Age and renal prostaglandin inhibition during exercise and heat stress

W. B. FARQUHAR AND W. L. KENNEY

Noll Physiological Research Center, Pennsylvania State University, University Park, Pennsylvania 16802-6900

Farquhar, W. B., and W. L. Kenney. Age and renal prostaglandin inhibition during exercise and heat stress. J. Appl. Physiol. 86(6): 1936–1943, 1999.—Aging is associated with a number of physiological changes that may cause the kidney to rely to a greater extent on vasodilatory PGs for normal functioning. Acute exercise has been shown to cause renal vasoconstriction that may be partially buffered by vasodilatory PGs. To determine the relative importance of renal PGs during exercise in older adults, we compared the renal effects of the PG inhibitor ibuprofen (1.2 g/day for 3 days) vs. a placebo control in a cohort of eight younger (24 ± 2 yr) and eight older (64 ± 2 yr) women during treadmill exercise (~57% maximal oxygen consumption) in the heat (36°C). This over-the-counter dose of ibuprofen reduced renal PG (i.e., PGE₂) excretion by 47% (P < 0.05). Acute exercise in the heat caused dramatic decreases in glomerular filtration rate, renal blood flow, and sodium excretion in both age groups. PG inhibition was associated with greater decreases in urine production and free water clearance (P < 0.05). There were no drug-related declines in glomerular filtration rate or renal blood flow. We conclude that PG inhibition has only modest effects on renal function during exercise. Also, the lack of hemodynamic changes with PG inhibition indicates that healthy well-hydrated older women are not in a renal PG-dependent state.

WE PREVIOUSLY REPORTED (9) that an over-the-counter (OTC) dose of the nonsteroidal anti-inflammatory drug (NSAID) ibuprofen (Ibu) depresses glomerular filtration rate (GFR) more than does a placebo (Pl) in a cohort of younger men and women during dehydrating exercise in the heat. Under these conditions, Ibu caused a 41 ± 2% decrease in GFR compared with a 31 ± 3% decrease in the Pl trial. Walker et al. (29) found that the NSAID indomethacin lowered renal blood flow (RBF), concluding that with sustained exercise indomethacin can compromise renal function and potentiate the risk of developing acute renal failure. There have also been anecdotal case reports linking NSAID use to acute renal failure during prolonged exercise (20, 27). Although effects are negligible under nonstressed conditions (35), NSAIDs such as Ibu and indomethacin have been shown to inhibit vasodilatory renal PGs, such as PGE₂ and PGI₂, up to 60% and to depress renal function during what have been termed renal PG-dependent states (21). Frequently cited examples of PG-dependent states include hypovolemia, salt depletion, chronic heart failure, and hepatic cirrhosis (7, 16, 28, 37), all of which are characterized by enhanced sympathetic outflow, increased circulating catecholamine concentrations, and increased angiotensin II. PGs are thought to partially modulate renal function during these high vasoconstrictor states.

Many of the physiological changes that accompany aging might be predicted to increase the kidney’s reliance on PGs, leading some to classify aging as a PG-dependent state. For example, aging is associated with decreases in GFR, RBF, and blood flow per unit mass of the kidney (8, 14, 18). In addition, the progressive loss of functioning nephrons in the older kidney increases the fluid and solute load per nephron (8). This decreases the functional reserve of the kidney and, assuming that this loss is analogous to the experimental reductions in renal mass in animals (i.e., two-thirds nephrectomy), may enhance the ability of NSAIDs to facilitate vasoconstriction (31). Also, at rest arterial plasma norepinephrine spillover rates are elevated in the older adult (26), possibly leading to enhanced renal vasoconstriction. However, the limited data do not support a direct link between NSAID use and renal dysfunction in healthy older adults during resting conditions. Asokan et al. (2) administered 75 mg/day of indomethacin for 1 wk to 10 healthy older adults (mean age 71 yr, 7 women and 3 men). No changes in GFR and renal plasma flow (RPF) were reported in the indomethacin trial compared with the Pl control. Allred et al. (1) reviewed patient data from 27 women (mean age 84 yr) taking NSAIDs for at least 3 wk and compared them with 27 control subjects (mean age 85 yr). There were no differences in serum urea, creatinine, or potassium concentrations between the two groups. Therefore, at least under resting conditions in the older adult, NSAIDs do not appear to impair renal function.

