J. Emerg. Med.* 2001; 19: 244–6.
30 Scala R, Naldi M, Archinucci I *et al.* Noninvasive positive pressure ventilation in patients with acute exacerbations of COPD and varying levels of consciousness. *Chest* 2005; 128: 1657–66.
31 Elliott MW, Confalonieri M, Nava S. Where to perform noninvasive ventilation? *Eur. Respir. J.* 2002; 19: 1159–66.
32 Silva GE, Sherrill DL, Guerra S *et al.* Asthma as a risk factor for COPD in a longitudinal study. *Chest* 2004; 126: 59–65.
33 Ulrik CS, Lange P. Decline of lung function in adults with bronchial asthma. *Am. J. Respir. Crit. Care Med.* 1994; 150: 629–34.
34 Vonk JM, Jongepier H, Panhuysen CI *et al.* Risk factors associated with the presence of irreversible airflow limitation and reduced transfer coefficient in patients with asthma after 26 years of follow up. *Thorax* 2003; 58: 322–7.

基礎からの睡眠医学

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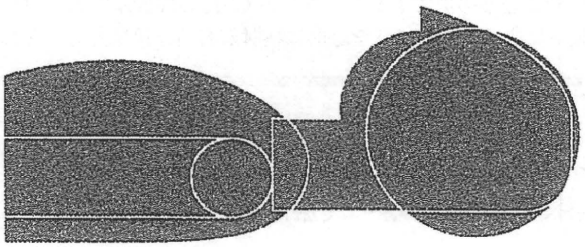

現代の“国民病”睡眠障害

24時間型・高齢化社会のなか増加する睡眠障害。
その臨床に必須の睡眠医学について、
基礎知識から各検査法および症状・診断・治療まで、
わかりやすく解説。医師、コ・メディカル、保健学系・医学系学生必携。

定価（本体5,800円十税） 名古屋大学出版会

8 各種疾患と睡眠障害
③生活習慣病

要旨

米国においては1,500万人の睡眠時無呼吸が存在するとの報告がみられる。閉塞性睡眠時無呼吸（OSA）の50％には高血圧があり40％がやがて糖尿病になり，高血圧患者の30％，糖尿病患者の23％はOSA患者とされる。また，重症のOSAの60〜70％以上はメタボリックシンドローム（Mets）を合併していると報告されている。Metsの管理は脳心血管障害の発症予防のために行われると記されているが，この目的は睡眠時無呼吸治療の目的と一致するものである。血液凝固系は脳心血管障害の発症に関与しているが，睡眠時無呼吸が血液凝固系に影響を与えるとの報告も多くみられる。中枢性無呼吸も心不全患者の予後を左右することも明らかになっている。睡眠時無呼吸は睡眠不足以外では日中の過度の眠気の最も頻度の高い原因である。顔面形態などの影響もあり，本邦のOSAの頻度は欧米と同程度とされる。睡眠時無呼吸は頻度が高く他領域に関連するので，学際的に検討が必要な領域と考えられる。

キーワード

○メタボリックシンドローム（metabolic syndrome：Mets）
○糖尿病　○代謝障害　○血液凝固　○肝障害

はじめに

睡眠時無呼吸は一見健康そうにみえる人達にみられ，しかもその頻度が高い。2003年に米国で二次性高血圧の原因の一つとされ[1]，2005年に診療機関受診の重症例では心血管障害，脳卒中の発症により予後が悪くなることが明らかにされたが[2]，2008年に一般人口においても同様な傾向のあることが明らかにされた[3・4]。ハリソン内科学書の最新版では，Douglas[5]が「閉塞性睡眠時無呼吸低呼吸症候群（obstructive sleep apnea hypopnea syndrome：OSAHS）は最近50年間で認識された最も重要な病態の一つである。OSAHSは世界的に主要な病態の一つであり，死亡の重要な原因の一つであり，日中の眠気の最も頻度の高い原因である」と述べており，関連ある病態として高血圧，心血管と脳血管障害，糖尿病，肝機能障害が挙げられている。2008年7月には国際糖尿病連合（International Diabetes Federation：IDF）から「睡眠時無呼吸と2型糖尿病に関するIDF合意声明」が発表され[6]，同声明では「2型糖尿病と睡眠呼吸障害（sleep-disordered breathing：SDB），特にSDBで最も頻度が高い閉塞性睡眠時無呼吸（obstructive sleep apnea：OSA）には関連がある可能性が，最近の研究によって示されている」「睡眠時無呼吸と2型糖尿病の関連への認識を高めることを目的としている。IDFは医療機関に，この2つの疾患の関連についての研究活動を促進することを求める。また，一つの疾患をもつ患者に対して他の疾患が伴う可能性が考慮されるべきである」と述べている[6]。同年9月

