demonstrated that 3 Gy is the tolerance dose in the lung in single fractional irradiation. It remains unknown why a single patient showed RP changes reaching the region exposed to the far lower dose of 3 Gy. Some immunologic processes induced by tissue destruction in single fractional high-dose irradiation might be involved in the extension of RP, and further observation of the radiation changes in the lung after single fractional high-dose irradiation is required.

In conclusion, KL-6 is a useful marker for the prediction of the occurrence of RP after single, fractional, high-dose stereotactic irradiation of lung tumors. The extent of RP might reach beyond the tolerance dose of single fractional lung irradiation, and it is necessary to examine the mechanism of RP as well as that of the increment of KL-6 after single, fractional, high-dose stereotactic irradiation.

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Reversal of Nocturnal Periodic Breathing in Primary Pulmonary Hypertension After Lung Transplantation*

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Nocturnal periodic breathing (PB) closely resembling Cheyne-Stokes respiration in congestive heart failure has been reported to occur in end-stage primary pulmonary hypertension (PPH). We herein describe the clinical course of a 56-year-old female patient with PPH and severe hypoxemia, hypocapnia, and right ventricular compromise in whom sleep-disordered breathing (SDB) resolved after successful double-lung transplantation. This case illustrates the crucial roles of blood gas alterations and hemodynamic impairment in the emergence of PB in PPH, and is in favor of a genuine association between advanced right heart failure and the development of SDB.

Key words: lung transplantation; periodic breathing; primary pulmonary hypertension

Abbreviations: AHI = apnea-hypopnea index; CHF = congestive heart failure; CI = cardiac index; CSR = Cheyne-Stokes respiration; DlCO = diffusion capacity of the lung for carbon monoxide; PAP = pulmonary artery pressure; PB = periodic breathing; PPH = primary pulmonary hypertension; SaO2 = oxygen saturation; SDB = sleep-disordered breathing; TST = total sleep time

We have recently reported that patients with advanced primary pulmonary hypertension (PPH) may have nocturnal periodic breathing (PB) closely resembling Cheyne-Stokes respiration (CSR) in congestive heart failure (CHF).1 Presumably, hemodynamic impairment with

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prolongation of circulation time of chemical stimuli of breathing plays an important role in the emergence of PB in PPH. Blood gas alterations, ie, hypoxemia and hypocapnia, are also likely to contribute to breathing instability in patients with PPH. We now describe the clinical course of a patient with PPH and PB in whom sleep-disordered breathing (SDB) disappeared after successful double-lung transplantation.

**Case Report**

A 56-year-old woman was first admitted to our hospital in May 1998. She reported shortness of breath during minimal physical exercise (New York Heart Association class III). On physical examination of the tachypneic patient, facial and acral cyanosis and distention of the jugular veins could be detected. Furthermore, slight ankle edema was noted. Pulmonary auscultation was normal. The second heart sound was split, and a holosystolic murmur was heard over the tricuspid valve area. Otorhinolaryngologic and neurologic evaluation did not reveal any abnormalities. Body weight was normal (body mass index of 26.1).

Pulmonary function testing with arterial blood gas analysis showed normal ventilation, a marked reduction of diffusion capacity of the lung for carbon monoxide (DLCO), and severe hypoxemia and hypocapnia. Transthoracic echocardiography demonstrated right atrial and ventricular enlargement, whereas the left ventricle had normal dimensions and contractility. Ultrasound Doppler measurements revealed high-grade tricuspid valve insufficiency and marked elevation of systolic pulmonary artery pressure (PAP) [Table 1].

