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Depression of peripheral chemosensitivity by a dopaminergic mechanism in patients with obstructive sleep apnoea syndrome

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Depression of peripheral chemosensitivity by a dopaminergic mechanism in patients with obstructive sleep apnoea syndrome. S. Osanai, Y. Akiba, S. Fujiuchi, H. Nakano, H. Matsumoto, Y. Ohsaki, K. Kikuchi. ©ERS Journals Ltd 1999.

ABSTRACT: In the present study, respiratory drives to chemical stimuli and peripheral chemosensitivity were evaluated in patients with obstructive sleep apnoea (OSAS). The effects of oral administration of domperidone, a selective dopamine D_2-receptor antagonist, were also examined, to study the respiratory effects of endogenous dopamine on peripheral chemoreceptors.

Sixteen patients with OSAS and nine normal control subjects were studied. Respiratory responses to hypercapnia and hypoxia were measured using the rebreathing method and isocapnic progressive hypoxia method, respectively. The hypoxic withdrawal test, which measures the decrease in ventilation caused by two breaths of 100% O_2 under mild hypercapnic hypoxic conditions (end-tidal oxygen and carbon dioxide tensions $\approx$8.0 kPa and 5.3–6.7 kPa, respectively), was used to evaluate peripheral chemosensitivity.

In the patients with OSAS, ventilatory responses to hypercapnia and hypoxia were significantly decreased compared with those of control subjects. Hypoxic withdrawal tests showed that peripheral chemosensitivity was significantly lower in patients with OSAS than in normal subjects. Hypercapnic ventilatory response and peripheral chemosensitivity were enhanced by administration of domperidone in the patients with OSAS, although no changes in either of these were observed in the control subjects. The hypoxic ventilatory response and peripheral chemosensitivity in the patients with OSAS were each significantly correlated with severity of hypoxia during sleep.

These findings suggest that peripheral chemosensitivity in patients with obstructive sleep apnoea syndrome may be decreased as a result of abnormality in dopaminergic mechanisms and that the reduced chemosensitivity observed in patients with obstructive sleep apnoea syndrome may affect the severity of hypoxia during sleep.
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Obstructive sleep apnoea syndrome (OSAS) is characterized by frequent episodes of upper airway closure during sleep [1]. This airway collapse is due to both a narrow upper airway and a decrease in muscle tone during sleep [2]. It has also been suggested that the critical trigger of apnoea might be instability of breathing during sleep [3] and that the duration of apnoea is influenced by individual respiratory drive [4, 5]. The ventilatory response in patients with OSAS has, therefore, been studied in detail over the last two decades. However, the role of peripheral chemoreception in this syndrome has not been adequately evaluated.

In the present study, the ventilatory response to chemical stimuli and peripheral chemosensitivity was measured in patients with OSAS using the hypoxic withdrawal test [6–8]. The respiratory effect of endogenous dopamine, a major neurotransmitter [9, 10] which might inhibit peripheral chemoreceptors [11, 12], was also assessed by administration of domperidone, a dopamine antagonist [13].

Table 1. – Characteristics of subjects

	Control subjects	Patients with OSAS
Sex M/F	7/2	14/2
Age yrs	43.7±4.7	46.6±3.1
	(24–62)	(24–65)
BMI $kg \cdot m^{-2}$	27.2±2.4	27.8±1.4
	(20.9–38.5)	(18.9–42.8)
VC % pred	100.1±3.9	105.0±2.6
	(78.4–113.1)	(82.7–117.2)
FEV1/FVC %	90.3±2.6	80.6±1.3*
	(79.3–106.4)	(73.7–93.3)
P_{a,CO_2} mmHg	40.8±0.5	43.6±0.7*
	(36.2–42.2)	(39.8–50.6)
P_{a,O_2} mmHg	91.2±1.2	83.8±2.4*
	(84.8–98.8)	(66.9–95.6)

Values are means±SEM with ranges shown in parentheses. OSAS: obstructive sleep apnoea syndrome; M: male; F: female; BMI: body mass index; VC: vital capacity; FEV1/FVC: forced expiratory volume in one second/forced vital capacity; P_{a,CO_2}: arterial carbon dioxide tension; P_{a,O_2}: arterial oxygen tension. *: $p<0.05$. (1 mmHg=0.133 kPa.)

