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IGF-I and ventilation after short-term progestin in postmenopausal women with chronic respiratory insufficiency

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Progestins stimulate respiration. We have previously shown prolonged ventilatory improvement in chronic respiratory failure with short-term medroxyprogesterone acetate (MPA). The mechanism of the sustained respiratory effect is unknown. Insulin-like growth factor-I (IGF-I) and insulin have anabolic effects which could also improve ventilation in the long-term. To better understand the interactions between hormones and control of breathing, we evaluated the degree and duration of changes in IGF-I, insulin and cortisol after short-term MPA therapy in chronic respiratory insufficiency.

Fourteen postmenopausal women with permanent or episodic hypercapnic or hypoxaemic respiratory failure were recruited for a placebo-controlled single-blind trial. After 14 days of placebo treatment and 7 days of washout, a daily dose of 60 mg MPA was administered for 14 days. Serum IGF-I, insulin and cortisol were measured five times at 3-week intervals: at baseline, after 14 days on placebo, after 14 days on MPA, and during the washout, on days 21 and 42.

Serum IGF-I levels were 15·2 (SD 4·6), 20·8 (SD 6·8) and 17·2 (SD 6·4) at baseline, on MPA and after a 3-week washout. Serum insulin levels did not change [12·5 mU l^{-1} (SD 4·1), 12·2mU l^{-1} (SD 4·8) and 14·5mU l^{-1} (SD 3·6), respectively]. Serum cortisol did not change. On MPA, IGF-I increased on average by 5·6 nmol l^{-1} [95% confidence interval (95% CI) 1·4 to 9·9] or 42·0 % (95% CI 6·3 to 77·8) from baseline. The IGF-I response coincided with the previously reported ventilatory improvement.

MPA 60 mg daily for 2 weeks increases serum IGF-I in postmenopausal women with chronic respiratory insufficiency. During follow-up after MPA, there was a trend towards increased IGF-I and insulin levels. The role of these two hormones to induce prolonged ventilatory stimulation could not be excluded and further studies in larger populations are warranted.

Key words: respiration; insulin-like growth factor-I; menopause; progesterone; hormone replacement therapy.

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Introduction

The incidence of sleep-disordered breathing (SDB) is higher among men and postmenopausal women compared with premenopausal women (1). Increasing occurrence of SDB in postmenopausal women is most often attributed to decline in progesterone concentration. However, many other endocrine changes also occur during the menopause, but their influence on SDB is not known. After menopause, levels of serum insulin-like growth factor-I (IGF-I) decrease faster than in premenopause. This appears not only to be related to age but the menopause *per se*. Healthy women who have experienced a natural menopause have lower IGF-I levels than healthy age-matched premenopausal women (2).

In severe sleep apnoea IGF-I level is decreased (3). Increased level of IGF-I is associated with a higher ventilatory sensitivity to carbon dioxide (CO_2) (3). There are also some data suggesting a possible direct effect of insulin on respiratory control (4). MPA may increase IGF-I (5) and insulin levels (6). Also the location of both IGF-I and insulin receptors in parts of the brain associated with both sensing of H^+ ion concentrations (brain stem) and integration of inputs from chemoreceptor areas (cerebellum) suggests that these two hormones might be involved in the control of breathing (7).

Progestins stimulate ventilation. Medroxyprogesterone acetate (MPA) is regarded as a central chemoreceptor stimulant (8), although there is also evidence for peripheral action (9). According to our previous results in postmenopausal women, MPA increases levels of waking blood gases

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for longer than the hormone is detectable in serum (10). The mechanism of the prolonged stimulatory effect of MPA is unknown. The endocrine alterations after parenteral MPA are known to subside slowly (11). Knowledge of prolonged hormonal interactions of orally administered MPA is limited to high doses (>100 mg) administered mainly as single daily doses.

MPA could be a suitable respiratory stimulant in postmenopausal women with chronic respiratory failure (10). MPA has also certain glucocorticoid properties. Suppression in serum cortisol secretion occurs even with daily doses of 100 mg of MPA (12). However, unlike glucocorticoids, MPA does not reduce growth rate in children (11). Glucocorticoid-like effects are observed in up to 30% of patients treated for longer than 6 weeks with daily doses of the order of 1500 mg MPA (13). Whether daily doses of less than 100 mg of MPA suppress serum cortisol, is not known.

