Effect of menopause on the chemical control of breathing and its relationship with acid-base status

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1School of Kinesiology and Health Studies, 2Department of Community Health and Epidemiology, and 3Department of Medicine, Queen’s University, and 4Department of Physiology, Queen’s University, and 5School of Kinesiology and Health Studies, 6Department of Medicine, Queen’s University and Kingston General Hospital, Kingston, Ontario, Canada

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Preston ME, Jensen D, Janssen I, Fisher JT. Effect of menopause on the chemical control of breathing and its relationship with acid-base status. Am J Physiol Regul Integr Comp Physiol 296: R722–R727, 2009. First published December 17, 2008; doi:10.1152/ajpregu.90865.2008. — This study examined the role of alterations in the chemoreflex control of breathing, acid-base balance, and their interaction in postmenopausal ventilatory adaptations. A modified iso-oxic hyperoxic and hypoxic CO2-rebreathing procedure was employed to evaluate central and peripheral chemoreflex drives to breathe, respectively, in 15 healthy postmenopausal and 20 premenopausal women of similar age. Arterialized venous blood samples were collected at rest for the estimation of arterial Pco2 (PaCO2) and H+ concentration ([H+]1), plasma strong ion difference ([SID]) and total weak acid ([A]tot) concentrations, and serum progesterone ([P4]) and 17β-estradiol ([E2]) concentrations. In post-compared with premenopausal women, PaCO2, [SID], and the central chemoreflex ventilatory recruitment threshold for Pco2 (VRTCO2) were higher, whereas [P4] and [E2] were lower (all P < 0.05), with no significant change in central or peripheral chemoreflex sensitivity, peripheral chemoreflex VRTCO2, and [A]tot. The acidifying effect of an increased PaCO2 was offset by the alkalizing effect of an increased [SID], such that [H+] was preserved in post-compared with premenopausal women. PaCO2 correlated positively with the central chemoreflex VRTCO2 (r = 0.67, P < 0.01), which in turn correlated positively with [SID] (r = 0.53, P < 0.01) within the pooled data. In conclusion, the relative alveolar hypoventilation and attendant arterial hypercapnia in healthy post-compared with premenopausal women could be explained, in part, by the interaction of 1) reduced central, but not peripheral, chemoreflex VRTCO2, 2) increased [SID], and 3) reduced circulating female sex steroid hormone concentrations.

The increasing menopausal demographic in North America raises several important questions regarding the underlying physiological status of this population of women, including the impact of menopause on ventilatory control, acid-base balance, and their complex interaction. Increases in circulating concentrations of progesterone ([P4]) and estrogen ([E2]), such as occurs in human pregnancy and across the menstrual cycle, are characterized by consistent increases in resting ventilation (Ve), with attendant reductions in arterial Pco2 (PaCO2) (25, 28, 40, 48, 51, 54). Hormone replacement therapy studies reported that medroxyprogesterone acetate (a synthetic progestin), administered alone and in combination with E2, consistently reduced resting PaCO2 by ~6 mmHg in postmenopausal women (39, 43–46). Withdrawal of these hormones would therefore be expected to decrease resting Ve, thereby increasing PaCO2 in otherwise healthy postmenopausal women. Although the underlying mechanisms of these ventilatory adaptations remain speculative, the combined facilitatory effects of P4 and E2 on central and/or peripheral chemoreflex drives to breathe may be involved (3, 4, 11, 26, 28, 29, 31, 48).

Classical concepts of H+ homeostasis and their link to the chemoreflex control of breathing have evolved from strict Henderson-Hasselbalch interpretations to embrace the physicochemical approach described by Stewart (52, 53). Stewart’s approach identifies PaCO2, total weak acid concentration ([A]tot), and the strong ion difference ([SID]), i.e., the concentration difference of strongly dissociated positive and negative ions in solution) as the three independent variables involved in the regulation of H+ concentration ([H+]1) in biological fluids (23, 24, 33). In keeping with the experimental results of Jennings (23, 24) and Oren et al. (37, 38), Duffin (12) recently demonstrated that the alkalizing effects of an increased plasma and cerebrospinal fluid (CSF) [SID] alters the relationship between the measured (Pco2) and presumptive ([H+]1) stimuli to the peripheral and central chemoreceptors, such that arterial and CSF [H+] are reduced at any given PaCO2 and CSF Pco2, respectively (see Figs. 7 and 14 in Ref. 52). Consequently, the chemoreflex ventilatory recruitment threshold for Pco2 (VRTCO2) is increased, which in turn decreases resting Ve, with attendant increases in PaCO2. Although evidence suggests that plasma [SID] may be higher in post- than in premenopausal women (18–21), this is the first study to examine the role of acid-base balance in the chemoreflex control of breathing in healthy postmenopausal women.

