Eur Respir J 2002; 20: 724–732
DOI: 10.1183/09031936.02.00250102
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European Respiratory Journal
ISSN 0903-1936

Inspiratory neural drive response to hypoxia adequately estimates peripheral chemosensitivity in OSAHS patients

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ABSTRACT: The aim of the present study was to examine the relationships between the responses to progressive isocapnic hypoxia and hypoxic withdrawal test in patients with obstructive sleep apnoea-hypopnoea syndrome (OSAHS) and to analyse the determinants of carotid body sensitivity in OSAHS.

Nineteen consecutive OSAHS patients and 13 healthy subjects were selected. Ventilatory ($\Delta V'_I/S_{a,O_2}$/BSA) and inspiratory neural drive ($\Delta P_{0.1}/S_{a,O_2}$) responses to progressive isocapnic hypoxia were determined. Peripheral chemosensitivity was evaluated by the hypoxic withdrawal test, which measures the decrease in ventilation caused by two breaths of 100% oxygen ($\%\Delta V'_I$).

Withdrawal response and ventilatory and inspiratory neural drive responses to hypoxia were lower in OSAHS patients than in control subjects. In patients with OSAHS, $\%\Delta V'_I$ correlated significantly with $\Delta V'_I/S_{a,O_2}$/BSA and with $\Delta P_{0.1}/S_{a,O_2}$. On stepwise multiple linear regression analysis, a strong correlation between $\%\Delta V'_I$ and $\Delta P_{0.1}/S_{a,O_2}$ was found. Moreover, $\%\Delta V'_I$, $\Delta V'_I/S_{a,O_2}$/BSA and $\Delta P_{0.1}/S_{a,O_2}$ were significantly correlated with minimum arterial oxygen saturation and with arousal index.

Obstructive sleep apnoea-hypopnoea syndrome patients have a strong relationship between peripheral chemosensitivity and respiratory response to hypoxia, suggesting that hypoxic stimulation of central chemoreceptors is minimally relevant in obstructive sleep apnoea-hypopnoea syndrome. Moreover, sensitivity of the carotid body in patients with obstructive sleep apnoea-hypopnoea syndrome is related to sleep disruption and to nocturnal hypoxia.

Eur Respir J 2002; 20: 724–732.

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Keywords: Carotid body
chemosensitivity
hypoxia
sleep apnoea

Received: June 1 2001
Accepted after revision: April 11 2002

This study was supported by FIS (96/1280 and 99/0252) and Neumomadrid (2000) Grants.

The study of peripheral chemosensitivity in patients with obstructive sleep apnoea-hypopnea syndrome (OSAHS) has been of considerable interest over several years [1–7]. The peripheral chemoreflexes are an important mechanism for regulation of both breathing and autonomic cardiovascular function [8]. In fact, abnormalities in chemoreflex mechanisms have been implicated in the increased cardiovascular stress in patients with OSAHS. The relationship between peripheral chemosensitivity and blood pressure profile suggests that recurrent obstructive apnoeas may reset the peripheral chemoreceptor output to a higher level, causing a chronic increase in sympathetic tone and initiating hypertension [9, 10]. Intersubject variation of heart rate changes during sleep apnoea could also be due to variations in response to hypoxia [11].

In spite of these pathophysiological implications, the role of peripheral chemoreception in OSAHS has not been adequately evaluated. The nature of the respiratory response to chemical stimuli in awake patients with OSAHS is still unclear. In these patients, depression of peripheral chemosensitivity has been reported [7]. In contrast, other investigators have concluded that response to hypoxia in OSAHS patients is normal [2–6] or increased [1].

These discrepancies in findings concerning chemical sensitivity in OSAHS could be due in part to confounding factors, such as obesity, age, sex, smoking habit, metabolic acidosis, hypercapnia, resting metabolic rate, alcohol abuse and genetic factors [12–15]. But the stimulation method employed in each study also seems to be responsible for some differences. The best established techniques for assessment of hypoxic response are progressive isocapnic hypoxic stimulation [16] and the hypoxic withdrawal test [17]. It has been demonstrated that progressive hypoxia does not adequately evaluate chemosensitivity of the carotid body because it stimulates peripheral and central chemoreceptors together [8]. Since the time required for central nervous system stimulation is considered to be about 20 s [18], the hypoxic withdrawal test eliminates peripheral chemoreceptor activity but leaves the humoral environment of the central respiratory system unchanged [17].

The aim of this study was to evaluate the relationship between responses to progressive isocapnic

hypoxia and the hypoxic withdrawal test in OSAHS patients. The determinants of carotid body sensitivity in patients with OSAHS were also studied.

Materials and methods

Study subjects

Nineteen consecutive OSAHS patients and 13 healthy subjects were selected to be studied. Patients were excluded from the study for the following reasons: unwillingness or inability to perform the testing procedure; obstructive or restrictive lung disease demonstrated by pulmonary function testing; known valvular heart disease; current drug or mechanical treatment for sleep apnoea; known neuromuscular disease; abnormal thyroid function; morbid obesity (body weight >150% ideal); and recent (<3 months) myocardial infarction or cerebrovascular accident. Control subjects were judged healthy by history, physical examination, electrocardiogram (ECG), spirometry and chest radiography.

Subjects were asked not to eat for 4 h before the study and they were also asked to refrain from using coffee, tea and alcohol for $\geqslant$12 h, and tobacco for $\geqslant$2 h before each study. The study was approved by the Institutional Ethics Committee at the hospital. All subjects gave their written informed consent prior to enrolment.

