Respiratory Insufficiency in Postmenopausal Women*

Sustained Improvement of Gas Exchange With Short-term Medroxyprogesterone Acetate

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Study objectives: The degree and duration of respiratory stimulation of medroxyprogesterone acetate (MPA) in postmenopausal women.

Design: A placebo-controlled single-blind trial.

Setting: University hospital in Turku, Finland.

Patients: Fourteen postmenopausal women with permanent or previous episodic hypercapnic or hypoxemic respiratory failure.

Interventions: A 12-week trial including 14-day treatment periods with placebo and MPA (60 mg daily) and a 6-week follow-up.

Results: Thirteen of 14 patients completed the trial. The mean (± SD) PaCO2 at baseline was 42.8 ± 4.5 mm Hg and the mean PaO2 was 71.2 ± 9.0 mm Hg. The average reduction of PaCO2 was 6.3 mm Hg (14.7%, p < 0.001) on MPA and 3.0 mm Hg (6.1%, p < 0.001) after a 3-week washout. At 6 weeks after MPA, the PaCO2 had returned to baseline. The mean changes in PaO2 (+6.0 ± 18.0 mm Hg on MPA and +3.8 ± 22.5 mm Hg after a 3-week washout) were not significant. The PaO2/PaCO2 ratio increased, and bicarbonate and base excess decreased (p < 0.001) on MPA but not during washout. The systolic BP did not change on MPA but decreased on average 14.8 ± 15.0 mm Hg (p = 0.016) after a 3-week washout. The diastolic BP remained unchanged.

Conclusions: Our results suggest that postmenopausal women with chronic respiratory insufficiency consistently improve on MPA at a dose of 60 mg daily for 14 days. Lower PaCO2 is sustained for at least 3 weeks after cessation of MPA. The sustained effects in gas exchange and favorable after-effects in BP warrant further studies into the therapeutic efficacy and possible benefits of MPA pulse therapy. (CHEST 1999; 115:1581–1587)

Key words: COPD; hypercapnia; hypoxemia; medroxyprogesterone acetate; menopause; respiratory stimulant; sustained effect; women

Abbreviations: BE = base excess; CI = confidence interval; FSH = follicle-stimulating hormone; LH = luteinizing hormone; LTOT = long-term oxygen therapy; MPA = medroxyprogesterone acetate; NIPPV = nasal intermittent positive-pressure ventilation; NS = not significant

Hypercapnic respiratory failure is the end stage and predictor of poor prognosis in severe lung disease. Nasal intermittent positive-pressure ventilation (NIPPV) has been suggested to control chronic respiratory failure caused by COPD. However, the efficacy of NIPPV in terms of quality of life or survival remains to be determined.1 Therefore, NIPPV is not recommended as the first-line therapy for chronic respiratory failure in stable COPD.2,3

Long-term oxygen therapy (LTOT) improves oxygenation and the prognosis of COPD with chronic respiratory failure.4,5 In a subgroup of patients, LTOT cannot be used because of aggravation of CO2 retention. Both NIPPV and LTOT require the cooperation of the patient, expensive devices, efficacy monitoring, and technical maintenance.

In patients with clinically stable COPD, progestins improve arterial hypoxemia and hypercapnia as well
as increase arterial pH. Progestins act through progesterone receptors. Marked variability in individual responses to progestins suggests differences in number, binding capacity, or function of progesterone receptors. Despite the fact that progesterone is a female hormone and has feminizing effects, it is surprising that the above-mentioned studies include 124 men but only 3 women.

It is generally accepted that the ventilatory effects subside within 14 days after cessation of medroxyprogesterone acetate (MPA). However, there is some evidence suggesting that patients with stable hypercapnia may continue to decrease their PaCO₂ even after 1 week of cessation of MPA.

The purposes of the present study were to evaluate the degree and duration of MPA effect as well as the tolerability in postmenopausal women with chronic respiratory insufficiency.

**Materials and Methods**

**Patient Selection**

Fourteen postmenopausal women with permanent or previous episodic hypercapnic or hypoxic respiratory failure were enrolled in the trial. The respiratory failure was caused by COPD, end-stage asthma, or late sequelae of pulmonary tuberculosis and assessed with daytime arterial blood gas measurements (Table 1). The criteria for postmenopausal status were age > 50 years, time since last menstruation at least 2 years, and serum concentrations of follicle-stimulating hormone (FSH) > 30 IU/L. Patients on estrogen were allowed to continue their hormone replacement therapy (Table 2).