Next, spiral and high-resolution CT scans of the chest were performed, which excluded the presence of proximal pulmonary emboli or parenchymal lung disease. Ventilation-perfusion scans were without evidence for central or peripheral pulmonary embolism. Sonorolog testing for collagen vascular or autoimmune disease was negative. Finally, Swan-Ganz catheterization (Edwards Lifesciences, Irvine, CA) with pharmacologic testing was done, showing severe precapillary pulmonary hypertension with a concomitant reduction in cardiac output (mean PAP, 59 mm Hg; pulmonary vascular resistance, 1,631 dyne·cm⁻²·m⁻³; pulmonary capillary wedge pressure, 6 mm Hg; cardiac index [CI], 1.53 L/min/m²; right ventricular ejection fraction, 6%). Based on these investigations, the diagnosis of PPH was established, and the patient was started on oral angiotensin-converting enzyme inhibitors and long-term oxygen therapy. Furthermore, regular daily inhalations with iloprost (Ventavis, Schering AG, Berlin, Germany), a stable prostacyclin analog, were initiated as previously described.²

As the patient reported nocturnal awakenings and excessive daytime sleepiness (Epworth sleepiness scale score of 12), full-night attended polysomnography was performed. Polysomnography was carried out with the help of a computerized system (SIDAS GS; IfM GmbH; Wettenberg, Germany) that continuously monitored the following parameters: EEG (electrodes at the positions C3/A2 and C4/A1 of the international 10–20 system), electrooculogram, electromyogram of the submental and pretibial muscles, oronasal flow (probes), thoracoabdominal breathing movements (inductive plethysmography), oxygen saturation (SaO₂) [pulse oximetry at the finger tip], and snoring (microphone). Analysis of sleep stages, arousals, and breathing while asleep was visually performed according to standard criteria.³ An obstructive apnea was diagnosed if complete cessation of oronasal flow occurred in the presence of thoracoabdominal breathing movements. If neither oronasal flow nor breathing efforts of the chest and abdomen could be detected, the apnea was scored as central.

Hypopnea was defined as a reduction in the respiratory amplitude of >50% compared to the preceding signals. All apneas and hypopneas were required to have a duration of at least 10 s. The apnea-hypopnea index (AHI) was obtained by dividing the total number of these events through the total sleep time (TST). An AHI of >10/h of sleep was considered to be diagnostic of SDB. PB was required to show a crescendo-decrescendo pattern of hyperventilatory phases between central apneas and hypopneas (at least three consecutive cycles). Furthermore, the obstructive AHI had to be <10/h. While breathing room air, the sleep recordings revealed the presence of severe PB with marked nocturnal oxygen desaturations (Table 2; Fig 1, top). During a second night, oxygen was administered via nasal prongs at a flow rate of 3 L/min. This led to an improvement in nocturnal SaO₂, however, the PB pattern persisted (AHI, 58/h; mean SaO₂, 91.5%; SaO₂ < 90% during 7% of TST; lowest SaO₂, 72%).

In June 1999, the patient was readmitted because of clinical deterioration. Lung function and blood gases had not significantly changed (DLCO, 60% of predicted; PaO₂, 44 mm Hg; PaCO₂, 27 mm Hg) but right-heart catheterization demonstrated a further progress of the pulmonary hypertension (mean PAP, 64 mm Hg; pulmonary vascular resistance, 2,023 dyne·cm⁻²·m⁻³; pulmonary capillary wedge pressure, 6 mm Hg; CI, 1.32 L/min/m²; right ventricular ejection fraction, 5%). Polysomnography performed under oxygen administration continued to show PB (AHI, 64/h; PaCO₂ 50% compared to the preceding signals. All

<table>
<thead>
<tr>
<th>Variables</th>
<th>Before Transplant</th>
<th>After Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI, no./h of TST</td>
<td>78</td>
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</tr>
<tr>
<td>AHI obstructive, no./h of TST</td>
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<td>1</td>
</tr>
<tr>
<td>AHI central, no./h of TST</td>
<td>70</td>
<td>2</td>
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<tr>
<td>PB, % of TST</td>
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<td>Nocturnal SaO₂ mean, %</td>
<td>90.5</td>
<td>93.5</td>
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<td>Lowest nocturnal SaO₂, %</td>
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<td>84</td>
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<tr>
<td>Nocturnal SaO₂ &lt; 90%, % of TST</td>
<td>34</td>
<td>3</td>
</tr>
<tr>
<td>NREM 1 + 2, % of TST</td>
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<td>58</td>
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<tr>
<td>NREM 3 + 4, % of TST</td>
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<tr>
<td>REM, % of TST</td>
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<td>22</td>
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<tr>
<td>Sleep efficiency, % of TIB</td>
<td>78</td>
<td>84</td>
</tr>
<tr>
<td>Arousal index, no./h of TST</td>
<td>65</td>
<td>12</td>
</tr>
</tbody>
</table>