Methods

Polysomnography. Healthy subjects and OSAHS patients underwent polysomnography from 23:00–07:00 h. Electroencephalogram (C3-A2, C4-A1), electrooculogram, chin electromyogram, electromyograms of the tibialis anterior of both legs, and ECG were continuously recorded. Breathing was monitored using nasal cannulas, oronasal thermistors and thoracoabdominal stain gauges. Simultaneously, arterial oxygen saturation (S_{a,O_2}) was monitored with a pulse oximeter (Pulsox DP-8, Minolta, Osaka, Japan). Sleep was analysed using the standard criteria [19] for epochs of 20 s and the following sleep variables were calculated: total sleep time, wake time after sleep onset and sleep efficiency, defined as the ratio of total sleep time to sleep episode duration. Micro-arousals were scored according to the American Sleep Disorders Association (ASDA) definition [20]. An obstructive apnoea/hypopnoea event was characterised by a >50% decrease from baseline in the amplitude of breathing for $\geqslant$10 s associated with either O_2 desaturation of >3% or an arousal in the presence of continued respiratory efforts [21]. The apnoea/hypopnoea index (AHI) was established as the number of apnoeas/hypopnoeas per hour of sleep. The number of arousals per hour of sleep was expressed as the arousal index (ARI). OSAHS was defined as excessive daytime sleepiness unexplained by other factors plus five or more obstructed breathing events per hour during sleep [21]. As indices of nocturnal O_2 saturation, the mean S_{a,O_2} throughout the night, the mean low S_{a,O_2} (mean of the minimum value for S_{a,O_2} in each 30-s epoch) and the minimum S_{a,O_2} (lowest values recorded during sleep) were computed.

Respiratory function. Immediately after awakening, pulmonary function tests were performed as previously described [22], with subjects seated, and always in the same order allowing enough rest between each manoeuvre. All procedures were performed by the same technician, blinded to the results.

Arterial blood gas values were measured with subjects in a seated position, while they breathed room air. Spirometry was performed by means of a pneumotachograph and static lung volumes were measured with a constant-volume body plethysmograph (MasterLab Body, Erich Jaeger GmbH, Würzburg, Germany), according to European Respiratory Society standardisation [23]. Resting O_2 uptake and carbon dioxide (CO_2) output were measured over 5 min, using an automated ergometry set up (Oxycon Alpha, Jaeger). Mean values of the last 4 mins were taken for analysis.

Maximal static inspiratory pressure ($P_{I,max}$) was measured using a differential pressure transducer (M-163; Sibelmed, Barcelona, Spain). Patients, comfortably seated and wearing a noseclip, performed maximal respiratory efforts either at residual volume or at total lung capacity against an obstructed mouthpiece with a small leak (internal diameter, 0.7 mm) to minimise oral pressure artifacts. The manoeuvres were repeated until three measurements sustained for $\geqslant$3 s and with <5% variability were recorded. The highest value obtained was used for analysis.

Mouth occlusion pressure at 0.1 s after the beginning of inspiration ($P_{0.1}$) was measured by the Whitelaw method [24]. Mouth pressure was recorded with a differential pressure transducer (Model DWD, Jaeger). Approximately every 15 s the inspiratory line was occluded without the subject's knowledge for <0.5 s by means of a pneumatic inflatable balloon (Series 9327; Hans-Rudolph, St. Louis, MO, USA). The mean of five or more measurements was determined. The values for dead space and resistance of the system up to a flow of 100 mL were 173 mL and 0.1 $kPa \cdot s \cdot L^{-1}$, respectively.

Ventilatory and $P_{0.1}$ responses to progressive isocapnic hypoxia were determined using the rebreathing method of Rebuck and Campbell [17]. S_{a,O_2} was measured continuously with a finger-pulse oximeter (model Oscar II, Datex, Helsinki, Finland). In the seated position with noseclips applied, subjects breathed room air through a mouthpiece *via* a three-way valve while expired gas was continuously sampled at the mouthpiece using a rapidly responding infrared CO_2 analyser (model Oscar II, Datex). The gas analyser was calibrated with gases previously analysed by the Scholander technique. After a stable end-tidal CO_2 concentration was achieved, subjects rebreathed through a 7-l bag containing the initial gas mixture: 21% O_2 and 7% CO_2 in nitrogen (N_2). CO_2 was held constant (end-tidal CO_2 tension (P_{et,CO_2})$\pm$1 mmHg) at the resting end-tidal level ("mixed-venous") using a variable CO_2 absorber bypass, containing soda lime CO_2 absorbent and a variable fan. Inspiratory minute

ventilation (V'_I) was measured by electrically integrating the inspiratory flow signal obtained with a heated (37°C) pneumotachograph (Screenmate Box, Jaeger). Approximately every 15 s without the subject's knowledge, $P_{0.1}$ was recorded as indicated previously. V'_I, $P_{0.1}$, S_{a,O_2} and P_{et,CO_2} were displayed on a 12-bit analogue digital board and a personal computer running LabVIEW software (National Instruments, Austin, Texas, USA). Signals were sampled at 100 Hz. $P_{0.1}$ was measured from each tracing. V'_I and $P_{0.1}$ were plotted against S_{a,O_2} on linear coordinates and the slopes were calculated by least-squares linear regression. The procedure was terminated when the S_{a,O_2} reached 80%.

