Medroxyprogesterone improves cardiac autonomic control in postmenopausal women with respiratory insufficiency

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**Summary**

**Objective**: To study the effect of medroxyprogesterone acetate (MPA) on autonomic cardiac control in respiratory insufficiency in postmenopausal women.

**Design**: A prospective, single-blind study.

**Subjects**: Eighteen postmenopausal women with respiratory insufficiency and eight asymptomatic postmenopausal women with nocturnal hypoxaemia as controls.

**Methods**: Oral MPA treatment was given at 30 mg twice daily for 2 weeks. All-night polysomnography including a two-channel electroencephalogram, an electro-oculogram, an electromyogram, an electrocardiogram, arterial oxyhaemoglobin saturation, maximum end-tidal CO\textsubscript{2} partial pressure, a ballistocardiogram and breathing movements were recorded at baseline and at the end of MPA treatment. Heart rate variability (HRV) was calculated in time and frequency domains during various sleep stages on and off MPA, and the results were correlated to respiratory variables.

**Results**: At baseline, patients had higher heart rate and lower HRV than controls, suggesting increased cardiac sympathetic output. MPA increased HRV in patients, but not in controls. End-tidal CO\textsubscript{2} partial pressure decreased, and respiratory rate increased during treatment in both groups.

**Conclusions**: HRV is compromised in women with respiratory insufficiency. Peroral MPA increases their HRV to levels comparable with those in controls. This suggests an improvement in vagal cardiac control beneficial to cardiovascular health.

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**Introduction**

Heart rate variability (HRV) is a measure of autonomic neural influences on the heart. In a healthy man, heart rate fluctuates constantly, and resting HRV is mainly under vagal control. Stress increases the relative influence of the sympathetic nervous system on the heart, thus decreasing HRV. \cite{1}
Reduced HRV increases the susceptibility for ventricular tachyarrhythmias and sudden cardiac death in the general population.\textsuperscript{1–3} HRV has been observed to be reduced in patients with respiratory insufficiency, and this reduction correlates strongly with the severity of the respiratory condition assessed with forced expiratory volume.\textsuperscript{1,5} Considering the effects of HRV on cardiovascular prognosis, this leads to an assumption of a major role of HRV in the increase of cardiac events observed in nocturnal respiratory disturbance states.\textsuperscript{6}

It has been suggested that oestrogen has a positive effect on cardiac autonomic modulation, thereby improving cardiac health.\textsuperscript{7} An increase in HRV is due to enhanced vagal activity, which is antifibrillatory and thus cardioprotective.\textsuperscript{8} Progestins are needed in oestrogen replacement therapy to protect the uterine endometrium.\textsuperscript{9} Progestins, like medroxyprogesterone acetate (MPA), are respiratory stimulants,\textsuperscript{10} although this effect requires higher dosage than in postmenopausal hormone replacement therapy. Therefore, progestins correct the abnormal balance of the arterial blood gases in respiratory insufficiency.\textsuperscript{11} On the other hand, the exact influence of progestins on autonomic control of the heart is not known. Recent studies, however, have suggested that combined HRT reduces HRV, thus possibly having negative effects on cardiovascular health, while unopposed oestrogen does not change HRV.\textsuperscript{12,13}

In order to evaluate whether MPA impairs the autonomic control of the heart, we decided to investigate the effect of plain MPA on cardiac autonomic control in a group of postmenopausal women with respiratory insufficiency and in a control group of asymptomatic postmenopausal women with partial upper airway obstruction-related nocturnal hypoxia.

\textbf{Subjects and methods}

In this study, sleep data with simultaneous all-night high-resolution electrocardiogram (ECG) recordings were used. Some of these data have also been used in an earlier study on the effect of MPA on sleep and breathing.\textsuperscript{14}

Eighteen postmenopausal women with stable-phase permanent or episodic hypercapnic or hypoxaemic respiratory insufficiency participated in the study. The respiratory insufficiency was caused by COPD (12 cases), end-stage asthma (three cases), or late sequelae of pulmonary tuberculosis (four cases). The patients had moderate to severe ventilatory impairment according to pulmonary function tests. At baseline, their mean $FEV_1$ (SD) was 0.91 (0.47) l or 36 (18)\%, mean $FVC$ 1.50 (0.65) l or 50 (19)\%, $FEV%$ 64 (18)\% of predicted, mean arterial pH 7.40 (0.03), $PaCO_2$ 5.6 (0.4) kPa, and $PaO_2$ 9.6 (1.1) kPa. They were selected from hospital patient records, and these 18 fulfilled inclusion criteria in a telephone and personal interview, passed a clinical examination and volunteered. These participants were required to be over 50 years of age and they had been postmenopausal for at least 2 years.

