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Nocturnal hypoxemia, night-day arterial pressure changes and left ventricular geometry in dialysis patients

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Nocturnal hypoxemia, night-day arterial pressure changes and left ventricular geometry in dialysis patients. It is well established that nocturnal hypoxemia in sleep apnea causes an inversion of the circadian arterial pressure rhythm and triggers nocturnal hypertension. Since sleep apnea is very frequent in dialysis patients, we hypothesized that nocturnal hypoxemia may be a factor that contributes to alter the 24-hour arterial pressure profile in these patients. To test the hypothesis 32 dialysis patients underwent 24-hour blood pressure (BP) monitoring and continuous monitoring of arterial O_2 saturation during the night-time. Hemodialysis patients were studied during the non-dialysis day. All patients underwent an echocardiographic study. Thirteen patients had no episode of nocturnal hypoxemia (group I), 7 had at least one episode overnight but less than 2 episodes/hr (group II) and 12 had $\geq$ 2 episodes/hr (group III). The average daytime systolic pressure was similar in the three groups. However, the average nocturnal systolic pressure fell in the first group ($-2.5 \pm 4.2\%$) and rose in the second ($+2.0 \pm 3.6\%$) and in the third ($+3.9 \pm 2.2\%$) group (one way ANOVA, $P < 0.005$). The relative wall thickness of the left ventricle (RWT) was significantly ($P < 0.05$) higher in group III than in group I, and in the aggregate ($N = 32$) there was an inverse relationship between average nocturnal SaO_2 and RWT ($r = -0.43$, $P = 0.015$). The proportion of patients with concentric remodeling or concentric hypertrophy was higher ($P = 0.05$) in the group with a more severe degree of nocturnal hypoxemia (group III, 8 of 12) than in the other two groups (group I, 3 of 13; group II, 2 of 7). Nocturnal hypoxemia is associated with the "non-dipping" arterial pressure profile in dialysis patients. Disturbed respiratory control during the night may represent an important cardiovascular risk factor in dialysis patients.

The inability to maintain the circadian profile is an important feature of the altered arterial pressure control in patients with chronic renal failure. Indeed, these patients very frequently fail to show the physiological decrease during night-time ("non-dipping" profile) [1–12]. Various hypotheses have been proposed to explain such alteration [2, 4, 5] (see **Discussion**). We thought that episodes of oxygen desaturation, triggered by sleep apnea, which is very frequent in the dialysis population [13–24; reviewed in 19], could be a contributory factor. Sleep apnea in the general population represents a well established cause of nocturnal hypertension [25, 26], and it is frequently associated with primary hypertension [reviewed in 27, 28], as well as with severe cardiovascular complications [29–31]. Therefore, in this study we sought whether nocturnal hypoxemia is related with altered night-day arterial pressure changes as well as with deranged left ventricular geometry in uremic patients.

Key words: sleep apnea, dialysis, chronic renal failure, non-dipping, hypoxemia, 24-hour arterial pressure, ambulatory monitoring, circadian rhythm.

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METHODS

Patients

Thirty-two patients (19 male and 13 female) out of 120 patients on chronic dialysis who were being treated at our institution and at an affiliated dialysis center accepted our request to take part in the study. The exclusion criteria were (*a*) pre-existing pulmonary disease in 27 patients (defined on the basis of medical history, physical examination, chest radiography and respiratory functional tests when indicated), (*b*) diabetes mellitus in 23, (*c*) symptomatic heart failure in nine, (*d*) severe hypertension contraindicating the withdrawal of antihypertensive treatment in one, (*e*) occluded brachial artery in five, and (*f*) AL amyloidosis in two. The remaining 21 patients either refused or could not participate for logistical reasons. Thus, the 32 patients who participated in the study represented the 60% of all eligible cases. Their mean age was 48 years (range 17 to 79 years) and the duration of dialysis treatment was six years (range 1 to 21 years). The cause of chronic renal disease was chronic glomerulonephritis in nine cases, polycystic kidney in five, interstitial nephritis in three, Alport syndrome in two, nephroangiosclerosis in one, cortical necrosis in one, pyelonephritis in one, Laurence-Moon-Bardet Biedle syndrome in one, gouty nephropathy in one, and undefined in eight cases. No patient had had myocardial infarction or cerebrovascular events. None was a habitual smoker or a heavy drinker or a frequent user of sedative drugs. Twenty-one patients were on hemodialysis and were being treated thrice weekly with standard bicarbonate dialysis (Na 138 mmol/liter, HCO_3 35 mmol/liter, K 1.5 mmol/liter, Ca 1.25 to 1.75 mmol/liter, Mg 0.75 mmol/liter) and 1.1 to 1.7 m^2 hollow-fiber or flat plat Cuprophan dialyzers. The average urea Kt/V in these patients was 1.32 ± 0.40. The remaining 11 patients were on CAPD (weekly Kt/V 1.82 ± 0.20).

