Sleep Apnea Syndrome and End-stage Renal Disease*

Cure After Renal Transplantation

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We report two patients undergoing maintenance hemodialysis who presented with sleep apnea syndrome (SAS). The first patient is a 36-year-old man with a terminal Berger's glomerulopathy and associated obstructive sleep apnea syndrome (OSAS) (apnea-hypopnea index [AHI] = 80). He was receiving home hemodialysis and was treated by nasal continuous positive airway pressure (CPAP). After successful renal transplantation, his symptoms completely disappeared, and control polysomnography greatly improved (AHI = 9). The second patient had hypokalemic nephropathy with severe, uncontrolled hypertension and hypertensive myocardopathy. He was receiving home dialysis and showed a central sleep apnea syndrome with an AHI of 51. He also was successfully treated by nasal CPAP. After renal transplantation, his sleep improved, insomnia disappeared, and polysomnography showed great improvement (AHI = 5). We discuss the role of periodic breathing related to end-stage renal disease associated metabolic abnormalities, as a pathogenetic factor of these SAS. Respiratory correction of chronic metabolic acidosis, “uremic toxins,” “middle molecules,” and hemodialysis are all evoked as etiologic factors and their own roles are discussed.

(Ches] 1993; 103:1330-35)

AHI = apnea/hypopnea index; CI = cardiac index; CPAP = continuous positive airway pressure; CSAS = central sleep apnea syndrome; ESRD = end-stage renal disease; OSAS = obstructive sleep apnea syndrome; PLM = periodic leg movement; RDI = respiratory disturbance index; SAS = sleep apnea syndrome; SRDB = sleep-related breathing disorder; UPPP = uvulopalatopharyngoplasty; WASO = wakefulness after sleep onset

Obstructive sleep apnea syndrome (OSAS) has a multifactorial origin. Each factor acts with its own preponderance in each subject. Opening or closure (partial or complete) of the upper airway depends on a subtle balance of forces among the following: respiratory drive that determines negative suction pressure; upper airway caliber; and respiratory control stability that influences synchrony (timing and activation intensity) between upper airway muscles and diaphragm.

The epidemiology of OSAS suggests the association of two or more predisposing factors in order to manifest the complete syndrome: subtle anatomic abnormalities need be associated with obesity or another “risk factor” such as periodic breathing (by itself multifactorial). Enlarging the upper airway rarely cures OSAS. However, in OSAS, periodic respiration is still described after tracheostomy or during spontaneous ventilation when awake.

OSAS has been described in patients with chronic renal insufficiency and end-stage renal disease and is thought to be related to metabolic factors. During metabolic acidosis, compensatory hyperventilation leads to hypocapnia thus more easily reaching the “apneic threshold” at sleep onset, generating periodic respiration and destabilization of respiratory control. "Uremic toxins" or other metabolic abnormalities related to renal failure influence respiratory control. Their action is controversial: dialysis has been reported to improve or worsen sleep-related breathing disorders (SRDB). The following cases illustrate how kidney transplantation improves OSAS as well as central sleep apnea syndrome (CSAS).

Case Reports

Case 1

In March 1990, a 36-year-old man was sent to our unit by an ear, nose, and throat surgeon to be submitted to polysomnography before undergoing a uvulopalatopharyngoplasty (UPPP). The patient had had Berger's disease since 1977 and had been receiving hemodialysis since 1988. He was treated by home dialysis three times per week with bicarbonate buffer on cellulose acetate membrane.

Hypertension appeared in 1986, and he was treated first by β-blockers and then by Ca" -antagonists (nifedipine). Arterial blood pressure was about 135/85 mm Hg under treatment. Clinically, he had no significant neuropathy, and he underwent a parathyroidectomy in 1989.

He had sustained an episode of altitude cardiogenic lung edema during a stay at a height of 1,200 m. Hyperkinetic myocardopathy (arteriovenous fistula and chronic anemia) had been assessed by cardiac catheterization: wedge pressure was 23 mm Hg, mean pulmonary arterial pressure was 55, cardiac index (CI) was 6.5 L/

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min/m², and cardiac output was 10 L/min.

He was a snorer (for approximately 10 years) but this recently caused marital trouble; he had been hypersomnolent for a few months, as his renal disease worsened.