には The American Heart Association and the American College of Cardiology Foundation (AHA/ACCCF) から Sleep Apnea and Cardiovascular Disease という Scientific Statement (科学的な声明) が出た[7]。このように，睡眠時無呼吸，特に OSA は，世界的に頻度が高く，心血管障害患者，糖尿病患者などではその頻度はさらに高くなるので，医療経済的にもその病態の理解と治療の必要性が高まっている。

1 概念・定義

成人の 5 人に 1 人は無呼吸低呼吸指数 (apnea-hypopnea index : AHI) 5 以上であり，15 以上は 15 人に 1 人にみられると報告されており[8]，他の報告でも AHI 5 以上は 9〜26 % とされている[9]。糖尿病，高血圧症，冠動脈疾患，心筋梗塞などの疾患を有する患者における OSA の有病率はさらに高いと報告されている[8]。メタボリックシンドローム (metabolic syndrome : Mets) の定義には，World Health Organization (WHO)[10], National Cholesterol Education Program (NECP)[11], International Diabetes Federation (IDF)[12]，本邦の定義[13]などがあり，頻度を比較するとき注意が必要である。

2 疫 学

OSA の 50 % には高血圧があり[7]，40 % がやがて糖尿病になり[6]，高血圧患者の 30 %[7]，糖尿病患者の 23 % は OSA 患者とされる[14]。また，諸家の報告をまとめると重症の OSA の 60〜70 % 以上は Mets を合併していることになる。現在までに OSA 患者の Mets 頻度については 5 編の論文が発表されており[15〜19]，5 編中 1 編のみが，一般社会人口に基づいた成績である。同論文では結果として一般人口より有意に肥満傾向のある方が対象となっている[17]。男女比が不明の論文があるが，いずれにおいても男性は体重に独立して OSA 患者では有意に Mets の頻度が高いと報告されている[15〜19]。一方，Mets の構成要因である糖尿病，高脂血症などの代謝障害は，OSA の重症度よりも体重に依存していたとの報告もあり[20]，OSA と Mets の関連における体重の影響については今後も検討が必要と思われる。

3 病態生理

閉塞性睡眠時無呼吸—低呼吸および無呼吸—低呼吸後の再呼吸により低酸素血症，低酸素血症からの回復，高 $PaCO_2$ 血症，過度の胸腔内圧の変動，短期覚醒などが起こる。この無呼吸中の低酸素血症および短期覚醒に伴って，交感神経活動が亢進し短期覚醒直後に頂点になる一過性の血圧の上昇がみられる。この無呼吸と短期覚醒に伴う血圧の変動のため，OSA 患者は夜間睡眠中に高血圧なるとされ，夜間の高血圧を伴う血圧変動が OSA 患者の昼間の高血圧合併に関与している可能性が示唆されてきた。また，睡眠時無呼吸および無呼吸後の再呼吸は，低酸素血症，低酸素血症からの回復を起こすので，虚血・再潅流と同様な組織障害を引き起こすのではないかと考えられている[21・22]。睡眠ポリグラフ検査 (polysomnography : PSG) 上の短期覚醒の数は交感神経機能亢進，酸素飽和度 90 % または 85 % 以下などの時間は持続的低酸素，1 時間あたりの無呼吸・低呼吸数，または 3 % あるいは 4 % の酸素飽和度の低下回数は間欠的低酸素の影響を代表する指標と考えられている。間欠的低酸素は虚血再潅流と同様な影響を血管内皮などに酸化ストレスとして与え，全身性の炎症も起こし動脈硬化に導