Eleven patients were on treatment with erythropoietin (6 hemodialysis patients and 5 CAPD patients). Eleven were taking antihypertensive drugs [Ca-channel blockers in 10 cases (which were associated with beta-blockers in 3, with clonidine in 1 and with captopril plus clonidine in 1) and clonidine in the remaining case]. Because antihypertensive drugs can interfere with the night-day arterial pressure changes in patients with chronic renal failure [32, 33], these medications were stopped at least one week before the study.

Protocol and methods

The protocol was conformed with the ethical guidelines of our institution and informed consent was obtained from each participant. The study was performed during the day off dialysis. The patients were admitted in the nephrology ward of our Unit between 7 a.m. and 7:30 a.m., in standard hospital rooms. Twenty-nine studies were performed with patients sleeping in a quiet single bed room. The remaining three patients slept in a double room. The bedmates of these three patients were in stable condition and did not need night care.

Arterial pressure monitoring

Twenty-four hour arterial pressure monitoring (Takeda 2420, model 7) was started between 7:00 and 7:30 a.m. Measurements were done every 15 minutes both during the day (7 a.m. to 11 p.m.) and during the night (11 p.m. to 7 a.m.). The calibration of the ambulatory recorder was performed against a mercury sphygmomanometer before each recording. Patients were instructed to maintain the level of activity of a normal day spent indoors at home.

Nocturnal pulse oximetry

Pulse oximetry was measured by means of the Ohmeda-Biox 3700 digital pulse oximeter (Pabish, Milan, Italy), placing the sensor on the patient's index finger. The recordings were done between 11 p.m. and 7 a.m. and for a further hour after awaking. A fall in oxygen saturation was considered to be significant if the oxygen desaturation during that episode was $> 4\%$ than minimum oxygen saturation during the control period in awake conditions [34]. The minimal oxygen saturation (SaO_2) and average nocturnal SaO_2 levels were obtained by using the standard software provided with the Ohmeda Biox pulse oximeter.

Echocardiography

The day after dialysis each patient underwent an echocardiographic study and all echocardiographic measurements were performed according to the recommendations of the American Society of Echocardiography [35] by an observer unaware of arterial pressure and SaO_2 recordings. Left ventricular mass (LVMI) was calculated according to the Devereux formula [36] indexed for body surface area. Relative wall thickness was calculated by the standard formula RWT = 2 PWT/LVEDD (cut-off value $\geq$ 0.45). Geometric analysis of the left ventricle was performed according to Koren et al [37]. Presence or absence of left ventricular hypertrophy (LVH) was defined on the basis of a LVMI greater than or less than 125 g/m^2. A normal RWT and no LVH was defined as normal geometry; LVH was classified as concentric when RWT was $\geq$ 0.45 and eccentric when RWT was $\leq$ 0.45. The pattern of increased RWT without LVH is defined concentric remodeling.

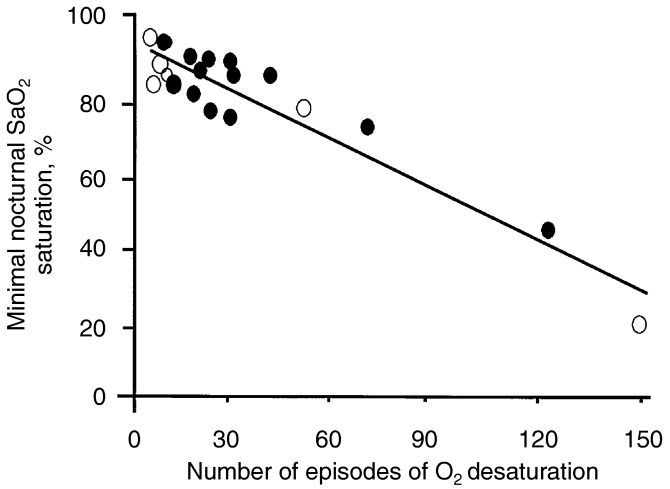

Fig. 1. Relationship between the number of episodes of nocturnal hypoxemia and the minimal SaO_2. Symbols are: (○) CAPD patients; (●) HD patients. $r = -0.94$; $P < 0.001$.