Sleep disturbances reported by the patient are numerous: many nocturnal awakenings, morning tiredness, and diurnal hypersomnolence that impaired work activity. Disruptive snoring appeared a few months before patient entry and his wife described nocturnal obstructive apneas.

The patient was 170 cm in height and 50 kg in weight. Results of pulmonary function tests were normal. He had never been a smoker or a drinker. Renal anemia was present: red blood cell count was 2.9; hemoglobin was 7.5 g/L; and hematocrit was 0.22. Arterial blood gases at rest were as follows: PaO₂, 82 mm Hg; PaCO₂, 34 mm Hg; and pH, 7.34. Serum bicarbonate level was 18 mmol/L; creatinine, 1.330 µmol/L; urea, 30 mmol/L before dialysis; respectively, 21 mmol/L, 500 µmol/L, and 12 mmol/L after dialysis. Chest radiograph was normal.

This patient presented with a slight retrognathia (dental overjet); unfortunately, cephalometric data are not available. The uvula was normal.

Polysomnography was performed the day after a dialysis session. Electroencephalogram (A2/C4, A1/C3), submental electromyogram (EMG), and electro-oculogram (EOG), were recorded to sleep stages according to the Rechtschaffen and Kales manual. Nasal and oral airflow were detected with thermistors and respiratory movement was detected with strain gauges; hemoglobin saturation was continuously recorded. Disordered breathing events (apneas and hypopneas) were defined according to standard criteria.

Polysomnography shows an OSAS with an apnea/hypopnea index (AHI) of 80 (Table 1) and other results typical of OSAS. However, it must be underlined that AHI was much more elevated in NREM sleep (97/H) than that in REM sleep (30/H), an unusual finding.

Because of our knowledge of interactions between chronic renal failure and OSAS, we do not recommend UPFF. Moreover, many predictable postanesthetic problems are an additional argument to favor continuous positive airway pressure (CPAP).

Nasal CPAP was successfully used (+ 10 cm H₂O) but compliance was poor because of nasal dryness and discomfort. On the other hand, renal transplantation was indicated and realized in April 1990. CPAP was stopped by the patient immediately after.

Another polysomnography examination was performed in October 1990. At this time, the patient had had sleeping without snoring, and nocturnal dyspnea disappeared. The patient was again alert all day long.

Arterial blood gases were normal with a pH of 7.41, PaCO₂ of 40, and PaO₂ of 86; serum creatinine level was 186 µmol/L; urea was 13.5 mmol/L; serum bicarbonate was 30 mmol/L; RBC count was 4.9 10¹²/L; and hemoglobin was 16.5 g/dL. Glomerular filtration (insulin clearance) was 47 ml/min.

Blood pressure was 125/75 mm Hg; hemodynamic study was not performed but high output probably persisted because arteriovenous fistula was still in function.

This second polysomnogram showed disappearance of OSAS (Table 1), but persistence of a slight periodic respiration. However, no hypopnea per se (50 percent reduction of respiratory flux associated with a 4 percent fall of saturation) was seen.

Objective sleep data improved, however, with an increase in wakefulness after sleep onset (WASO) related to first half-night difficulties to stably fall asleep, associated with a possible "sleep lab effect" that was prominent because of disappearance of hypersomnolence.

CASE 2

The second patient was a 37-year-old man who had a hypokalemic-induced nephropathy secondary to long-term evolution of mental anorexia (1969 to 1974). His weight was 48.5 kg; his height was 1.65 m.

He had severe uncontrolled hypertension since 1981. Despite multiple treatments, blood pressure reached 200/140 mm Hg. Hypertensive myocardopathy developed with the first episode of cardiogenic lung edema in 1989. Doppler echography showed a severe hypertrophic "restrictive" myocardopathy with severe left ventricular compliance alteration.

Dialysis began in February 1990 when the patient presented in overt refractory cardiac failure. Home dialysis was realized three times per week for 4 h, with acetate buffer.

Sleep disturbances were reported since December 1989 with associated nocturnal insomnia and daytime hypersomnolence. Insomnia was related to breathing disturbances corresponding probably to nocturnal lung edema: orthopenia, nocturnal cough, laryngeal crackles. The patient's wife described apneas during sleep. He was an occasional snorer; resumption of breathing was said to be noisy.

