Eur Respir J 2001; 18: 989–995
DOI: 10.1183/09031936.01.00099401
Printed in UK – all rights reserved

European Respiratory Journal
ISSN 0903-1936

Medroxyprogesterone in postmenopausal females with partial upper airway obstruction during sleep

T. Saaresranta*,#, P. Polo-Kantola*,¶, E. Rauhala+, O. Polo*,#

Medroxyprogesterone in postmenopausal females with partial upper airway obstruction during sleep. T. Saaresranta, P. Polo-Kantola, E. Rauhala, O. Polo. ©ERS Journals Ltd 2001.

ABSTRACT: The aim of the present study was to evaluate the degree and duration of respiratory stimulation caused by medroxyprogesterone acetate (MPA), and compare the effect of MPA to that of nasal continuous positive airway pressure (nCPAP) in sleep-disordered breathing.

Ten postmenopausal females with predominantly partial upper airway obstruction during sleep had an overnight sleep study at baseline, on the fourteenth day of treatment with MPA and after a 3-week washout period. Six subjects on nCPAP were also studied 3 months later.

At baseline, the overnight mean±SD end-tidal pressure of carbon dioxide (P_{et,CO_2}) was 5.5±0.4 kPa the arterial oxygen saturation (S_{a,O_2}) 93.0±1.2%, S_{a,O_2} nadir 80.0±6.7%, and frequency of oxygen desaturation ⩾4% (ODI_4) per hour 2.2±1.3. MPA decreased P_{et,CO_2} by 0.8 kPa (14.5%, p<0.001). After washout, the mean P_{et,CO_2} remained at 0.5 kPa (9.1%, p<0.001) lower than at baseline. S_{a,O_2} did not change. P_{et,CO_2} was lower on MPA than on nCPAP (4.7±0.2 kPa *versus* 5.0±0.3 kPa; p=0.037) but S_{a,O_2} was similar. Apnoea/hypopnoea index tended to be lower on CPAP than on MPA.

Medroxyprogesterone acetate at a daily dose of 60 mg improves ventilation in postmenopausal females with partial upper airway obstruction during sleep without compromising sleep. The ventilatory improvement is sustained for at least 3 weeks post-treatment. Medroxyprogesterone acetate was more efficient in decreasing the partial pressure of carbon dioxide but continuous positive airway pressure was superior in decreasing respiratory efforts.

Eur Respir J 2001; 18: 989–995.

*Dept of Pulmonary Diseases, Turku University Hospital, Turku, #Dept of Physiology, Sleep Research Unit, Turku University, Turku, ¶Dept of Obstetrics and Gynaecology, Turku University Hospital, Turku, and +Dept of Clinical Neurophysiology, Satakunta Central Hospital, Pori, Finland.

Correspondence: T. Saaresranta, Dept of Pulmonary Diseases, Turku University Central Hospital, Kiinamyllynkatu 4–8, FIN-20520 Turku, Finland.
Fax: 358 23133328

Keywords: Medroxyprogesterone acetate, menopause, nasal continuous positive airway pressure, partial upper airway obstruction, sleep, sustained effect

Received: December 11 2000
Accepted after revision July 10 2001

This work was supported by grants from the Finnish Sleep Research Society, The Finnish Anti-Tuberculosis Association Foundation, The Research Foundation for Pulmonary Diseases, The Väinö and Laina Kivi Foundation and The Turku University Foundation. O. Polo was supported by The Paulo Foundation.

The menopause has a major impact on sleep and breathing. Although the increase in breathing abnormalities after the menopause [1] is attributed to decreased progesterone secretion, the role of progesterone replacement therapy as a respiratory stimulant has not been established.

In addition to obesity and structural abnormalities in the upper airway, a decrease in the drive to breathe is likely to be involved in sleep-disordered breathing in postmenopausal females. Episodes of hypopnoea are relatively more common than apnoea in females [2]. Furthermore, in females, the apnoea/hypopnoea index (AHI) may underestimate the severity of upper airway dysfunction, since females can be symptomatic with an AHI <5 [3].

Conventional postmenopausal hormone replacement therapy aims to control climacteric vasomotor symptoms. Since the postmenopausal state predisposes to hypoventilation, some females might benefit from progesterone replacement therapy. The efficacy of short-term treatment with medroxyprogesterone acetate (MPA) on sleep and breathing in postmenopausal women with nocturnal hypoventilation related to partial upper airway obstruction during sleep was therefore evaluated. In a subgroup, the effects of MPA were compared to those of nasal continuous positive airway pressure (nCPAP), which is known to relieve partial upper airway obstruction without any immediate effect on respiratory drive.