Eight postmenopausal hysterectomised women served as control group. These women were selected from a group of 71 postmenopausal women with no respiratory symptoms or previously diagnosed diseases.\textsuperscript{15} The controls were asymptomatic and had normal flow-volume spirometry values, but had presented with partial upper airway obstruction-related nocturnal hypoxaemia during a previous sleep recording, and thus were supposed to benefit from high-dose MPA therapy. Their mean $FEV_1$ was 2.53 (0.30) l or 98 (8)\%, mean $FVC$ 2.91 (0.39) l or 91 (9)\%, and $FEV%$ 87 (5)\% of predicted.

The controls were thus selected to avoid the possible side effects of high-dose progestins in completely healthy postmenopausal women. Their mean arterial pH was 7.41 (0.01), $PaCO_2$ 5.4 (0.3) kPa, and $PaO_2$ 10.8 (1.7) kPa.

Exclusion criteria included major systemic disease, alcohol or drug abuse or current smoking, long-term oxygen therapy and contraindications to progestin therapy. One participant in the control group and one in the patient group used unopposed oestrogen replacement therapy. Beta blockers were used by two controls and one patient, diuretics by one control and five patients, calcium channel blockers by two patients, nitrates by five patients, and digoxin by one patient. Fifteen patients used inhaled and three oral corticosteroids, 12 anticholinergic drugs and 15 $\beta_2$ agonists.

The study design is shown in Fig. 1. Seven days after the baseline measurements, a 2-week oral progestin therapy was started in the asymptomatic controls. 30 mg of MPA (Lutopolar, Orion Pharma, Espoo, Finland) was administered 2 h before going to bed and 30 mg at bedtime. The participants with respiratory insufficiency were given a 2-week placebo treatment beginning 7 days after baseline, but this regimen was not included in this analysis. The 2-week MPA regimen was started 7 days after the placebo treatment. Originally, we intended to make a double-blind, crossover study, but a pilot study in the controls showed that the respiratory effects of MPA had a carry-over effect of over 3 weeks. As exacerbations of the patients’ pulmonary...
disease could have devastated a crossover study with a lengthy washout period, we decided, for the patients' safety, to opt for a single-blind design where placebo was administered before MPA.

The sleep data consisted of a whole-night polysomnography including a two-channel electroencephalography, electro-oculography, ECG, submandibular electromyography, arterial oxyhaemoglobin saturation measured with a finger probe pulse oximeter (Biox Ohmeda 3700e, BOC Company, Louisville, Colorado), and end-tidal carbon dioxide partial pressure measurement (end-tidal $P_{CO_2}$) (Datex Normocap CO$_2$ and O$_2$ Monitor, Instrumentarium, Finland). With end-tidal $P_{CO_2}$ we wished to gain an estimation of arterial $P_{CO_2}$, and our estimates agree with our previous finding on blood gas analyses in patients with respiratory insufficiency. Breathing movements and a ballistocardiogram were recorded with a static charge sensitive bed (Biomatt, Biorec, Turku, Finland). Sleep recordings were obtained at baseline and at the end of the MPA treatment.

HRV was analysed from 3 to 6-min periods of stage 2, slow wave sleep (combined stages 3 and 4), and rapid eye movement sleep, each at the first appearance. Periods of the awake state were not sampled due to a high amount of movement artifact. The sleep stages during these 3–6-min periods were scored in 30-s epochs according to standard criteria. Stage 2 and slow wave sleep periods were classified as quiet sleep. The epochs were carefully chosen not to include body movements or extrasystolia. Respiratory rate was calculated from the respiratory signal of the static charge sensitive bed to evaluate its possible effect on HRV. Mean arterial oxyhaemoglobin saturation and maximum end-tidal $P_{CO_2}$ were also calculated from each analysed period.

HRV was assessed in both time and frequency domain. In time domain, we calculated standard deviation of the interbeat interval (SDNN), root mean square of successive interbeat interval differences (RMSSD), its coefficient of variance (CVS) and the percentage of successive interbeat intervals with over 50 ms differences in duration (pNN50). SDNN reflects overall HRV, and estimates overall parasympathetic tone. RMSSD and pNN50, although they are the products of different mathematical formulae, are closely intercorrelated and measure the beat-to-beat variation in heart rate that is under the control of rapid variations in vagal outflow. CVS indicates the ratio of RMSSD to mean heart rate in per cent, extracting the effect of changing heart rate from the obtained information.