Biologic data (September 1990) are the following: hemoglobin, 7.3 g/dl; hematocrit, 0.20; and RBCs, 2.32 10¹²/L. Predialysis bicarbonate serum level was 21 mmol/L; creatinine was 814 µmol/L; and urea was 37 mmol/L; postdialysis values are, respectively, 19 mmol/L, 362 µmol/L, and 13 mmol/L. The drop of bicarbonate should be explained by acetate buffer and some degree of acetate intolerance as described by Vinay et al. Arterial blood gases drawn 6 h after dialysis were pH of 7.52, PaCO₂ of 33 mm Hg, and PaO₂ of 51 mm Hg. Spirometric data showed a slight restrictive impairment with a FVC at 78 percent and a TLC at 64 percent of theoretical values. Ventilatory responses to hypoxia were 3.6 1/min/mm Hg CO₂; 0 L/min intercept was at 32 mm Hg of PaCO₂. The patient had no clinical evidence of upper airway narrowing. Again we did not dispose of cephalometric radiograph.

Before renal transplantation, the patient underwent two polysomnographic studies. Methodology was the same as for the first patient, but with recording of esophageal pressure. The first polygraphy was performed during the acute phase before dialysis (February 1990), the second after "stabilization" of clinical status several months after initiation of regular home dialysis (September 1990).

Both showed (Table 2, data obtained after hemodialysis initiation are in brackets) highly pathologic respiratory disturbance index (RDI) central of origin (assessed by esophageal pressure). The first polysomnogram showed a CSAS with an AHI of 51/h; in the second

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<th>Table 1—Patient I*</th>
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<td>Apnea index</td>
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<tr>
<td>Apnea hypopnea index</td>
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<tr>
<td>Mean saturation</td>
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<td>% TST under 90 %</td>
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<td>% TST under 85 %</td>
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<td>% TST under 80 %</td>
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<td>Minimal saturation</td>
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<td>Total TST, min</td>
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<td>WASO, %SPT</td>
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<td>Stage 1, %SPT</td>
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<td>Stage 2, %SPT</td>
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<td>SWS, %SPT</td>
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<td>REM, %SPT</td>
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<td>Arousal/h</td>
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*TST = total sleep time; SPT = sleep period time (time spent in bed between sleep onset and final morning awakening); WASO = wakefulness after sleep onset. See text for explanations (case 1).
Table 2—Patient 2*

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<thead>
<tr>
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<tr>
<td>Apnea index</td>
<td>[39] 51</td>
<td>5</td>
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<tr>
<td>Apnea hypopnea index</td>
<td>[72] 51</td>
<td>10</td>
</tr>
<tr>
<td>Mean saturation</td>
<td>[67] 94</td>
<td>97</td>
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<tr>
<td>% TST under 90 %</td>
<td>[61] 12</td>
<td>1</td>
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<tr>
<td>% TST under 85 %</td>
<td>[86] 5</td>
<td>0</td>
</tr>
<tr>
<td>% TST under 80 %</td>
<td>[6] 0</td>
<td>0</td>
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<tr>
<td>Minimal saturation</td>
<td>[70] 77</td>
<td>87</td>
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<tr>
<td>Desaturation index</td>
<td>[86] 80/h</td>
<td>3/h</td>
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<tr>
<td>Mean desaturation</td>
<td>12</td>
<td>4</td>
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<tr>
<td>Total TST, min</td>
<td>[255] 312</td>
<td>349</td>
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<tr>
<td>Sleep latency, min</td>
<td>[10] 20</td>
<td>25</td>
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<tr>
<td>WASO, %SPT</td>
<td>[35] 33</td>
<td>24</td>
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<tr>
<td>Stage 1, %SPT</td>
<td>[18.5] 16.2</td>
<td>10.5</td>
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<tr>
<td>Stage 2, %SPT</td>
<td>[34.5] 25.8</td>
<td>51</td>
</tr>
<tr>
<td>SWS, %SPT</td>
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<td>4.42</td>
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<tr>
<td>REM, %SPT</td>
<td>[5.32] 10.2</td>
<td>10.3</td>
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<tr>
<td>Arousals/h</td>
<td>[68] 70</td>
<td>30</td>
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*TST = total sleep time; SPT = sleep period time (time spent in bed between sleep onset and final morning awakening); WASO = wakefulness after sleep onset. See text for explanations (case 2).
†Data obtained after hemodialysis initiation in brackets.