In the present study, we postulated that reductions in circulating female sex hormone concentrations, alone or in combination with the alkalizing effect of an increased plasma [SID], contribute significantly to the relative hypoventilation and attendant arterial hypercapnia observed after the onset of menopause. We hypothesized that these outcomes would be mechanistically linked to reductions in central and peripheral chemoreflex drives to breathe. Our primary objective, therefore, was to determine whether resting PaCO2 was increased in healthy post-compared with premenopausal women of similar age and to identify whether this difference was associated with reductions in [P4], [E2], and central and/or peripheral chemoreflex drives to breathe. Our second objective was to determine whether increases in plasma [SID] contribute to a higher resting PaCO2 in postmenopausal women by increasing the chemoreflex VRTCO2.
METHODS

Subjects. Subjects included healthy, nonsmoking, physically active premenopausal (n = 20) and postmenopausal (n = 15) women between 42 and 54 yr of age. Subjects were excluded if they were perimenopausal (i.e., sporadic and irregular menstrual cycles); they were taking any form of medication, including oral contraceptives and hormone replacement therapy, within 6 mo of participation; they had a history of cardiopulmonary, metabolic, hematologic, and/or eating disorder(s); they were born at and/or had recently returned from a trip at high altitude; or their menopause was surgically induced. Detailed overnight polysomnography was not performed to rule out the presence of sleep-disordered breathing. Nevertheless, no individual in either group presented with daytime somnolence or a clinical diagnosis of sleep-disordered breathing, and available evidence suggests that obstructive sleep apnea has no independent effect on the central and peripheral chemoreflex response to hypercapnia and hypoxia, respectively (8, 50). Before participation, subjects completed the revised Physical Activity Readiness Questionnaire (www.csep.ca/forms.asp) and obtained medical clearance from their primary healthcare provider. Premenopausal women were eumenorrheic and reported no menstrual cycle irregularities or disturbances before and throughout study participation. Postmenopausal status was defined as the absence of menses for ≥1 yr before study participation (56).

Study design. This was a controlled, cross-sectional study for which written informed consent was obtained from all subjects. The study protocol and consent form were approved by the Queen’s University and Affiliated Teaching Hospitals Health Sciences Human Research Ethics Board in accordance with the Declaration of Helsinki. Subjects were tested on two occasions, separated by ≥3 days, and abstained from caffeine, alcohol, and strenuous exercise on each test day. No restrictions were placed on menstrual cycle phase for the first laboratory visit. During the second laboratory visit, however, premenopausal women were tested in the follicular phase of their menstrual cycle (confirmed by serum [P4] and [E2] measurements), which was determined using the 1st day of their last menstrual cycle and the average length of at least three previous menstrual cycles (9).

During the first laboratory visit, basic physical characteristics, including body height and mass, blood pressure, and routine spirometry, were recorded, and each subject performed a modified iso-oxic hypercapnic CO2-rebreathing procedure (see below) for familiarization purposes. During the second laboratory visit, subjects completed a modified iso-oxic hypercapnic and hypoxic CO2-rebreathing procedure (see below). These tests were separated by ≥45 min, and the order was randomized between subjects. After a rest period of ≥90 min, breath-by-breath measurements of Ve, tidal volume (VT), breathing frequency (fr), estimated alveolar ventilation (V̇A), O2 consumption (V̇O2), and CO2 production (V̇CO2) were collected during 10 min of quiet resting breathing in accordance with previously published methods (17). During the 6th min of this rest period, arterialized venous blood samples for the estimation of arterial blood gas and acid-base status, serum [P4] and [E2], and plasma osmolality concentrations were collected and analyzed in accordance with previously published methods from our laboratory (25, 34, 51).

