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Clinical reports

Respiratory failure due to morbid obesity in a patient with Prader-Willi syndrome: an experience of long-term mechanical ventilation

Masashi Nishikawa[1], Taro Mizutani[2], Tomohei Nakao[3], Tomohiro Kamoda[5], Shinji Takahashi[4], and Hidenori Toyooka[4]

[1] Department of Anesthesiology, University of Tsukuba Hospital, Tsukuba, Japan
[2] Department of Critical Care Medicine, Institute of Clinical Medicine, University of Tsukuba, 1-1-1 Tennoudai, Tsukuba, 305-8575, Japan
[3] Department of Pediatrics, University of Tsukuba Hospital, Tsukuba, Japan
[4] Department of Anesthesiology, Institute of Clinical Medicine, University of Tsukuba, Tsukuba, Japan
[5] Department of Pediatrics, Institute of Clinical Medicine, University of Tsukuba, Tsukuba, Japan

Abstract
Prader-Willi syndrome (PWS) is characterized by obesity, mild mental retardation or learning disability, and behavior problems, especially in association with food and eating. A 19 year-old man, 150 cm, 140 kg (body mass index [BMI], 62.2 $kg \cdot m^{-2}$), whose condition had been diagnosed as PWS, received 41-day mechanical ventilation because of respiratory failure, chiefly due to morbid obesity. Because the patient frequently developed bronchoconstriction, metered-dose inhalers of a corticosteroid (beclomethasone dipropionate) and a β2 agonist (salbutamol) were needed. To achieve adequate sedation, which was also crucial to control the bronchoconstriction, the concurrent use of midazolam, fentanyl, ketamine, and propofol was required. Pressure-control ventilation was useful to avoid high airway pressure due to low respiratory system compliance associated with the morbid obesity. Because it appeared that the basic problem leading to respiratory failure in this patient was morbid obesity, body weight reduction was considered to be mandatory. Thus, caloric intake was limited to 1000 $kcal \cdot day^{-1}$, resulting in body weight reduction by 50 kg during the patient's stay in the intensive care unit (ICU). The patient was successfully extubated on ICU day 35.

Key words Prader-Willi syndrome · mechanical ventilation · respiratory failure · obesity

Introduction

Prader-Willi syndrome (PWS) is characterized by obesity, mild mental retardation or learning disability, and behavior problems, especially in association with food and eating, resulting in a debilitating physical and developmental disability in adolescence and adulthood [1]. It has been reported that sleep-related ventilatory abnormalities, e.g., sleep apnea, occur in patients with PWS [2–4]. We experienced 41-day mechanical ventilation in a 19-year-old male patient with PWS who was morbidly obese.

Address correspondence to: T. Mizutani
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Case report

A 19 year-old man, 150 cm, 140 kg (body mass index [BMI], 62.2 $kg \cdot m^{-2}$) was brought to our hospital in an ambulance because of loss of consciousness and a fall. His condition had been diagnosed as PWS at the age of 1 year, also being diagnosed as a sleep apnea syndrome and mild mental retardation later. Chromosomal analysis in his infancy showed a microdeletion in 15q11-13, by which the diagnosis of PWS was confirmed. During the ambulance transportation, $S_{P_{O_2}}$ decreased to 60%–70%. Over the previous 3 years, the patient's body weight had gradually increased from 100 kg to 140 kg, and he experienced dyspnea.

On admission, arterial blood gas values were: pH, 7.22; P_{CO_2}, 77 mmHg; and P_{O_2}, 112 mmHg, while oxygen was delivered at a flow of 4 $l \cdot min^{-1}$ via a nasal cannula. On chest X-ray, elevation of the diaphragm and low volume in both lungs were seen. Blood chemistry revealed increases in liver enzymes (aspartate aminotransferase [AST], 98 $IU \cdot l^{-1}$; alanine aminotransferase [ALT], 109 $IU \cdot l^{-1}$) and mild hyperglycemia (140 $mg \cdot dl^{-1}$). On hospital day 2, arterial blood gases were: pH, 7.17; P_{CO_2}, 98 mmHg; and P_{O_2}, 100 mmHg. Because the hypercapnia had worse ned, he was moved to the high-care unit, and noninvasive positive pressure ventilation, using the BiPAP S/T-D device (Respironics, Carlsbad, CA, USA) was attempted. However, due to his mental retardation, it became obvious, within half an hour, that using the BiPAP continuously was impossible. Because the patient remained hypercapnic and became unconscious, mechanical,