Subjects

Initially, 71 healthy hysterectomized postmenopausal females were recruited for polygraphical sleep studies by announcements in newspapers [4]. The static-charge sensitive bed (SCSB) recordings showed episodes of increased respiratory resistance (IRR) [5], with prolonged hypoxaemia in 11 subjects, of whom 10 agreed to participate in the present study. Their median age was 60 (range 54–68) yrs, median body mass index 31.3 (range 23.5–37.6) $kg \cdot m^{-2}$, and the mean Epworth sleepiness score was 6.4±5.0. Five of 10 subjects reported snoring at least during three nights of the week. Their postmenopausal status was verified by measurements of serum follicle-stimulating

hormone (FSH >30 IU·L^{-1}). None of the subjects were current smokers or suffered from any major disease.

Written informed consent was obtained from all participants. The protocol was approved by The Joint Commission on Ethics of Turku University and Turku University Central Hospital.

Methods

Study design

MPA treatment was started 7 days after the baseline sleep study. A second sleep study was performed on the fourteenth day of treatment with MPA, and a third sleep study 3 weeks post-treatment.

MPA (60 mg) of (Lutopolar®, Orion Pharma, Finland) was administered orally at 21:00–23:00 h. Compliance was confirmed by tablet counts, patient interviews and measurements of serum MPA concentration. After 3 months (range 66–104 days), six of the 10 subjects agreed to undergo another sleep study with nCPAP, using a self-titrating device (Sullivan Autoset®, Rescare Ltd, Sydney, Australia).

Questionnaires

The subjects completed a structured diary with 20 separate items concerning their daily symptoms (including degree of dyspnoea) and possible adverse effects of MPA for 14 days before visits 2 and 3. The severity of symptoms was assessed on a scale from 0–5. After a sleep study, the subjects completed a questionnaire on their subjective sleep quality during the study night.

Blood tests

Serum concentrations of MPA were measured the morning after each sleep study. At the baseline visit, arterial blood samples were obtained with a single arterial puncture in patients lying awake in the supine position.

Sleep studies

Overnight polygraphical sleep recordings included electroencephalogram (EEG), electro-oculogram, electromyogram, and electrocardiogram. The adequacy of respiration was monitored by a finger probe oximeter (Ohmeda Biox 3700 Pulse Oximeter, BOC Health Care, Louisville, CO, USA), side-stream capnograph (Datex Normocap® CO_2 and O_2 Monitor, Instrumentarium, Finland) and a static charge sensitive bed [5, 6]. AHI and respiratory irregularity index were determined with the Sullivan Autoset® (Rescare Ltd) in the diagnostic mode. During CPAP study, Autoset® was used in the treatment mode.

Sleep stages were scored according to the criteria of Rechtschaffen and Kales [7] criteria and expressed as percentage of total sleep time. Sleep efficiency was defined as percentage sleep during the sleep period time. Arousal was defined as an appearance of EEG-alpha activity for >3 s [8].

The SCSB recordings were analysed using conventional criteria [5]. Four types of periodic breathing, episodes of IRR and periodic movements were analysed in 3-min epochs and were expressed as percentage of time in bed. Percentage of time was used instead of event index because episodes of IRR do not occur as short repetitive events, but are typically prolonged from 1–30 min [5].

Breathing abnormalities recorded by the SCSB were considered clinically significant if they represented >5% of the time in bed. This limit corresponds to an AHI of 5 [9]. Periodic breathing pattern (P)-1 and obstructive periodic breathing pattern (OP)-1 represent patterns of periodic breathing with moderate or high respiratory effort, whereas OP-2 and OP-3 patterns reflect episodes of obstructive apnoea [5].

Statistical analyses

The overall comparisons between repeated measurements were performed using either the nonparametric Friedman's test or parametric analysis of variance (ANOVA) of repeated measurements. In nonparametric cases, the Wilcoxon signed-rank test was used and in parametric cases the F-test was used. In multiple comparisons, Bonferroni's correction was used for p-values and confidence intervals. The differences between MPA and CPAP were evaluated with a paired t-test or Wilcoxon signed-rank test. A p-value of <0.05 was considered significant.