The sustained ventilatory effect on MPA that was demonstrated in our previous study (10), led us to suspect possible endocrine interactions. To better understand the relations between hormones and breathing, we analysed the frozen serum samples to evaluate the degree and duration of changes in IGF-I and insulin in postmenopausal women with chronic respiratory insufficiency, induced by short-term MPA therapy. Patients with chronic respiratory failure often use corticosteroids, and therefore may have adrenal suppression. To evaluate the safety of MPA in terms of possible adrenal suppression, cortisol concentrations were assessed also.

Methods

SUBJECTS

Fourteen postmenopausal women with permanent or previous episodic hypercapnic or hypoxaemic respiratory failure were enrolled in the trial. The respiratory failure was due to chronic obstructive pulmonary disease (COPD), end-stage asthma or late sequlae of pulmonary tuberculosis and assessed with daytime arterial blood gas measurements. Their mean age was 67·0 years (SD 6·30). The detailed clinical characteristics of the subjects have been described previously (10). The criteria for postmenopausal status were age over 50 years, time since last menstruation at least 2 years and serum concentrations of follicle stimulating hormone (FSH) $>30\,\mathrm{IU\,l^{-1}}$. One subject on vaginal oestrogen therapy was allowed to continue with her hormone replacement therapy.

The exclusion criteria were malignancies, heart diseases (except cor pulmonale), hepatic, renal, psychiatric, and neurological diseases, thromboembolic events, unstable hypertension, severe rheumatoid arthritis, insulin dependent diabetes, total serum cholesterol $>9{\cdot}5\,\mathrm{mmol\,l^{-1}}$, serum triglycerides $>2{\cdot}5\,\mathrm{mmol\,l^{-1}}$, use of any alternative medicine, medication with effects on the central nervous system, progestins except for MPA given by the research team, contraindications to MPA therapy, long-term oxygen therapy, or current smoking. We also excluded patients with abnormalities in white blood cell count, serum creatinine, alanine aminotransferase, oestradiol, progesterone, FSH, luteinizing hormone, prolactin, sex-hormone binding globulin and TSH. Before the baseline visit, patients were further evaluated by taking a medical-history and physical examination.

Written informed consent was obtained from all patients. The protocol was approved by the Joint Commission on Ethics of Turku University and Turku University Central Hospital and the National Agency for Medicines.

STUDY DESIGN

The 12-week study was a placebo-controlled single-blind trial (Fig. 1). Seven days after the baseline visit the patients started fortnight of placebo treatment. A 7-day placebo washout period was then followed by MPA orally 30 mg b.i.d. for another fortnight. The follow-up was 6 weeks after treatment. Patients were weighed and blood samples for serum MPA, IGF-I, insulin and cortisol were collected at 3-week intervals: at baseline, after 2 weeks on placebo, after 2 weeks on MPA, and after a 3-week and a 6-week washout period.

Thirty mg of oral MPA (Lutopolar®, Orion Pharma, Espoo, Finland) was administered twice in the evening, at 21·00 hours and 23·00 hours, to achieve maximum plasma concentrations and respiratory stimulation throughout the night. Identical placebo tablets for the placebo treatment were also provided by Orion Pharma, Finland. Compliance was assessed by tablet counts, patient interviews and measurements of serum MPA concentrations. Blood samples for MPA, IGF-I, insulin and cortisol were collected after an overnight fast in seated subjects at 08·00 hours at baseline, on the 14th day on placebo, on the 14th day on MPA, and after a 3-week and a 6-week washout.

LABORATORY ASSAYS

IGF-I was determined with IRMA kit (Nichols Institute Diagnostics, U.S.A.). Insulin was determined with Phadeseph® Insulin RIA kit (Pharmacia, Uppsala, Sweden). Cortisol was determined with heterogeneous competitive magnetic separation assay (Technicon Immuno-1 system, U.S.A.). Serum MPA concentrations were determined by liquid chromatography–tandem mass spectrometry (HP 1090 series II/L® liquid chromatograph Hewlett-Packard, Avondale, CA, U.S.A. and API III® triple quadrupole mass spectrometer, PE Sciex, Thornhill, Ontario, Canada).