ventilation, using the BEAR 1000 device (VIASYS Healthcare, Conshohocken, PA, USA) was started, following orotracheal intubation, which was carried out without difficulties. Initial ventilator settings were as follows: synchronized intermittent mandatory ventilation (SIMV) mode, using volume-control SIMV (VC-SIMV); $F_{I_{O_2}}$, 0.6; tidal volume (V_T), 500 ml; frequency of SIMV (f), 18; positive end-expiratory pressure (PEEP), 5 cmH_2O; and pressure-support ventilation (PSV), 8 cmH_2O. At that time, peak inspiratory pressure (PIP) amounted to 35–40 cmH_2O. After the initial stabilization period, arterial blood gas values were: pH, 7.49; P_{CO_2}, 48 mmHg; and P_{O_2}, 114 mmHg, with the same ventilator settings as those above and at an $F_{I_{O_2}}$ of 0.4. On hospital day 8, the patient was transferred to the intensive care unit (ICU) to be treated more intensively.

Four difficulties regarding mechanical ventilation had to be overcome. First, it was extremely difficult to obtain appropriate sedation using common sedative agents, such as midazolam and propofol. The patient needed relatively deep sedation, because his agitation triggered bronchoconstriction, as described below. Because 1% propofol, at a rate of 200–250 $mg \cdot h^{-1}$, alone, was inadequate, midazolam, 7.5–15 $mg \cdot h^{-1}$, was added. However, this combination was replaced by another combination, i.e., fentanyl 0.2–0.25 $mg \cdot h^{-1}$ and midazolam, 20–50 $mg \cdot h^{-1}$ after several days to avoid the high caloric intake associated with massive propofol infusion. Still, the combined infusion of fentanyl and midazolam for 4 days could not bring about adequate sedation. Thus, ketamine 40–120 $mg \cdot h^{-1}$ was added, but it became more and more difficult to obtain adequate sedation over the next 10 days. Finally, propofol, 50–100 $mg \cdot h^{-1}$ was added again, resulting in an acceptable sedation level, using four sedative agents concurrently. The second difficulty was that the patient frequently developed bronchoconstriction, which caused transient hypoxia and hypercapnia, although he had no previous history of asthma. To prevent and control this asthma-like attack, it appeared to be effective to use metered-dose inhalers of a corticosteroid (beclomethasone dipropionate), and a β2 agonist (salbutamol), utilizing an in-line chamber device (ACE MDI Spacer; DHD Healthcare, Wampsville, NY, USA) regularly. The third difficulty was that, during mechanical ventilation, the airway pressure tended to be very high, due to low respiratory system compliance (Crs) associated with the morbid obesity as well as the repeated bronchoconstriction. Therefore, immediately after the beginning of mechanical ventilation, the ventilatory mode was changed from VC-SIMV to pressure-control SIMV (PC-SIMV) with PIP of 32 cmH_2O, by which V_T ranging from 300 to 450 ml was obtained. Also, the levels of PSV and PEEP were raised to 24 and 8 cmH_2O, respectively. Shortly thereafter, ventilatory mode was changed to pressure-control ventilation (PCV), using an inspiratory time of 1 s, because the ventilator had fixed PSV termination criteria, thereby causing premature inspiratory termination during PSV breathing. The fourth difficulty was that as the basic problem leading to the respiratory failure appeared to be the morbid obesity, body weight reduction was considered to be mandatory. Thus, caloric intake was limited to 1000 $kcal \cdot day^{-1}$, resulting in body weight reduction by 50 kg during the patient's 40-day ICU stay. For the initial 1 week of his ICU stay, total parenteral nutrition was utilized, because of a relatively large volume of gastric regurgitation. Subsequently, enteral nutrition was introduced, from 100 $ml \cdot day^{-1}$ to 1000 $ml \cdot day^{-1}$ over 4 weeks. During this period, he developed no hyper-, or hypoglycemia, and no ketosis. Fluid and electrolyte balance was evaluated and corrected on a daily basis, along with daily body weight measurement (Century CC; Hill-Rom, Batesville, IN, USA).