In frequency domain, HRV was assessed using power spectral analysis based on the Fast Fourier transformation algorithm. Trends were removed from the signal by subtracting the regression line. The signal was resampled at a sampling frequency of 4 Hz, using linear interpolation, and windowed using the Hanning window function. The Fast Fourier transformation analysed spectra were subjected to triangular smoothing, with a range of 0.01 Hz. We calculated total power (0 Hz to either 0.50 Hz or half the mean interbeat interval), which is closely correlated to SDNN. The calculated sub-bands were very low frequency power (0–0.04 Hz), low-frequency power (0.04–0.15 Hz), and high-frequency power (0.15–0.40 Hz). The very low frequency band is regulated by parasympathetic oscillation and modulated by the renin–angiotensin–aldosterone system. The baroreflex-related low-frequency band is modulated by both sympathetic and parasympathetic nervous systems. The high-frequency oscillations represent respiratory variation, and they are closely correlated to RMSSD and pNN50. The low-to-high-frequency ratio was calculated for assessment of the sympathovagal balance.

Ethics

The study was approved by the Joint Committee on Ethics of the University of Turku and Turku
University Central Hospital. All subjects gave their written informed consent after receiving oral and written information.

**Statistical analysis**

Group differences were calculated at baseline and during MPA treatment, as well as from the MPA treatment effect by the Wilcoxon two-sample test with the $t$ distribution approximation (SAS software release 8.1, SAS Institution Inc., Cary, NC). The sleep-stage-induced differences in measured variables were similarly calculated at baseline, during MPA treatment, and from the treatment-induced difference. For interactions between sleep stage and patient group, a repeated measures analysis of variance with two factors was conducted. Skewed distributions were corrected using logarithmic, third root (pNN50), or 16th power (mean SaO2) transformation. A $P$ value of $<0.05$ was considered statistically significant. Values are given as median (range).

**Results**

One patient from the respiratory insufficiency group withdrew from the study after her baseline night, and another had to be excluded because of acute aggravation of her chronic obstructive pulmonary disease. One woman in the control group had to be excluded because of frequent extrasystolia. The ultimate size of the study group was thus 23 women, of whom 16 had respiratory insufficiency and seven were controls.

The median heart rate was higher in patients with respiratory insufficiency than in controls (70 (56–100) bpm versus 61 (51–76) bpm, $P<0.0001$). All HRV variables were reduced in women with respiratory insufficiency, except the low-to-high-frequency ratio, which was similar to controls (Table 1, Fig. 2).

The effect of MPA was highly different between groups. During MPA treatment, a difference in heart rate between groups was still observed (74 (52–113) bpm versus 65 (57–83) bpm, $P=0.018$). In patients with respiratory insufficiency, MPA did not change mean heart rate, but it increased the total power of HRV. The separate power bands, however, were not affected. MPA also increased RMSSD, CVS, and pNN50. In the control group, MPA increased mean heart rate and decreased RMSSD slightly, but had no other effects on HRV (Table 1, Fig. 2).

Respiratory rate was higher and end-tidal $PCO_2$ lower in women with respiratory insufficiency than in controls. MPA increased respiratory rate and median arterial oxyhaemoglobin saturation in both groups. The increase in arterial oxyhaemoglobin saturation on MPA was inversely proportional to the baseline value ($r=−0.84$). MPA reduced end-tidal $PCO_2$ in a similar way in both groups ($−3.5$ ($−14.6–6.2$) mmHg in respiratory insufficiency patients versus $−5.9$ ($−11.6–0.1$) mmHg in controls, $P=0.07$) (Table 2).

Sleep stage had no effect on time domain HRV. In frequency domain, there were differences between quiet and rapid eye movement sleep in the very low- and high-frequency domains (Fig. 2). There were no group differences in the sleep stage-influenced pattern of HRV.