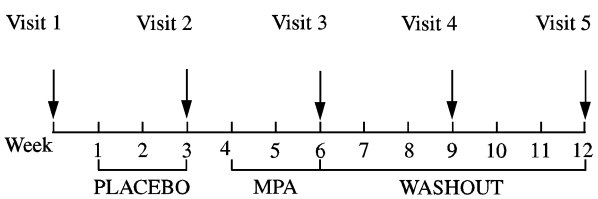

FIG. 1. Study design.

The limit of quantitation was 0·02 ng ml^{-1} of MPA in plasma. Metabolites of MPA were not measured.

STATISTICAL ANALYSES

The analyses were started with assessment of distribution and variance. Serum cortisol was analysed with Friedman's χ^2-test, and further analysis with Wilcoxon Sign Rank test. Weight, IGF-I and insulin were tested using the analysis of variance for repeated measures, followed by contrasts based on Fisher's F-test with Bonferroni correction. Comparisons between the first and the second sessions tested the placebo effect, between the first and the third sessions the immediate MPA effect and between the first and the fourth and the first and the fifth the sustained effect of MPA. Confidence intervals (CI) with Bonferroni corrections for the means of the differences were determined. In all tests, $P<0{\cdot}05$ was considered significant. To identify possible correlations between IGF-I level and previously reported P_{aCO_2} and P_{aO_2} levels (10), Pearson correlation coefficients were calculated. Chi-square analysis was utilized to evaluate the responder distributions. Statistical computing was performed with SAS System for Windows, release 6·12/1996 (SAS Inc., Cary, NC 1990).

Results

Thirteen out of 14 patients completed the trial. One subject discontinued because of fever and viral respiratory tract infection after her second visit. Other patients were clinically stable. At baseline the mean BMI was 26·7 kg m^{-2} (SD 5·22). Weight and BMI did not change during the trial (Table 1). As earlier reported (10), range of MPA while on treatment was 2·28–8·39 ng ml^{-1} (mean 4·33 ng ml^{-1}). At the 3-week washout, MPA was under the detection limit in three out of 13 subjects (23%). In the remaining 10, the range of MPA was 0·032–0·196 ng ml^{-1} (mean 0·06 ng ml^{-1}). At 6 weeks, MPA was undetectable in all subjects.

MPA increased the mean IGF-I from 15·2 nmol l^{-1} (SD 4·63) to 20·8 nmol l^{-1} (SD 6·85). The average change was 5·6 nmol l^{-1} (95% confidence interval (95% CI 1·4 to 9·9) or 42·0% (95% CI 6·3 to 77·8). At the 3-week washout, the average IGF-I was still 13·2 % above the baseline but the difference was not significant (95 % CI -2·5 to 28·9). At the 6-week washout IGF-I had returned to baseline (Fig. 2).

Changes in IGF-I levels did not correlate with simultaneously measured blood gas changes except at the 6-week washout, when increase in IGF-I was related with decrease in P_{aO_2} ($r=-0{\cdot}68$, $P=0{\cdot}0097$). In most subjects IGF-I and P_{aO_2} increased on MPA and remained increased at least 3 weeks after cessation of MPA (Table 2 and 3). P_{aCO_2} decreased in most subjects on MPA and remained decreased at 3 weeks after cessation of MPA (Table 3). The differences were evaluated with χ^2-tests knowing that the test is not powerful with low n-values. None of the tests was statistically significant. The long-term effects of the acute MPA-induced IGF-I increase on blood gases during the follow-up are demonstrated in Figs 3 and 4. At 3 weeks after cessation of MPA, the majority of subjects still remained responders in terms of blood gases, whereas at 6 weeks a random distribution was observed (Figs 3 and 4).

The mean serum insulin level was 12·5 mU^{-1} (SD 4·1) at baseline, 12·5 mU l^{-1} (SD 3·9) on placebo, 12·2 mU l^{-1} (SD 4·8) on MPA, 14·5 mU l^{-1} (SD 3·6) at the 3-week washout and 14·2 mU l^{-1} (SD 4·4) at the 6-week washout (Table 1). The percentage changes are shown in Fig. 2. The median serum cortisol levels were 470 nmol l^{-1} (interquartile range, IQR 219), 536 nmol l^{-1} (IQR 91), 454 nmol l^{-1} (IQR 268), 508 nmol l^{-1} (IQR 80), 568 nmol l^{-1} (IQR 229), respectively (Table 1). No differences observed in insulin and cortisol were significant.

