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Primary Pulmonary Hypertension With Central Sleep Apnea

— Sudden Death After Bilevel Positive Airway Pressure Therapy —

Toshiaki Shiomi, MD; Christian Guilleminault, MD*; Ryujiro Sasanabe, MD; Yoshitaka Oki, MD; Rika Hasegawa, MD; Kazuo Otake, MD; Katsuhisa Banno, MD; Kengo Usui, MD; Masato Maekawa, MD; Hitoshi Kanayama, MD**; Ryoutaro Takahashi, MD**; Tadashi Kobayashi, MD

An obese 23-year-old man with sleep-disordered breathing and primary pulmonary hypertension (PPH) had been administered oral beraprost sodium, anticoagulant warfarin, and home oxygen therapy, at another hospital as treatment for the PPH, but he had not experienced any symptomatic improvement. The patient had a body mass index of 32.4 kg/m^2, and complained of fatigue, shortness of breath on exertion, excessive daytime sleepiness, and snoring. Arterial blood gas analysis showed a PaO_2 and a $PaCO_2$ of 70.9 and 31.2 mmHg, respectively. A polysomnographic study revealed central sleep apnea with an apnea–hypopnea index (AHI) of 29.7 episodes/h. The patient showed improvement of daytime sleepiness after starting nocturnal nasal bilevel positive airway pressure (BiPAP) therapy for the central sleep apnea, but his pulmonary hypertension, measured in the daytime, worsened. The patient died suddenly while walking to the bathroom in the morning 1 month after initiation of BiPAP therapy. It is necessary to consider the possibility of sudden death when nasal BiPAP therapy is given to a PPH patient with central sleep apnea. (*Jpn Circ J* 2000; **64:** 723–726)

Key Words: Central sleep apnea; Nasal bilevel positive airway pressure; Primary pulmonary hypertension; Sleep-related breathing disorders; Sudden death

Primary pulmonary hypertension (PPH), a general term for precapillary pulmonary hypertension of unknown etiology,[1–3] is usually progressive with a very poor prognosis. Death occurs within an average of 2.8 years[3] and sudden death occurs in 7% of these patients.[4] PPH is treated medically with calcium antagonists, prostacyclin, anticoagulants, or surgically using techniques such as atrial septostomy, lung transplantation and combined heart–lung transplantation.[2,5] Sleep apnea syndrome (SAS) is characterized by two major symptoms (ie, excessive daytime sleepiness and nocturnal apnea accompanied by snoring) and is associated with a high incidence of cardiovascular disease, including hypertension, ischemic heart disease, and pulmonary hypertension. The incidence of pulmonary hypertension among SAS patients without apparent cardiopulmonary disease is 15–20%.[6,7] However, the relationship between PPH and sleep-related breathing disorders such as SAS is unclear. To further the body of knowledge about this condition, we report a case of PPH and repetitive central sleep apnea.

Case Report

The patient was a 23-year-old man, 161 cm tall and weighing 84 kg, with a body mass index of 32.4 kg/m^2. As a teenager he had partaken in normal physical activities, but he reported development in the recent past of inexplicable fatigue, which progressively worsened, and development of shortness of breath on exertion. The medical examination, performed at a previous hospital, showed a blood pressure of 108/74 mmHg, a heart rate of 76 beats/min, and a respiration rate of 24 breaths/min. Arterial blood gas analysis showed an oxygen partial pressure (PaO_2) of 70.9 mmHg and a carbon dioxide partial pressure ($PaCO_2$) of 31.2 mmHg. Chest X-ray showed enlarged central pulmonary arteries and cardiac dilatation with a cardiothoracic ratio of 63%. The electrocardiogram showed right ventricular hypertrophy, with right ventricular and atrial dilatation