Modified rebreathing procedure. A modified version of the rebreathing procedure of Read (40a), which included 5 min of prior hypercapnic breath by breath maintenance of a constant iso-oxic hyperoxic breathing procedure of Read (40a), which included 5 min of prior hypercapnic breath by breath maintenance of a constant iso-oxic hyperoxic breathing procedure (13). This sub-V̇RTC02 ventilation value (V̇EB) was taken as an estimate of nonchemoreflex drives to breathe (14, 49) and 2) measurement, rather than extrapolation, of the chemoreflex V̇RTC02.

After hyperventilation, subjects expired to residual volume and then were switched from breathing room air to a rebreathing bag containing a hyperoxic-hypercapnic (24% O2-6% CO2-balance N2) or a hypoxic-hypercapnic (4.5% O2-6% CO2-balance N2) gas mixture. Rebreathing began with three to five deep breaths causing rapid equilibration of the ṖCO2 in the rebreathing bag, lungs, and arterial blood with ṖCO2 of the mixed venous blood, thereby minimizing the central (or brain tissue) ṖCO2-ṖaCO2 difference. This equilibration ensures that J changes in ṖETCO2 accurately reflect changes in arterial and central ṖCO2/[H+] and 2) hypercapnia- and hypoxia-induced increases in cerebral blood flow have little or no effect on central ṖCO2/[H+] and, therefore, determination of the slope (sensitivity) of the ventilatory response to CO2. Equilibration was verified by the observance of a plateau in ṖETCO2, and was a prerequisite for continuing the test. After equilibration, subjects were instructed to relax and breathe as they felt the need.

During rebreathing, ṖETCO2 increased progressively from hypo- to hypercapnia while iso-oxia was maintained at a hyperoxic (150 mmHg) or hypoxic (50 mmHg) ṖETCO2 by a computer-controlled flow of 100% O2 to the rebreathing bag. Arterial O2 saturation and heart rate were monitored continuously with an ear oximeter (OXI, Radiometer Copenhagen, Copenhagen, Denmark). Rebreathing was terminated when Ve exceeded 100 l/min, ṖETCO2 exceeded 60 mmHg, and/or the subject experienced discomfort.

During rebreathing, subjects were comfortably seated, wore nose clips, and breathed through a mouthpiece connected to a three-way T-shaped wide-bore manual directional valve (model 2100a, Hans Rudolph, Kansas City, MO) that permitted switching from room air to the rebreathing bag. Subjects rebreathed from a 10-liter plastic bag connected to a low-resistance bidirectional volume turbine (model VMM-2A, Alpha Technologies, Laguna Niguel, CA). ṖETCO2 and ṖETO2 were measured at the mouth via a respiratory mass spectrometer (model MGA 1100, Perkin Elmer) at a sampling flow rate of 64 ml/min. The rebreathing system was calibrated with precision analyzed gases of known concentrations and a 3-liter volume syringe before each test. A 12-bit analog-to-digital converter (DAQCard-6062E, National Instruments, Austin, TX) digitized the analog output signals from all monitoring devices for computer analysis using custom-written software (Labview 6.1, National Instruments). The data acquisition software calculated Ve, V̇E, Ve, ṖETCO2, and ṖETO2 on a breath-by-breath basis.

Data from rebreathing experiments were imported into an analysis program designed specifically for this purpose (Labview 6.1). Measured volumes were corrected to body temperature and pressure, saturated with water vapor. Data from the first equilibration at the start of rebreathing and any aberrant points (e.g., sighs, swallows) were excluded from further analysis. Breath-by-breath ṖETCO2 was then plotted against time and fitted with a least-squares regression line, the slope of which depends on V̇O2. The equation for this line provided a predicted value of ṖETCO2 vs. time, thereby minimizing interbreath variability. Thereafter, Ve was plotted against the predicted ṖETCO2 and fitted with a model made up of the sum of two segments separated by a single breakpoint (13). All segments were fitted through an iterative process whereby the breakpoint and other parameters were varied to obtain an optimal fit to the observed data by minimizing the sum of squares (Levenberg-Marquardt algorithm). The ventilatory response to hyperoxic and hypoxic hypocapnia below the V̇RTC02, respectively, was modeled as an exponential decay to a final value (13). This sub-V̇RTC02 ventilation value (V̇EB) was taken as an estimate of nonchemoreflex drives to breathe (14, 49). The ṖETCO2 at which Ve increased with progressive increases in ṖETCO2 was taken as the V̇RTC02. Finally, the slope of the linear relation between Ve and ṖETCO2 above the V̇RTC02 was taken as an estimate of chemoreflex sensitivity (VeS). We assumed that the V̇RTC02 and VeS measured under iso-oxic hyperoxic conditions originated from the central che-
morefex alone, inasmuch as hyperoxia attenuates the peripheral chemoreflex response to CO₂ (10), whereas the same measurements recorded under iso-oxy hypoxic conditions represented the sum of central and peripheral chemoreflex stimulation.