Definitions and data analysis

Patients were arbitrarily classified as "non-dippers" when their night-day systolic pressure ratio was $\geq 100\%$ because this threshold approximates the 95th percentile of the night-day ratio in 4765 normotensive subjects reported in a recent meta-analysis [38]. A ratio $\geq 100\%$ mathematically corresponds with a night-time systolic pressure equal to or higher than daytime pressure. This ratio depends less on BP level than on the nocturnal BP fall and is to be preferred in the definition of dipping status [38].

Data are presented as mean$\pm$ SD and median (interquartile range) and analyzed by parametric and non-parametric tests, as appropriate. Between groups comparisons were made by one-way ANOVA followed by the Newman-Keuls test for multiple comparisons or by Kruskall Wallis statistic. Proportions were compared by the chi-square test. Relationships between paired parameters were analyzed by the least square method (continuous variables) or by the Spearman rank test (discontinuous variables). Multifactorial hypotheses were tested by multiple regression analysis.

RESULTS

Overnight oxygen saturation profile

During the control period in awake conditions, the average oxygen saturation (SaO_2) in the whole group of dialysis patients was 97.3 $\pm$ 1.4%. During night-time nineteen patients had at least one desaturation episode, while the remaining thirteen had no episode. The median of the number of oxygen desaturation episodes overnight was 16 (interquartile range 6 to 37 episodes), while the mean values of the average nocturnal SaO_2 and of the average minimum SaO_2 were 95.4 $\pm$ 3.0% and 80.8 $\pm$ 15.0%, respectively. In the patients with at least one episode of nocturnal hypoxemia the number of oxygen desaturation episodes was inversely and very strictly related to the severity of oxygen desaturation ($r = -0.94$, $P < 0.001$) without any difference between hemodialysis and CAPD patients (Fig. 1). On the basis of the results of the nocturnal pulse oximetry study, patients were divided into three groups: thirteen patients with no episode of

Table 1. Clinical and biochemical data, ambulatory monitoring and pulse oximetry in the three groups

	Group I (no episode of O_2 des.) $N = 13$	Group II (at least 1 episode of O_2 des. overnight but <2/hr) $N = 7$	Group III (≥2/hr episodes of O_2 des.) ($N = 12$)
Age *years*	45.2 ± 19.7	54.6 ± 19.3	46.4 ± 12.6
Males/females	9/4	2/5	8/4
BMI kg/m^2	23.4 ± 3.5	25.8 ± 3.5	26.4 ± 3.9
Duration of dialysis treatment *years* (median, interquartile range)	2.0 (1.0–13.0)	2.0 (1.0–7.0)	3.0 (2.25–6.5)
Serum Na *mMol/liter*	139 ± 4	138 ± 6	138 ± 4
Serum K *mmol/liter*	4.8 ± 0.8	4.70 ± 1.0	5.3 ± 0.7
Serum albumin *g/dl*	4.0 ± 0.6	4.2 ± 0.1	4.3 ± 0.5
Hematocrit %	32 ± 7	31 ± 3	33 ± 7
PTH *pg/ml* (median, interquartile range)	74 (10–306)	95 (5–342)	322 (101–594)
Pulse			
Min SaO_2 in awake conditions %	92.7 ± 3.6	94.7 ± 2.3	91.7 ± 3.9
Min SaO_2 during night-time %	91.1 ± 3.2	88.1 ± 4.3	76.6 ± 17.4
Average nocturnal SaO_2	97.2 ± 1.2	96.2 ± 2.1	94.9 ± 3.3
Number of O_2 des. episodes/hr (median, interquartile range)	0 (0–0)	0.6 (0.2–0.7)	3.2 (2.0–7.7)
Ambulatory monitoring			
Arterial pressure			
24 hr average systolic pressure	138 ± 22	141 ± 27	143 ± 30
24 hr average diastolic pressure	75 ± 13	77 ± 11	86 ± 19
Heart rate			
24 hr average HR	75 ± 11	78 ± 6.3	81 ± 9.8

desaturation (group I), seven with at least one episode of desaturation during the whole recording period but less than two episodes/hr (group II), and twelve with a consistent desaturation pattern (≥ 2 desaturation episodes/hr; group III).