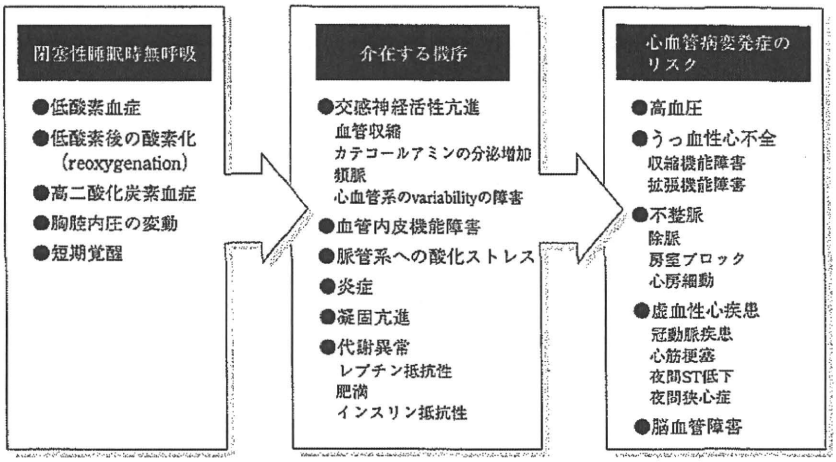

図1　閉塞性睡眠時無呼吸（OSA）と脳・心血管病変の関連（文献21より引用改変）

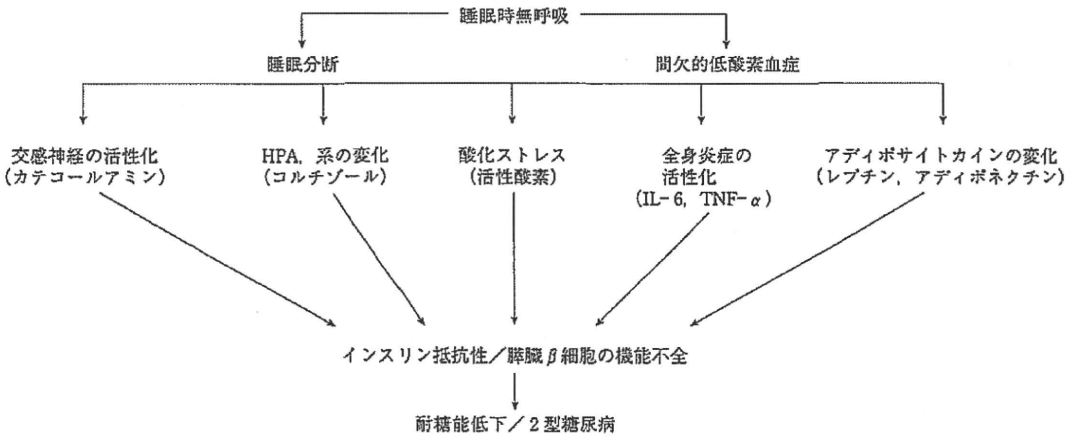

図2　睡眠時無呼吸と耐糖能低下を結びつけるメカニズム（文献6より引用改変）
HPA：視床下部一下垂体一副腎皮質。

くとの考えが示されている。なお，持続的低酸素はhypoxia-inducible factor-1（HIF-1），間欠的低酸素はNF-κBなどの転写因子を誘導し，その下流の様々の因子が全身病態を作り出すとの報告が増えている[22]。図1のようにOSAによる低酸素血症などは交感神経機能活動の亢進，血管内皮機能不全，血管への酸化ストレス，炎症，凝固機能の亢進，代謝機能障害を起こし，脳・心血管障害を誘発すると考えられつつある[7]。また，IDFの「睡眠時無呼吸と2型糖尿病に関するIDF合意声明」[6]では，OSAによる睡眠分断，間欠的低酸素血症が交感神経機能の活性化，視床下部一下垂体一副腎皮質系の変化，酸化ストレス，全身性炎症の活性化，アディポサイトカインの変化を介してインスリン抵抗性，膵臓のβ細胞の機能不全を招き，耐糖能低下／2型糖尿病へとつながるメカニズムが記されている（図2）。