The purpose of the present study was to determine whether NSAIDs depress renal function during exercise and heat stress in the healthy older adult. Heat stress combined with exercise is associated with greater decreases in RBF and GFR compared with exercise in normothermic conditions. Exercise is associated with increased renal sympathetic activity, increased circulating catecholamine concentrations, and increased renin-angiotensin II, which, as stated above, may be predicted to evoke a renal PG-dependent state. The aforementioned physiological changes seen with aging would likely augment the deleterious effects of PG inhibition with NSAIDs. To determine whether the relative importance of PGs in the control of renal function changes with advancing age, comparisons between older and younger subjects were made. We
Methods

Subjects. Sixteen healthy women (8 younger and 8 older; see Table 1 for subject characteristics) gave their oral and written consent to participate in this institutionally approved study. The older women were postmenopausal and not taking hormone-replacement therapy. Men were not included in the study because urinary PGE2 excretion only reflects urinary PGE2 production in women [men produce PGs from nonrenal sources such as the seminal vesicles (33)]. Subject screening was performed under the auspices of the Noll Laboratory General Clinical Research Center and consisted of a physical examination by a physician, resting electrocardiogram (ECG), body composition assessment using skinfold calipers (15), and a maximal graded exercise test on a motor-driven treadmill where the ECG was monitored for the older subjects only. Maximal oxygen consumption (V\text{O}_2\text{max}) was measured during exercise in the older kidney, (i.e., a greater decrease in renal function during PG inhibition with Ibu in the older subjects).

Table 1. Subject characteristics

<table>
<thead>
<tr>
<th></th>
<th>Younger</th>
<th>Older</th>
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<tbody>
<tr>
<td>Age, yr</td>
<td>24 ± 2</td>
<td>64 ± 2*</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>60.6 ± 4.9</td>
<td>59.4 ± 2.3</td>
</tr>
<tr>
<td>Height, cm</td>
<td>164.7 ± 2.2</td>
<td>159.5 ± 1.3</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>22.8 ± 3</td>
<td>32.9 ± 3.0*</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.64 ± 0.07</td>
<td>1.61 ± 0.03</td>
</tr>
<tr>
<td>V\text{O}_2\text{max}, ml·kg\textsuperscript{-1}·min\textsuperscript{-1}</td>
<td>41.2 ± 2.2</td>
<td>29.1 ± 1.7*</td>
</tr>
<tr>
<td>24-h Creatinine clearance, ml·min\textsuperscript{-1}·1.73 m²\textsuperscript{-1}</td>
<td>105 ± 4</td>
<td>79 ± 8*</td>
</tr>
</tbody>
</table>

Values are means ± SE. V\text{O}_2\text{max}, maximal O₂ consumption. *Different from younger, P < 0.05.
where $[P]_{PAH}$, $[U]_{PAH}$, $[P]_{inulin}$, and $[U]_{inulin}$ are the plasma and urine concentrations of PAH and inulin, respectively (mg/dl); $V$ is the urine flow rate in milliliters per minute; and Hct is the hematocrit. An extraction ratio of 0.90 was used for PAH when calculating RPF, which has been previously shown to not change during moderate-intensity exercise (4, 13). PAH and inulin were assayed using standard spectrophotometric techniques (5, 30). A continuous-flow autoanalyzer (Technicon Instruments, Tarrytown, NY) and a spectrophotometer (Spectronic 21D-Milton Roy, Rochester, NY) were utilized for the PAH and inulin assays, respectively. Hemodynamic variables were all standardized to a body surface area of 1.73 m². Filtration fraction (%) was calculated as (GFR/RPF) \times 100.