Table 2—Sleep Study Results Before and After Double-Lung Transplantation*

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CHEST / 125/1 / JANUARY, 2004

345

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*NREM = nonrapid eye movement sleep; REM = rapid eye movement; TIB = time in bed.
mean $\text{Sa}_2$, 90.2%; $\text{Sa}_2 < 90\%$ during 3% of TST; lowest $\text{Sa}_2$, 66%). The patient was switched to IV iloprost and set on a transplant waiting list. At this time, left-heart catheterization was performed and ruled out significant coronary artery disease, intracardiac shunting, or left ventricular dysfunction.

In September 2000, the patient received a double-lung transplant (at the University Hospital of Homburg/Saar; Dr. Schäfers). The postoperative clinical course was complicated by acute renal failure requiring intermittent hemodialysis and cytomegalovirus infection of the transplanted lungs, but finally the patient recov-
ered. Four months later, polysomnography was again performed with the patient breathing room air and without any cardiac medications. At this time, blood gases were normal and echocardiography was without evidence for any persistent pulmonary hypertension (Table 1). The patient reported a better sleep quality and a reduction in her daytime sleepiness (Epworth sleepiness scale score of 9). The sleep study now showed completely normal breathing with well-preserved nocturnal SaO₂ (Table 2; Fig 1, bottom).

**Discussion**

In our opinion, this case illustrates the complex interaction of blood gas alterations and hemodynamic impairment in the emergence of PB in patients with PPH. In the patient under discussion, multiple factors were present predisposing to PB: a reduced CI, a pronounced decrease of PaCO₂ to a point that was presumably below the apneic threshold, and marked hypoxemia that increases chemoreflex gain. Following lung transplantation, hemodynamic parameters, circulation time, and blood gases were normalized, and the SDB was no longer observed. The same is true for CSR in CHF, which disappears after successful cardiac transplantation.⁶

In our original series of 20 patients with PPH, a beneficial effect of nasal oxygen administration on nocturnal PB was observed in the majority of the affected patients.¹ In the present case, the PB was unresponsive to oxygen therapy. Similar observations have been made in CSR-CHF patients in whom the SDB persists despite optimal medical therapy and oxygen supplementation. In these patients, noninvasive positive pressure ventilation may be initiated and has been shown to result in better overall survival.⁷ In contrast, as suggested by a case study, treatment with continuous positive airway pressure or bilevel ventilation might be harmful to patients with PPH and PB,³ and therefore we did not start this form of therapy in our patient.

A possible limitation of the polysomnographic recordings employed in the present study is that they were carried out without esophageal probes. We decided not to insert such a device in this severely ill, anticoagulated patient, and to rely on the characteristics of the thoracoabdominal breathing movements when differentiating between obstructive and central apneas.

The fact that we did not obtain invasive hemodynamic data after lung transplantation might be regarded as a further drawback. However, we think that the echocardiographic examination performed after lung transplantation sufficiently excluded any persistent pulmonary hypertension.

In summary, we herein describe for the first time the reversal of nocturnal PB in patients with PPH by successful lung transplantation. In our opinion, this case report underlines the importance of blood gas alterations and hemodynamic impairment for the development of PB in patients with PPH. In addition, as there was no evidence for CHF or a neurologic disease process, a genuine association between severe right-heart failure and the development of SDB might be inferred from the present study.

**References**