The exclusion criteria were malignancies, heart diseases (except for COPD), end-stage asthma, or late sequelae of pulmonary tuberculosis and assessed with daytime arterial blood gas measurements (Table 1). The criteria for postmenopausal status were age > 50 years, time since last menstruation at least 2 years, and serum concentrations of follicle-stimulating hormone (FSH) > 30 IU/L. Patients on estrogen were allowed to continue their hormone replacement therapy (Table 2).

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**Table 1—Baseline Characteristics of Patients**

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>67.0</td>
<td>6.30</td>
</tr>
<tr>
<td>Age at menopause, yr</td>
<td>49.2</td>
<td>4.71</td>
</tr>
<tr>
<td>Time since menopause, yr</td>
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<td>9.45</td>
</tr>
<tr>
<td>Smoking, pack-yr</td>
<td>5.9</td>
<td>10.66</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.7</td>
<td>5.22</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>0.78</td>
<td>0.34</td>
</tr>
<tr>
<td>FVC, L</td>
<td>1.23</td>
<td>0.44</td>
</tr>
<tr>
<td>FEV₁, %</td>
<td>32</td>
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</tr>
<tr>
<td>FVC, %</td>
<td>44</td>
<td>15.62</td>
</tr>
<tr>
<td>FEV¹/FVC, %</td>
<td>64</td>
<td>14.17</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.40</td>
<td>0.03</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>42.8</td>
<td>4.88</td>
</tr>
<tr>
<td>PaO₂, mm Hg</td>
<td>71.2</td>
<td>9.15</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>155</td>
<td>20.81</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>78</td>
<td>14.71</td>
</tr>
</tbody>
</table>

*BMI = body mass index. Values of PaCO₂ > 45 mm Hg are considered hypercapnic, and values of PaO₂ < 75 mm Hg hypoxemic.

**Table 2—Baseline Characteristics of Patients**

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Patients (N = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD</td>
<td>9 69</td>
</tr>
<tr>
<td>Ashima</td>
<td>3 23</td>
</tr>
<tr>
<td>Late sequelae of pulmonary tuberculosis</td>
<td>4 31</td>
</tr>
<tr>
<td>α₁-antitrypsin deficiency</td>
<td>2 15</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>2 15</td>
</tr>
<tr>
<td>Tracheobronchial collapse</td>
<td>1 8</td>
</tr>
<tr>
<td>Pulmonary fibrosis</td>
<td>1 8</td>
</tr>
<tr>
<td>Suspected asbestosis</td>
<td>1 8</td>
</tr>
<tr>
<td>Past smokers</td>
<td>8 62</td>
</tr>
<tr>
<td>Current smokers</td>
<td>0 0</td>
</tr>
<tr>
<td>Current use of vaginal estrogen therapy</td>
<td>1 8</td>
</tr>
</tbody>
</table>

Cholesterol > 9.5 mmol/L, serum triglycerides > 2.5 mmol/L, use of any alternative medicine, medication with effects on the CNS, progestins except for MPA given by the research team, contraindications to MPA therapy, LTOT, current smoking, and current participation in any other clinical study.

The prestudy visit included measurements of blood hemoglobin concentration, hematocrit, WBC count, serum creatinine, alanine aminotransferase, total cholesterol, triglycerides, high-density lipoprotein, estradiol, progesterone, FSH, luteinizing hormone (LH), prolactin, sex hormone-binding globulin, and thyroid-stimulating hormone. Blood samples were collected between 7:00 AM and 9:00 AM after an overnight fast. The prestudy visit also included detailed taking of medical history and clinical 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 National Agency for Medicines.

**Study Design**

The 12-week study was a placebo-controlled single-blind trial. Seven days after the baseline measurements, all patients started with placebo treatment for 14 days. The placebo measurements were made in the morning after the last evening placebo dose. After a 7-day interval, MPA treatment for 14 days was started, and the MPA measurements were made as after placebo treatment. The washout measurements were similarly done in the morning, 3 and 6 weeks after cessation of MPA (Fig 1).

Thirty milligrams of oral MPA (Lutopolar; Orion; Espoo, Finland) was administered twice in the evening, at 9 and 11 PM. MPA reaches its peak serum concentration within 1 to 3 h and declines quite sharply thereafter. MPA was divided in two doses given 2 h apart because we wanted sufficient MPA concentrations from falling asleep to waking up. Identical placebo tablets for the placebo treatment were also provided by Orion. Compliance was assessed by tablet counts, patient interviews, and measurements of serum MPA concentrations. The visit protocol was performed five times at 3-week intervals: at baseline, after 14 days on placebo, after 14 days on MPA, and after 3- and 6-week washout periods.