Materials and methods

Study groups

The present experiments were performed with 16 patients with OSAS and nine control subjects (table 1). The diagnosis of OSAS had been reached by standard full-night polysomnography [1, 14]. The patients with OSAS fulfilled the criteria for OSAS proposed by GUILLEMINAULT *et al.* [1]. All of the patients with OSAS snored and

had excessive daytime sleepiness. The clinical characteristics of the patients with OSAS are shown in table 2. At the time of the study, no patient with OSAS had any evidence of hypothyroidism or heart failure. Five patients with OSAS had hypertension treated with calcium channel blockers or angiotensin-converting enzyme inhibitors. All medications were withdrawn under careful observation 1 week before the studies. No patient required administration of these medications during the study period. The control subjects were recruited from among hospital staff members who were naive concerning respiratory physiology. No control subjects had health problems and none were receiving any medication. Sleep-disordered breathing in the control subjects was screened for using a questionnaire and overnight measurement of arterial oxygen saturation (S_{a,O_2}) with a pulse oximeter (Pulsox 7; Minolta, Osaka, Japan). Oral informed consent was obtained from each subject before the study. The study protocol was approved by the Institutional Review Board of Asahikawa Medical College. All subjects were instructed to refrain from drinking caffeine-containing beverages on the day of the study.

Respiratory drives

The effects on respiratory drive of chemical stimuli were assessed by the ventilatory response and mouth occlusion pressure response. All subjects fasted and were in a stable resting state for at least 30 min before the tests. They were seated in a comfortable chair, breathed through a low-resistance valve (Model 2700; Hans Rudolph, St Louis, MO, USA) and wore a rubber mouthpiece, noseclips and headphones, which supplied music devoid of strong rhythmic content. Inspiratory airflow was monitored by a Fleish-type pneumotachograph (MFP-1T-S; Nihon Koden, Tokyo, Japan) connected to the inspiratory site of the valve. Inspiratory tidal volume was derived by integration of the flow signal. During each test, inspiratory minute ventilation (V'_I) at body temperature, ambient pressure and water saturation (BTPS) conditions, tidal volume and breathing frequency were measured continuously. On the inspiratory valve, an electromagnetic shutter was inserted to measure mouth occlusion pressure ($P_{0.1}$), which is the pressure generated 0.1 s after occlusion by the inspiratory muscles at functional residual capacity. Measurement of $P_{0.1}$ was performed randomly every 5–10 breaths during the hypercapnia and hypoxia tests as follows. Respiratory gas was sampled continuously from the mouthpiece for measurements of breath-by-breath end-tidal carbon dioxide tension (P_{ET,CO_2}) and end-tidal oxygen tension (P_{ET,O_2}) using a mass spectrograph (Med Spect II; Chemetron, USA). S_{a,O_2} was measured using the pulse oximeter. The electrocardiogram was monitored to determine cardiac frequency and detect incidental arrhythmias due to hypoxia.

Table 2. – Patients with obstructive sleep apnoea syndrome

Patient No.	AI h^{-1}	$DSR_{4\%}$ %	$DSR_{10\%}$ %
1	18.7	4.0	0.5
2	56.3	20.2	5.8
3	13.9	7.7	0.8
4	20.3	22.0	7.2
5	10.2	25.6	4.5
6	47.5	56.2	28.5
7	48.0	18.2	2.2
8	18.7	4.0	1.0
9	51.4	72.1	13.7
10	45.5	52.2	16.3
11	38.5	43.0	21.0
12	26.2	13.1	1.2
13	43.0	15.3	4.1
14	21.4	63.1	4.9
15	40.1	16.5	8.7
16	60.0	19.0	11.0
Mean±SEM	35.0±8.7	28.3±7.1	8.2±2.1

AI: apnoea index; $DSR_{4\%}$: 4% desaturation ratio; $DSR_{10\%}$: 10% desaturation ratio.