Assuming a mean difference for the partial pressure of carbon dioxide (P_{CO_2}) of 0.7 kPa between groups and a SD of 0.5 kPa, eight subjects would be needed to show a difference at an alpha of 0.05 and a statistical power of 90%. Predicting a drop-out rate of 20%, a total of 10 subjects was needed.

Results

Four out of eight subjects had a daytime oxygen tension in arterial blood (P_{a,O_2}) <10 kPa. The carbon dioxide tension in arterial blood (P_{a,CO_2}) was within reference range in all subjects. At baseline, mean arterial pH was 7.41±0.01 (mean±SD), mean P_{a,CO_2} 5.4±0.30 kPa, mean P_{a,O_2} 10.8±1.7 kPa.

At baseline, no episodes of OP-3 of OP-2 pattern were observed but partial upper airway obstruction was frequent (average IRR 23.4±1.5% and average OP-1 5.5±5.9% of time in bed). The Autoset® nasal pressure profile analysis showed significant upper airway flow limitation in all subjects. The median AHI determined by the Autoset® was 10.6 (interquartile range, (IQR) 6.2) and respiratory irregularity index 31.0 (IQR 17.4). The mean arterial oxygen saturation (S_{a,O_2}) was 93.0±1.2%, maximum S_{a,O_2} 98.7±1.4%, nadir S_{a,O_2} 80.0±6.7% and the mean frequency of oxygen desaturation $\geqslant$4% (ODI_4) per hour was 2.2±1.3. The percentage of sleep Stage 1 was 7.9±3.5, Stage 2 56.4±6.0, slow-wave sleep 10.4±5.0 and

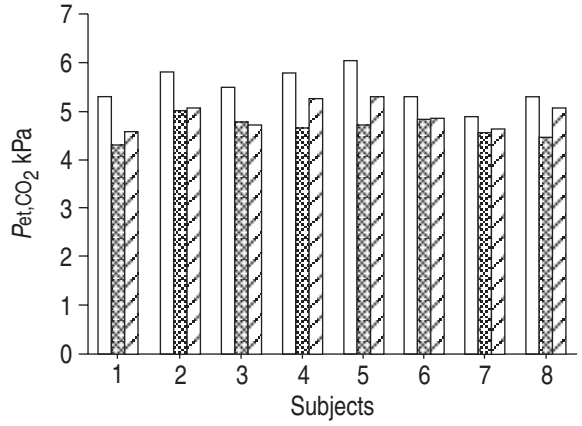

Fig. 1.–End-tidal pressure of carbon dioxide (P_{et,CO_2}) in eight subjects at baseline (□), on medroxyprogesterone acetate (MPA: ■) and 3 weeks after cessation of MPA (▨).

rapid eye movement (REM) 18.4±8.4. The median EEG-arousal index (arousals·h^{-1}) was 5.6 (IQR 1.4) and the median sleep efficiency 95.0 (IQR 4.6)%.

Medroxyprogesterone acetate concentrations

After the 2-week treatment, the median concentration of MPA was 5.13 ng·mL^{-1} (range 1.94–8.68 ng·mL^{-1}). After a 3-week washout, MPA was below the detection limit in one patient, and in the other seven the median concentration was 0.06 ng·mL^{-1} (range 0.02–0.17).

Questionnaires

Subjective sleep quality as well as daytime alertness remained unchanged during the study period. Body weight, mental symptoms and dyspnoea scores also remained constant.

Nocturnal breathing

The effect of medroxyprogesterone acetate. MPA induced both immediate and sustained decreases in the end-tidal pressure of carbon dioxide (P_{et,CO_2}) (fig. 1). At baseline the average of P_{et,CO_2} was 5.5±0.44 kPa. With MPA, there was a decrease in P_{et,CO_2} of 0.8 kPa (95% confidence interval (CI) 0.8–1.2, p<0.001) or 14.5%. After a 3-week washout period, the mean P_{et,CO_2} (5.0±0.29 kPa) remained at 0.5 kPa (95% CI 0.3–0.77, p<0.001) or 9.1% lower than at baseline. Oxygenation remained similar on MPA and after washout. The AHI and respiratory irregularity index were initially low and did not change. Central events were rare in the study subjects at baseline, on MPA and after washout. Two out of eight subjects completing the study showed sporadic episodes of central apnoea (8 and 1 central event·night^{-1}) at baseline, two on MPA (3 and 1 events), and three after a 3-week washout (3, 2 and 1 events).