All blood samples were collected into EDTA-containing, heparin-containing, and serum-separator vacutainers (Becton Dickinson, Franklin Lakes, N J) and immediately placed on ice. Hemoglobin concentration and Hct were determined by using a Coulter hematology analyzer (Coulter MicroDiff 16, Coulter, Miami, FL). All samples were subsequently centrifuged, and the plasma was frozen. Urine volume was measured by using a graduated cylinder with an aliquot frozen in 15-ml polypropylene Falcon tubes (Becton Dickinson, Franklin Lakes, N J).

Rectal temperature (T_re) was used as an index of core temperature. A rectal thermistor (YSI series 400) was inserted by the subjects 10 cm past the anal sphincter. A temperature-controlled water bath (verified with a mercury thermometer) was used to calibrate the thermistor. T_re was recorded before, every 5 min during, and every 10 min after exercise. Heart rate was recorded before, every five 5 during, and every 10 min after exercise by using a Polar monitor in the younger subjects and a single-lead ECG (CM5, Marquette Electronics) in the older subjects.

Serum and urine osmolality were determined by using the freezing-point depression technique with an Advanced Digi-Matic Osmometer model 3D2 (Advanced Instruments, Norwood, MA). Free water clearance ($CL_{H2O}$) was calculated by using the following formula

$$CL_{H2O} = V - \frac{(U_{osm} \cdot V)}{P_{osm}}$$

where $U_{osm}$ and $P_{osm}$ are equal to urine and plasma osmolality, respectively (mosmol/kgH₂O). Percent change in plasma volume (resting in the seated position vs. exercise in the standing position) was calculated by using the changes in the hemoglobin concentration and Hct (6). Because posture was not the same during the resting and exercise periods, it is not possible to determine the independent effects of exercise on plasma volume. Creatinine clearance for the 24-h urine sample was determined by using standard spectrophotometric techniques with a continuous-flow autoanalyzer (Technicon Instruments, Tarrytown, NY; Jaffe method) and used to estimate GFR on the day preceding the experimental trial.

Serum sodium and potassium concentrations were measured by using an automatic flame photometer (model IL943TM, Instrumentation Laboratories, Lexington, MA). PGE₂ concentration in the urine (34) was measured by using a commercially available radioimmunoassay [¹²⁵I] kit (DuPont Medical Products, Boston, MA). All excretion rates were calculated using the following formula: volume (l) \cdot time (min) \cdot concentration (meq/l or pg/ml).

Statistical analysis. All data are reported as means ± SE. A repeated-measures ANOVA (SAS statistical software) was used to determine age, drug, and time effects ($2 \times 2 \times 5$; there were actually 6 clearance periods, but only 1 resting clearance period was used for analysis to simplify the model). A P value of 0.05 was considered significant. Differences in physical characteristics between younger and older subjects were determined by using a two-tailed independent t-test. Because time was not a factor for the variables determined from the 24-h urine sample as well as changes in plasma volume and PGE₂ excretion, a two-tailed dependent t-test was used to evaluate drug effects. Post hoc comparisons were done by using the Scheffe’s method.

RESULTS

Subject characteristics are presented in Table 1. As expected, baseline 24-h creatinine clearance was significantly lower in the older subjects. Older subjects also had a higher percent body fat and a lower $V_{O2max}$ ($P < 0.05$).