The respiratory response to hypercapnia was measured using the rebreathing method [15]. In brief, a 6-L bag, which was filled with gas composed of 5% CO_2, 50% O_2 and 45% N_2, was connected to the breathing valve and the subject rebreathed into the bag until P_{ET,CO_2} was >9.3 kPa (70 mmHg). During the tests, the P_{ET,O_2} was maintained >13.3 kPa (100 mmHg). One rebreathing test was usually terminated within 5 min. The respiratory response to hypoxia was measured by the isocapnic progressive hypoxia method [16]. In brief, P_{ET,O_2} was lowered from 16.0 to 6.0 kPa (120 to 45 mmHg) over 7 min by the addition of N_2. CO_2 was added in amounts sufficient to maintain isocapnia. The respiratory drive was assessed by the slopes of V'_I and $P_{0.1}$ as functions of P_{ET,CO_2} and S_{a,O_2}.

Hypoxic withdrawal responses

The hypoxic withdrawal test [6–8] was used to evaluate the contribution of peripheral chemoreceptors to the ventilatory response. At the beginning of the test, V'_I and P_{ET,CO_2} were measured while the subject was breathing room air in a rubber bag. N_2 and CO_2 were then added to room air in the rubber bag. The P_{ET,O_2} was gradually lowered to 8.0 kPa (60 mmHg). At the same time, the P_{ET,CO_2} was elevated to 0.7 kPa (5 mmHg) above the P_{ET,CO_2} during breathing of room air in order to stabilize ventilation. In this mildly hypercapnic hypoxic state, the hypoxic inspiratory gas was changed to 100% O_2 during two breaths without indicating this to the subject. 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 $\%\Delta V'_I$ ($\Delta V'_I/V'_{I,0} \times 100$) was used as an index of the peripheral chemoreceptor activity (fig. 1). One exposure to hypoxia in this test was usually terminated within 7 min. This 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.

Drugs and protocol

A double-blind study was performed to compare domperidone (Kyowa-Hakkou, Tokyo, Japan) with placebo on separate test days in a random order. The dose of domperidone was 0.5 $mg \cdot kg^{-1}$ *per os*. The medicines were prepared

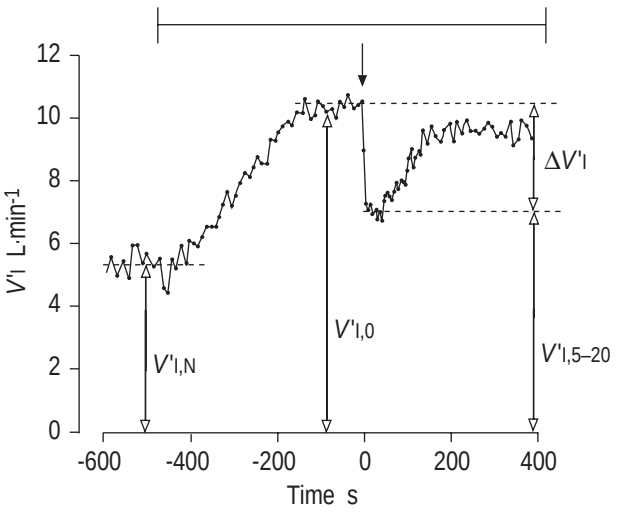

Fig. 1. – Representative recording of hypoxic withdrawal test results for a normal subject. Inspiratory minute ventilation (V'_I) was plotted against time (s). Initially, the subject breathed room air, and V'_I ($V'_{I,N}$) and end-tidal carbon dioxide tension (P_{ET,CO_2}) were measured. Then, the end-tidal oxygen tension (P_{ET,O_2}) was gradually lowered to 8.0 kPa (60 mmHg) and at the same time the P_{ET,CO_2} was elevated to 0.7 kPa (5 mmHg) above the level of air ventilation (solid horizontal line). In this hypoxic state, the hypoxic inspiratory gas was changed to 100% O_2 during two breaths (filled vertical arrow). The ventilation after these two breaths of O_2 was observed for about 120–180 s. The V'_I before breathing of 100% O_2 was defined as $V'_{I,0}$, and 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 $\%\Delta V'_I$ ($\Delta V'_I/V'_{I,0} \times 100$) was used as an index of peripheral chemoreceptor activity.

by a controller and the investigators were blind to them until the end of the protocol for each patient. Drugs were administered to subjects 30 min before each test.