The increased resistance pattern was common and remained unchanged (23.4±1.5% at baseline, 24.0±19.6% on MPA, 20.7±21.1% after washout). Similarly, the frequency of the OP-1 pattern did not change (5.5±5.9%, 3.2±4.6%, 4.4±5.1%, respectively). Only one subject had the P-1 pattern and none showed OP-2 or OP-3 patterns.

Comparison of medroxyprogesterone acetate and nasal continuous positive airway pressure. MPA lowered P_{et,CO_2} by 0.3 kPa (95% CI 0.03–0.66, p=0.037) more than CPAP (table 1). The effects on S_{a,O_2} nadir, mean S_{a,O_2}, and ODI_4·h^{-1} were similar with each treatment. Mean S_{a,O_2} was 0.83% higher on MPA (p=0.042, 95% CI 0.04–1.62). CPAP was marginally (p=0.062) superior to MPA in decreasing AHI, the AHI decreased 4.6·h^{-1} (95% CI -22.2–0.4) more on CPAP.

The frequency of increased resistance during baseline study, MPA and CPAP was 26.1±18.7%, 25.4±21.9%, and 5.2±4.7%, respectively. CPAP was more effective than MPA in decreasing resistance IRR (mean change -21.1±20.5%, p=0.006). No treatment effect on OP-1 was seen.

Sleep variables

The effect of medroxyprogesterone acetate. MPA had no immediate or long-term effects on sleep (fig. 2), but

Table 1.–Comparison of changes of respiratory parameters on medroxyprogesterone acetate (MPA) and on continous positive airway pressure (CPAP)

Parameter	Average at baseline	Change from baseline on MPA	Change from baseline on CPAP	p-value (ΔMPA *versus* ΔCPAP)
AHI·h^{-1}	12.1±5.9	-4.4±8.5	-7.2±4.4	NS
IRR %	26.3±18.7	-0.8±13.9	-21.1±20.5	0.006
OP-1 %	5.6±6.2	-1.7±4.4	-4.7±5.2	NS
P_{et,CO_2} kPa	5.5±0.4	-0.8±0.4	-0.5±0.6	0.037
S_{a,O_2} max %	98.7±1.5	0.3±1.4	-0.5±1.9	0.042
S_{a,O_2} mean %	93.0±1.3	0.8±1.4	0.5±1.4	NS
S_{a,O_2} nadir %	82.2±3.7	0.0±7.8	-7.0±23.3	NS
ODI_4·h^{-1}	1.4±1.3	-0.7±1.5	-0.6±2.9	NS

Data are presented as mean±SD except for apnoea/hypopnoea index (AHI), where median (interquartile range) is used. n=6. NS: nonsignificant; IRR: increased respiratory resistance; OP-1: obstructive periodic breathing pattern; ODI_4: frequency of oxygen desaturation ⩾4%; P_{et,CO_2}: end-tidal pressure of carbon dioxide; S_{a,O_2}: arterial oxygen saturation.

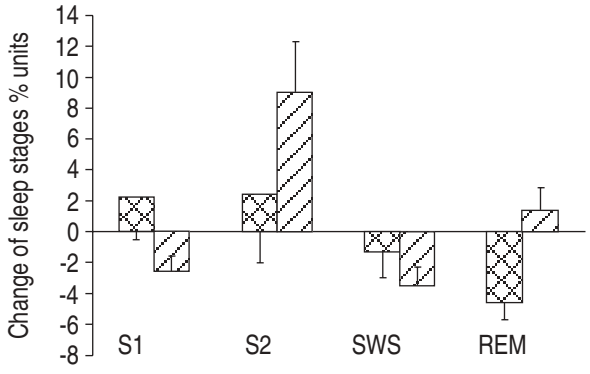

Fig. 2. – The immediate (■) and sustained effects (▨: after 3 weeks of washout) of medroxyprogesterone acetate (MPA) on sleep stages compared to baseline. The changes were not significant. S1: sleep Stage 1; S2: sleep Stage 2; SWS: slow-wave sleep; REM: rapid eye movement sleep.

during washout the median sleep efficiency improved further from 95.0% (IQR 4.6) at baseline to 97.9% (IQR 2.0) during washout. The median EEG arousal frequency was $5.6 \cdot h^{-1}$ at baseline, 6.8 on MPA and 5.3 during washout. Compared to baseline, no change in the median arousal indices were observed during treatment (+0.16, IQR 2.0) or washout (-0.65, IQR 1.3).