**Statistical analysis.** A conventional power calculation formula for the comparison of two independent populations of unequal sizes was used to estimate the minimum sample size with assumption of 80% power and α = 0.05. The outcome variables considered most important were PaCO₂, [SID], hyperoxic and hypoxic VT/CO₂, and V̇E/S, respectively. Standard deviations from Slatkovska et al. (51) were used to calculate sample sizes capable of detecting between-group differences of 2 mmHg and 2.5 meq/l for PaCO₂ and [SID], respectively. Standard deviations from Jensen et al. (27) were used to calculate sample sizes capable of detecting between-group differences of 2.0 l·min⁻¹·mmHg⁻¹ and 2.5 mmHg for hyperoxic and hypoxic V̇E/S and VT/CO₂, respectively. The resulting estimates were 11, 14, 15, and 14 subjects per group for PaCO₂, [SID], and hyperoxic/hypoxic V̇E/S and VT/CO₂, respectively.

Independent t-tests were used to identify between-group differences for the general physical characteristics, resting cardiorespiratory variables, and blood biochemistry parameters. A general linear model for repeated measures was used to identify significant associations between PaCO₂ and each of V̇E/B, V̇E/S, VT/CO₂, and [SID]. Serum [P₄] and [E₂] were not used in the correlational analysis because of inherent between-group differences in their circulating concentrations. P < 0.05 was used for all analyses. Values are means ± SD. Statistical analyses were performed using SPSS 14.0 software (SPSS, Chicago, Illinois).

**RESULTS**

The mean age of the pre- and postmenopausal groups differed significantly by ~7 yr (Table 1). Group vs. age comparisons demonstrated that menopausal status served as a better predictor of the between-group differences in measured variables (i.e., age did not improve predictability of any of the variables after we accounted for menopausal status), which suggests that the between-group differences presented here reflect the effect(s) of menopausal status, rather than age.

Subject characteristics are presented in Table 1. Pre- and postmenopausal groups were well matched for important physical characteristics other than age. Postmenopausal women had not experienced a menstrual period for ≥1 yr (1.8 ± 1.2 yr, range 1–5 yr) before testing. Menopause-related changes in

<table>
<thead>
<tr>
<th>Variable</th>
<th>Premenopausal (n = 20)</th>
<th>Postmenopausal (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>45.3 ± 3.2</td>
<td>52.1 ± 1.8*</td>
</tr>
<tr>
<td>Height, cm</td>
<td>165.4 ± 5.9</td>
<td>162.2 ± 8.0</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>68.2 ± 14.3</td>
<td>63.4 ± 8.5</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.8 ± 4.6</td>
<td>24.5 ± 2.9</td>
</tr>
<tr>
<td>PEFR, l/s (%predicted)</td>
<td>5.4 ± 0.8 (86 ± 12)</td>
<td>5.4 ± 0.7 (91 ± 15)</td>
</tr>
<tr>
<td>FVC, liters (%predicted)</td>
<td>3.2 ± 0.4 (98 ± 10)</td>
<td>3.1 ± 0.3 (98 ± 15)</td>
</tr>
<tr>
<td>FEV₁, liters (%predicted)</td>
<td>2.6 ± 0.3 (97 ± 11)</td>
<td>2.5 ± 0.3 (103 ± 16)</td>
</tr>
<tr>
<td>PEFR/FVC, % (%predicted)</td>
<td>83.0 ± 7.1 (108 ± 9)</td>
<td>79.6 ± 9.6 (106 ± 12)</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>118.5 ± 10.6</td>
<td>118.3 ± 8.0</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>72.1 ± 8.0</td>
<td>75.3 ± 6.6</td>
</tr>
</tbody>
</table>

Values are means ± SD; n, number of subjects. BMI, body mass index; PEFR, peak expiratory flow rate; FVC, forced vital capacity; FEV₁, forced expired volume in 1 s; SBP, systolic blood pressure; DBP, diastolic blood pressure. *Significantly different from premenopausal (P < 0.01).