4　症状・徴候

(1)　閉塞性睡眠時無呼吸（OSA）と内臓脂肪

OSA の肥満型は内臓脂肪蓄積型肥満との報告が多い[23・24]。AHI と内臓脂肪量が 1 次相関を示したとの報告がみられている。OSA 患者の内臓脂肪量は持続陽圧呼吸（continuous positive airway pressure：CPAP）療法により体重の変化なしに有意に低下したとの報告されている[25・26]。OSA における肥満の脂肪沈着の分布が内臓脂肪優位型であるとの報告以外にも上気道にも有意に脂肪が沈着し，気道を有意に狭窄させているのではないかとも考えられている。したがって，OSA が体内の脂肪の分布に影響を与える可能性も否定できない。

(2)　閉塞性睡眠時無呼吸（OSA）と耐糖能

2 つの大規模人数のインスリン抵抗性を homeostasis model assessment method（HOMA）index で測定した報告では，OSA とインスリン抵抗性は体重とは独立して関連していると報告されている[27・28]。また，クランプ法で調べた報告でも OSA は体重とは独立にインスリン抵抗性に関連していたが，特に非肥満群において OSA の影響は大であった[29]。筆者らの成績でも，CPAP 治療初日よりインスリン値は変化を認めなかったが血糖値の低下をみている[30]。

上記のようにすでに多くの臨床研究が睡眠呼吸異常（主に OSA）と糖代謝異常の関連を指摘していたが，米国での最近の大規模コホート（n＝2,656：Sleep Heart Health Study：SHHS）研究では，睡眠呼吸異常が睡眠 1 時間当たり 5～14.9 回の軽度睡眠時呼吸異常ではオッズ比 1.27（95％信頼区間：0.98，1.64），15 回以上の中等度から重度の睡眠時呼吸異常ではオッズ比 1.46（95％信頼区間：1.09，1.97）の空腹時血糖での耐糖能異常（$p<0.01$）が認められている[31]。睡眠呼吸異常に関連した低酸素血症が年齢，性，BMI，腹部周囲径と独立して耐糖能異常に関連していたと報告されている（図 3）[31]。

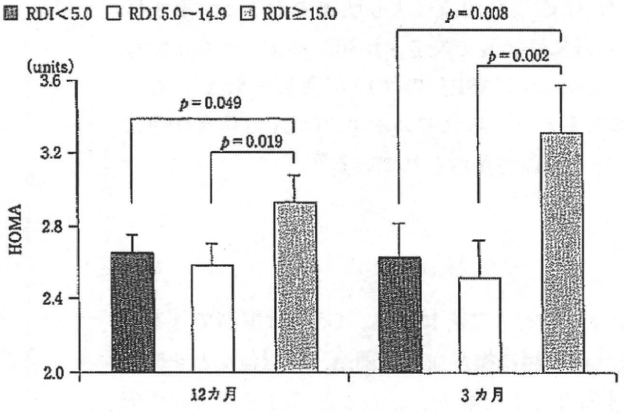

図 3　年齢，性，喫煙歴，BMI，腹部周囲径，および自己申告の睡眠時間によって補正された HOMA 指数と RDI の関連
（文献 31 より引用改変）

睡眠呼吸検査と血液検査の間隔が 12 カ月（n＝1,067）と 3 カ月（n＝405）のデータ。睡眠呼吸検査と血液検査の間隔が短いほど呼吸異常が HOMA 指数に大きな影響を与えている。RDI は AHI にほぼ同意。
HOMA 指数：homeostatis model assessment method index. RDI：respiratory disturbance index（睡眠呼吸障害指数）。

また，4 時間以上の CPAP 治療により血糖値，HbA1c の改善も報告されている[32]。このような背景のもと，世界糖尿病連合から声明が発表[6]されたと考えられる。

(3)　閉塞性睡眠時無呼吸（OSA）と脂質代謝

Ip ら[33]の報告によると 6 カ月の CPAP 治療により，体重の変化がないにも関わらず血清の中性脂肪値が有意に低下したとされる。さらにまた，1 カ月の CPAP 治療で total cholesterol が低下したと報告[34]されたが，著者らの検討でも，8 カ月以上の CPAP 治療によりコレステロール値が有意に低下している[27]。