Peripheral chemosensitivity was detected as a fall of ventilation following sudden elimination of mild hypoxia [7, 25]. At the beginning of the test, V'_I and P_{et,CO_2} were measured while the subject was breathing room air from a rubber bag. N_2 and CO_2 were then added to obtain a end-tidal O_2 tension (P_{et,O_2}) of 60 mmHg and P_{et,CO_2} 5 mmHg higher than the control. Two breaths of O_2 were then given by turning a three-way stopcock near the inlet of the respiratory valve, to raise P_{et,O_2} >200 mmHg. P_{et,CO_2} was also decreased by 2–3 mmHg because inspired CO_2 pressure decreased to zero at this time [25]. After two breaths of 100% O_2, the inspiratory gas was switched back to the hypercapnic hypoxic gas. The V'_I during room-air breathing was defined as $V'_{I,N}$. The V'_I before breathing 100% O_2 during the mildly hypercapnic hypoxic state was defined as $V'_{I,0}$. The V'_I between 5 and 20 s after changing the inspiratory gas was defined as $V'_{I,5–20}$. The difference between $V'_{I,0}$ and $V'_{I,5–20}$ was defined as the withdrawal response ($\Delta V'_I$) and $\%\Delta V'_I$ ($\Delta V'_I/V'_{I,0}\times100$) was used as an index of the peripheral chemoreceptor activity. The withdrawal test was performed three or more times at intervals of 20 min. The subject breathed room air between tests to avoid the effects of hypoxic ventilatory depression [7]. To eliminate the effects of body size and sex, the indices of each ventilatory response were corrected by body surface area (BSA).

Table 1. – Anthropometric characteristics, lung function and sleep architectures in control subjects and patients with obstructive sleep apnoea-hypopnoea syndrome (OSAHS)

	Control subjects	Patients with OSAHS
Sex M:F	10:3	14:5
Age yr	56±13	54±8
Weight kg	81±14	88±14
Height m	1.62±0.11	1.69±0.09
BMI $kg\cdot m^{-2}$	30.9±3.0	30.8±3.6
Smokers %	31	21
Total sleep time min	373±42	316±24
Sleep efficiency %	85±8	71±6*
Sleep onset latency min	33±12	10±8**
WASO min	32±36	105±22**
AHI h^{-1}	2.4±1.4	47.3±22.9**
ARI h^{-1}	2.0±1.3	34.4±13.4**
Mean S_{a,O_2} %	96±1	93±5
Mean low S_{a,O_2} %	90±1	79±9**
Minimum S_{a,O_2} %	89±2	74±8**
FVC L	3.30±1.01	3.78±0.79
FEV1 L	2.52±0.86	3.08±0.74
TLC L	5.75±1.29	6.32±1.03
FRC L	3.22±0.84	2.94±0.61
RV L	2.40±1.05	2.40±0.59
$P_{I,max}$ kPa	10.0±2.2	11.1±3.1
pH	7.41±0.03	7.40±0.03
P_{a,O_2} mmHg	79.4±4.4	73.9±9.1
P_{a,CO_2} mmHg	37.5±3.1	38.9±3.8
V'_{O_2} $L\cdot min^{-1}$	0.284±0.053	0.303±0.080
V'_{CO_2} $L\cdot min^{-1}$	0.242±0.052	0.257±0.076
$P_{0.1}$ kPa	0.139±0.019	0.205±0.045**

Data are presented as mean±SD. M: male; F: female; BMI: body mass index; WASO: wake after sleep onset; AHI: apnoea-hypopnoea index; ARI: arousal index; S_{a,O_2}: arterial oxygen saturation; FVC: forced vital capacity; FEV1: forced expiratory volume in one second; TLC: total lung capacity; FRC: functional residual capacity; RV: residual volume; $P_{I,max}$: maximal static inspiratory pressure; P_{a,O_2}: oxygen tension in arterial blood; P_{a,CO_2}: carbon dioxide in arterial blood; V'_{O_2}: oxygen consumption; V'_{CO_2}: carbon dioxide output; $P_{0.1}$: mouth occlusion pressure. *: $p<0.05$ for the comparison with control group; **: $p<0.01$ for the comparison with control group.

Analysis

The comparisons between the patients with OSAHS and the control subjects were performed by the Mann-Whitney U-test. Coefficient of variability was computed as 100× standard deviation (SD) of the repeated determinations divided by the mean value ($100\times SD\cdot mean^{-1}$). Correlations between respiratory responses to progressive isocapnic hypoxic stimulation and the

Table 2. – Respiratory responses to chemical stimuli in control subjects and patients with obstructive sleep apnoea-hypopnoea syndrome (OSAHS)

	Control subjects	Patients with OSAHS
$\Delta V'_I/S_{a,O_2}$/BSA L/min/%/m^2	0.455±0.006	0.261±0.003**
$\Delta P_{0.1}/S_{a,O_2}$ kPa/%	0.0033±0.0003	0.0024±0.0004**
$\Delta V'_{I,N}$/BSA L/min/m^2	5.45±0.36	5.43±0.46
$\Delta V'_{I,0}$/BSA L/min/m^2	10.9±1.78	6.55±0.78**
$\Delta V'_I$/BSA L/min/m^2	3.60±0.50	1.57±0.30**
$\Delta V'_I$ %	33.0±2.8	24.0±3.6**

Data are presented as mean±SD. $\Delta V'_I/S_{a,O_2}$/BSA: ventilatory response to progressive isocapnic hypoxic stimulation; $\Delta P_{0.1}/S_{a,O_2}$: central inspiratory drive response to progressive isocapnic hypoxic stimulation; $\Delta V'_{I,N}$/SA: inspiratory minute ventilation during room air breathing; $\Delta V'_{I,0}$/BSA: inspiratory minute ventilation during mildly hypercapnic hypoxic state; $\Delta V'_I$: withdrawal response. **: $p<0.01$ for the comparison with control group.

hypoxic withdrawal test were analysed by linear regression analysis, using Spearman's rank correlation coefficient (r). In order to determine which independent variables were correlated with hypoxic withdrawal response, stepwise multiple linear regression analysis was performed [26]. Independent variables entered into the regression included AHI, ARI, mean lowest S_{a,O_2}, minimum S_{a,O_2}, O_2 uptake and CO_2 production. Stepwise criteria were a probability of F-Snedecor test to enter <0.05 and a probability of F-Snedecor test to remove >0.10. In all cases, p-values of <0.05 were considered to be significant. Data are expressed as mean±SD.