Data analysis

In the sleep study, apnoea was defined as cessation of flow at the nose and mouth for at least 10 s. An apnoea index (total number of apnoeic episodes divided by the total sleep time in hours) was defined and computed as described by GUILLEMINAULT *et al.* [1]. Baseline S_{a,O_2} was determined with the awake subject in a supine position. The periods with desaturations of >4 or 10% compared with the baseline S_{a,O_2} were calculated; then the durations of desaturation as percentages of total sleep time were calculated as the 4% desaturation ratio (DSR4%) and 10% desaturation ratio (DSR10%), respectively. The slopes of the V'_I and $P_{0.1}$ responses to hypercapnia and hypoxia were calculated by least-squares regression analysis with P_{ET,CO_2} and S_{a,O_2}, respectively. To eliminate the effects of body size and sex, the indices of each ventilatory response were corrected by body surface area (BSA) in square metres [17].

Values reported in the text and tables are means±SEM. Differences were tested for significance with the Wilcoxon test for intragroup comparison and the Mann–Whitney U-test was used for two independent groups. Correlations were assessed by calculating Spearman correlations coefficients. A p-value <0.05 was considered to indicate statistical significance.

Results

The characteristics of the two groups are shown in table 1. There was no significant difference in anthropometric values between patients with OSAS and control subjects. The mean values of forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) and arterial oxygen tension (P_{a,O_2}), although within the generally accepted normal range [18], were lower in patients with OSAS. The mean value of arterial carbon dioxide tension (P_{a,CO_2}) was higher in the group of patients with OSAS, since this group included five patients with chronic hypoventilation (P_{a,CO_2} ≤6.0 kPa (45 mmHg)).

The ventilatory responses to hypercapnia and hypoxia are shown in table 3. The mean values of the hypercapnic ventilatory response in the patient group was lower than that in the control group. Domperidone increased the respiratory drive to hypercapnia only in the patients with OSAS. In the patients with OSAS, each parameter of respiratory drive to hypoxia was significantly lower than that in the corresponding value in the control group. Domperidone did not alter the respiratory drive to hypoxia in either group.

There was no significant difference in $V'_{I,N}$ between the two groups (table 4). The $V'_{I,0}$/BSA, $\Delta V'_I$/BSA and $\%\Delta V'_I$ for patients with OSAS were lower than those for the control subjects. Domperidone increased $V'_{I,N}$ in neither the patients with OSAS nor the control subjects. Domperidone increased the $\Delta V'_I$/BSA and $\%\Delta V'_I$ in patients with OSAS, but not in control subjects. No difference was found in $\Delta V'_I$/BSA or $\%\Delta V'_I$ during administration of domperidone between the two groups. On subgroup analysis, no differences were observed in ventilatory responses to chemical stimuli or peripheral chemoreception between the OSAS patients without chronic hypercapnia and those with chronic hypercapnia (data not shown).

Correlations between ventilatory drive parameters and the results of polysomnography for the patients with OSAS are given in table 5. There was no significant correlation between the respiratory drive to hypercapnia and any of the indices of disturbance of ventilation during sleep. Hypoxic ventilatory response exhibited a negative correlation with DSR4% (fig. 2). There were significant correlations between DSR4% and $\%\Delta V'_I$, and between DSR10% and $\%\Delta V'_I$. The apnoea index was correlated with neither hypoxic ventilatory response nor hypercapnic ventilatory response. Scatter plots of significant correlations in table 5 are illustrated in figure 2. Values for the OSAS patients with hypercapnia are indicated as open circles and they appeared to superimpose on each relationship. These findings showed that subgroup analysis was unlikely to alter the comprehensive findings of this study.

Discussion

The present study showed that: 1) respiratory drive to chemical stimuli was attenuated in patients with OSAS; 2) peripheral chemosensitivity was reduced in patients with OSAS; 3) domperidone increased the hypercapnic ventilatory response and the hypoxic withdrawal response in patients with OSAS; and 4) the hypoxic ventilatory response and hypoxic withdrawal response during wakefulness were negatively correlated with the severity of desaturation during sleep in patients with OSAS.