**Visit protocol:** Body weight, BP, arterial blood gases, serum MPA, and flow-volume spirometry (Vitalograph Compact II; Vitalograph Ltd; Buckingham, England) were assessed. BP was measured in the morning by the same individual, using the auscultatory method in seated subjects. Arterial blood samples were obtained with a single arterial puncture in patients lying awake in supine position. Blood hemoglobin and hematocrit were measured at 3-week intervals except during placebo treatment.
**Statistical Analysis**

The analyses were started with assessment of distribution and variance. The repeated measurements except BP were tested using the analysis of variance for repeated measures, followed by determination of contrasts based on Student’s t test with Dunnert’s adjustment. Systolic and diastolic BP 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 second sessions tested the placebo effect, between the first and third sessions the immediate MPA effect, between the first and fourth and the first and fifth sessions the sustained effect of MPA. Questionnaire responses about symptoms and possible adverse events were analyzed with Friedman’s χ² test. If statistically significant changes were found, further analysis was performed using the Wilcoxon sign-rank test with Bonferroni correction. Correlations between MPA and blood gas values as well as the frequency and intensity of headache were determined by Spearman rank-order correlation. In all tests, p < 0.05 was considered significant. Statistical computing was performed with appropriate computer software (SAS for Windows, version 6.12; SAS Institute; Cary, NC).

**RESULTS**

Thirteen of 14 patients completed the trial. One subject discontinued because of fever and viral respiratory tract infection after her second visit. Serum creatinine, WBC count, prolactin, estradiol, progesterone, TSH, SHBG, LH, and FSH were within the normal range at baseline, and serum lipids were within the inclusion criteria. One subject had mild anemia (hemoglobin, 115 g/L; reference range, 117 to 153 g/L) and another had mild polycythemia (hemoglobin, 162 g/L; hematocrit, 0.49; upper limit of normal range, 0.47). The reference values of our laboratory were 33.8 to 45.0 mm Hg for PaCO₂ and 75.0 to 105.0 mm Hg for PaO₂. At baseline, 5 of 13 patients (38%) had PaCO₂ > 45 mm Hg and 11 (85%) had PaO₂ < 75 mm Hg. In four patients PaCO₂ and PaO₂ were simultaneously beyond the reference ranges. After the 2-week treatment, the mean concentration of MPA was 4.33 ng/mL (range, 2.28 to 8.39 ng/mL). After a 3-week washout MPA was under the detection limit in three patients, and in the other 10 the mean concentration was 0.06 ng/mL (range, 0.032 to 0.196 ng/mL). After a 6-week washout, MPA was not detected in any subject. Changes in the blood gases did not correlate with the serum concentrations of MPA.

**Immediate Effects of MPA on Gas Exchange**

Compared with baseline, MPA improved the PaCO₂ values in 12 (Fig 2) and PaO₂ in 11 of 13 patients. MPA reduced the mean PaCO₂ from 42.8 ± 4.88 mm Hg (mean ± SD) to 36.8 ± 5.25 mm Hg. The average reduction was 6.3 mm Hg (95% confidence interval [CI], 4.5 to 8.2) or 14.7% (95% CI, 9.3 to 20.1; Table 3 and Fig 3). The mean HCO₃⁻ was reduced from 25.3 to 22.6 mmol/L (average decrease, 2.6 mmol/L; 95% CI, 1.5 L to 3.7) and base excess (BE) from 0.97 to −2.23 mmol/L (average decrease, 3.2 mmol/L; 95% CI, 1.96 to 4.4). The mean PaO₂ at baseline was 71.2 mm Hg and 76.5 mm Hg on MPA, the average change of 5.2 mm Hg or 8.5% being statistically not significant (NS; Fig 3). The PaO₂/PaCO₂ ratio, representing the combined effect on gas exchange, improved 28.5% (from 11.8 to 45.1) on MPA (Fig 3).
Sustained Effects of MPA

The blood gases were reevaluated after 3- and 6-week washout periods. At the 3-week washout, Pa$\text{CO}_2$ and Pa$\text{O}_2$ values remained improved in 11 and 8 patients, respectively. At 3 weeks after cessation of MPA, the mean Pa$\text{CO}_2$ was still 3.0 mm Hg (95% CI, 0.75 to 4.5) or 6.1% (95% CI, 2.3 to 9.9; Fig 3) lower than baseline, whereas at 6 weeks the mean Pa$\text{CO}_2$ had returned to the baseline level. The Pa$\text{O}_2$, Pa$\text{O}_2$/Pa$\text{CO}_2$ ratio (Fig 3), HCO$_3^-$, and BE (Fig 4) followed a similar sustained effect pattern, but the changes were NS. The pH changed neither on MPA nor during the washout (Fig 4).

