High Ventilatory Response to Hypoxia in Hypertensive Patients with Sleep Apnea

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ABSTRACT

The ventilatory response to hypoxia (VRH) in relation to daytime arterial blood pressure was studied in 37 patients with the sleep apnea syndrome (SAS). The patients were divided into hypertensives (n=16) and normotensives (n=21). The hypertensive group had a significantly higher VRH (ventilatory increase 1.48 l/min BTPS per percent decrease in arterial oxygen saturation) than the normotensive group (0.69 l/min/ %, P<0.01).

The observed difference raises the question whether a high chemoreceptor sensitivity to hypoxaemia can contribute in causing arterial hypertension among cases with SAS.

INTRODUCTION

The sleep apnea syndrome (SAS) is characterized by frequent apneas, heavy snoring and day time sleepiness (9, 15). Many SAS patients suffer from systemic hypertension and a considerable proportion of patients with essential hypertension also has SAS (5, 13). A relationship between snoring and essential hypertension has also been suggested (14, 7).

Although there are some explanations for the increase in systemic arterial blood pressure during sleep in patients with SAS, the mechanisms by which the systemic hypertension becomes permanent are still obscure (15). One of the known factors which contribute to the rise in arterial pressure during apnea is the stimulation of peripheral chemoreceptors (PC) by hypoxaemia.

In this retrospective study of SAS patients we investigated the relationship between daytime systemic hypertension and the ventilatory response to hypoxia (VRH), which may be associated with the sensitivity of the peripheral chemo-receptors during wakefulness.

PATIENTS AND METHODS

The study comprised patients attending the Department of Lung Medicine at the University Hospital, Uppsala, with (a) the diagnosis of well established

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obstructive SAS, (b) the absence of other diseases known specifically to influence arterial blood pressure, and (c) willingness to participate in the test of VRH. Thirty-seven patients fulfilled the three criteria and entered the study. The patients were then divided into two groups according to their arterial pressure, a hypertensive group and a normotensive group. The hypertensive group consisted of 15 men and one woman (Table 1). They were all previously known to be hypertensive and were being treated with various antihypertensive agents. Twelve patients were taking beta blockers (6 propranolol, 4 metoprolol, 2 pindolol), mainly in combination with diuretics, three patients were taking methyldopa and one was receiving clonidine. The normotensive group consisted of 21 male SAS patients (Table 1).

The diagnosis of SAS was made after a whole-night polysomnographic study according to Gislason (6). Sleep was monitored and analysed according to the recommendations of Rechtschaffen and Kales (21). Respiratory movements were monitored by use of a static charge sensitive bed (Biorec OY, Kuusisto, Finland) and also with movement sensors (Siemens 230). Air flow was detected by means of nose and mouth thermistors and also by attaching a stetoscope near the trachea for recording the tracheal sounds.

Apnea was defined in this study as complete cessation of air flow through the upper airways for more than 10 seconds, and the pathological apnea index as 5 apneas or more per hour of sleep (9).

The VRH was assessed using the rebreathing method described by Rebuck and Campbell (20). Gas for the end-tidal CO_2 and O_2 tensions (PetCO$_2$ and PetO$_2$, respectively) was sampled from the mouthpiece and continuously analysed with a Beckman LB-2 non-dispersive infrared instrument and a Beckman OM-11 polarographic analyzer (Beckman Instruments AB, Stockholm, Sweden) respectively. The level of the PetCO$_2$ was maintained constant with a system of valves by which the flow of the expired air could be shunted through a CO_2-absorber. During the procedure isocapnic hypoxia, monitored with a Biox 3700 Pulse Oximeter (Ohmeda, Boulder, Colorado, USA) equipped with an ear probe, developed as a consequence of oxygen consumption. The VRH was calculated as the average increase in ventilation in 1/min BTPS per percent decrease in arterial oxygen saturation (1/min/% SaO$_2$).

Statistic probability was assessed by Student's unpaired t-test, and when appropriate by the chisquared test with Yates' continuity correction.

RESULTS

The prevalence of arterial hypertension in our SAS patients was 43 per cent. Using Student's unpaired t-test no statistically significant difference was found in the mean age, body mass index (W/H^2), or duration of apneas or apnea index between the hypertensive and normotensive groups (Table 1). The hyper-

tensive patients had significantly higher systolic (P<0.001), diastolic
(P<0.01) and mean arterial pressures (P<0.01) than the normotensive ones,
although they were already under antihypertensive therapy.

Table 1. Ventilatory response to hypoxia in normotensive and hypertensive
patients with the sleep apnea syndrome. W/H^2 = body mass index;
AI = apnea index; AD = apnea duration; SBP, DBP = systolic and
diastolic blood pressures; Mean = mean arterial pressure.