Table 3. – Ventilatory responses to hypercapnia and hypoxia

	Control subjects		Patients with OSAS	
	Placebo	Domperidone	Placebo	Domperidone
$\Delta V'_I/\Delta P_{ET,CO_2}$/BSA L·min^{-1}·mmHg^{-1}·m^2	0.96±0.09	0.85±0.16	0.71±0.10†	1.10±0.16*
$\Delta P_{0.1}/\Delta P_{ET,CO_2}$ cmH_2O·mmHg^{-1}	0.79±0.15	0.65±0.15	0.29±0.04†	0.49±0.08*
$\Delta V'_I/\Delta S_{a,O_2}$/BSA L·min^{-1}·mmHg^{-1}·m^2	0.55±0.08	0.62±0.11	0.34±0.06†	0.37±0.05
$\Delta P_{0.1}/\Delta S_{a,O_2}$ cmH_2O·%$^{-1}$	0.65±0.10	0.56±0.06	0.28±0.04†	0.22±0.05†

Values are means±SEM. OSAS: obstructive sleep apnoea syndrome; V'_I: inspiratory minute ventilation; P_{ET,CO_2}: end-tidal carbon dioxide tension; BSA: body surface area; $P_{0.1}$: mouth occlusion pressure; Δ: difference; S_{a,O_2}: arterial oxygen saturation. (1 mmHg=0.133 kPa.) *: p<0.05 placebo *versus* domperidone; †: p<0.05 control subjects *versus* patients with OSAS.

The nature of the ventilatory response to chemical stimuli in awake patients with OSAS is still unclear. Ventilatory drive in OSAS patients has been reported to be diminished [19, 20]. In contrast, other investigators have concluded that ventilatory responses in OSAS patients are normal [21]. These discrepancies in findings concerning chemical ventilatory control in OSAS are due in part to differences in patient populations between these studies. Chronic hypercapnia is well recognized, though uncommon among OSAS patients during wakefulness [20, 22]. Hypercapnic OSAS patients have decreased respiratory drive compared with that in normocapnic OSAS patients [19, 20, 22] and the chronic hypercapnia observed during wakefulness in patients with OSAS has been thought to reflect the impact of oxygen desaturation during sleep [23]. The findings obtained for ventilatory drive in patients with OSAS might be affected by the inclusion of hypercapnic OSAS patients in study populations. However, no differences were found in the chemical drives between the normocapnic patient group and the hypercapnic patient group in the present study. Previous studies have shown that tracheostomy and nasal continuous positive airway pressure enhanced ventilatory drive in OSAS patients with normocapnia and those with hypercapnia [20, 24]. These findings suggest that the ventilatory drive in normocapnic patients with OSAS is probably depressed.

It has been demonstrated that ventilatory responses are negatively correlated with the degree of hypoxaemia during sleep in OSAS patients [4]. Hypercapnic OSAS patients have greater oxygen desaturation during sleep than those with eucapnic OSAS [5]. It is possible that frequent asphyxia during sleep causes adaptation and resetting of the ventilatory responses to chemical stimuli in OSAS patients.

Results of twin studies suggest that ventilatory drives are controlled by genetic factors [25]. Familial aggregation of blunt ventilatory responses to chemical stimuli have been demonstrated for healthy members of the families of OSAS patients [26]. The findings of the present study and previous studies suggest that both genetic and acquired factors contribute to the changes in ventilatory drives observed in patients with OSAS.

In order to determine peripheral chemoreceptor activity in awake humans, the hypoxic withdrawal test was used to exclude factors other than the peripheral chemoreceptor activity. The merits of withdrawal tests in the evaluation of peripheral chemoreception have been reported by MILLER *et al.* [27]. In the present study, the change in V'_I during the 5–20-s period following the end of the first O_2 inspiration was defined as the withdrawal response. Since the time required for circulation from the lung to the central nervous system is considered to be about 20 s, the hypoxic withdrawal test eliminates peripheral chemoreceptor activity but leaves the humoral environment of the central respiratory regulating system unchanged. $\Delta V'_I$ and $\%\Delta V'_I$ are, therefore, due to the transient cessation of peripheral chemoreceptor activity.

A preliminary study by the authors estimated the spontaneous variation in five repeated tests of hypoxic withdrawal responses in single subjects. The mean of the coefficient of variance of $\Delta V'_I$ was 12.8% (range 8.8–15.6%) in six healthy subjects. This value was equal to indices of ventilatory responses given in previous reports.