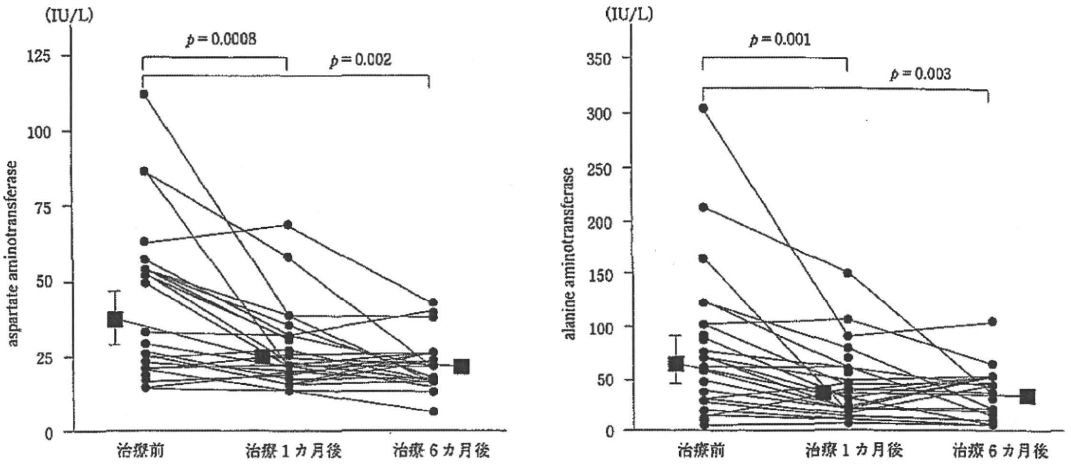

図4　持続陽圧呼吸（CPAP）治療後の肝機能の変化（文献36より引用改変）
●は個々の症例，■は平均値を示す。

(4)　閉塞性睡眠時無呼吸（OSA）と血液凝固障害

OSAにおける血液凝固障害については1995年頃から報告されている。フィブリノーゲン，血液粘性度，凝固因子の報告がみられ，最近ではD-ダイマー，PAI-1についても，OSAによる低酸素または間欠的低酸素が過凝固，血栓形成方向に働いているとの報告が多い[35]。

(5)　閉塞性睡眠時無呼吸（OSA）と肝障害

肥満患者においてウィルス肝炎以外の肝障害では脂肪肝の頻度は高いと考えらるが，肥満があるOSA患者の肝障害（恐らく大部分は脂肪肝と思われるが）はCPAP治療により改善することが示されている（図4）[36]。肥満人口の増加とともに，高度の脂肪肝に肝実質の炎症・壊死，線維化所見が加わった非アルコール性脂肪性肝炎（nonalcoholic steatohepatitis: NASH）の増加が注目されている。NASHはしばしば肝硬変に進行し予後不良の肝疾患になると考えられているが，OSAは体重に独立して肝酵素上昇，NASHのリスクファクターの一つである可能性が示されている[37]。

5　診断・鑑別

OSAであることをPSGなどで診断後，CPAP治療などを行うことにより，OSAは解消できるので，その後の経過をみて，内臓脂肪量，糖代謝，脂質代謝の諸指標，血液凝固系，肝機能などを経時的経過観察することにより，OSAの影響を明らかにすることができる。このときCPAPなどの治療機器の使用時間を客観的に計測して，CPAPなどが，使用されているか否かを確かめる必要がある。一般的に週5日，1日4時間以上の使用，すなわち週20時間以上の使用があればアドヒアランスありと判断されることが多い。実際，1日4時間以上のCPAP使用で耐糖能，内臓脂肪量，死亡率の改善の報告が最近もみられている[2・26・32]。また，1日平均3時間の使用で拡張期血圧の低下をみたと報告されている[38]。

様々なパラメータが変化したときにCPAPの効果か否かを明らかにするには，プラセボであると

考えられるsham-CPAPが必要であるとされるが，sham-CPAPによる数cmH_2OのCPAP圧であってもAHIはある程度は減少する。また，実際の臨床上でsham-CPAPを本邦で使用することは倫理上困難である。血糖値，脂質の値はわずかの体重の増減で変化するので，CPAP治療などによる効果か否かが判別困難なことも多いが，血圧に次いで最近ではOSAと糖代謝は関連があるとの考えが強くなりつつある[6,7]。