Around hospital day 10, the patient developed mild right heart failure associated with pericardial effusion, diagnosed by chest X-ray and echocardiography, which was treated successfully with furosemide. The patient received frequent positional changes and meticulous skin care by the ICU nurses. During the whole period of his ICU stay, he remained afebrile, without apparent signs of infection or pressure sores.

Gradually the patient's respiratory condition became better. The frequency of bronchoconstriction decreased and Crs improved (Fig. 1). Therefore, weaning, i.e., decreases in f, PEEP, and the PSV level proceeded step by step. Also, the doses of sedative drugs, i.e., propofol, midazolam, and ketamine were gradually reduced, to 150 $mg \cdot h^{-1}$, 10 $mg \cdot h^{-1}$, and 40 $mg \cdot h^{-1}$, respectively. Propofol and ketamine were discontinued several hours before extubation. Just prior to the extubation, his respiratory rate and V_T were 14–20 $breaths \cdot min^{-1}$ and 280–300 ml, respectively, with continuous positive airway pressure mode being used, with 6 cmH2O PSV. Finally, the patient was extubated successfully on ICU day 35. Three hours after the extubation, arterial blood gas values were: pH, 7.39; P_{CO_2}, 53 mmHg; and P_{O_2}, 155 mmHg, while oxygen was delivered at a flow of 7 $l \cdot min^{-1}$, using a face mask.

Discussion

Respiratory failure is well known to be a frequent cause of death in patients with PWS [4]. We believe that this is the first case report of a young adult with PWS who required long-term mechanical ventilation due to morbid obesity, although an ex-premature neonate with PWS who required 55-day mechanical ventilation after birth has been reported [5].