Comparison of medroxyprogesterone acetate and continuous positive airway pressure. The initial sleep efficiency was already good and any further improvement was not expected. Using MPA or wearing nCPAP for the first night did not impair sleep quality.

Adverse events

Eight out of ten subjects completed the study. One subject quit because of irritation by the nasal prongs. Another subject had cerebral infarction in the right hemisphere after 8 days on MPA. According to the side-effect diary, no symptoms were observed during the week before the stroke. There was sinus rhythm and all blood clotting factors were normal.

Discussion

The present study was based on a previous observation by the authors that 17% of healthy postmenopausal females spent a significant proportion of their sleep time with partial upper airway obstruction [10]. Since partial obstruction predisposes to CO_2 retention [11], the effects of respiratory stimulants such as MPA are of interest. The present results show that MPA used at a dose of 60 mg daily for 14 days improves ventilation in the affected females. The improvement was maintained beyond 3 weeks post-treatment. nCPAP was more efficient than MPA in decreasing respiratory efforts but the P_{et,CO_2} decreased more with MPA.

The observations in postmenopausal females with partial upper airway obstruction should be extrapolated with caution to females with obstructive sleep apnoea. The current knowledge on the efficacy of progestins to control obstructive sleep apnoea is based on studies in males. In postmenopausal females with sleep-disordered breathing, only three studies have used MPA in combination with oestrogen [12–14] and one as a single therapy [15]. Their common conclusion was that there was some decrease in AHI or shortening of apnoea duration. None of the studies measured partial upper airway obstruction or CO_2 and none compared the response with that of nCPAP.

As with previous observations by the authors, in postmenopausal females with chronic respiratory failure [16], the ventilatory improvement in the present study was sustained for at least 3 weeks after cessation of MPA. This contradicts an earlier observation that the ventilatory effects subside within 14 days of cessation of MPA [17]. However, there is also evidence to support a prolonged ventilatory effect. In a study of the obesity hypoventilation syndrome, a normal P_{a,CO_2} was maintained for up to 4 months after cessation of intramuscular progesterone therapy [18].

There are at least three possible reasons for the sustained ventilatory improvement, which relate to obesity, female gender or abnormal breathing. In obese subjects, abundant adipose tissue may result in increased metabolism of endogenous steroids to oestradiol [19], which is needed for upregulation of progesterone receptors. Combining oestrogen with progesterone prolongs the ventilatory effects in healthy males. Obesity does not, however, explain the sustained ventilatory improvement observed earlier in nonobese females with chronic respiratory insufficiency [16]. Therefore, other factors must also be involved.

Another possibility is related to the female sex. Although the oestrogen levels of postmenopausal females are comparable to those of males, the response to female hormone therapy could be more prolonged. The number of progesterone receptors might be greater or their distribution different in females. The progesterone receptors in females might also be more readily upregulated during treatment.

A third factor contributing to the prolonged respiratory stimulation seen in the present subjects with mild sleep-disordered breathing but not in healthy study subjects [17] might be the underlying ventilatory abnormality itself. The natural homeostatic mechanisms aim at correcting altered functions. In the case of sleep-disordered breathing, the altered function is hypoventilation; whereas, in healthy controls taking MPA, the altered function is the drug effect of excessive respiratory stimulation. In the former case, the homeostatic mechanisms act parrallel to the MPA effect when trying to correct hypoventilation. In the later case, the homeostatic efforts to correct the excessive ventilation oppose the action of MPA. The synergic action of two correcting mechanisms could explain the enhanced treatment effect of the MPA patients in the present study.

The sustained ventilatory effect of short-term MPA suggests that periodic administration might be sufficient to improve ventilation in females. In terms of

sleep efficiency, periodic administration might even be superior to continuous therapy.