There were by half central hypopneas. Despite the shift of apneas to hypopneas, oxygenation worsened at the second recording. Again, RDI was much more important in NREM (75) than in REM.14

Awating renal transplantation, the patient was treated by nasal CPAP (+ 8 cm H2O). Desaturations and sleep-disordered breathing events were suppressed or greatly improved under treatment that was observed a mean of 6 h per night.

Renal transplantation was performed in August 1991, and the patient stopped nasal CPAP. Polysomnography after transplantation was performed in September 1991, and again showed great improvement, near curve (Table 2).

Post transplantation biologic data are partial because the patient refused to undergo arterial blood gas studies and a second test of ventilatory responses to hypoxic normocapnia and hypercapnia. Blood pressure was 140/70 mm Hg; glomerular filtration (insulin clearance), 43 ml/min; serum creatinine level, 164 µmol/L; serum urea level, 8.1 mmol/L; and bicarbonate, 25 mmol/L.

**DISCUSSION**

This report describes sleep apnea syndrome (SAS) in two patients with end-stage renal disease (ESRD). Prevalence of OSAS is 10 percent to 50 percent in ESRD.4-10 To our knowledge, however, this is the first description of improvement in SAS-associated ESRD by kidney transplant.

Physiopathologic factors involved are numerous. Respective role of renal disease by itself and/or dialysis procedures are discussed. No definitive statement exists about causes of ESRD-associated SAS.

Discussion will focus on how instability of respiratory control can lead to OSAS as well as CSAS, and factors of respiratory instability in ESRD with or without maintenance dialysis.

**Periodic Breathing and SAS**

Central sleep apnea syndrome can be considered as an extremely obvious kind of PB. Therefore, interactions between CSAS and PB are clear. It is much more interesting to focus on relations between OSAS and PB.

Onal and Lopata1 have found that in tracheostomized OSAS patients, some degree of periodic breathing persists. This fact leads us to postulate that periodic breathing could be involved in OSAS. Further experiments12,13 emphasized these data: periodic breathing may induce sleep apnea; it is easier if inspiratory resistances are increased.

It can be hypothesized that any factor of periodic breathing (hypoxia, hypocapnia, acidosis, increased respiratory control gain, delayed responses, reduced cardiac output, diminished damping of respiratory responses, etc)14,15 can favor OSAS, especially if increased inspiratory resistances occurred, even at moderate level. Periodic breathing and increased inspiratory resistances could be thought to conjugate themselves at various ratios (probably individual) to generate OSAS.1,12-16

Inspiratory resistances can be due to anatomic narrowing or to a “functional” one, as in the case of increased respiratory drive, ie, increased inspiratory flow, according to Bernoulli’s law (“dynamic” narrowing).

The role of periodic breathing (presumed of central origin created by “respiratory rhythm generator”) in OSAS needs to be explained. Increased upper airway resistances have been described during Cheyne-Stokes breathing18-22 and is presumably due to two essential phenomena.

**First,** ambivalence has been reported17 between the inspiratory muscles and the upper airway dilators. Thus, the inspiratory muscles are activated before the upper airway muscles, or more than them. This condition leads to increased collapsing force at pharyngeal level.

**Secondly,** Onal and Lopata19 have shown that this activation ambivalence is not a necessary condition to generate upper airway obstruction. In fact, fluctuating drive leads to fluctuation of muscle tonus; if the inspiratory flow is only slightly (or not at all) reduced, suction forces are increased according to fluid mechanic physical law. This phenomenon can be named “dynamic narrowing” of the upper airway. Probably, suction forces increase more if the upper airway is narrowed.

Concerning the second patient, the noise heard at resumption of breathing corresponds to partial obstruction an upper airway. This finding is frequently reported in cardiogenic periodic breathing.20-22

**ESRD and SAS**

**Chronic Renal Insufficiency and SAS:** SAS has been described in ESRD with or without dialysis. This
finding argues toward the own responsibility of chronic renal insufficiency in SAS.