Urine production from the 24-h urine samples collected on the day before the experimental trial (1 day after the start of Ibu or Pl) was consistently lower in the Ibu trial (compared with the Pl trial) for both the younger and older subjects (in 14 of 16 subjects): 1.1 ± 0.2 and 1.3 ± 0.2 ml/min in the older and 0.9 ± 0.1 and 1.2 ± 0.2 ml/min in the younger for the Ibu and Pl trials, respectively ($P < 0.05$). Sodium excretion was 58 ± 5 and 79 ± 9 meq/min in the older ($P > 0.05$, Pl vs. Ibu) and 91 ± 9 and 103 ± 13 meq/min in the younger ($P > 0.05$, Pl vs. Ibu) during the Ibu and Pl trials, respectively (no statistical differences). Creatinine clearance from the 24-h urine sample was 96 ± 6 and 103 ± 8 ml·min⁻¹·1.73 m⁻² in the younger subjects and 71 ± 8 and 62 ± 10 ml·min⁻¹·1.73 m⁻² in the older subjects during the Ibu and Pl trials, respectively, representing a significant age ($P < 0.05$) effect but no drug effect. Renal PGE₂ production was significantly lower in the Ibu compared with the Pl trial ($P < 0.05$; see Fig. 1).

Resting measures during the infusion on the experimental day indicated that older subjects excreted less sodium (Fig. 2) and had a significantly lower $V_{O2max}$ (Fig. 3) and RBF (Fig. 4; $P < 0.05$). Urine production (Fig. 5) was also lower in the older subjects ($P < 0.05$). Sodium excretion was significantly lower in the older subjects ($P < 0.05$; see Fig. 2). Sodium and potassium concentrations were measured by using an automatic flame photometer (model IL943TM, Instrumentation Laboratories, Lexington, MA). PGE₂ concentration in the urine (34) was measured by using a commercially available radioimmunoassay [¹²⁵I] kit (DuPont Medical Products, Boston, MA). All excretion rates were calculated using the following formula: volume (l) \cdot time (min) \cdot concentration (meq/l or pg/ml).
Fig. 2. Sodium excretion in younger (A; n = 8) and older (B; n = 8) subjects during resting conditions, exercise (2 clearance periods), and recovery (also 2 clearance periods). PL, placebo; IBU, ibuprofen. Values are means ± SE. Repeated-measures ANOVA indicated significant age (††P < 0.007) and time (*P < 0.0001) effects as well as significant interactions between age and drug and age and time (P < 0.02) and age and time (P = 0.0001).

Fig. 3. Glomerular filtration rate (GFR) in older (n = 8) and younger (n = 8) subjects during resting conditions, exercise (2 clearance periods), and recovery (also 2 clearance periods). Values are means ± SE. Repeated-measures ANOVA indicated significant age (††P, 0.02) and time (*P, 0.0001) effects as well as a significant age and drug interaction (P < 0.05).

Fig. 4. Renal blood flow (RBF) in older (n = 8) and younger (n = 8) subjects during resting conditions, exercise (2 clearance periods), and recovery (also 2 clearance periods). Values are means ± SE. Repeated-measures ANOVA indicated significant age (††P < 0.006) and time (*P < 0.0001) effects as well as a significant age and time interaction (P < 0.0001).
and free water clearance (Fig. 6) were similar in the older and younger subjects. Filtration fraction averaged 28% in the younger subjects and 29% in the older subjects (with no drug effect).