Table 1 Hemodynamic Data* Before and After BiPAP

	Before BiPAP	*After BiPAP*
Systemic BP, systolic (mmHg)	*116*	*108*
Systemic BP, diastolic (mmHg)	*83*	*74*
Systemic BP, mean (mmHg)	*94*	*85*
PAP, systolic (mmHg)	*77*	*91*
PAP, diastolic (mmHg)	*33*	*38*
PAP, mean (mmHg)	*50*	*58*
PCWP (mmHg)	*5*	*10*
Transpulmonary gradient (mmHg)	*45*	*48*
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	*2.17*	*2.44*
pH	*7.41*	*7.48*
$PaCO_2$ (mmHg)	*31.2*	*32.5*
PaO_2 (mmHg)	*70.9*	*79.6*
SaO_2 (%)	*94.5*	*95.8*

**All mesurements dose while patient was awake. Right-heart catheter data and arterial blood gas samples taken before and after 2 weeks of nasal bilevel positive airway pressure (BiPAP) therapy.*
PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; Transpulmonary gradient, mean PAP–PCWP.

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*The Third Department of Internal Medicine, Aichi Medical University School of Medicine, Aichi, Japan, *Sleep Research Center, Stanford University School of Medicine, Stanford, California, USA and **Department of Medicine, Kamo Hospital, Toyota, Japan*
Mailing address: Toshiaki Shiomi, MD, The Third Department of Internal Medicine, Aichi Medical University, 21 Karimata, Yazako, Nagakute-cho, Aichi-gun, Aichi 480-1195, Japan

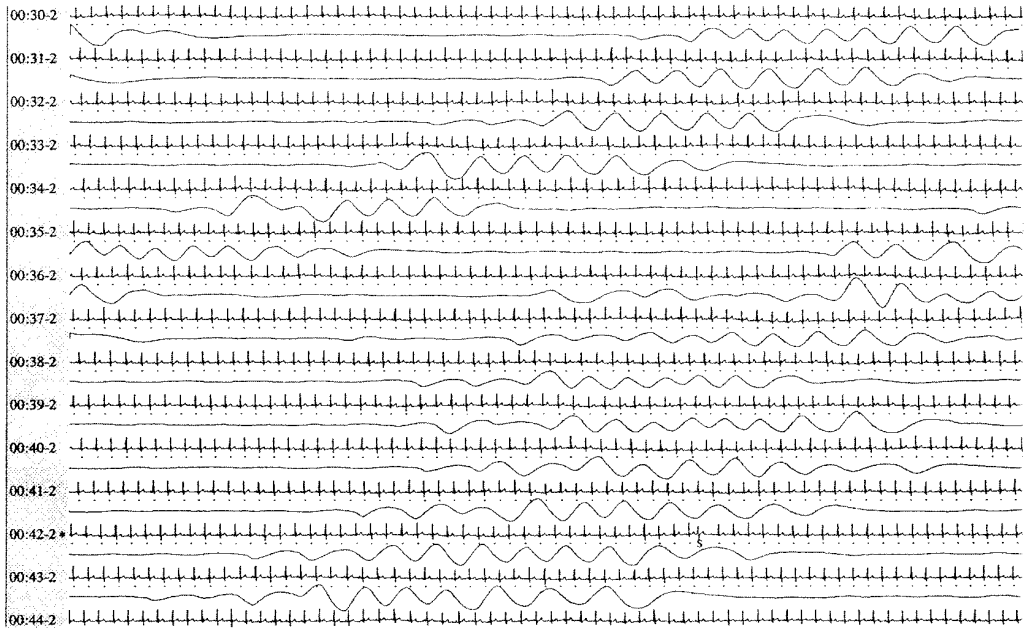

Fig 1. Holter monitoring with nasal air flow shows the repeated episodes of sleep apnea.