Results

The anthropometric characteristics of the patients with OSAHS and the control subjects are shown in table 1. There was no significant difference in sex, age, body mass index or smoking habit between both groups.

The mean values of lung volumes, $P_{I,max}$, arterial blood gases, O_2 uptake and CO_2 production were similar in both groups. Of the basal lung function tests, only $P_{0.1}$ was significantly higher ($p<0.001$) in the OSAHS patients than in the control subjects.

The respiratory responses to hypoxia are shown in table 2. Compared with control subjects, patients with OSAHS had lower ventilatory and inspiratory neural drive responses to progressive isocapnic hypoxic stimulation ($p<0.001$). There was no significant difference in V'_I during room air breathing. The mean values of V'_I during mildly hypercapnic hypoxic state ($\Delta V'_{I,0}$/BSA) and withdrawal response ($\Delta V'_I$/BSA and $\%\Delta V'_I$) for patients with OSAHS were lower than those for the control subjects.

In control subjects, withdrawal response was correlated with ventilatory and $P_{0.1}$ responses to progressive isocapnic hypoxic stimulation (fig. 1). As

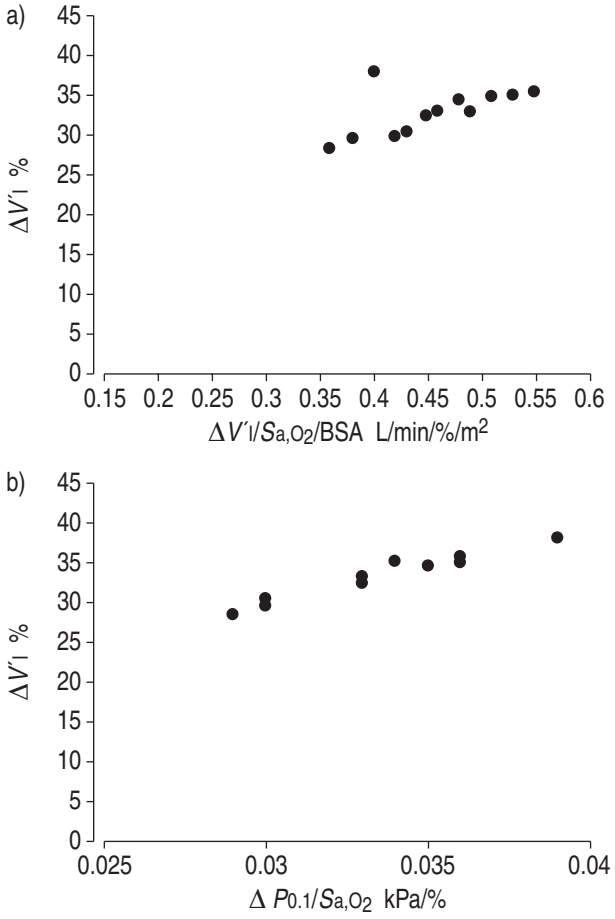

Fig. 1.–a) Ventilatory and b) inspiratory neural drive responses to progressive isocapnic hypoxic stimulation plotted against hypoxic withdrawal in control subjects. $\Delta V'_I$: withdrawal response; $\%\Delta V'_I$: $\Delta V'_I/V'_{I,0}\times100$, where $V'_{I,0}$ is V'_I before breathing 100% O_2 during the mildly hypercapnic hypoxic state. S_{a,O_2}: arterial oxygen saturation; BSA: body surface area; $\Delta V'_I/S_{a,O_2}$/BSA: ventilatory response to progressive isocapnic hypoxic stimulation; $P_{0.1}$: mouth occlusion pressure; $\Delta P_{0.1}/S_{a,O_2}$: central inspiratory drive response to progressive isocapnic hypoxic stimulation. (a) r=0.685, p=0.010; b) r=0.961, p=0.000).

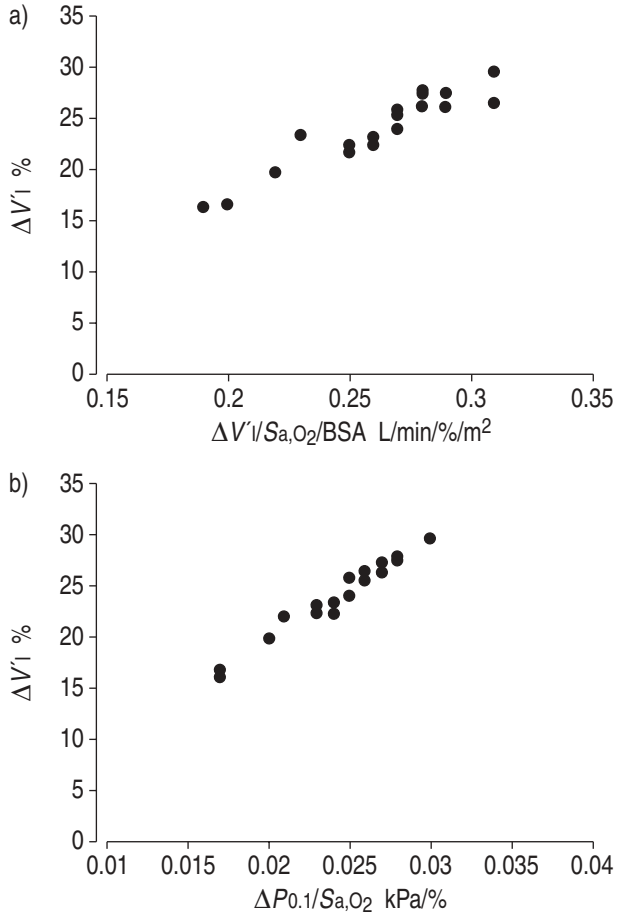

Fig. 2.–a) Ventilatory and b) inspiratory neural drive responses to progressive isocapnic hypoxic stimulation plotted against hypoxic withdrawal in patients with obstructive sleep apnoea-hypopnoea syndrome (OSAHS). $\Delta V'_I$: withdrawal response; $\%\Delta V'_I$: $\Delta V'_I/V'_{I,0}\times100$, where $V'_{I,0}$ is V'_I before breathing 100% O_2 during the mildly hypercapnic hypoxic state. S_{a,O_2}: arterial oxygen saturation; BSA: body surface area; $\Delta V'_I/S_{a,O_2}$/BSA: ventilatory response to progressive isocapnic hypoxic stimulation; $P_{0.1}$: mouth occlusion pressure; $\Delta P_{0.1}/S_{a,O_2}$: central inspiratory drive response to progressive isocapnic hypoxic stimulation. a) r=0.976, p=0.000; b) r=0.926; p=0.000.