Discussion

EFFECTS OF MPA ON SERUM IGF-I

The present study shows that serum concentration of IGF-I increases during MPA treatment in postmenopausal

TABLE 1. Mean values (SD in parentheses) of serum IGF-I, insulin and weight, and median values (interquartile range in parentheses) of morning cortisol, $n=13$. MPA: medroxyprogesterone acetate, washout (3 wk): 3 weeks after the cessation of MPA administration, washout (6 wk): 6 weeks after the cessation of MPA administration; P: Fisher's F-test (serum IGF-1, insulin and weight) or Wilcoxon Sign Rank test (cortisol) with Bonferroni correction, n.s.: non-significant.

Factor (reference value)	Baseline	Placebo	P	MPA	P	Washout (3 week)	P	Washout (6 week)	P
IGF-I	15·2	14·9	n.s.	20·8	0·008	17·2	n.s.	15·5	n.s.
(5·0–28 nmol l^{-1})	(4·6)	(4·7)	($P=1{\cdot}00$)	(6·8)		(6·4)	($P=0{\cdot}112$)	(4·3)	($P=1{\cdot}00$)
Insulin	12·5	12·5	n.s.	12·2	n.s.	14·5	n.s.	14·2	n.s.
(5–20 mU l^{-1})	(4·1)	(3·9)	($P=1{\cdot}00$)	(4·8)	($P=1{\cdot}00$)	(3·6)	($P=0{\cdot}078$)	(4·4)	($P=0{\cdot}725$)
Cortisol	470	536	n.s.	454	n.s.	508	n.s.	568	n.s.
(150–650 nmol l^{-1})	(219)	(91)	($P=1{\cdot}00$)	(268)	($P=1{\cdot}00$)	(80)	($P=1{\cdot}00$)	(229)	($P=0{\cdot}230$)
Weight (kg)	68·4	68·4	n.s.	68·0	n.s.	68·5	n.s.	68·5	n.s.
	(14·5)	(14·4)	($P=1{\cdot}00$)	(14·1)	($P=1{\cdot}00$)	(14·7)	($P=1{\cdot}00$)	(14·0)	($P=1{\cdot}00$)

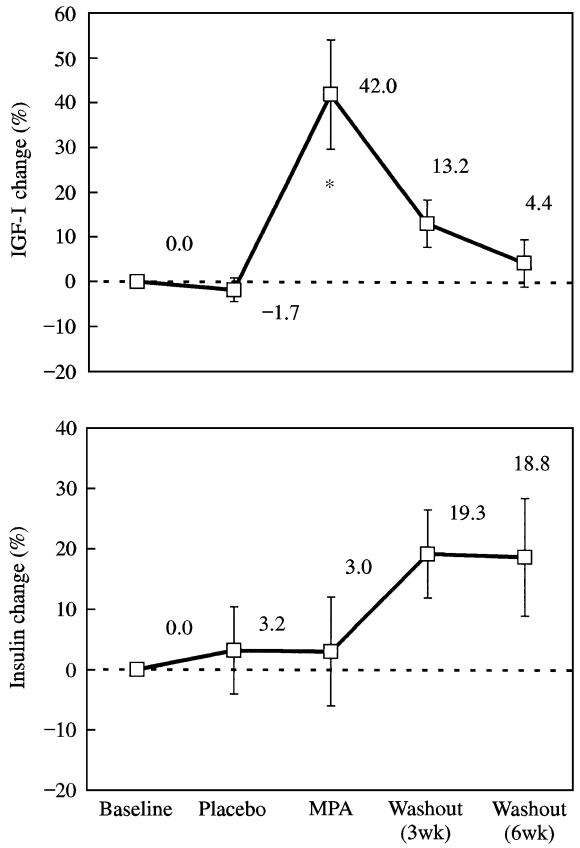

FIG. 2. IGF-I and insulin after a 14-day medroxyprogesterone acetate (MPA) therapy. Values are percentage changes from baseline on placebo, on MPA, and after 3- and 6-week washouts. * = $P < 0{\cdot}05$.

TABLE 2. Frequencies of changes in P_{aCO_2} and serum IGF-I during the study period. P_{aCO_2}: partial pressure of arterial carbon dioxide, ↓ decrease in value; ↑ increase in value; † no change in value in one subject.