MPA did not improve the AHI. There was no significant difference between CPAP and MPA nights but this may be due to the small number of subjects. In previous studies, MPA has shown no consistent effect on AHI. No change [20], decreasing trend [21] or slight decrease of AHI [13, 14] has been reported with MPA alone or in combination with oestrogen. By decreasing P_{et,CO_2} MPA may also induce respiratory instability resulting in an increase in the number of apnoeic and hypopnoeic episodes if P_{a,CO_2} decreases below the apnoeic threshold. However, this was not supported by the present data, where the frequency of central apnoea did not increase with MPA. It is likely that the MPA-induced net effect on the number of apnoeic and hypopnoeic events depends on the subtle balance between sufficient or overdriven ventilation.

The presence of periodic breathing (OP-1) is in line with the observation that these females showed mainly partial upper airway obstruction. MPA had no effect on the frequency of periodic breathing but the high variance and small number of subjects weaken the power of this interpretation. CPAP decreased the OP-1 and IRR patterns. An important observation was that the IRR pattern, indicating increased respiratory efforts, remained unchanged on MPA but decreased on CPAP. This observation is in agreement with the hypothesis that the ventilatory drive remains similar with MPA, but it is achieved at lower levels of CO_2 [22]. This may also explain why MPA did not increase the sensation of dyspnoea.

Whereas the AHI seems a surrogate variable to describe the severity of sleep-disordered breathing in postmenopausal females, the IRR phenomenon seems to be characteristic of sleep-disordered breathing in postmenopausal females. This pattern indicates increased respiratory efforts, corresponding to intrathoracic pressures $<$-20 cmH_2O [23]. The pattern consists of high frequency respiratory components that appear when expiration becomes active. There is a high correlation between the IRR spike amplitude and the P_{et,CO_2} level [11].

MPA concentrations were unmeasurable or near the detection limit within 2 [17] or 3 weeks (present study) of cessation of treatment. In postmenopausal females, FSH and luteinizing hormone remain decreased at least 3 weeks after MPA therapy [24]. It is possible that the MPA-induced ventilatory effects outlast measurable serum concentrations.

Neither objective nor subjective sleep quality altered with MPA. Previously, MPA has been reported to have either no effect on sleep [15], to decrease REM sleep [25], or to decrease [13] or increase arousals [26]. In the present subjects, sleep efficiency was surprisingly high at baseline and on MPA but improved still further during washout. This delayed MPA effect is in line with an earlier report of decrease in Stages 1 and 2 sleep and increase in REM sleep after MPA [20] and supports the view that short-term MPA therapy may have favourable rebound effects on sleep. The present findings of extremely high sleep efficiency and low arousal index are not, however, the first observations of this kind. In a previous study, by the authors, on healthy postmenopausal females, the median EEG arousal index was 3.2 (range 0.2–12.4, n=32) and the median sleep efficiency was 93.4% (range 74.4–98.6, n=63) [27]. These findings were not scorer-related, since they were analysed by different scorers. Sleep efficiency decreases with age, although less so in females than in males. Whether there is an interaction between high CO_2 and low arousal index in these particular subjects, remains to be elucidated.

All of the postmenopausal females in the present study considered themselves healthy and were not seeking treatment. Although their mean S_{a,O_2} and P_{et,CO_2} during sleep were within reference ranges, they had frequent episodes of increasing P_{et,CO_2} and hypoxaemia with mean S_{a,O_2} nadir as low as 80%. This contrasts with their exceptionally good sleep quality, high sleep efficiency and low arousal frequency. Although the current study was experimental, the results prompt the question whether or not the females benefited from the intervention. Although, on direct questioning, some symptoms suggested upper airway obstruction (*e.g.* dreams of cats sitting on ones throat), excessive sleepiness was not reported. Therefore, any possible therapeutic benefit in such patients would certainly not be related to improving sleep quality and daytime performance.

Recent literature has produced controversial results about the possible cardiovascular effects of sleep-disordered breathing on one hand and female sex hormone replacement on the other. Not only sleep-disordered breathing but also atherosclerosis, rapidly increase after the menopause. In females, snoring increases the risk of stroke independent of other factors [28]. Partial upper airway obstruction with nocturnal CO_2 retention offers a plausible cause of intracellular acidosis that might result in endothelial dysfunction and reduced nitric oxide (NO) production. Increasing evidence suggests that high CO_2 levels are involved in the pathogenesis of vascular disease. In postmenopausal females, resting P_{et,CO_2} is an independent determinant of systolic blood pressure and carotid artery intima-media thickness [29]. Decreasing high or borderline CO_2 during sleep might therefore improve endothelial function and prevent cardiovascular sequelae. Increased endothelial NO production could be mediated by MPA-induced insulin-like growth factor 1 production [30, 31].