**Table 2. Resting cardiorespiratory and blood biochemistry**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Premenopausal (n = 20)</th>
<th>Postmenopausal (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minute ventilation, l/min</td>
<td>8.0 ± 1.7</td>
<td>8.5 ± 4.5</td>
</tr>
<tr>
<td>V̇E, ml</td>
<td>638.9 ± 228.0</td>
<td>498.7 ± 105.8*</td>
</tr>
<tr>
<td>Estimated alveolar ventilation, l/min</td>
<td>13.5 ± 3.2</td>
<td>17.0 ± 4.9*</td>
</tr>
<tr>
<td>Metabolic rate of O₂ consumption, ml/min</td>
<td>6.2 ± 1.4</td>
<td>5.3 ± 0.7*</td>
</tr>
<tr>
<td>Metabolic rate of CO₂ production, ml/min</td>
<td>295.1 ± 39.7</td>
<td>298.1 ± 71.6</td>
</tr>
<tr>
<td>Ventilatory equivalent for O₂</td>
<td>32.4 ± 6.2</td>
<td>29.6 ± 6.1</td>
</tr>
<tr>
<td>Ventilatory equivalent for CO₂</td>
<td>38.4 ± 2.0</td>
<td>38.7 ± 2.6</td>
</tr>
<tr>
<td>Arterial PCO₂, mmHg</td>
<td>37.7 ± 3.9</td>
<td>41.2 ± 4.3*</td>
</tr>
<tr>
<td>[SID], meq/l</td>
<td>37.0 ± 1.4</td>
<td>38.7 ± 1.9†</td>
</tr>
<tr>
<td>[HCO₃⁻], mmol/l</td>
<td>23.7 ± 1.4</td>
<td>25.5 ± 1.5†</td>
</tr>
<tr>
<td>[A₉¹, meq/l</td>
<td>16.4 ± 0.6</td>
<td>16.5 ± 0.7</td>
</tr>
<tr>
<td>Osmolality, mosmol/kgH₂O</td>
<td>280.2 ± 3.6</td>
<td>283.9 ± 3.2‡</td>
</tr>
<tr>
<td>[P₄], nmol/l</td>
<td>6.7 ± 9.7</td>
<td>11.1 ± 0.8*</td>
</tr>
<tr>
<td>[E₂], pmol/l</td>
<td>306.1 ± 255.6</td>
<td>67.3 ± 49.1‡</td>
</tr>
</tbody>
</table>

Values are means ± SD; n, number of subjects. V̇E, tidal volume; fB, breathing frequency; [H⁺], arteralized venous H⁺ concentration; [SID], strong ion difference concentration; [A₉¹], total weak acid concentration; [HCO₃⁻], bicarbonate concentration; [P₄], serum progesterone concentration; [E₂], 17β-estradiol concentration. Significantly different from premenopausal: *P < 0.05; †P < 0.01.

resting cardiorespiratory parameters are shown in Table 2: V̇E, V̇O₂, and V̇CO₂ were not significantly different between groups; however, V̇A/O₂ and V̇T were consistently lower, whereas fB was consistently higher, in the post- than in the premenopausal women.

**Blood biochemistry.** Blood biochemistry measurements were not available for one of the premenopausal subjects. Resting PaCO₂, [SID], HCO₃⁻ concentration ([HCO₃⁻]), and plasma osmolality were consistently higher, whereas [E₂] and [P₄] were significantly lower, in the post- than in the premenopausal women (Table 2). Increases in PaCO₂ and [SID], in the setting of an unchanged [A₉¹], offset each other, such that [H⁺] did not differ between groups (Table 2).