	P_{aCO_2}↓		P_{aCO_2}↑	
	IGF-I↓	IGF-I↑	IGF-I↓	IGF-I↑
Placebo†	2	5	3	2
MPA	1	11	0	1
Washout (3 weeks)	1	10	0	2
Washout (6 weeks)	3	3	4	3

women with chronic respiratory insufficiency. This coincides with the decrease in P_{aCO_2} and the increasing trend in P_{aO_2} [Tables 2 and 3 and Saaresranta *et al.* (10)]. The MPA induced increase in IGF-I is in accordance with the earlier observations that MPA increases plasma IGF-I levels both in healthy women (5) and in women with advanced breast cancer (14). Although IGF-I did not remain significantly increased 3 weeks after cessation of MPA, the observed

TABLE 3. Frequencies of changes in P_{aO_2} and serum IGF-I during the study period. P_{aO_2}: partial pressure of arterial oxygen, ↓ decrease in value; ↑ increase in value; † no change in value in one subject.

	P_{aO_2}↓		P_{aO_2}↑	
	IGF-I↓	IGF-I↑	IGF-I↓	IGF-I↑
Placebo†	2	4	3	3
MPA	0	2	1	10
Washout (3 weeks)	1	4	0	8
Washout (6 weeks)	3	5	4	1

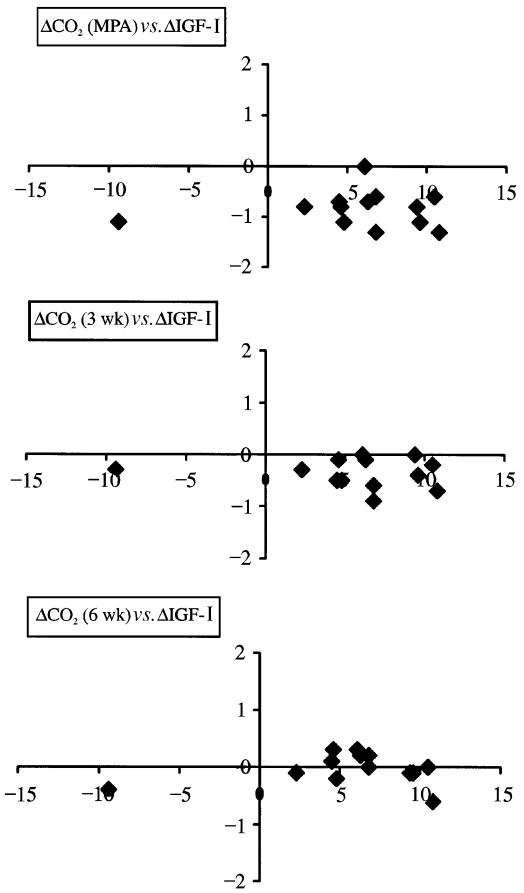

FIG. 3. The MPA-induced increase in IGF-I and the acute and long-term changes on P_{aCO_2}. MPA: medroxyprogesterone acetate; P_{aCO_2}: partial pressure of arterial carbon dioxide, 3 wk: a 3-week washout; 6 wk: a 6-week washout.

increasing tendency in serum concentrations during the washout period suggests that the MPA induced increase in IGF-I was not short-lived.

Our results are also in line with the observations of Malarkey *et al.* (15) in postmenopausal women. Combining

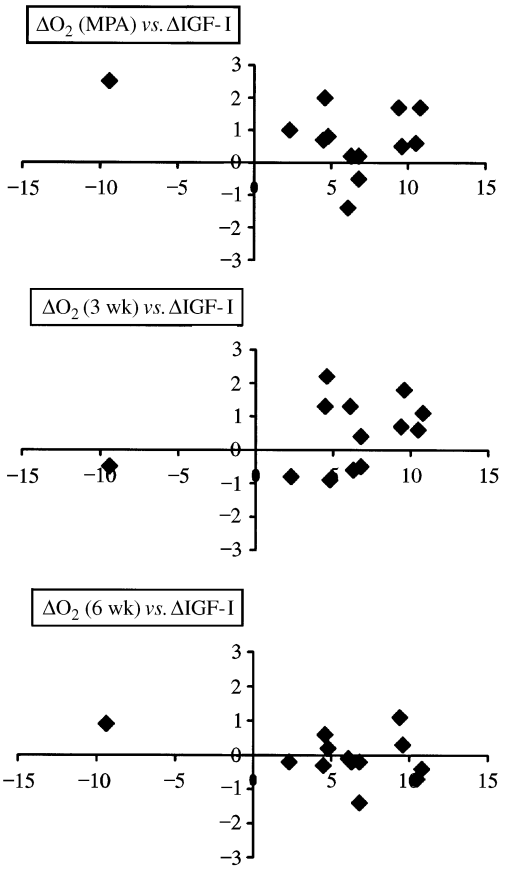

FIG. 4. The MPA-induced increase in IGF-1 and the acute and long-term changes on Pa_{O_2}. MPA: medroxyprogesterone acetate; Pa_{O_2}: partial pressure of arterial oxygen, 3 wk: a 3-week washout; 6 wk: a 6-week washout.