Exercise in the heat caused dramatic decreases in GFR, RBF, urine production, sodium excretion, and free water clearance in both age groups ($P < 0.0001$). Ibu depressed urine production ($P < 0.03$ vs. PI) and free water clearance ($P < 0.02$ vs. PI) in both age groups. No drug effects were seen for RBF, GFR, and sodium excretion in either age group. PGE$_2$ excretion during exercise was $83.3 \pm 18.5$ and $53.9 \pm 17.9$ pg/min in the PI and Ibu trials, respectively. Although these excretion values tended to be lower in the Ibu trial, they did not reach significance ($P > 0.10$). Preexercise rectal temperatures in the younger subjects were $37.19 \pm 0.09$ and $37.28 \pm 0.04^\circ C$ and increased during exercise to $38.74 \pm 0.08$ and $38.81 \pm 0.10^\circ C$ in the Ibu and PI trials, respectively, with no drug effect. The older subjects' preexercise rectal temperatures were $36.91 \pm 0.07$ and $36.94 \pm 0.12^\circ C$ (Ibu and PI trials, respectively) and increased to $38.50 \pm 0.16$ and $38.45 \pm 0.13^\circ C$ during exercise. Although no drug effects were noted for either age group, the older group's preexercise and exercise temperatures were significantly lower than those of the younger subjects. Preexercise heart rates were not affected by drug or age and averaged 76 beats/min. Peak exercise heart rates were $164 \pm 3$ and $158 \pm 4$ beats/min in the younger subjects and $132 \pm 8$ and $133 \pm 8$ beats/min in the older subjects in the Ibu and PI trials, respectively, representing a similar percentage of maximal heart rate in the older and younger subjects. Oxygen consumption was $24.6 \pm 2.0$ and $25.0 \pm 1.8$ ml·kg$^{-1}$·min$^{-1}$ in the younger subjects and $15.8 \pm 1.6$ and $15.8 \pm 1.3$ ml·kg$^{-1}$·min$^{-1}$ in the older subjects during the Ibu and PI trials, respectively. This represented $\sim 55$ and $60\% V\dot{O}_{2\max}$ for the older and younger subjects, respectively. Percent change in plasma volume was $-13 \pm 2$ and $-10 \pm 2\%$ in the younger and $-2 \pm 2$ and $-8 \pm 2\%$ in the older subjects for the Ibu and PI trials, respectively. The only drug effect was a smaller change in plasma volume in the older subjects during the Ibu trial ($P < 0.03$).

All measured and calculated variables started to return to baseline during the 1-h recovery period. Ibu appeared to have longer lasting effects in the older subjects, demonstrated by the depressed urine production and free water clearance in the second recovery clearance period.
DISCUSSION

This purpose of this study was to investigate the renal effects of PG inhibition with OTC Ibu during exercise in older adults. Because NSAID use among younger and especially older adults is prevalent (12), it was thought that this type of investigation would yield usable information for these populations. Another aim was to understand the importance of renal PGs in the regulation of the kidney during exercise and to determine whether this changed with advancing age.

Renal PGs can be important determinants of renal function during certain physiological and pathological conditions; therefore, inhibiting PGs with NSAIDs can depress renal function. By using exercise and heat stress as physiological perturbations, we predicted that PG inhibition would have a selectively greater effect in the older adults due to an age-related decrease in renal function. The major finding of this study was that OTC Ibu inhibited renal PG production and caused significant decreases in urine production and free water clearance. Contrary to what we anticipated, Ibu did not depress GFR or RBF in either age group. The lack of a significant Ibu-induced change in GFR was demonstrated under resting conditions via 24-h creatinine clearance the day preceding exercise and with inulin clearance on the experimental day. Although there are no comparative data in older adults, Zambraski et al. (36) found that aspirin use was associated with minor changes in free water clearance but no changes in creatinine clearance after treadmill exercise in nonhydrated (no food or drink for 10 h before exercise) younger men. These results also differ from our earlier work (9), where a slightly lower GFR was found with Ibu in younger subjects during exercise. However, the previous subjects were dehydrated before the exercise bout; therefore the kidney was probably stressed to greater extent in the prior report (9).

Ibu-induced reductions in urine production and free water clearance may have been mediated through the actions of arginine vasopressin (AVP). Previous studies (3, 10) report that PGs inhibit the intrarenal actions of AVP on the collecting tubule within the renal medulla. Therefore, when renal PG production declines, there is a release of inhibition of AVP, which results in enhanced water reabsorption. Because this probably occurs without any appreciable change in circulating AVP, we did not attempt to measure plasma AVP concentration.