Table 4. – Results of hypoxic withdrawal test

	Control subjects		Patients with OSAS	
	Placebo	Domperidone	Placebo	Domperidone
$\Delta V'_{I,N}$/BSA L·min^{-1}·m^{-2}	5.4±0.2	6.0±0.5	5.2±0.2	5.0±0.0
$\Delta V'_{I,0}$/BSA L·min^{-1}·m^{-2}	10.2±1.1	9.9±1.4	6.7±0.6†	7.3±1.0
$\Delta V'_I$/BSA L·min^{-1}·m^{-2}	3.2±0.4	3.0±0.4	1.3±0.2†	2.4±0.2*
$\%\Delta V'_I$ %	31±3	32±4	19±3†	36±3*

Values are means±SEM. OSAS: obstructive sleep apnoea syndrome; $V'_{I,N}$: inspiratory minute ventilation during breathing of room air; BSA: body surface area; $V'_{I,0}$: inspiratory minute ventilation during hypercapnic hypoxia; $V'_{I,5–20}$: V'_I between 5 and 20 s after changing the inspiratory gas; $\Delta V'_I$: $V'_{I,0}$ - $V'_{I,5–20}$; $\%V'_I = V'_I/V'_{I,0} \times 100$. *: p<0.05 placebo *versus* domperidone; †: p<0.05 control subjects *versus* patients with OSAS.

Table 5. – Coefficients of correlation between apnoea index (AI), oxygen desaturation ratios and ventilatory responses in patients with obstructive sleep apnoea syndrome

	AI	$DSR_{4\%}$	$DSR_{10\%}$
Hypercapnic response			
$\Delta V'_I/\Delta P_{ET,CO_2}$/BSA	-0.073	-0.116	-0.041
$\Delta P_{0.1}/\Delta P_{ET,CO_2}$	0.31	-0.048	0.088
Hypoxic response			
$\Delta V'_I/\Delta S_{a,O_2}$/BSA	-0.378	-0.687*	-0.577
$\Delta P_{0.1}/\Delta S_{a,O_2}$	-0.112	-0.447	-0.416
Hypoxic withdrawal response			
$\%\Delta V'_I$	-0.141	-0.654*	-0.644*

$DSR_{4\%}$: 4% desaturation ratio; $DSR_{10\%}$: 10% desaturation ratio; Δ: difference; V'_I: inspiratory minute ventilation; P_{ET,CO_2}: end-tidal carbon dioxide tension; BSA: body surface area; $P_{0.1}$: mouth occlusion pressure; S_{a,O_2}: arterial oxygen saturation. *: p<0.05.