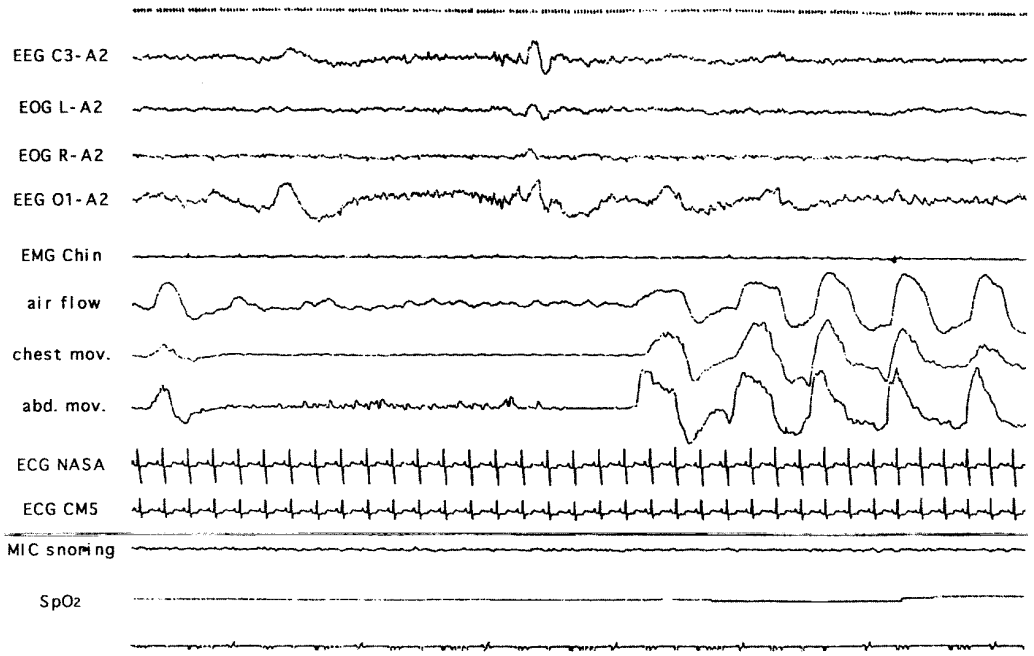

Fig 2. Polysomnographic recording shows the central sleep apnea in a primary pulmonary hypertension (PPH) patient.

apparent on echocardiography. The cardiac function was New York Heart Association class III. Abdominal ultrasonography showed hepatomegaly and congestion of the liver. Lung ventilation-perfusion scintigraphy and femoral vein ultrasonography yielded no findings suggestive of thrombi. Pulmonary angiography and right heart catheterization had been previously performed and there had not been any signs of thrombi in the pulmonary vascular tree. The pulmonary artery pressure (PAP) was 77/33 mmHg and the pulmonary capillary wedge pressure was 5 mmHg, supporting a diagnosis of PPH (Table 1). Oral administration of 120 μg/day of beraprost sodium, 3.5 mg/day of anticoagulant warfarin, and home oxygen therapy had been started at the previous hospital to treat PPH, but had not lead to symptomatic improvement. The presence of SAS was also suspected due to snoring and excessive daytime sleepiness in an obese subject. The Holter monitoring with nasal airflow showed repeated episodes of apnea during nocturnal sleep[11] (Fig 1). The patient was then referred to us for sleep evaluation, nocturnal polysomnography (PSG) and

treatment, including the possible use of continuous positive airway pressure (CPAP) during sleep.

The PSG included the following: electroencephalogram (EEG, $C_3/A_2-O_1/A_2$); electrooculogram (EOG); chin electromyogram (EMG); electrocardiogram (ECG); and pulse oximetry. Respiration was monitored by measurement of airflow (oro-nasal thermistors), thoracic and abdominal movements, and neck microphone. The PSG study determined sleep states, sleep stages, apnea, and hypopnea in accordance with the international criteria[12] The total sleep time was 475 min, the sleep latency was 8 min, and the rapid eye movement (REM) latency was 74 min. There were 72% of stage 1, 6% of stage 2, 2% of stage 3, 1% of stage 4, and 16% of REM sleep, results indicative of very abnormal sleep. The apnea–hypopnea index (AHI; number of apneas and hypopneas per hour of sleep) was 29.7 episodes/h and the lowest arterial oxygen saturation (SaO_2) was 74.3%. Most of the apnea episodes were central (91.2%), 2.3% were obstructive, and 6.5% of the events were scored as hypopnea. There was no Cheyne-Stokes breathing (defined as a pattern of crescendo/decrescendo breathing). The conclusion of the study was that the patient had predominantly central sleep apnea (Fig 2).