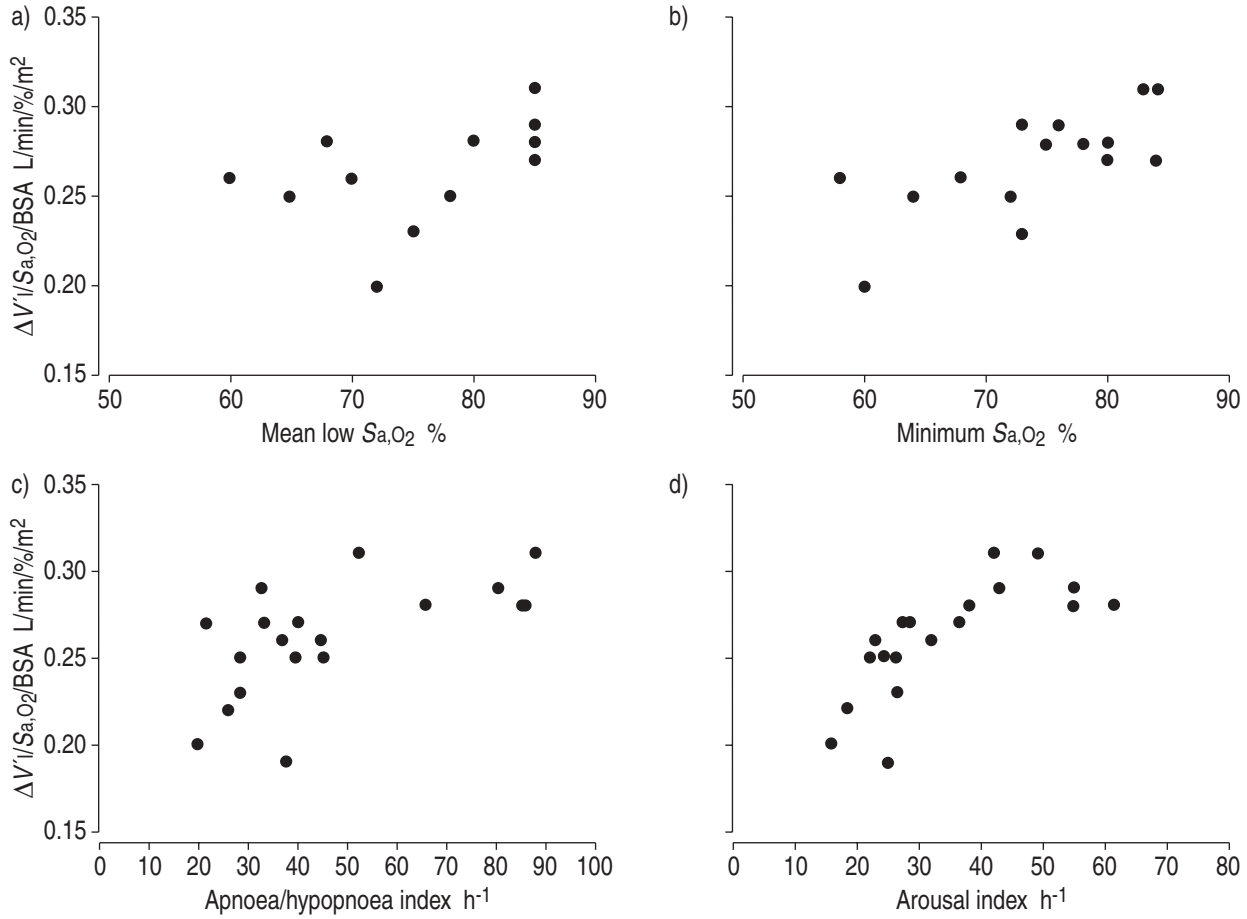

Fig. 3. – Relationship between a) mean nocturnal arterial oxygen saturation (S_{a,O_2}), b) minimum S_{a,O_2}, c) apnoea/hypopnoea index and d) arousal index with ventilatory response to progressive isocapnic hypoxia ($\Delta V'_I/S_{a,O_2}$/BSA). BSA: body surface area; $\Delta V'_I$: withdrawal response. a) r=0.732, p=0.002; b) r=0.697, p=0.004 c) r=0.649, p=0.003; d) r=0.864; p=0.000.

shown in figure 2, patients with OSAHS had significant correlations between $\Delta V'_I/S_{a,O_2}$/BSA and $\%\Delta V'_I$, and between $\Delta P_{0.1}/S_{a,O_2}$ and $\%\Delta V'_I$. On stepwise multiple linear regression analysis, $\%\Delta V'_I$ significantly correlated with $\Delta P_{0.1}/S_{a,O_2}$ (multiple r^2=0.970, p=0.000) in patients with OSAHS.