The development of a stroke in one of the study subjects is contradictory to the thinking that MPA might have immediate beneficial endothelial effects. The incidence of thromboembolic complications encountered during high-dose MPA treatment in breast cancer with or without chemotherapy is 2.1% [32]. However, neoplastic diseases [33] may also enhance coagulability. MPA may change blood-clotting factors to favour thrombosis [32], but cerebral infarction during MPA treatment is an extreme rarity. A Medline database search found one case report of medullary infarction during MPA treatment [34]. The role of MPA therapy in the development of cerebral infarction in the patient from this study, therefore, remains unclear. The patient was neither hypertensive nor a smoker, ethanol consumption was moderate and

serum lipids and blood-clotting factors were within reference ranges. Oestrogen replacement therapy had previously been used without complications. However, the patient was a heavy snorer, which increases the risk of stroke [28].

To conclude, medroxyprogesterone acetate used at a dose of 60 mg daily for 14 days improves nocturnal ventilation in postmenopausal females with partial upper airway obstruction during sleep. This effect is maintained for at least 3 weeks. Medroxyprogesterone acetate is at least equally effective in reducing P_{et,CO_2} as nasal continuous positive airway pressure but it may be less effective in reducing episodes of apnoea or hypopnoea. Long-term intervention studies are needed to evaluate whether postmenopausal females would have any respiratory or cardiovascular benefit from lower nocturnal carbon dioxide levels, achievable with appropriate hormone replacement therapy.

Acknowledgements. The authors would like to thank E. Wallius for statistical assistance, and the drug company Orion Pharma, Espoo, Finland, who supplied the medication and assessments of medroxyprogesterone acetate concentrations.