6 治療

CPAPなどによるOSAの治療が糖代謝，内臓脂肪蓄積量，血清脂質，脂肪肝による肝機能などの改善に効果がみられるとの報告があるが，いまだ確定したわけではない。OSA患者の7割以上は肥満傾向を認めるので，肥満を是正すれば，糖代謝，内臓脂肪量，血清脂質，脂肪肝による肝機能とともにOSAも改善する。一般的に10％の体重減量により，AHIは26％改善し，10％の体重増加により，AHIは30％増加するとされる。しかし，4年間の経過で10％以上の体重を減量できた者は全体の3％のみであったので[39]，CPAPなどの治療を行いながら，減量を心がけたほうがよいと指導すべきだろう。

7 予後

重症OSA患者であっても，CPAP治療4時間により対照群および軽中等症群と予後に差がなくなったと報告されている[2]。また，CPAPを1日1時間以上行うと予後に差がなかったとの報告もみられる[40]。Mets，代謝障害，血液凝固障害などは結果として脳心血管障害を起こして予後の悪化を招くことが多いので，予後に関しては，上記各個パラメータの改善も含めて毎日あるいは週5日以上CPAPを4時間以上装着する，あるいはそれが困難なら，毎日，床に入れば必ずCPAP装着することを励行すべきだと思われる。

おわりに

睡眠時無呼吸，特にOSAとMets，代謝障害，血液凝固，脂肪肝などの生活習慣病のうち，糖尿病と関連の強さがIDFの声明通り認識されつつある。しかしながら，他にも，例えば肝障害などのように多くの報告がなされつつある領域もあり，睡眠時無呼吸と生活習慣病の関連については今後ますます検討が増えていくと考えられる。

（陳 和夫）

文 献

1）Chobanian AV, Bakris GL, Black HR, et al: Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment on High Blood Pressure. Hypertension 42: 1208-52, 2003
2）Marin JM, Carrizo SJ, Vicente E,et al: Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet 365: 1046-53, 2005
3）Young T, Finn L, Peppard PE, et al: Sleep disordered breathing and mortality: eighteen-year follow-up of the Wisconsin Sleep Cohort. Sleep 31: 1071-8, 2008
4）Marshall NS, Wong KK, Liu PY, et al: Sleep apnea as an independent risk factor for all-cause mortality: The Busselton Health Study. Sleep 31: 1079-85, 2008