Within-day coefficients of variation for chemosensitivity indices as assessed in all OSAHS patients for three study sessions were 6.1% (range, 2.0–8.5%) for $\Delta V'_I/S_{a,O_2}$ /BSA, 5.8% (range, 1.7–8.0%) for $\Delta P_{0.1}/S_{a,O_2}$, and 8.3% (range, 3.2–12.4%) for $\%\Delta V'_I$. Day-to-day coefficients of variation as assessed in eight patients with OSAHS on three different days, were 9.1% (range, 3.3–13.5%) for $\Delta V'_I/S_{a,O_2}$/BSA, 8.9% (range, 4.1–12.6%) for $\Delta P_{0.1}/S_{a,O_2}$, and 12.6% (range, 5.2–18.1%) for $\%\Delta V'_I$.

In OSAHS patients, $\Delta V'_I/S_{a,O_2}$/BSA correlated with mean low S_{a,O_2} (r=0.732, p=0.002), minimum S_{a,O_2} (r=0.697, p=0.004), AHI (r=0.649, p=0.003) and ARI (r=0.864, p=0.000) (fig. 3). $\Delta P_{0.1}/S_{a,O_2}$ also correlated with mean low S_{a,O_2} (r=0.824, p=0.000), minimum S_{a,O_2} (r=0.771, p=0.001), AHI (r=0.650, p=0.003) and ARI (r=0.902, p=0.000) (fig. 4). Indeed, $\%\Delta V'_I$ correlated with mean low S_{a,O_2} (r=0.816, p=0.000), minimum S_{a,O_2} (r=0.768, p=0.001), AHI (r=0.676, p=0.001) and ARI (r=0.913, p=0.000) (fig. 5). O_2 uptake and CO_2 production were related with $\Delta P_{0.1}/S_{a,O_2}$ (r=0.582, p=0.009 and r=0.576, p=0.010, respectively) and with $\%\Delta V'_I$ (r=0.553, p=0.014 and r=0.560, p=0.013, respectively), but they did not correlate with $\Delta V'_I/S_{a,O_2}$/BSA (r=0.375, p=0.114 and r=0.386, p=0.103, respectively). No correlations were found between the withdrawal response and mean nocturnal S_{a,O_2} (r=-0.238, p=0.455), pH (r=-0.234, p=0.336), CO_2 tension in arterial blood (P_{a,CO_2}) (r=0.086, p=0.726), functional residual capacity (r=0.290, p=0.242), $P_{I,max}$ (r=0.175, p=0.473) or central inspiratory drive (r=-0.192, p=0.430). On stepwise multiple linear regression for $\%\Delta V'_I$ as dependent variable, the variables entered into the more significant model (r=0.882, adjusted r^2=0.740) were ARI (standardised coefficient beta=0.551, p=0.009) and minimum S_{a,O_2} (standardized coefficient beta=0.422, p=0.034).

Discussion

The main results of the present study are the following: peripheral chemosensitivity is reduced in OSAHS patients in comparison with control subjects;