**Hyperoxic and hypoxic CO₂ rebreathing responses.** Despite prior familiarization, three premenopausal women and one postmenopausal woman were unwilling to complete both rebreathing trials because of the discomfort/anxiety associated with performing this test. Therefore, complete rebreathing data

![Fig. 1. Central ventilatory chemoreflex response to hyperoxic hypercapnia in a representative pre- and postmenopausal subject. PṙCO₂, end-tidal PCO₂.](http://ajpregu.physiology.org/DownloadedFrom/a)
were available from 17 pre- and 14 postmenopausal women. Pre- and postmenopausal groups remained well matched for important physical characteristics but still differed with respect to age. Menopause-related changes in the ventilatory response to iso-oxic hyperoxic and hypoxic CO₂ rebreathing are presented in Fig. 1 and Table 3. Sub-VRTCO₂ ventilation was not significantly different between groups. Hyperoxic and hypoxic VRTCO₂ values were consistently higher (by 3.5 and 2.9 mmHg, respectively) in post- than in premenopausal women (Table 3). The magnitudes of these differences were quantitatively similar, indicating that the central, but not peripheral, chemoreflex VRTCO₂ increased from pre- to postmenopause. Hyperoxic and hypoxic V̇ES values tended to be reduced in post- compared with premenopause; however, these differences did not reach statistical significance (Table 3). The magnitude of these differences, although not statistically significant, were quantitatively similar in post- and premenopause (1.1 and 1.0 l·min⁻¹·mmHg⁻¹, respectively), suggesting that central, but not peripheral, chemoreflex sensitivity tended to be reduced in the former. V̇ES and V̇ES were higher, and VRTCO₂ was lower, under hypoxic than hyperoxic rebreathing conditions, independent of menopausal status.

**Correlations.** Significant relationships were observed between resting PaCO₂ and each of the following independent variables within the pooled data: hyperoxic \( r = -0.36, P < 0.05 \) and hypoxic \( r = -0.36, P < 0.05 \) \( V̇ES \) and hyperoxic \( r = 0.67, P < 0.01 \); Fig. 2) and hypoxic \( r = 0.54, P < 0.01 \) VRTCO₂. Plasma [SID] correlated positively with hyperoxic \( r = 0.53, P < 0.01 \) (Fig. 2) and hypoxic \( r = 0.46, P < 0.01 \) VRTCO₂ within the pooled data.

**DISCUSSION**

The results of our study provide several novel observations regarding the control of ventilation and its relationship with acid-base balance in healthy post- compared with premenopausal women of similar age. 1) Postmenopausal women possessed a reduced central, but not peripheral, chemoreflex drive to breathe, as evidenced by an increased VRTCO₂ and modestly reduced V̇ES response to iso-oxic hyperoxic hypercapnia. 2) The reduced central chemoreflex drive to breathe was associated with decreased circulating female sex steroid hormone concentrations and resulted in a modest alveolar hypoventilation with attendant arterial hypercapnia. 3) Postmenopausal women experienced acid-base adaptations characterized by increased plasma [SID] that compensated for the arterial hypercapnia and maintained \([H^+]\) in healthy post-compared with premenopausal women.

Effect of menopause on chemoreflex control of breathing. Resting PaCO₂ was consistently higher by an average of 3.5 mmHg in postmenopausal women. This difference could be explained, in large part, by a 3.5-mmHg increase in the central chemoreflex VRTCO₂ in post- vs. premenopausal women (Figs. 1 and 2). These observations suggest that reductions in central chemoreflex drives to breathe are responsible for the increased PaCO₂ in healthy postmenopausal women.

Mechanisms of increased resting PaCO₂ in postmenopausal women. Several hormone replacement therapy studies have demonstrated that medroxyprogesterone acetate administered alone, and in combination with estrogen, consistently reduces resting PaCO₂ in J) postmenopausal women with (45, 46) and without respiratory insufficiency (39) and 2) healthy men (6, 22, 36, 47, 58) and ovariohysterectomized women (7, 28, 41, 48). It is unclear whether female sex hormones alter resting PaCO₂ by acting directly on central chemoreceptor cells and/or indirectly on neuromodulatory structures involved in the processing, integration, and translation of central chemoreceptor activity into pulmonary ventilation (1–4, 11, 26, 42). Regardless of the cellular mechanism(s) involved, our data support the
view that reductions in circulating [P₄] and [E₂] are responsible, at least in part, for the increased resting PaCO₂ in healthy postmenopausal women via their direct/indirect effects on central chemoreflex drives to breathe.