There was a significant (P < 0.02) age and drug interaction in sodium excretion. Sodium excretion was slightly higher at each of the five time points (rest, exercise, and recovery; see Fig. 2) in the younger subjects during the Ibu trial but lower at four of the five time points in the older adults. Sodium excretion the day before exercise (24-h urine sample) was 12 (P > 0.05) and 27%
Similarly, in a related exercise study, Poortmans et al. (22) noted that renal PGs normally function to inhibit Na\textsuperscript{+}-K\textsuperscript{+}-ATPase activity in the tubular cells, which augments sodium transport across the basolateral membrane. These data imply that renal PGs can significantly effect sodium handling associated with PG inhibition. The renal effects of higher anti-inflammatory doses of Ibu and the effects of Ibu during dehydrating exercise in older adults are not known. In conclusion, older women do not appear to be in PG-dependent state under basal or exercise conditions.

Renal PGE\textsubscript{2} excretion has been shown to be a valid index of renal PGE\textsubscript{2} production in female dogs (34) and has therefore been used as a surrogate measure of renal PGE\textsubscript{2} production in humans (33). The ability of OTC to inhibit renal PGE\textsubscript{2} excretion in the present study is shown in Fig. 1. During exercise, the response was particularly variable, especially in the younger subjects. These variable responses were also noted by Zambraski et al. (33) in a cohort of younger women during exercise. Nevertheless, in the present study, Ibu was associated with a 36% reduction (P > 0.10) in PGE\textsubscript{2} excretion. Similarly, in a related exercise study, Poortmans et al. (23) found a 75% reduction in PG 6-keto-F\textsubscript{1}\textsubscript{2} excretion after 2 min of strenuous exercise in a group of 10 healthy men taking Ibu (compared with a PI). However, because Ibu and other NSAIDs do not completely abolish renal PG synthesis, the remaining PGs may still contribute to the control of renal function.

These data do not support the notion that older adults are in a constant PG-dependent state under basal or exercise conditions. PG-dependent states are usually characterized by significant declines in renal hemodynamic function and profound sodium retention with the administration of a PG inhibitor, neither of which occurred within this cohort of older adults. The exercise protocol utilized caused dramatic reductions in renal function in both age groups. In the PI trial, GFR and RBF decreased ~30–50%. Similarly, urine production decreased 60–70% in both age groups. Declines in renal function during exercise are intensity dependent (11) and generally in the range of 30–60% (32). The slightly greater reductions in urine production in the present study can be attributed to the added burden of heat stress and the fact that all subjects were very well hydrated, as evidenced by the high urine flow rates preceding exercise (~5.0 ml/min). The subjects were all well hydrated to avoid dehydration and to ensure adequate urine volumes for accurate analysis. Nevertheless, the renal responses were consistent with previous data. For example, Poortmans (22) noted that urine flow decreased ~80% in hyperhydrated (urine flow 7–17 ml/min) subjects after short but exhaustive exercise.

There was a highly significant (P < 0.0001) age and time interaction for RBF. It appears as though the return of RBF to baseline in the recovery was sluggish in the older subjects. A similar response was noted by Kenney and Zappe (18) in their investigation of younger and older men. At present, no conclusive mechanistic explanation can be provided, other than stating that PG inhibition does not alter this response. Overall, few studies (24) have investigated the renal hemodynamic responses to acute exercise in older adults, especially in postmenopausal women. These data are therefore important because they show that older women not taking hormone-replacement therapy respond in a similar fashion as do younger women and men.

In summary, OTC Ibu use in well-hydrated older subjects does not result in declines in renal hemodynamic function during acute exercise. There are, however, significant changes in the renal handling of water associated with PG inhibition. There are also age-related changes in renal sodium handling associated with PG inhibition. The renal effects of higher anti-inflammatory doses of Ibu and the effects of Ibu during dehydrating exercise in older adults are not known. In conclusion, older women do not appear to be in PG-dependent state under basal or exercise conditions.

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Address for reprint requests: W. B. Farquhar, HRCA Research and Training Institute, Laboratory for Cardiovascular Research, 1200 Centre St., Boston, MA 02131 (E-mail: farquhar@mail.hrca.harvard.edu).

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REFERENCES