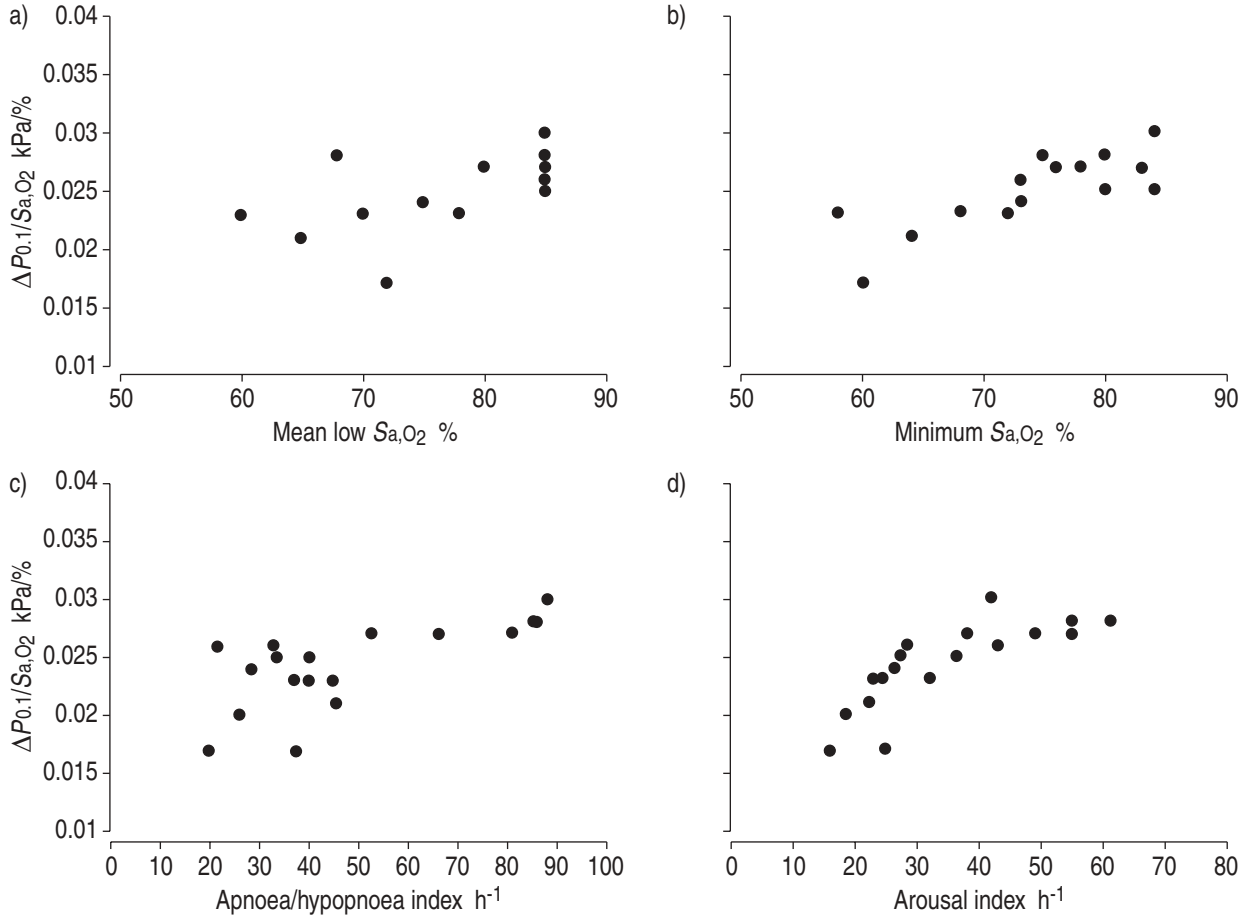

Fig. 4. – Relationship between a) mean nocturnal arterial oxygen saturation (S_{a,O_2}), b) minimum S_{a,O_2}, c) apnoea/hypopnoea index and d) arousal index with inspiratory neural drive response to progressive isocapnic hypoxia ($\Delta P_{0.1}/S_{a,O_2}$). $P_{0.1}$: mouth occlusion pressure. (a) r=0.824, p=0.000; b) r=0.771, p=0.001; c) r=0.650, p=0.003; d) r=0.902, p=0.000).

the sensitivity of carotid body is strongly related with inspiratory neural drive response to progressive isocapnic hypoxic stimulation; and peripheral chemosensitivity of OSAHS patients is related to sleep disruption and to nocturnal hypoxaemia.

There are several factors to be considered when interpreting the decreased peripheral chemosensitivity of the patient group. Differences in age, body size and lung volumes could modify responses to chemical stimuli [27]. However, none of these varied between the OSAHS and control subjects. It is also known that chemosensitivity is highly dependent on the acid-base status of the patient. The respiratory response to hypoxia is sensitive to variations in arterial pH induced by partial pressure of CO_2 changes. Specifically, acidosis and hypercapnia increase the response to hypoxia [27]. Only one of 19 OSAHS patients had a P_{a,CO_2} >45 mmHg (46.8 mmHg). $\Delta V'_I/S_{a,O_2}$/BSA, $\Delta P_{0.1}/S_{a,O_2}$ and $\Delta V'_I$ of this subject (0.27 L/min/%/m^2, 0.0250 kPa/% and 24.2%, respectively) were higher than mean values of the OSAHS group (table 2). A hypercapnia-related increase in peripheral chemosensitivity could not be excluded in this patient. Thus, it is possible that the results slightly underestimate the true depression of peripheral chemosensitivity of OSAHS patients. The contribution of metabolic rate to the decrease in peripheral chemosensitivity should also be evaluated. The present results, which show similar levels of O_2 consumption and CO_2 production between OSAHS patients and control subjects, suggest that changes in the sensitivity of the carotid body of these patients are not due to lower basal metabolism.

A strong relationship between peripheral chemosensitivity and respiratory responses to progressive isocapnic hypoxic stimulation in OSAHS patients was found. These findings suggest that hypoxic stimulation of central chemoreceptors is minimally relevant in OSAHS patients. Thus, inspiratory neural drive response to hypoxia could be used to estimate peripheral chemosensitivity in these patients. Furthermore, a limitation of the withdrawal test should be considered. In the withdrawal test, the level of the stimulus varies with the tidal volume and frequency of the hyperoxic breaths, the initial alveolar O_2 pressure, and the distribution of ventilation in the lungs [8]. Clearly, it would be difficult to apply this test in OSAHS patients in whom maldistribution of ventilation would prevent the relatively abrupt institution of a hyperoxic state, such as would occur in normal subjects.

This limitation of the withdrawal test in OSAHS patients could explain the slightly higher coefficients