Using Stewart’s physicochemical principles (52, 53), Duffin (12) recently described the role of acid-base balance in the chemoreflex control of breathing. He concluded that increases in [SID] would decrease [H⁺] (the presumptive stimulus to the chemoreceptors) at any given PCO₂ (the measured stimulus to the chemoreceptors), thereby increasing the chemoreflex VRTC0₂, which in turn increases resting PaCO₂. Our findings in postmenopausal women strongly support this hypothesis, since we found that 1) the acidifying effects of an increased PaCO₂, were effectively offset by the alkalizing effects of an increased [SID], such that arterial [H⁺] was unchanged compared with that in premenopausal women; 2) the central chemoreflex VRTC0₂ was consistently higher in post- than in premenopausal women; and 3) PaCO₂ correlated positively with the central chemoreflex VRTC0₂ (Fig. 2), which in turn correlated positively with plasma [SID] (Fig. 2). Collectively, these findings support the novel hypothesis that increases in plasma [SID] contributed to the increased PaCO₂ in healthy post-compared with premenopausal women, by increasing the central chemoreflex VRTC0₂, secondary to its effects on the PaCO₂-[H⁺] relationship.

The cross-sectional design of our study does not permit detailed examination of the time course of ventilatory, renal, and humoral adaptations during the pre- to peri- to postmenopausal transition. Therefore, we do not know whether 1) the acidifying effect of progressive increases in resting PaCO₂ (secondary to the above-mentioned direct/indirect effects of reduced [P₄] and [E₂] on central chemoreflex drives to breathe) initiate a compensatory (renal) increase in plasma [SID], so as to maintain arterial [H⁺] constant, or 2) the alkalizing effect of progressive increases in [SID] (secondary to the direct effects of reduced [P₄] and [E₂] on the activity of the renin-angiotensin-aldosterone system (35)) initiates a compensatory decrease in alveolar ventilation via reductions in central chemoreceptor efferent activity, which in turn increases PaCO₂, so as to regulate arterial [H⁺] at a constant level.

Methodological considerations. A constraint of our study is the cross-sectional design, in addition to the modest, but anticipated, between-group difference in age. Menopause is an age-related biological phenomenon; therefore, we chose not to match our groups for age, since this would introduce a bias due to the preselection of women who were pre- or postmenopausal beyond and before the age normally reported, respectively. We attempted to ameliorate the effects of our cross-sectional design by studying well-matched groups of healthy pre- and postmenopausal women that were “relatively” similar in age. Furthermore, we recruited a sample size from which we could detect physiologically meaningful between-group differences in our primary outcome variables based on a priori power calculations. Finally, we utilized statistical methods to ensure that that the between-group differences reported here reflected primarily differences in menopausal status as opposed to age. Therefore, the results of our study suggest that controlled, longitudinal studies of the ventilatory, hormonal, and acid-base adaptations during the pre- to peri- to postmenopausal transition would provide significant insight into the underlying causes of age-related ventilatory adaptations.

Perspectives and Significance

To the best of our knowledge, this is the first study to systematically examine the role of central and peripheral chemoreflex drives to breathe, acid-base balance, and their interaction in the ventilatory adaptations associated with menopause. The novel results of this study indicated that central, but not peripheral, chemoreflex drives to breathe were attenuated in postmenopausal women (as evidenced by a reduced hyperoxic VRTC0₂ and that this change was associated with decreased concentrations of female sex steroid hormones and complex acid-base interactions, resulting in an increased resting PaCO₂. A methodological strength of our study was the comparison with premenopausal women of similar age.

Research examining the impact of menopause on ventilatory control is timely given the rapidly growing postmenopausal demographic in North America and the increased need to understand the physiological milieu on which age- and sex-related respiratory disorders are imposed. The results of the present study, therefore, have potentially important clinical and physiological implications with respect to our understanding of 1) the increased prevalence of sleep-disordered breathing following the onset of menopause (5, 57) and 2) the effects of sex (27, 32, 55) and hormone replacement therapy (39, 43, 45) on ventilatory control and acid-base balance at rest and during exercise in health and disease.

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REFERENCES