oestrogen with MPA, the previously on oestrogen only observed decrease in serum IGF-I level was inhibited (15). Contradictory to that, Bellantoni *et al*. (16) did not observe a significant alteration of GH and IGF-I levels on MPA treatment in healthy non-obese postmenopausal women.

MPA may increase IGF-I directly or indirectly through a number of possible mediator hormones. The IGF-I increase may also be secondary to altered environment including improved ventilation, improved nutritional status or improved sleep quality.

In physiological conditions, GH stimulates IGF-I secretion. Most of the 24-h GH secretion occurs during the night and the secretory pulses are sleep dependent. Contrary to this, there is no circadian or sleep-related variation in the serum IGF-I concentration (17). The proper assessment of diurnal GH profile demands frequently repeated blood samples. We decided not to measure the GH profiles, and are therefore not able to evaluate the possible role of GH in inducing the increase in IGF-I secretion. Sleep disturbances are common in respiratory failure. With improved ventilation, MPA could lead to improved sleep, proportion of slow wave sleep, and amount of GH secreted during that sleep stage. Increase in slow wave sleep (sleep stages 3 and 4) increases the secretion of pulsatile GH (18). However, there is no evidence that MPA increases the amount of slow-wave sleep (19). On the contrary, MPA is known to suppress the sleep-induced peak in GH secretion (20). Acromegalic patients with increased hypercapnic ventilatory response had lower $etCO_2$ (end tidal CO_2) levels and higher IGF-I levels than those with decreased hypercapnic ventilatory response (21). In transsexuals and male sex offenders, MPA (400 mg i.m. weekly) caused an increase in plasma IGF-I concentration but not in GH (22). This suggests that MPA increases the IGF-I through other than GH-mediated mechanisms.

Another explanation for increased IGF-I could be an increase of plasma IGF-I binding proteins. IGF-I is bound tightly to several binding proteins in plasma whereas only less than 1% is free (23). Insulin-like growth factor binding protein-3 (IGFBP-3), the most abundant IGFBP in the circulation, is related in exponential fashion to serum IGF-I levels (24). We measured the amount of total plasma IGF-I concentrations by using the IRMA kit (Nichols Institute Diagnostics, U.S.A.). In this method, the sample is acidified to separate the IGF-I from IGFBPs. Thereafter excess IGF-2 is added to the assay to block the IGFBP binding sites from recombining with the released IGF-I. IGFBPs were not measured and therefore their possible role cannot be determined.

Nutritional status and dietary intake influence the IGF-I levels (25). Our patients had normal weight. We did not control diet during the 12-week study period, and the subjects were allowed to maintain their habitual diets. However, it is unlikely that change in nutritional status would have increased the IGF-I levels because no weight gain was observed and none of the patients reported a change in appetite.

It cannot be excluded that the increase in IGF-I is secondary to improved ventilation during MPA. Hypercapnia and hypoxaemia may suppress IGF-I secretion, and the increase in IGF-I would result from a release of this suppression. This is supported by the observations in patients with sleep apnoea. The more severe the sleep apnoea, the lower the IGF-I levels (26). Reversal of sleep apnoea by nasal CPAP essentially restored the IGF-I levels (26).

The impact of IGF-I on breathing is not well understood. However, the simultaneous increases in progesterone, IGF-I and ventilation, and decrease in Pa_{CO_2} are also observed in conditions such as pregnancy (27,28) and the luteal phase of the menstrual cycle (5,27) suggesting that a rise in IGF-I is involved in increasing ventilation. Sleep-related hypoxaemia in sleep apnoea results in alterations in metabolic regulatory peptides, insulin, IGF-I and IGF-II in particular (29). Chronic hypoxaemia in newborns is associated with a decrease in IGF-I without any change in GH (30). Our adult patients with respiratory failure had moderate hypoxaemia, which tended to improve simultaneously with the IGF-I increase on MPA (10).