Twenty-four hour arterial pressure monitoring

As shown in Table 1, the average 24-hour arterial pressure in patients with nocturnal hypoxemia (group III) tended to be higher than in those without (group I), but the difference was not significant. The daytime systolic pressure was almost identical in the three groups (group I, 143 ± 22 mm Hg; group II, 141 ± 23 mm Hg; group III, 143 ± 31 mm Hg). However, the average nocturnal systolic pressure changes showed a different pattern in the three groups (one way ANOVA, $P < 0.005$) because there was a −2.5 ± 4.2% decrease in the group without nocturnal hypoxemia (group I), an inverted pattern in the group with nocturnal hypoxemia (group III) with a +3.9 ± 2.2% increase ($P < 0.01$ vs. group I), and an intermediate behavior in group II with average increase +2.0 ± 3.6% ($P < 0.05$ vs. group I; Fig. 2). In the aggregate the night-day systolic pressure % change was inversely related with the number of episodes of nocturnal hypoxemia (r_S −0.40, $P = 0.02$). The average daytime diastolic pressure tended ($P = 0.07$) to be higher in group III (88 ± 20 mm Hg) than in the other two groups (group I, 78 ± 16 mm Hg; group II, 80 ± 8 mm Hg), but nocturnal diastolic pressure changes did not differ significantly (group I, +0.6 ± 6.4%; group II −5.0 ± 3.5%; group III, −0.3 ± 5.2%).

The average 24-hour heart rate was similar in the three groups (Table 1), and the daytime heart rate as well as night-time changes were again very similar (group I, 78 ± 7 beats/min, −6.5 ± 11.1%; group II, 80 ± 7 beats/min, −5.2 ± 3.9%; group III, 83 ± 7 beats/min, −6.6 ± 6.0%).

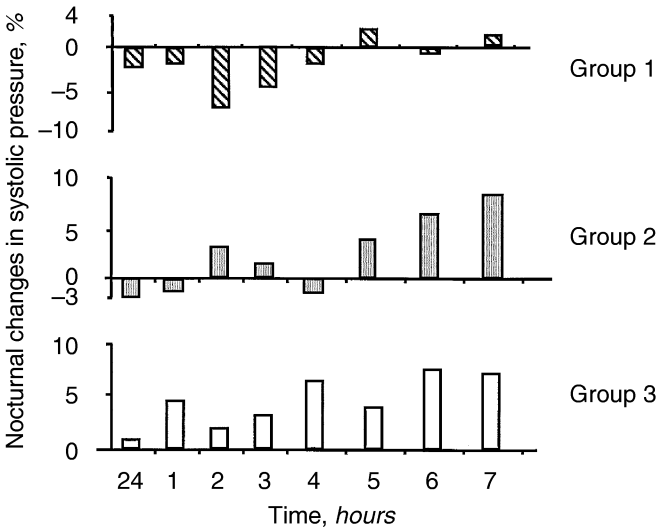

Fig. 2. Average nocturnal % changes in systolic pressure in the three groups. Nocturnal % Changes were calculated (hour by hour) by the formula:

$$\frac{\text{Night-time systolic pressure (hourly averages)} - \text{Average daytime systolic pressure}}{\text{Average daytime systolic pressure}} \times 100$$

Negative values indicate a fall in systolic pressure at night.

Table 2. Echocardiographic data in the three groups

	PWT	IVST	LVEDD	LVMI	
	cm			g/m^2	RWT
Group I	0.98 ± 0.20	1.10 ± 0.28	5.1 ± 0.64	127.8 ± 41.8	0.19 ± 0.04
Group II	1.00 ± 0.24	1.11 ± 0.25	4.6 ± 0.61	106.0 ± 35.4	0.22 ± 0.05
Group III	1.17 ± 0.28	1.19 ± 0.19	4.8 ± 0.53	131.6 ± 54.3	0.24 ± 0.05[a]

Abbreviations are: PWT, posterior wall thickness; IVST, interventricular septum thickness; LVEDD, left ventricular end diastolic diameter; LVMI, left ventricular mass index; RWT, relative wall thickness.