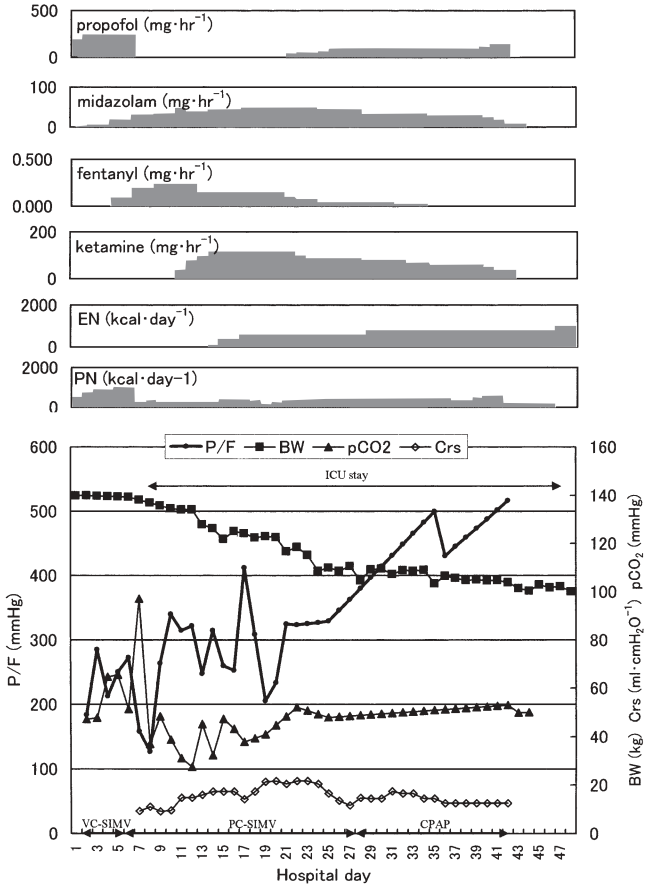

Fig. 1. Changes in dosages of sedative drugs and in amounts of enteral nutrition (*EN*) and parenteral nutrition (*PN*), including lipid administration associated with propofol infusion are shown in the *upper graphs*. Changes in the $P_{O_2}/F_{I_{O_2}}$ ratio (*P/F*), body weight (*BW*), arterial carbon dioxide partial pressure (pCO_2), respiratory system compliance (*Crs*), and ventilatory mode, i.e., volume-control synchronized intermittent mandatory ventilation (*VC-SIMV*), pressure-control SIMV (*PC-SIMV*), and continuous positive airway pressure (*CPAP*) are shown in the *lower graph*. *ICU*, intersive care unit

In sedated and paralyzed morbidly obese patients, markedly reduced functional residual capacity, an increased alveolar-arterial oxygenation gradient, the presence of an inflection point in the pressure-volume curve, and increased resistance of the respiratory system have been observed [6]. These findings appeared to be attributable to a reduction in lung volume due to the excessive unopposed intraabdominal pressure [6], and the basic pathophysiology in our patient's respiratory failure seemed to be consistent with the above findings. Very high airway pressure was a problem during mechanical ventilation, especially while volume-control ventilation (VCV) was being used in the early phase of the patient's ICU stay. In this regard, PCV is useful to avoid excessively high airway pressure in patients with low-compliance lungs, such as in acute respiratory distress syndrome (ARDS) [7,8].

During mechanical ventilation, according to the clinical practice guidelines [9], mainly midazolam or propofol, and fentanyl have been used to sedate patients in our ICU. In this patient, however, as many as four sedative and analgesic agents were used simultaneously to achieve optimal sedation. The exact mechanism of this "tolerance" was unclear, although it has been shown that the daily dose requirements of midazolam and propofol for adequate sedation increased progressively over time [10]. Because ketamine has a bronchodilatory action [11], ketamine administration seemed to be effective in ameliorating the bronchoconstriction in our patient. Although ketamine is not a common sedative agent in adult ICU patients, it has been used safely in pediatric patients [12] and patients with head injuries [13]. Propofol is available as an emulsion in a phospholipid vehicle, which provides 1.1 kcal·ml^{-1} from fat, and should be counted as a caloric source [9]. Hypertriglyceridemia due to long-term or high-dose propofol infusion has been documented [10]. Because only a 1% preparation was available in Japan at that time [14], we were very cautious not to give a large amount of propofol.

During our patient's ICU stay, enteral feeding was initiated as soon as possible according to the relevant guidelines [15]. About 40 kg of body weight reduction was thought to be needed, because he had had no respiratory problems 3 years earlier when his body weight was 100 kg, although his ideal body weight was 47.8 kg. According to the Harris-Benedict equation [16], the basal energy expenditure of a 150-cm tall, 19-year old male at 100 kg and 47.8 kg would be 2063 and 1345 kcal, respectively. Therefore, the caloric intake set at 1000 kcal·day^{-1} in this patient appeared to be not unrealistic and not unsafe. In addition, extreme caution was used to assure the safety of the body weight reduction, by means of laboratory tests and daily body weight measurements. We believe the successful weaning from mechanical ventilation was largely attributable to the body weight reduction [17].

Bronchoconstriction, which often appeared during the early period of our patient's ICU stay, was successfully treated and prevented by using metered-dose inhalers of a corticosteroid and a β2 agonist on a regular basis. If these measures had been ineffective, inhalational anesthetics such as sevoflurane might have been worth trying.

In conclusion, in a young adult patient with PWS, we experienced long-term mechanical ventilation due to morbid obesity. A variety of measures, including body weight reduction, use of the PCV mode, meticulous sedation, and treatment of bronchoconstriction were necessary to accomplish successful weaning from the mechanical ventilation.

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