Sleep stage did not affect heart rate in patients with respiratory insufficiency. However, heart rate changed with sleep stage in controls ($P=0.008$ for interaction between group and sleep stage effects at baseline and $P=0.017$ on MPA). At baseline, sleep stage did not affect respiratory rate in patients with respiratory insufficiency, but in the control group, respiratory rate was lower in quiet than in rapid eye movement sleep ($P=0.029$). On MPA, respiratory rate decreased in rapid eye movement sleep compared to quiet sleep in patients, while it remained unchanged in controls ($P=0.011$). Median arterial oxyhaemoglobin saturation was markedly lower in patients than in controls in stage 2 sleep on MPA, while in the other sleep stages, there was no marked difference ($P=0.047$). The difference in pNN50 between quiet and rapid eye movement sleep was smaller in patients than in controls on MPA ($P=0.05$).

**Discussion**

The present study shows that MPA affects HRV in postmenopausal women. MPA improved the disturbed cardiac autonomic regulation observed in those with severe respiratory insufficiency. In asymptomatic controls, MPA administration only increased heart rate, having neither positive nor negative effects on HRV.

HRV was severely compromised in patients with respiratory insufficiency. This is in line with previous studies that show markedly reduced HRV in several conditions affecting gas exchange, e.g. asthma, chronic obstructive pulmonary disease, and obstructive sleep apnea syndrome.4,5,24 This reduction is probably secondary to the underlying disorder. The patients are likely to benefit from the
Table 1  Group effect and MPA versus baseline effect on time domain variables of heart rate variability.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th></th>
<th>Medroxyprogesterone acetate</th>
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<th>MPA effect</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Stage 2</td>
<td>Slow wave sleep</td>
<td>REM sleep</td>
<td>Stage 2</td>
<td>Slow wave sleep</td>
</tr>
<tr>
<td>Mean interbeat interval (ms)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory insuff.</td>
<td>860 (599;1066)</td>
<td>866 (742;1055)</td>
<td>861 (729;985)</td>
<td>998 (946;1050)</td>
<td>880 (705;1126)</td>
</tr>
<tr>
<td>Controls</td>
<td>996 (945;1183)</td>
<td>993 (899;1105)</td>
<td>949 (796;1040)</td>
<td>&lt;0.001</td>
<td>922 (777;996)</td>
</tr>
<tr>
<td>Group effect</td>
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<td></td>
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<tr>
<td>SDNN (ms)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory insuff.</td>
<td>27 (5;119)</td>
<td>21 (10;90)</td>
<td>28 (14;87)</td>
<td>36 (5;132)</td>
<td>35 (9;148)</td>
</tr>
<tr>
<td>Controls</td>
<td>42 (29;151)</td>
<td>35 (14;161)</td>
<td>42 (26;139)</td>
<td>0.007</td>
<td>37 (23;62)</td>
</tr>
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<td>Group effect</td>
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<td>RMSSD</td>
<td></td>
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<tr>
<td>Respiratory insuff.</td>
<td>26 (4;140)</td>
<td>32 (7;89)</td>
<td>16 (5;138)</td>
<td>35 (4;152)</td>
<td>29 (8;184)</td>
</tr>
<tr>
<td>Controls</td>
<td>48 (27;249)</td>
<td>38 (13;276)</td>
<td>25 (13;231)</td>
<td>0.020</td>
<td>31 (11;51)</td>
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<tr>
<td>Group effect</td>
<td></td>
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<td>CVS</td>
<td></td>
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<tr>
<td>Respiratory insuff.</td>
<td>3.1 (0.7;16.4)</td>
<td>3.2 (0.8;12.0)</td>
<td>1.7 (0.7;18.9)</td>
<td>3.4 (0.7;20.2)</td>
<td>3.2 (1.1;24.0)</td>
</tr>
<tr>
<td>Controls</td>
<td>4.0 (2.7;23.0)</td>
<td>3.4 (1.5;27.2)</td>
<td>3.2 (1.5;23.8)</td>
<td>3.7 (1.6;6.6)</td>
<td>3.4 (1.4;5.5)</td>
</tr>
<tr>
<td>Group effect</td>
<td></td>
<td></td>
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<tr>
<td>pNN50(%)</td>
<td></td>
<td></td>
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<tr>
<td>Respiratory insuff.</td>
<td>2 (0;48)</td>
<td>1 (0;59)</td>
<td>0 (0;28)</td>
<td>11 (0;45)</td>
<td>8 (0;52)</td>
</tr>
<tr>
<td>Controls</td>
<td>32 (2;57)</td>
<td>20 (0;61)</td>
<td>1 (0;40)</td>
<td>12 (0;39)</td>
<td>10 (0;38)</td>
</tr>
<tr>
<td>Group effect</td>
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Significances in italics indicate difference in MPA effect between groups. Sleep stages are pooled together. SDNN = standard deviation of the interbeat interval, RMSSD = root mean square of successive interbeat interval differences, CVS = coefficient of variance for RMSSD, pNN50 = percentage of successive interbeat intervals with more than 50 ms difference in duration, respiratory insuff. = respiratory insufficiency, REM sleep = rapid eye movement sleep, MPA = medroxyprogesterone acetate.
improvement of cardiac autonomic regulation as measured with HRV, because it has been shown that overall and cardiovascular mortality risks are reduced with increasing HRV.\(^2,3\)