The central sleep apnea was initially treated by oral administration of acetazolamide (500 mg/day), but this was quickly discontinued when the patient developed nausea and numbness of hands and feet several days after beginning the treatment[13] Following this, nocturnal nasal bilevel positive airway pressure (BiPAP) therapy was initiated (the patient signed an informed consent prior to the start of treatment)[8–10] Calibration of BiPAP was performed with PSG, and all central sleep apneas were controlled with an inspiratory positive airway pressure of 6 cmH_2O and an expiratory positive airway pressure of 3 cmH_2O. The lowest SaO_2 during the night was 88%. Table 1 shows the results of right heart catheterization performed in the daytime, and compares the results obtained at the previous hospital before treatment with those obtained after 2 weeks of BiPAP. The interval between catheterizations was 56 days. Symptoms such as snoring and daytime sleepiness improved during BiPAP therapy, but the catheterization showed an increase of the PAP to 91/38 mmHg. One month after initiation of BiPAP therapy, the patient died suddenly when walking to the bathroom in the morning while hospitalized. An autopsy was not performed as consent could not be obtained from the family.

Discussion

Primary pulmonary hypertension is more common than obstructive SAS in women. The cause of death in Japanese patients with PPH is right-heart failure in 53% of cases and sudden death in 37%, with these 2 mechanisms comprising 90% of deaths. Life expectancy after the onset of signs of right-heart failure is extremely short (mean, 18 months; range, 7 months to 5 years)[14,15] Although the complication of pulmonary hypertension caused by hypoxic vasoconstriction is well known in patients with severe SAS, no clinical studies have been conducted on SAS associated with PPH. If PPH occurs in an obese man, such as the present patient, it is difficult to establish a diagnosis because of the difficulty in distinguishing this condition from obstructive SAS complicated by obesity hypoventilation syndrome, Pickwickian syndrome, or severe pulmonary hypertension. However, patients with obesity hypoventilation syndrome or Pickwickian syndrome usually have not only daytime hypoxemia, but also hypercapnemia. The low $PaCO_2$ (31.2 mmHg) supported a diagnosis of PPH, because there was not any evidence of pulmonary thromboembolism on scintigraphy[16] Hyperventilation appears to be the main cause of hypocapnemia in PPH[17] and we believe that the low $PaCO_2$ also played an important role in causing the central sleep apnea in our case.

Thalhofer et al reported that nasal BiPAP therapy was an effective treatment for pulmonary hypertension in patients with central sleep apnea;[18] but Palasiewicz et al reported that CPAP increased pulmonary intravascular pressure, but that BiPAP did not affect central pulmonary hemodynamics[19] In the present case, oral acetazolamide therapy for the central sleep apnea was quickly discontinued because of the side effects and nasal BiPAP therapy instituted after the PSG titration study. Unfortunately, we were unable to evaluate the effect of BiPAP on the evolution of the PAP during central sleep apnea, but as shown by the follow-up PSG and repeated clinical evaluation, nasal BiPAP lead to symptomatic improvement and better sleep. Oxygen desaturation improved, but pulmonary hypertension measured in the daytime worsened (Table 1). The patient died suddenly 1 month after initiation of BiPAP therapy, at a time when his level of daytime activity was gradually increasing.

It seems that either central sleep apnea is unrelated to pulmonary hypertension, or that the nocturnal BiPAP treatment alone is unable to reverse an already advanced daytime pulmonary hypertension. Attention must be paid to the patient's daytime activity level after nocturnal BiPAP therapy is instituted. Combination therapy may be appropriate in such a case; that is, nocturnal BiPAP therapy and continuous daytime intravenous infusion of epoprostenol (prostacyclin, PGI_2) without oral beraprost sodium. Even if a fatal arrhythmia or a pulmonary thromboembolism was suspected, the cause of the present patient's death remains unclear because the autopsy was not performed. Our experience suggests that consideration of sudden death is necessary if nasal BiPAP therapy is given for central sleep apnea in a PPH patient.

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