5) Douglas NJ : Sleep apnea. In : Harrison's Principle of Internal Medicine. 17th ed, pp. 1665-68, The McGraw-Hill, 2008
6) The IDF consensus statement on sleep apnoea and type 2 diabetes, 2008
7) Somers VK, White DP, Amin R, et al : Sleep apnea and cardiovascular disease. AHA/ACCF Scientific Statement. Circulation 118 : 1080-111, 2008
8) Young T, Skatrud J, Peppard PE : Risk factors for obstructive sleep apnea in adults. JAMA 291 : 2013-6, 2004
9) Basner RC : Continuous positive airway pressure for obstructive sleep apnea. N Engl J Med 356 : 1751-8, 2007
10) Jean-Louis G, Zizi F, Clark LT, et al : Obstructive sleep apnea and cardiovascular disease : role of the metabolic syndrome and its components. J Clin Sleep Med 4 : 261-72, 2008
11) Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP). Expert panel on detection, evaluation and treatment of high blood cholesterol in adults (adult treatment panel). JAMA 285 : 2486-97, 2001
12) Alberti KG, Zimmet P, Shaw J : Metabolic syndrome—a new world-wide definition. A Consensus Statement from the International Diabetes Federation. Diabes Med 23 : 469-80, 2006
13) メタボリックシンドローム診断基準検討委員会：メタボリックシンドロームの定義と診断基準．日内会誌 94 : 794-809, 2005
14) West SD, Nicoll DJ, Stradling JR : Prevalence of obstructive sleep apnoea in men with type 2 diabetes. Thorax 61 : 945-50, 2006
15) Coughlin SR, Mawdsley L, Mugarza JA, et al : Obstructive sleep Apnea is independently associated with an increased prevalence of metabolic syndrome. Eur Heart J 25 : 735-41, 2004
16) Gruber A, Horwood F, Sithole J, et al : Obstructive sleep apnoea is independently associated with the metabolic syndrome but not insulin resistance state. Cardiovasc Diabetol 5 : 22, 2006
17) Lam JCM, Lam B, Lam C, at al : Obstructive sleep apnea and metabolic syndrome in community-based Chinese adults in Hon Kong. Respir Med 100 : 980-7, 2006
18) Sasanabe R, Banno K, Otake K, et al : Metabolic syndrome in Japanese patients with obstructive sleep apnea syndrome. Hypertens Res 29 : 315-22, 2006
19) Parish JM, Adam T, Facchiano L : Relationship of metabolic syndrome and obstructive sleep apnea. J Clin Sleep Med 13 : 355-62, 2007
20) Sharma SK, Kumpawat S, Goel A, et al : Obesity, and not obstructive sleep apnea, is responsible for metabolic abnormalities in a cohort with sleep-disordered breathing. Sleep Med 8 : 12-7, 2007
21) Shamsuzzaman AS, Gersh BJ, Somers VK : Obstructive sleep apnea : implication for cardiac and vascular disease. JAMA 290 : 1906-14, 2003
22) McNicholas WT, Ryan S : Obstructive sleep apnoea syndrome : translating science to clinical practice. Respirology 11 : 136-44, 2006
23) Vgontzas AN, Bixler EO, Chrousos GP : Sleep apnea is a manifestation of the metabolic syndrome. Sleep Med Rev 9 : 211-24, 2005
24) Shinohara E, Kihara S, Yamashita S, et al : Visceral fat accumulation as an important risk factor for obstructive sleep apnoea syndrome in obese subjects. J Intern Med 241 : 11-8, 1997
25) Chin K, Shimizu K, Nakamura T, et al : Changes in intra-abdominal visceral fat and serum leptin levels in patients with obstructive sleep apnea syndrome following nasal continuous positive airway pressure therapy. Circulation 100 : 706-12, 1999
26) Trenell MI, Ward JA, Yee BJ, et al : Influence of constant positive airway pressure therapy on lipid storage, muscle metabolism and insulin action in obese patients with severe obstructive sleep apnoea syndrome. Diabetes Obes Metab 9 : 679-87, 2007
27) Punjabi NM, Sorkin JD, Katzel LI, et al : Sleep-disordered breathing and iusulin resistance in middle-aged and overweight men. Am J Respir Crit Care Med 165 : 677-82, 2002
28) Ip MS, Lam B, Ng MM, et al : Obstructive sleep apnea is independently associated with insulin resitance. Am J Respir Crit Care Med 165 : 670-6, 2002
29) Harsch IA, Schahin SP, Radespiel-Troger M, et al : Continuous positive airway pressure treatment rapidly improve insulin sensitivity in patients with obstructive sleep apnea syndrome. Am J Respir Crit Care Med 169 : 156-62, 2004
30) Shimizu K, Chin K, Nakamura T, et al : Plasma leptin levels and cardiac sympathetic function in patients with obstructive sleep apnoea-hypopnoea syndrome. Thorax 57 : 429-34, 2002
31) Punjabi NM, Shahar E, Redline S, et al : Sleep-disordered breathing, glucose intolerance, and insulin resistance.

The Sleep Heart Health Study. Am J Epidemiol 160 : 521-30, 2004
32) Babu AR, Herdegen J, Fogelfeld L, et al : Type 2 diabetes, glycemic control, and continuous positive airway pressure in obstructive sleep apnea. Arch Intern Med 165 : 447-52, 2005
33) Ip MS, Lam KS, Ho C, et al : Serum leptin and vascular risk factors in men with obstructive sleep apnea. Chest 118 : 580-6, 2000
34) Robinson GV, Pepperell JCT, Segal HC, et al : Circulating cardiovascular risk factors in obstructive sleep apnoea : data from randomised controlled trails. Thorax 59 : 777-82, 2004
35) 小賀徹：睡眠時無呼吸と血液凝固異常ー血管障害の危険因子ー(睡眠呼吸障害の合併症ーMultiple risk factor としての睡眠時無呼吸). 医学のあゆみ 224 : 919-22, 2008
36) Chin K, Nakamura T, Shimizu K, et al : Effects of obstructive sleep apnea syndrome on serum aminotransferase levels in obese patients. Am J Med 114 : 370-6, 2003
37) Tanne F, Gagnadoux F, Chazouilleres O, et al : Chronic liver injury during obstructive sleep apnea Hepatology 41 : 1290-6, 2005
38) Chin K, Nakamura T, Takahashi K, et al : Falls in blood pressure in patients with obstructive sleep apnoea after long-term nasal continuous positive airway pressure treatment. J Hypertens 24 : 2091-9, 2006
39) Peppard PE, Young T, Dempsey JMP, et al : Longitudinal study of moderate weight change and sleep disordered breathing. JAMA 248 : 3015-21, 2000
40) Campos-Rodriguez F, Pena-Grinan N, Reyes-Nunez N, et al : Mortality in obstructive sleep apnea-hypopnea patients treated with positive airway pressure. Chest 128 : 624-33, 2005