References

1. Block AJ, Wynne JW, Boysen PG. Sleep-disordered breathing and nocturnal oxygen desaturation in postmenopausal women. *Am J Med* 1980; 69: 75–79.
2. O′Connor C, Thornley KS, Hanly PJ. Gender differences in the polysomnographic features of obstructive sleep apnea. *Am J Respir Crit Care Med* 2000; 161: 1465–1472.
3. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 1993; 328: 1230–1235.
4. Polo-Kantola P, Erkkola R, Irjala K, Pullinen S, Virtanen I, Polo O. Effect of short-term transdermal estrogen replacement therapy on sleep: a randomized, double-blind crossover trial in postmenopausal women. *Fertil Steril* 1999; 71: 873–880.
5. Polo O. Partial upper airway obstruction during sleep. Studies with the static-charge-sensitive bed (SCSB). *Acta Physiol Scand* 1992; 145: Suppl. 606, 1–118.
6. Alihanka J, Vaahtoranta K, Saarikivi I. A new method for long-term monitoring of the ballistocardiogram, heart rate and respiration. *Am J Physiol* 1981; 240: 384–392.
7. Rechtschaffen A, Kales A. A manual of standardized terminology techniques and scoring systems for sleep stages of human subjects. Washington D.C., National Institute of Health, 1968.
8. American Sleep Disorders Association Task Force. EEG arousals: scoring rules and examples. *Sleep* 1992; 15: 175–184.
9. Polo O, Tafti M, Fraga J, Porkka VK, Déjean Y, Billiard M. Why don′t all heavy snorers have obstructive sleep apnea? *Am Rev Respir Dis* 1991; 143: 1288–1293.
10. Polo-Kantola P. Sleep, menopause and estrogen replacement therapy. *Annales Universitatis Turkuensis* D367, 1999; pp. 1–176.
11. Kirjavainen T. High-frequency respiratory movements during sleep. Physiological determinants and diagnostic usefulness of SCSB spiking. *Annales Universitatis Turkuensis* 1997; D263. pp. 1–145.
12. Pickett CK, Regensteiner JG, Woodard WD, Hagerman DD, Weil JV, Moore LG. Progestin and estrogen reduce sleep-disordered breathing in postmenopausal women. *J Appl Physiol* 1989; 66: 1656–1661.
13. Keefe DL, Watson R, Naftolin F. Hormone replacement therapy may alleviate sleep apnea in menopausal women: a pilot study. *Menopause* 1999; 6: 196–200.
14. Cistulli PA, Barnes DJ, Grunstein RR, Sullivan CE. Effect of short term hormone replacement in the treatment of obstructive sleep apnoea in postmenopausal women. *Thorax* 1994; 49: 699–702.
15. Block AJ, Wynne JW, Boysen PG, Lindsey S, Martin C, Cantor B. Menopause, medroxyprogesterone and breathing during sleep. *Am J Med* 1981; 70: 506–510.
16. Saaresranta T, Polo-Kantola P, Irjala K, Helenius H, Polo O. Respiratory insufficiency in postmenopausal women: sustained improvement of gas exchange with short-term medroxyprogesterone acetate. *Chest* 1999; 115: 1581–1587.
17. Skatrud JB, Dempsey JA, Kaiser DG. Ventilatory response to medroxyprogesterone acetate in normal subjects: time course and mechanism. *J Appl Physiol* 1978; 44: 939–944.
18. Lyons HA, Huang CT. Therapeutic use of progesterone in alveolar hypoventilation associated with obesity. *Am J Med* 1968; 44: 881–888.
19. Schneider G, Kirschner MA, Berkowitz R, Ertel NH. Increased estrogen production in obese men. *J Clin Endocrinol Metab* 1979; 48: 633–638.
20. Rajagopal KR, Abbrecht PH, Jabbari B. Effects of medroxyprogesterone acetate in obstructive sleep apnea. *Chest* 1986; 90: 815–821.
21. Collop NA. Medroxyprogesterone acetate and ethanol-induced exacerbation of obstructive sleep apnea. *Chest* 1994; 106: 792–799.
22. Bonekat HW, Dombovy ML, Staats BA. Progesterone-induced changes in exercise performance and ventilatory response. *Med Sci Sports Exerc* 1987; 19: 118–123.
23. Kirjavainen T, Polo O, McNamara S, Vaahtoranta K, Sullivan CE. Respiratory challenge induces high frequency spiking on the static charge sensitive bed (SCSB). *Eur Respir J* 1996; 9: 1810–1815.
24. Saaresranta T, Irjala K, Polo-Kantola P, Helenius H, Polo O. Prolonged endocrine responses to medroxyprogesterone in postmenopausal women with respiratory insufficiency. *Obstet Gynecol* 2000; 96: 243–249.
25. Dolly FR, Block AJ. Medroxyprogesterone acetate and COPD. Effect on breathing and oxygenation in sleeping and awake patients. *Chest* 1983; 84: 394–398.
26. Daskalopoulou E, Patakas D, Tsara V, Zoglopitis F, Maniki E. Comparison of almitrine bismesylate and medroxyprogesterone acetate on oxygenation during wakefulness and sleep in patients with chronic obstructive lung disease. *Thorax* 1990; 45: 666–669.
27. Polo-Kantola P, Erkkola R, Irjala K, Helenius H, Pullinen S, Polo O. Climacteric symptoms and sleep quality. *Obstet Gynecol* 1999; 94: 219–224.
28. Hu FB, Willett WC, Manson JE, *et al.* Snoring and

risk of cardiovascular disease in women. *J Am Coll Cardiol* 2000; 35: 308–313.
29. Anderson DE, Scuteri A, Metter EJ, Chesney MA. Association of high resting end tidal CO_2 with carotid artery thickness in women, but not men. *J Hypertens* 2001; 19: 459–463.
30. Tsukahara H, Gordienko DV, Tonshoff B, Gelato MC, Goligorsky MS. Direct demonstration of insulin-like growth factor-I-induced nitric oxide production by endothelial cells. *Kidney Int* 1994; 45: 598–604.
31. Saaresranta T, Irjala K, Polo-Kantola P, Helenius H, Polo O. IGF-I and ventilation after short-term progestin in postmenopausal women with chronic respiratory insufficiency. *Respir Med* 2000; 94: 909–916.
32. Yamamoto H, Noguchi S, Miyauchi K, *et al.* Changes in hematologic parameters during treatment with medroxyprogesterone acetate for breast cancer. *Jpn J Cancer Res* 1991; 82: 420–425.
33. Rickles FR, Edwards RL. Activation of blood coagulation in cancer: Trousseau′s syndrome revisited. *Blood* 1983; 62: 14–31.
34. Oon C, Lee YS. Medullary infarction - was it Depo-Provera? *Singapore Med J* 1980; 1980: 717–719.