[a] $P < 0.05$ vs. group I. The difference in PWT between group I and III just failed to reach statistical significance ($P = 0.06$).

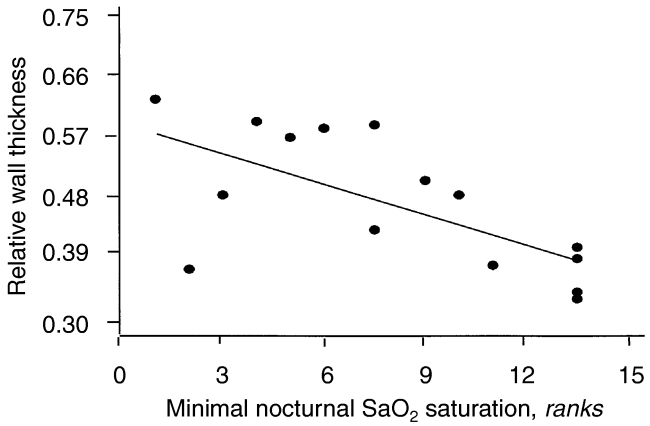

Fig. 3. Relationship between minimal nocturnal oxygen saturation (SaO_2) and relative wall thickness (RWT) in non-dippers dialysis patients. Abscissa, ranked SaO_2 data: rank 1 is the most severe case (minimal SaO_2 = 53%) and rank 15 the less severe case (minimal SaO_2 = 93%). $r = -0.66$; $P = 0.008$.

When patients were categorized on the basis of the individual night-day arterial pressure ratio into non-dippers (ratio ≥ 100%) and dippers (ratio <100%), 15 patients fell into the first category. The median number of SaO_2 desaturation episodes was much higher ($P = 0.005$) in non-dippers (14 episodes, interquartile range 4 to 37) than in dippers (0, interquartile range: 0 to 7).

Echocardiographic data

The PWT ($P = 0.06$) tended to be higher in patients with nocturnal hypoxemia (group I), while the IVST, the LVEDD and the LVMI were similar in the three groups (Table 2). The RWT was significantly increased in patients with nocturnal hypoxemia in comparison with those without hypoxemia (one-way ANOVA $P = 0.044$, group III vs. group I, $P < 0.05$) and in the aggregate there was an inverse relationship between average nocturnal SaO_2 and RWT ($r = -0.43$, $P = 0.0015$). Furthermore, separate analysis of dippers and non-dippers revealed a highly significant inverse correlation ($r = -0.66$, $P = 0.008$) between minimal nocturnal SaO_2 and RWT in non-dippers (Fig. 3), while no such correlation was found in the dippers ($r = 0.06$, NS).

Correlates of left ventricular geometry

The hematocrit, nocturnal hypoxemia (either expressed as average nocturnal SaO_2 or as number of nocturnal episodes of O_2 desaturation) and serum parathyroid hormone (PTH) were the only parameters to be significantly related with the echocardiographic measures of the left ventricle (Table 3). The hematocrit predicted both the PWT and the LVMI while nocturnal hypoxemia predicted the PWT as well as the RWT (Table 3). Parathyroid hormone was directly related with the RWT. In a multiple regression model average nocturnal SaO_2 and serum PTH predicted the 27% of RWT ($r = 0.52$, $P = 0.013$; SaO_2, $\beta = -0.38$; PTH, $\beta = 0.31$), while age, duration of dialysis treatment, body mass index (BMI), arterial pressure and hematocrit did not add any significant prediction power to the model. The proportion of patients with concentric remodeling or concentric hypertrophy was higher ($\chi^2 = 3.809$, $P = 0.05$) in the group with nocturnal hypoxemia (8 of 12) than in the other two groups (group I, 3 of 13; group II, 2 of 7; Fig. 4).

DISCUSSION

In this study nocturnal hypoxemia in dialysis patients was associated with the non-dipping profile and, independently of arterial pressure, with concentric hypertrophy and remodeling.