Metabolic acidosis is a constant feature of ESRD. Chronic respiratory compensation of metabolic acidosis leads to chronic hypcapnia.

If we consider the definition by Dempsey and Skatrud4 of an "apneic" threshold, we can believe that hypcapnia leads to further risk of sleep-induced apnea.23 It has been shown that there is an improvement in OSAS by CO₂ inhalation.26 Moreover, during periodic breathing induced by hypcapnia or hypoxia, increased upper airway resistance and obstructive apneas have been described.16-19

Increased respiratory controller gain (induced by acidosis stimulation, increased CO₂ sensitivity related to dialysis and hypoxia) is a supplemental factor of periodic breathing.14,15 A shift from central apnea to obstructive apnea has been described during induced metabolic acidosis.20 Unfortunately, to our knowledge, studies on respiratory control in chronic renal insufficiency give no definitive conclusion.27-29

On the other hand, anemia is a factor of respiratory destabilization25 that is improved by renal transplantation. The role of erythropoietin in ESRD-induced SAS probably deserves an evaluation.

It can be speculated that some metabolic "toxins" (as urea or others, known or unknown) can alter respiratory center function6-10 and thus create or worsen respiratory instability and/or ambivalence between upper airway muscles and diaphragm. Correlation has been reported between AHI and serum urea levels.6 However, we cannot rely on SAS and urea level because this finding is not confirmed by others, and because hemodialysis does not improve sleep-induced respiratory disturbances. Furthermore, blood urea itself does not depend only on dialysis efficacy, but strongly depends on nutritional status.

Kimmel16 questioned the reversibility of SAS in ESRD. He postulated that as in neuropathy and myopathy in uremia, SAS should not be reversible. This report provides a positive answer to his questions.

Nevertheless, renal transplantation did not completely cure renal insufficiency. The renal function assessed by inulin clearance hardly reached half the value of normal renal function (43 and 47 ml/min/L, 73 m² for each patient, respectively). It seems that acid-base equilibrium is the most improved, whereas protein metabolism (impairment by chronic antirejection corticosteroid therapy) and "middle molecule" metabolism are not totally corrected. Therefore, it can be postulated that most of the improvement observed is due to acid-base metabolism correction.

Predominance of SRDB in NREM reinforces the hypothesis of metabolically induced respiratory disturbances, because in NREM, respiratory control seems dependent only on metabolic factors.30

Cardiac dysfunction is a factor of periodic breathing, central sleep apnea, upper airway obstruction, and OSAS.30 For these patients, high output cardiac failure was induced by dialysis, arteriovenous fistula, and renal anemia. Moreover, the second patient's hypertensive myocardopathy (patient 2) superimposes its effects on high output cardiac failure.

Improvement in sleep quality (reduction of arousals and stages shifts, increased stage 3, reduction in stage 1) is probably due to the SAS cure. However, treatment of uremia can lead to better sleep stability.

It is not totally excluded (though improbable) that part of the reduction in sleep-disordered breathing events is related to better sleep stability.

Numerous awakenings (related or not to periodic leg movements [PLMs]) are not rare in patients with ESRD; thus, unstable sleep can lead to periodic breathing by constant shifts between wakefulness and sleep and the corresponding oscillations between two ways of respiratory control.5,16,20 PLMs should explain sleep disruption and respiratory instability, thus explaining part of the abnormalities. However, in the report by Kimmel et al,8 SRDBs are not related to PLMs. Furthermore, in these two patients, CPAP probably should have improved PLMs; a recent article reports rather a worsening of PLMs with CPAP in predisposed patients. Thus, if SRDBs are related to PLMs, they should not be improved by nasal CPAP.

Inspiratory resistances may have been reduced because of a reduction in generalized edema, particularly lung and upper airway edema. This fact does not seem of importance in our patients because night quality after dialysis was not improved: they were still insomniac or snoring and thus probably apneics. The second patient seems rather worse after dialysis in regard to nocturnal oxygenation.