Lung volumes decline with age. Aging is also related to decreased lean body mass (31), basal and stimulated GH secretion, basal IGF-I levels (32,33) and increased

somatostatin level (34). GH seems to correlate with plasma oestradiol levels. Basal and stimulated GH secretion are greater in women than in men throughout the adulthood until women achieve the menopause. In elderly women and men, the effects of both gender and age on GH secretion markedly diminish (32). Although GH has direct metabolic effects on peripheral tissues, most of its growth-promoting properties are mediated through the IGF family, especially IGF-I. There is a greater decrease in IGF-I in healthy postmenopausal women than in age-matched women who still remain premenopausal (2).

In chronic respiratory insufficiency, the respiratory muscle pump often functions close to the limit of its capacity to maintain effective ventilation. Increased load on respiratory muscles causes muscle fatique which is deleterious to muscle function. It is well established that GH increases the expression of systemic IGF-I, as well as autocrine/paracrine IGF-I in the skeletal muscle, and it is believed that IGF-I is a major regulator of muscle growth (35). IGF-I mediates most of the anabolic growth-promoting effects of GH in muscle and skeletal muscle tissues (35, 36) and also in cultured fibroblasts derived from human lung produce IGF-I (35). GH treatment increases ventilation, central inspiratory drive, and CO_2 response in children with Prader–Willi syndrome (37). The authors suggest that the improved ventilation might be attributed to an improved inspiratory muscle performance. If the anabolic effects of IGF-I induce improvement in ventilation by strengthening the respiratory muscles and thereby giving time for muscles to recover, the ventilation should remain improved beyond the point when the effects of IGF-I are subsiding.

EFFECTS OF MPA ON SERUM INSULIN

In our study, insulin levels tended to increase during washout (Fig. 2) but, at least in this study population, the increase did not reach statistical significance. IGF-I induces hypolycaemia but also decreases insulin levels (38). The increasing trend in insulin levels during the washout could be a rebound effect. Insulin is an anabolic agent and might possibly be involved in the previously observed prolonged improvement of ventilation (10). The effects of MPA on insulin are not consistent, since there has been no change (39) or increase (6). In mice, diabetes reduced hypercapnic ventilatory response during wakefulness and sleep. The reduction was not related to plasma leptin levels and obesity suggesting a possible direct effect of insulin on ventilatory control (4).

EFFECTS OF MPA ON SERUM CORTISOL

Contradictory to most other studies with higher doses of MPA (12,13), serum morning cortisol remained unchanged in our patients. This suggests that MPA with a dosage regimen of 60 mg in the evening for 2 weeks can be safely administered without steroid-withdrawal symptoms in postmenopausal women. Our finding may be explained by at least two factors. Firstly, we used a lower dose compared with most other studies evaluating the suppressive effect of MPA on cortisol. Secondly, MPA is usually divided into three daily doses administered regularly throughout the day. It is well established that glucocorticoids suppress cortisol levels to a lesser extent when administered once daily or on alternating days compared with multiple doses throughout the day. We administered MPA divided into two doses, both taken in the evening. This dosage regimen could be one reason why cortisol suppression was not observed. However, with a low *n*-value, exclusion of cortisol suppression is done with a high risk for type II error.

Conclusions

Impaired ventilation in aging women is often attributed to a decrease in progesterone concentration. However, a decrease in lung volumes or lean body mass, weakening of respiratory muscle capacity probably due to decreased IGF-I induced anabolic effects, and the alterations in various other hormones are also likely to compromise breathing in the elderly. Oestrogens modulate the progesterone action by regulating the progesterone receptors (40). The increased release of somatostatin (34) suppresses central respiratory drive (41) and reduces GH controlled IGF-I production.

We conclude that MPA 60 mg daily for 2 weeks increases serum IGF-I in postmenopausal women with chronic respiratory insufficiency. The pattern of IGF-I rise is similar to previously reported ventilatory improvement (10) which suggests that the IGF-I secretion and respiratory stimulation are linked, either through a common controller or through an interactive relationship. Insulin levels tended to increase during washout but this observation needs confirmation. Cortisol secretion was not altered suggesting that MPA with this dosage regimen could safely be used without glucocorticoid withdrawal symptoms.

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