Chronic renal failure is commonly associated with a blunted or inverted circadian arterial pressure curve [1–13]. Mainly on theoretical considerations, this phenomenon has been attributed to extracellular volume expansion [2], overactivity of the sympathetic system [4], uremic neuropathy [6], and frequent arousals associated with periodic leg movements and restless legs syndrome [39]. Episodes of nocturnal hypoxemia triggered by sleep apnea represent a potential cause of nocturnal hypertension that has not been previously considered. Seminal studies by Millman et al [14], Fein et al [15] and Kimmel, Miller and Mendelson [16] in the eighties as well as more recent studies [17–24] clearly established that sleep apnea syndrome, mainly of the obstructive type, is very frequent in the dialysis population with a prevalence ranging from 21% to 47% [21], and equally common in hemodialysis and CAPD patients [19]. Sleep apnea in the general population is consistently associated with an altered circadian arterial pressure rhythm [25, 26], and the severity of nocturnal hypoxemia is strictly related with the night-day systolic pressure change [25]. Hypoxemia is considered the primary factor responsible for the cardiovascular effects of sleep apnea [26, 27] because it induces a chemoreceptor mediated increase in efferent sympathetic activity, triggers the release of epinephrine in the adrenal medulla and alters the endothelial production of nitric oxide. Furthermore, sleep apnea is now considered an important cardiovascular risk factor [29–31], and in a follow-up study it was associated with a high incidence of myocardial infarction and stroke, while these cardiovascular complications were almost fully prevented by tracheostomy [30].

Table 3. Correlation matrix of the relationships between echocardiographic parameters and clinical, biochemical, ambulatory monitoring and pulse oximetry results

	PWT	LVEDD	LVMI	RWT
		r (P)		
Age	0.23 (0.20)	0.13 (0.48)	0.10 (0.58)	0.33 (0.06)
Duration of RDT	0.08 (0.66)	0.09 (0.63)	0.19 (0.29)	0.07 (0.72)
BMI	0.07 (0.68)	0.014 (0.94)	0.08 (0.66)	0.25 (0.17)
Hematocrit	−0.42 (0.01)	−0.18 (0.32)	−0.37 (0.04)	−0.27 (0.13)
Albumin	0.04 (0.83)	0.08 (0.67)	0.0 (0.83)	0.05 (0.79)
PTH	0.32 (0.08)	−0.13 (0.49)	0.21 (0.25)	0.36 (0.05)
24 hr systolic BP	0.05 (0.78)	0.28 (0.12)	0.15 (0.42)	0.10 (0.57)
24 hr diastolic BP	0.07 (0.68)	0.06 (0.72)	0.01 (0.94)	0.02 (0.89)
Daytime systolic BP	0.04 (0.84)	0.29 (0.10)	0.15 (0.41)	−0.14 (0.46)
Daytime diastolic BP	0.04 (0.82)	0.05 (0.77)	0.03 (0.88)	−0.01 (0.93)
night-time syst	0.08 (0.65)	0.23 (0.20)	0.15 (0.41)	−0.04 (0.82)
night-time diast	0.12 (0.49)	0.08 (0.65)	0.02 (0.92)	0.07 (0.66)
night-day systolic ratio	0.13 (0.46)	0.05 (0.78)	0.07 (0.71)	0.20 (0.28)
night-day diastolic ratio	0.21 (0.24)	0.10 (0.56)	0.11 (0.55)	0.21 (0.25)
Min. nocturnal SaO_2	−0.27 (0.13)	0.12 (0.52)	0.02 (0.89)	−0.34 (0.06)
Average nocturnal SaO_2	−0.34 (0.06)	−0.16 (0.38)	−0.05 (0.78)	−0.43 (0.01)
Number of episodes of O_2 des.	0.34 (0.05)	0.15 (0.40)	0.01 (0.94)	0.41 (0.02)

Abbreviations are in Table 2.