BP Effects

The systolic BP followed a distinct sustained-effect pattern, with no change on MPA but significant lowering after a 3-week washout period (from 155.2 mm Hg at baseline to 140.5 mm Hg; average reduction, 14.8 mm Hg [95% CI, 2.6 to 27.0] or 9.8% [95% CI, 2.0 to 18.0]; Fig 5). The diastolic BP did not change during the follow-up (Fig 5).

Adverse Effects of High-Dose MPA Therapy

Two of the 13 women had undergone a hysterectomy. Three (27%) women without hysterectomies had withdrawal bleeding after cessation of MPA and went through a gynecologic examination. A benign endometrial polyp was found to be a predisposing factor in one subject, and another had used local estrogen therapy promoting the proliferation of endometrial mucosa. In the third subject no endometrial abnormalities could be identified to predispose for withdrawal bleeding.

Some months after the termination of the present study, the observed effects on breathing were reported to the subjects on the phone. Twelve of 13 (92%) expressed their willingness to continue MPA therapy even after the trial. The subject with endometrial polyp and withdrawal bleeding preferred not to continue.

Body weight, body mass index, FEV$_1$, FVC, the FEV$_1$/FVC ratio, hemoglobin, and hematocrit remained constant throughout the study. Also, there was no effect of MPA on the sensation of dyspnea measured with the visual analog scale. No changes in mental disorders, headache, palpitation, swelling, tenderness of breasts, thirst, dizziness, or GI or dermatologic disorders were observed in the daily diary card questionnaire.

**Discussion**

Our results in women with chronic respiratory failure provide evidence that a significant proportion of the improvement of gas exchange achieved with the 14-day MPA therapy is maintained beyond 3 weeks after cessation of the hormone therapy. This high-dose of MPA was also well tolerated by postmenopausal women. These results warrant further studies into the efficacy of MPA pulse therapy compared with continuous administration. As far as BP responses are concerned, our preliminary observations suggest that periodic MPA therapy might have some benefits over continuous administration.

The time course of the respiratory stimulation effect of MPA has previously been studied in healthy men. The initial effect of 60 mg MPA per day appears at 48 h and maximal stimulation is achieved in 7 days. After MPA therapy for 2 weeks, the ventilatory effects subside within 14 days. These findings are contradictory to ours, inasmuch as we found a marked residual respiratory stimulation even after 3 weeks of cessation of MPA. This could be explained by several factors. First, our subjects were not healthy but suffered from severe pulmonary disease with chronic or episodic respiratory failure. The duration of the MPA effect has not directly been addressed in pulmonary patients, but some studies provide evidence for a prolonged effect of MPA. Delaunois et al administered MPA 75 mg/d to 15 men with stable COPD for 7 days and observed that in four subjects the PaCO$_2$ continued to decrease 1 week after cessation of MPA. They suggested that those subjects might have had temporary worsening of their condition during MPA with spontaneous improvement coinciding with the checkpoint at 1 week after cessation. This could not have been the case in our study, in which the condition of all
patients remained stable and their spirometric values did not change during the study period. Lyons and Huang used IM progesterone in eight patients (two men and six women) with severe obesity hypoventilation and followed up the PaCO₂ in five of them after 18 to 30 days of hormone therapy. The therapeutic effect achieved with progesterone was maintained in three subjects (two men and one woman) for 1 to 4 months, before returning to chronic hypercapnia. We previously studied eight postmenopausal women who presented with nocturnal CO₂ retention that was related to partial upper airway obstruction during sleep. Also in those women we were able to demonstrate sustained improvement of end-tidal CO₂ during sleep, measured 3 weeks after cessation of MPA.

The prolonged effect of MPA observed in the present study could also be explained by the fact that

![Figure 3](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21920/)

**Figure 3.** Changes (± SEM) in PaO₂, PaCO₂, and PaO₂/PaCO₂ ratio on MPA and after 3- and 6-week washouts. Changes are percentages from the baseline. ***** = p < 0.001.

![Figure 4](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21920/)

**Figure 4.** Changes in pH, BE, and HCO₃⁻ from the baseline. Changes (± SEM) are absolute for pH and BE, and as a percentage from baseline for HCO₃⁻. The mean of baseline in pH is 7.40 and 0.97 mmol/L in BE. ***** = p < 0.001.