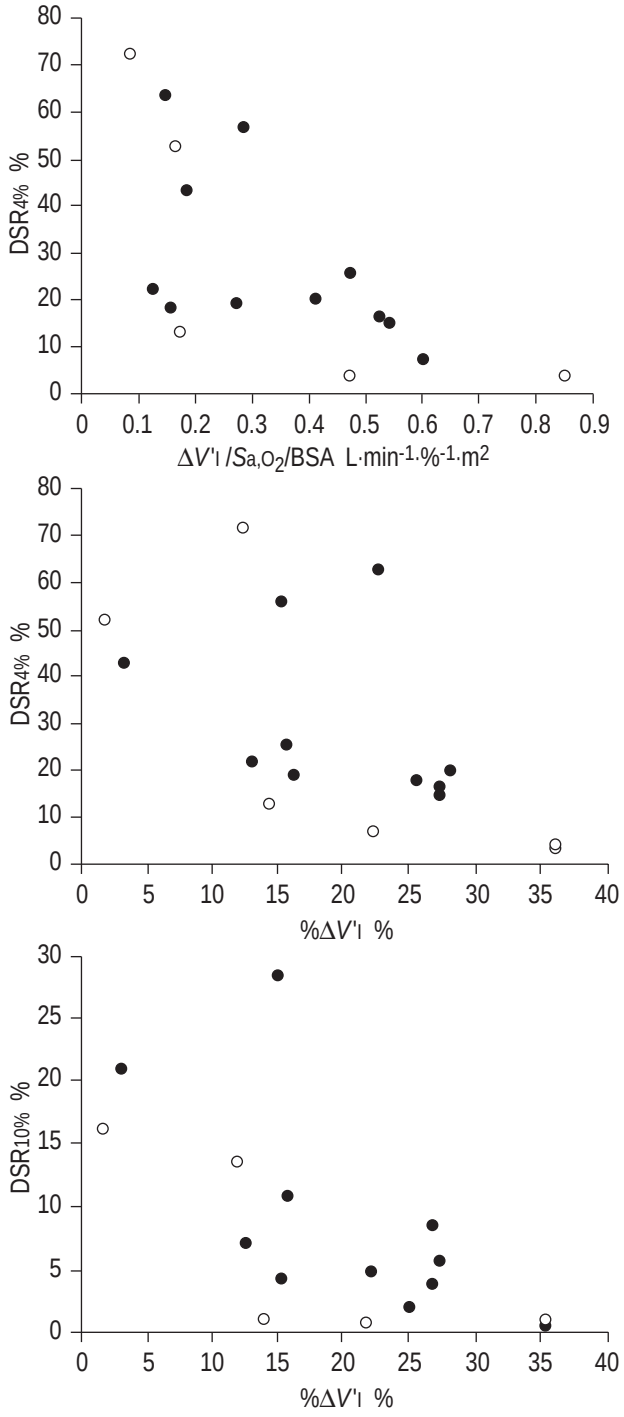

Fig. 2. – Scatter plots of significant correlations between oxygen desaturation ratio during sleep and ventilatory response in obstructive sleep apnoea syndrome with normocapnia (●) and those with chronic hypercapnia (○). $DSR_{4\%}$: 4% desaturation ratio; $DSR_{10\%}$: 10% desaturation ratio; Δ: difference; $\dot{V}'_I$: inspiratory minute ventilation; S_{a,O_2}: arterial oxygen saturation; BSA: body surface area.

The magnitude of change in responses to treatment with domperidone appeared to be significant, compared with spontaneous variation in the indices of ventilatory responses observed in the present study.

Dopamine is a major transmitter in the carotid body [9, 10]. In an animal study, exogenous dopamine reduced ventilatory responses to chemical stimuli owing to the inhibition of carotid chemoreception and dopamine antagonists augmented the ventilatory response [28]. Human studies have also shown that *i.v.* dopamine administration reduces the ventilatory responses to both hypoxia and hypercapnia [12, 29]. Dopamine appears to be an inhibitory transmitter in the mammalian carotid body.

Domperidone is a selective dopaminergic receptor antagonist (D_2) and only minimally crosses the blood–brain barrier [13]. It has been shown that, unlike other such antagonists, domperidone has no α_2-adrenoreceptor-blocking activity [30]. Therefore, domperidone was used to examine the roles played by endogenous dopamine in peripheral chemoreceptors.

It has been demonstrated in animal studies that the hypercapnic ventilatory response [31] and carotid chemosensory discharge response to hypercapnia [32] are enhanced by domperidone. The hypercapnic ventilatory response was not enhanced by domperidone in carotid body-denervated animals [31]. These findings appear to support the hypothesis that domperidone potentiates hypercapnic ventilatory responses in humans *via* the effects on peripheral chemosensitivity. The findings of the present study appear to be compatible with those of the animal studies noted above.

Delpierre *et al.* [33] reported that *i.v.* administration of domperidone increased hypoxic ventilatory response in healthy subjects. In the present study, domperidone changed neither the ventilatory responses to chemical stimuli nor peripheral chemosensitivity in control subjects. This discrepancy in findings between the previous studies and the present investigation might be explained by differences in serum concentrations of domperidone. A safe dose of orally administered domperidone was used in the present study to avoid serious cardiac side-effects [34]. This dose of domperidone has been demonstrated clearly to modulate the effects of dopamine in the gastrointestinal tract [35]. However, the same dose of domperidone increased peripheral chemosensitivity in the patients with obstructive sleep apnoea syndrome in the present study. One interpretation of these findings is that patients with obstructive sleep apnoea syndrome have an abnormality of dopaminergic mechanisms in peripheral chemoreceptors. More specifically, the effects of dopamine on the peripheral chemoreceptors of patients with obstructive sleep apnoea syndrome might be increased and in such patients these receptors might be more sensitive to dopamine receptor antagonists than are those of healthy subjects. However, this hypothesis requires more systematic pharmacological study for testing and direct evidence of abnormality of dopaminergic mechanisms in patients with obstructive sleep apnoea syndrome.

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