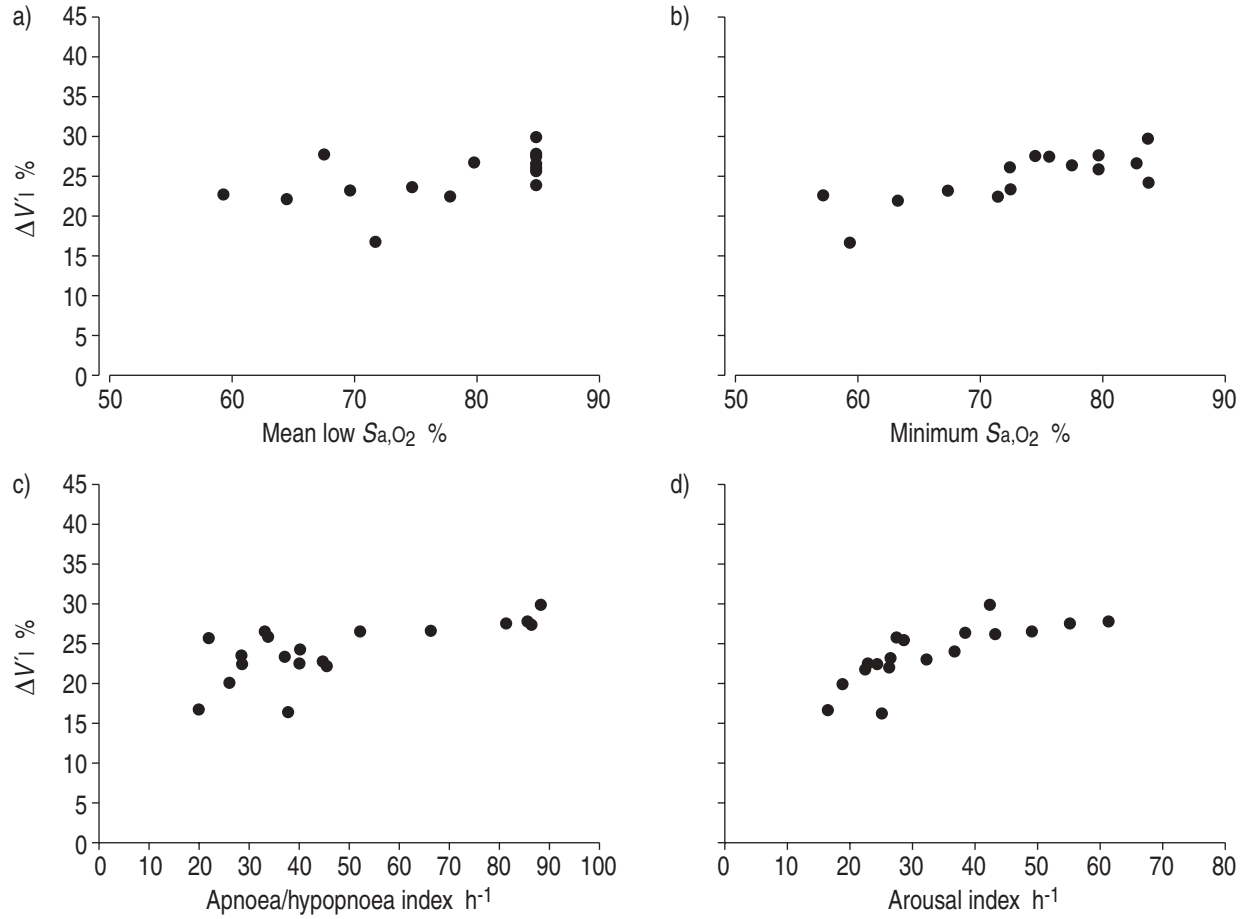

Fig. 5. – Relationship between a) mean nocturnal arterial oxygen saturation (S_{a,O_2}), b) minimum S_{a,O_2}, c) apnoea/hypopnoea index and d) arousal index with hypoxic withdrawal response ($\Delta V'_I$). (a) r=0.816, p=0.000; b) r=0.768; p=0.001; c) r=0.676; p=0.001; d) r=0.913, p=0.000).

of variation for $\%\Delta V'_I$ than for $P_{0.1}$ or ventilatory response to hypoxia found in this study. However, variability of both tests is moderate. Within-subject variability of hypoxic withdrawal response in the OSAHS patients (12.6%) was equal to spontaneous variation estimated by OSANAI *et al.* [7] in healthy subjects. The coefficient of variability for $P_{0.1}$ response to hypoxia found in the OSAHS patients (8.9%) was also similar to the coefficients of variability described by WHITE *et al.* [28] and the present authors' [29] in healthy subjects.

The mechanism of the reduced peripheral chemosensitivity in OSAHS patients is not well established. It seems probable that the diminished sensitivity of the carotid body represents a specific adaptation to the repeated hypoxia induced during apnoeas [30]. It is known that a reduction in ventilatory response to hypoxia occurs during both short- and long-term hypoxic exposure [31]. Although only very limited data exist on ventilatory changes during repeated hypoxia [30], the reduced peripheral chemosensitivity of OSAHS patients could represent an adaptive response to the hypoxic environment. Previous studies have shown that adaptation to sustained hypoxia may result from changes in either carotid chemoreceptors or central hypoxic sensitivity. The latter may be due either to altered central processing of afferent carotid body stimuli or to a change in direct central nervous system sensitivity to hypoxia [31]. The results of the present study do not exclude alterations in central processing of afferent stimuli, but show that central hypoxic stimulation is scarcely relevant.

In accordance with the role of hypoxia as an inducer of peripheral chemosensitivity alterations, a significant relationship between sensitivity of the carotid body and minimum nocturnal O_2 saturation was found. Previously, it has been demonstrated that ventilatory responses to hypoxia are negatively correlated with the degree of hypoxaemia during sleep in OSAHS patients [32]. OSANAI *et al.* [7] reported that the hypoxic withdrawal response showed negative correlations with 4%- and 10%-desaturation ratios. Contrary to these authors [7], the present authors found that peripheral chemosensitivity is also positively correlated with AHI. The importance of sleep structure as a contributing factor to peripheral chemosensitivity changes in OSAHS patients is not well known. Despite a reduction of ventilatory response to hypoxia after sleep deprivation having been demonstrated in healthy males [28], no relationship between diurnal sleepiness and chemosensitivity has been established. Previously, the present authors

have proposed that repetitive abrupt arousals from sleep could be important contributors to the increase of the peripheral chemosensitivity in OSAHS patients [9]. The relationship between ARI and hypoxic withdrawal response found in the OSAHS patients in the present study might suggest a contribution of sleep disruption to changes in peripheral chemosensitivity. In consequence, it could be hypothesised that the sensitivity of the carotid body in OSAHS patients might be determined by a balance between hypoxic depression and arousal stimulation.

The sequence of events leading to a decrease in peripheral chemosensitivity in OSAHS patients is unresolved, but it has been proposed that these subjects have an abnormality of dopaminergic mechanisms in the peripheral chemoreceptors [7]. Since dopamine appears to be an inhibitory transmitter in mammalian carotid bodies, the effects of dopamine on the carotid body of patients with OSAHS might be increased [7]. On the other hand, familial aggregation of blunt ventilatory responses to chemical stimuli has been reported for healthy family members of OSAHS patients [33]. Thus a contribution of genetic factors to the changes in peripheral chemosensitivity observed in patients with OSAHS cannot be excluded.

To conclude, this study shows a strong relationship between peripheral chemosensitivity and the respiratory response to hypoxia in obstructive sleep apnoea-hypopnoea syndrome patients, suggesting that hypoxic stimulation of central chemoreceptors is minimally relevant in these patients. Moreover the sensitivity of the carotid body in patients with obstructive sleep apnoea-hypopnoea syndrome is related to the apnoea-hypopnoea index and with nocturnal oxygenation.

Acknowledgements. The investigators acknowledge the excellent technical assistance provided by A. Alvarez, P. Librán, A. Pérez and C. Suárez.

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