<table>
<thead>
<tr>
<th>Table 3—Arterial Blood Gas Values (N = 13)*</th>
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<tr>
<td></td>
</tr>
<tr>
<td>pH</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
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<tr>
<td>PaO₂, mm Hg</td>
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<tr>
<td>HCO₃⁻, mmol/L</td>
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<tr>
<td>BE, mmol/L</td>
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*Values are given as mean ± SD. Student’s t test with Dunnett’s correction was used.
we, unlike most others, only included female patients. Although progesterone and estrogen levels in postmenopausal women correspond to those of men, there is a marked difference in serum LH and FSH concentrations. Hormone replacement therapy is therefore likely to have a much more complex interactive role with trophic effects in women. For example, estradiol increases the number of progesterone receptors.\textsuperscript{20} In ovariectomized rats, MPA does not stimulate breathing until progesterone receptors are upregulated with estrogen.\textsuperscript{21} In healthy men, the parenteral progesterone-induced decrease of PA\textsubscript{CO\textsubscript{2}} was not enhanced but prolonged when estrogen was combined.\textsuperscript{22} MPA metabolites may have weak intrinsic estrogenic activity or may be partially converted to estrogens.\textsuperscript{23}

We administered MPA 60 mg daily, which is the most common dose in studies using MPA to stimulate respiration. There is marked individual variation in the dose of MPA required for respiratory stimulation, the minimum dose ranging from 7.5 to 60 mg/d.\textsuperscript{24} The sustained effects of MPA could be attributed to slow elimination of MPA in our patients. This is not supported by the observations that MPA concentrations are below or near the detection limit after 2\textsuperscript{16} or 3 weeks (our study) of cessation of the MPA therapy. Formation of long-acting active metabolites of MPA could be another explanation. MPA has many metabolites, the physiologic significance and biological activity of which are largely unknown. The turnover of MPA may also differ in various tissues. In rats, the MPA-related substances disappear slowly from the lung, skeletal muscle, and brain.\textsuperscript{25}

Progestins increase the ventilatory response to hypercapnia and hypoxia.\textsuperscript{26} The time course of increased chemosensitivity is not known. The prolonged effect of MPA may be caused by modification of peripheral or central chemoreceptor action or by central processing of the carotid body neural output.\textsuperscript{27} It is possible that MPA resets the respiratory center for a new response level, which is preserved for a prolonged period. Long-term effects may also arise from changes in the body CO\textsubscript{2} stores and the acid-base buffer system acquired during 2 weeks of high-dose MPA. Finally, short-term MPA may alter the endocrinologic steady state, which may need weeks to recuperate.

Although no change in BP was found after 2 weeks of MPA, there was a significant decrease of the systolic BP at the 3-week washout. This finding was not expected and there is a high likelihood of a random observation; however, cardiovascular effects have been monitored during MPA therapy with controversial results, but to our knowledge the washout period has not been followed up. Regensteiner et al\textsuperscript{28} found that neither estrogen nor MPA (60 mg/d for 1 week) alone had an effect on BP, whereas combination of the two hormones lowered the systolic and diastolic BP in normotensive postmenopausal women. Prelevic and Beljic\textsuperscript{29} reported that combining cyclic MPA (5 mg/d for 10 days) with estrogen increased the BP in healthy postmenopausal women. High doses of MPA (up to 400 to 800 mg/d) used in postmenopausal women for metastatic breast cancer increased BP.\textsuperscript{30} No change in BP was found in healthy women undergoing the menopause transition who were treated with oral estrogens and cyclic MPA (MPA 10 mg/d for 14 days).\textsuperscript{31} In subjects with high-altitude polycythemia, diastolic BP decreased with MPA in subjects with normal lung function but not in those with lung disease.\textsuperscript{32} Our result could be interpreted in line with the observation that hypercapnic BP response is greater during the luteal phase of the menstrual cycle.\textsuperscript{32} During hormone therapy, the MPA-induced BP increase is counteracted by low CO\textsubscript{2}, resulting in no change, whereas during the washout period, the BP decreases because MPA is withdrawn but the CO\textsubscript{2} remains low.

MPA is known to improve arterial blood gases. Our results provide evidence that a therapeutically sufficient response could be achieved with intermittent MPA therapy in postmenopausal women with respiratory insufficiency. Mimicking the physiologic

![Graph](http://journal.publications.chestnet.org/pdfaxaccess.ashx?url=/data/journals/chest/21920/)
pattern of female hormone rhythmicity might result in better dynamic interactions with other hormones than what perhaps would be achieved with continuous administration. To whom, how, and how much remain to be answered.

REFERENCES

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