	HYPERTENSIVES		NORMOTENSIVES		DIFFERENCE	
	Mean	SD	Mean	SD	t	P
Age, years	55	9	51	9	1.52	NS
W/H^2, kg/m^2	33	3	31	5	1.34	NS
AI	55	29	41	28	1.54	NS
AD, sec	23	5	23	7	0.18	NS
SBP, mm Hg	156	13	135	12	4.92	<0.001
DBP, mm Hg	94	5	85	4	2.97	<0.01
Mean, mm Hg	114	6	102	6	2.85	<0.01
VRH, l/min/% SaO$_2$	1.48	1.04	0.69	0.32	2.94	<0.01

VRH was significantly higher in the hypertensive group (average 1.48 l/min/%
SaO_2) than in the normotensive one (P<0.01). Using the two-tailed chisquared
test with Yates' correction, it was found that at a VRH greater than 1, the
fraction of hypertensive patients was significantly higher (X^2=7.38, P<0.01)
than that of the normotensive patients.

The end-tidal CO_2 tension before the VRH test was in average 5.40 kPa (SD=
0.51) in the 21 normotensive patients, and 5.55 kPa (SD=0.51) in the 16 hyper-
tensive patients. The difference between the two averages is not statistically
significant.

DISCUSSION

The arterial blood pressure, in terms of systolic, diastolic, mean and pulse
pressures, is increased during a sleep apnea, with its zenith immediately
after the resumption of ventilation (24). The mechanism underlying this pheno-
menon is a complicated process in which the progressive hypoxia seems to play
an incremental and critical role (23, 24). Hypoxia, stimulating peripheral
chemoreceptors with consequent central nervous effects, especially when (as in
the case of an apnea) their action is not opposed by an increase in venti-
lation, causes peripheral vasoconstriction (12) through the sympathetic ner-
vous system (16). Previous studies have found the VRH to be either decreased
in relation to the awake response (2, 4, 22) or unaltered (8, 22), depending
on the experimental conditions. But even in cases when the VRH during sleep
is decreased, it is directly related to the VRH during wakefulness (2).

The sympathetic outburst during the arousal following apnea (3), added to
the simultaneous increase in cardiac output, has been judged to cause the rise
in arterial pressure. According to some authors (8, 21, 22) the role of hypox-

aemia as an arousing factor, potentiating the activation of the sympathetic nervous system, is rather weak (4, 8, 22), and others (18) have even suggested that hypoxic arousal does not require activation of peripheral chemoreceptors.

It has been found that young men with mild hypertension have an increased hypoxic drive (25), and it has been proposed that hypertension may augment the sensitivity of peripheral chemoreceptors (1). However, the question whether an increased sensitivity of chemoreceptors is a cause of hypertension, or whether hypertension increases the sensitivity of chemoreceptors, is difficult to answer. The carotid body in man differs both structurally and functionally from that in animals. Autopsy studies in humans have shown that carotid body hyperplasia, which may occur in systemic hypertension or severe hypoxia, probably does not involve the oxygen sensitive tissue (10). On the other hand, patients who had undergone bilateral carotid body resection but had intact baroreceptors were found to show a decrease in their baseline arterial pressure during hypoxia, in contrast to control subjects who showed an increase (17). It is therefore probable that also in man hypoxia causes increased arterial pressure through the mediation of peripheral chemoreceptors.

Przbylski has formulated the hypothesis that increased sensitivity of chemoreceptors may induce systemic hypertension (19). The present results give indirect support to that hypothesis, and suggest that such an effect is effective in SAS where cessation of breathing, a brief episode of hypoxaemia and transient arterial hypertension coexist.

The significant difference in VRH, observed between hypertensive and normotensive patients with SAS in the present study, indicates that a high sensitivity of the ventilatory effect of peripheral chemoreceptors during wakefulness may be related to the development of arterial hypertension in SAS. A reasonable question is whether there were other reasons for the difference in VRH between the two groups. The influence of beta-blockers on the sensitivity of ventilation to hypoxia is not well known but probably inhibitory rather than excitatory (11). Diuretics may cause mild hypokalemic alkalosis and slight elevation of arterial $PaCO_2$, but this probably does not contribute to the observed difference in VRH since our hypertensive patients had a normal blood-electrolyte status and since there was no difference in end-tidal PCO_2 between the two groups.

We conclude that hypertensive SAS patients have a higher VRH than normotensive ones, but the role of VRH in development of hypertension in habitual snoring still remains to be determined.

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