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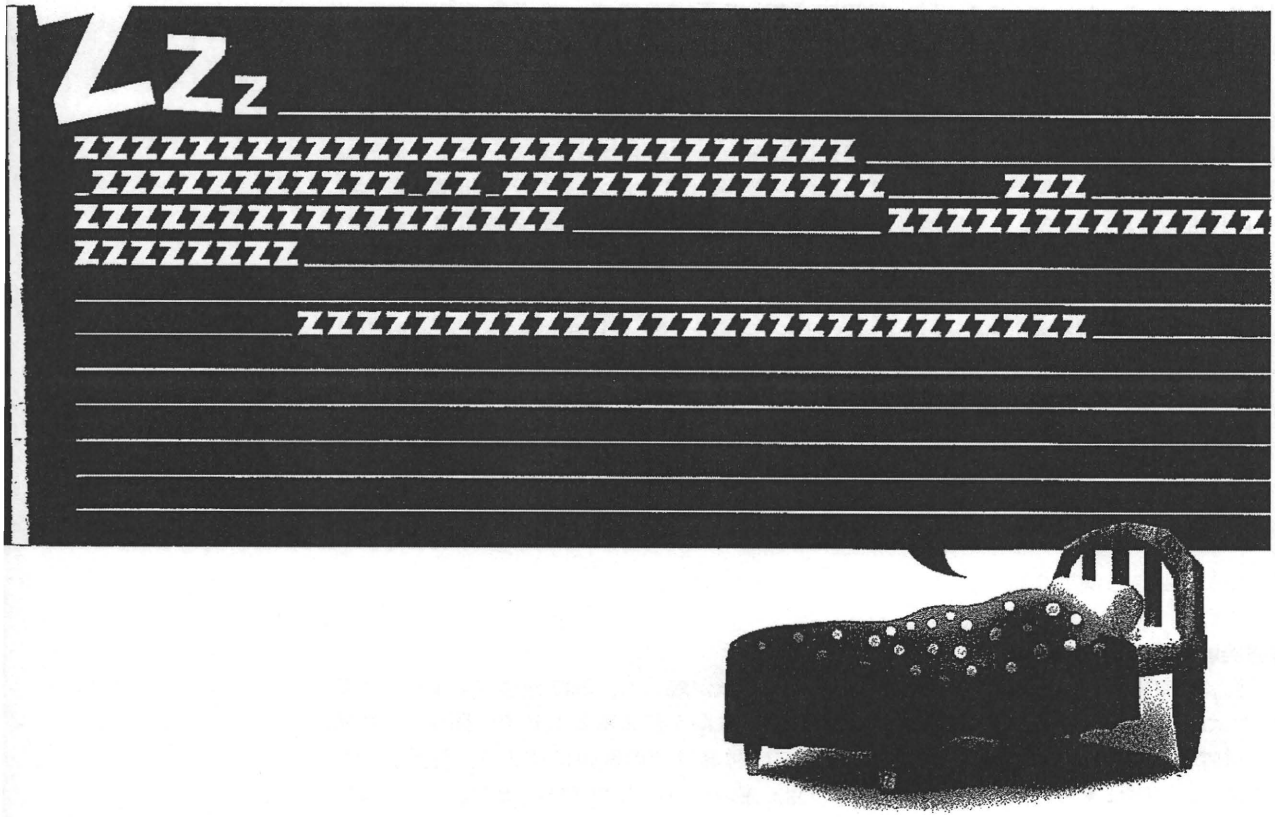

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