MPA increased heart rate in the control group, which is supported by a previous study on the effects of combined HRT in healthy women.\(^12\) In contrast, however, although natural progesterone changes autonomic cardiac control, the mean heart rate and blood pressure are not affected by the menstrual cycle.\(^25\)

We found that in postmenopausal women MPA increased respiratory rate and decreased end-tidal \(PCO_2\). This is in line with a previous study, where combined oestrogen and progesterone administration decreased end-tidal \(PCO_2\), and increased carotid body neural response and hypoxic ventilatory responsiveness in cats.\(^26\) MPA enhances minute ventilation, as well as the hypoxic and hypercapnic ventilatory responses.\(^10\) The chronic \(CO_2\) retention in chronic obstructive pulmonary disease is corrected by MPA.\(^11\) In this study, MPA increased arterial oxyhaemoglobin saturation in those patients with the most severe nocturnal hypoaxaemia. MPA administration is known to increase arterial oxygen partial pressure (\(PO_2\)),\(^27\) which is reflected in an increase of arterial oxyhaemoglobin saturation. However, on the oxygen–haemoglobin dissociation curve, even fairly strong increases in arterial \(PO_2\) do not markedly change an arterial oxyhaemoglobin saturation that is above 90%. A \(PO_2\) increase of a similar magnitude significantly increases an arterial oxyhaemoglobin saturation that is below 85%. This may explain why the median arterial oxyhaemoglobin saturation did not change even though lower saturations were clearly improved.

In rats, hypoxia only influences HRV when combined with changes in \(PCO_2\), whereas isocapnic hypoxia does not change HRV.\(^28\) Furthermore, supplemental oxygen does not decrease the number of nocturnal hypoxic arousals in chronic obstructive pulmonary disease.\(^29\) In a subgroup of patients with chronic obstructive pulmonary disease, long-term oxygen therapy increases arterial \(CO_2\) partial pressure.\(^30\) The increase in end-tidal \(PCO_2\) and an increase in circulating \(CO_2\) have been shown to centrally modulate sympathetic preganglionic output.\(^31,32\) Based on these findings, we hypothesise that hypercapnia, but not hypoxia, is responsible for the changes in HRV. The effect of MPA on HRV in patients with respiratory insufficiency may also be affected by improved respiration.

Most of our patients with respiratory insufficiency regularly used inhaled and systemic corticosteroids and sympathomimetics, medications that undoubtedly affect autonomic nervous function. However, oral prednisone, which decreases plasma noradrenaline concentrations and muscle

![Figure 2](image-url)
nerve sympathetic activity, has no effect on heart rate and blood pressure in a group of 15 healthy volunteers (12 men and three women). Moreover, an acute inhalation of nebulisator doses of salbutamol does not have an effect on HRV in patients with chronic obstructive pulmonary disease, although in healthy subjects $\beta_2$ agonists decrease HRV and increase heart rate. Therefore, the medication used by our patients with respiratory insufficiency is unlikely to explain the group differences. While the medication remained constant throughout the study, it is not likely to have influenced the MPA effect.

In both respiratory insufficiency patients and controls, the effect of sleep stage on HRV was similar to that observed in our previous study in healthy postmenopausal women. This suggests that women with severe hypoxaemic disorders, although their cardiac autonomic control is otherwise compromised, have normal sleep stage-related patterns of HRV change.

We conclude that high-dose oral MPA has an impact on cardiac autonomic regulation. The MPA effect on HRV seems to depend on the severity of the underlying respiratory condition. In subjects with chronic respiratory insufficiency, the HRV changes suggest a beneficial effect of MPA on cardiovascular regulation. In asymptomatic women, although hypoxaemic during sleep, no negative impact of high-dose MPA on HRV can be detected.

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References