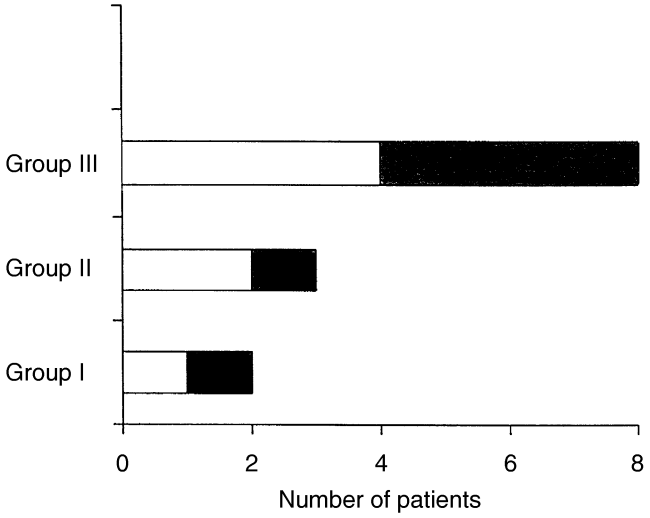

Fig. 4. Patients with concentric remodeling (■) and concentric hypertrophy (□) in the three groups.

In the present study we found that the night-day systolic pressure change is reversed in dialysis patients with nocturnal hypoxemia and that this alteration is inversely related with the number of episodes of hypoxemia. Accordingly, the number of episodes of nocturnal hypoxemia was much higher in non-dippers than in dippers. This study is the first to associate the non-dipping phenomenon to nocturnal hypoxemia in dialysis patients. Having not performed polysomnographic recordings, nocturnal hypoxemia in our patients may not necessarily reflect sleep apnea. However, none of our patients had concomitant diseases or factors interfering with respiratory control. Nocturnal pulse oximetry is very useful in ruling out sleep apnea (negative predictive value of 97%). Its diagnostic sensitivity (98%) is also very high but the positive predictive value of this method is rather limited (61%) [34]. Pulse oximetry reliably detects hypoxemia in dialysis patients [39]. Thus, we believe that the most likely cause of hypoxemia in our patients was a disturbed respiratory control during sleep. Whatever the relationship between hypoxemia and sleep apnea in dialysis patients, it is important to note that studies in rats submitted to recurrent episodic hypoxia [40] or to continuous hypobaric hypoxia [41], as well as experimental observations in healthy humans [42] have consistently demonstrated that hypoxemia *per se* activates a series of reflex cardiovascular responses, which, mainly via sympathetically mediated vasoconstriction, provoke an important arterial pressure increase. It is worth noting that although the link between hypoxemia and the night-day arterial pressure changes in this study was a consistent one, it remains to be seen whether it entails a causal relationship or represents a mere association. Continuous positive airway pressure lowers arterial pressure in hypertensive patients with sleep apnea [43, 44], and the stepwise reduction of this treatment is associated with a proportional arterial pressure increase [45], suggesting a causal link. It should be noted that the average nocturnal fall in systolic pressure in non-hypoxemic patients was rather small (−2.5%) and less than that observed in age-matched healthy subjects [38], which indicates that factors other than hypoxemia play an important role in the altered circadian arterial pressure profile in dialysis patients.

Independently of hypertension, patients with sleep apnea display an increase in left ventricular mass as well as in posterior wall, and interventricular septum thickness in the presence of unaltered left ventricular end diastolic diameter [46] (that is, a geometric pattern indicating concentric hypertrophy). Similarly, we noted that nocturnal hypoxemia in dialysis patients was associated with concentric hypertrophy or remodeling. Concentric hypertrophy as well as concentric remodeling [47] entail an elevated risk for cardiovascular disease and death that is independent of arterial pressure. In dialysis patients concentric hypertrophy has an adverse clinical outcome [48] and the expected median survival in these patients is only 48 months. Thus, our finding that nocturnal hypoxemia is associated with concentric hypertrophy or remodeling, independently of other well established predictors of left

ventricular hypertrophy such as older age, hypertension and anemia while on dialysis [48], suggests that it may represent an important cardiovascular risk factor in dialysis patients. A limitation of our study is the relatively small sample size. Further studies of larger dimensions are warranted to investigate the role of nocturnal hypoxemia in the high cardiovascular risk of dialysis patients.

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APPENDIX

Abbreviations in this article are: BP, blood pressure; IVST, interventricular septum thickness; LVEDD, left ventricular end diastolic diameter; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; PWT, posterior wall thickness; RWT, relative wall thickness; SaO_2, oxygen saturation.

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