Hemodialysis and SAS: From one report in which ESRD-related SAS is improved by hemodialysis,7 it seems that dialysis does not significantly improve sleep-breathing disorders.9 For at least two patients, hemodialysis worsened or induced these troubles. For another patient it created a shift of central to obstructive apnea. Thus, hemodialysis seems to have adverse effects on respiratory disorders, as follows:

(1) increased CO₂ sensitivity occurs during hemodialysis20 and leads to increased hyperventilation. Then respiratory stability and/or upper airway stability are further jeopardized.

(2) acetate dialysis has been shown to induce cardiovascular impairment by myocardial depressant effects.31,32

(3) hypoxia during acetate dialysis is a frequent feature and superimposes its action in destabilization of respiratory control.

Mechanisms of hypoxia during dialysis11,31,32 are numerous and are briefly reviewed.
The leading factor is hypoventilation induced by loss of bicarbonates caused by acetate metabolism and by loss of bicarbonates across dialyzer (in case of acetate dialysis). During bicarbonate dialysis, hypoventilation is due to rapid alkalization of body fluids. Bicarbonate dialysis generally induces slighter levels of hypoxemia.

The second important factor seems to be an alteration of diffusion capacity by lung leukostasis. This leukostasis is dependent on complement activation and seems “membrane” dependent.

Thus, choice of dialysis duration, bath, and membrane is important because cardiovascular, pulmonary, and metabolic effects differ between techniques.

Consistently, nocturnal desaturation worsened for the second patient after steady-state hemodialysis. This finding is not surprising because this patient was dialyzed against acetate buffer which seems more deleterious.

Improvement of OSAS after beginning hemodialysis is not found by all,4 it can thus be postulated that the role of metabolic factors is not so important in generating ESRD-associated SAS. However, improvement in these two patients argue in favor of the role of metabolic factors, and lack of benefits observed while receiving dialysis may be due to the following factors: abrupt metabolic modifications seen during hemodialysis do not act as a chronic stabilization on respiratory control. For example, metabolic acidosis comes back quickly after the end of hemodialysis session; thus ventilatory correcting factors do too. In this sense, even if “peripheral” (blood) acid-base abnormalities are corrected, ventilation is still stimulated by a high concentration of $H^+$ which persists toward the central chemoreceptors.27-30

Finally, it has been shown that perfusion of branched amino acids provides some improvement in ESRD-associated sleep disorders and particularly in ESRD-associated SAS.31 This finding may favor the existence of “toxic products” resulting from metabolic deviation, in uremia.

Why Did Some Respiratory Disturbances Persist?
In the first patient, persistence of periodic breathing is not surprising because anatomic narrowing of the upper airway still persists; this condition is considered by some authors as a periodic breathing factor.13,24

It is possible, however, that the myocardopathy was not completely cured, because of definitive myocardial damage (mainly induced by hypertension) and because of persistence of arteriovenous fistula.

Despite renal graft, persistence of unknown periodic breathing metabolic factors cannot be excluded. As a matter of fact, renal transplantation did not completely cure ESRD, and renal function after transplantation has not entirely recovered. Thus “uremic toxins” may be still present.

**CONCLUSIONS**

The physiopathology of OSAS is partially unknown and probably involves several factors such as periodic breathing and increased upper airway resistance (“anatomic” narrowing and functional factors called “dynamic” narrowing).

We report cured SAS in two patients after successful renal transplantation and analyze possible causes of these findings. We emphasize periodic breathing’s role in SAS physiopathology. Successful renal transplantation has probably permitted respiration stabilization by curing metabolic factors leading to periodic respiration.

SAS has been reported during ESRD just before or during long-term maintenance hemodialysis. The role of buffer or membrane has been discussed elsewhere, considering the well-known hypoxemia during the dialysis session. Sufficient data are lacking to draw conclusions on the impact of buffer and membranes on SAS.

Our report clearly shows that improvement of renal function may decrease sleep disorders during chronic renal failure. Despite renal function remaining moderate (glomerular filtration about 45 ml/min/1.73 m²), nutritional status and muscular metabolism may improve and “uremic toxins” accumulated during ESRD may disappear.

SAS (particularly its cardiovascular consequences) must be considered when evaluating therapeutic strategy in ESRD. SAS may worsen preexistent renal hypertension and thus impair cardiac function.

In this way, kidney transplantation, instead of dialysis, may provide a new indication to resolve SAS in severe renal disease.

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