Cardiopulmonary Baroreflex in NaCl-Induced Hypertension in Borderline Hypertensive Rats

Abstract Borderline hypertensive rats fed an 8% NaCl diet develop increased arterial pressure in association with increased cardiopulmonary baroreflex sensitivity compared with rats fed a 1% NaCl diet. We performed experiments to localize the site of sensitization within the cardiopulmonary baroreflex. To determine whether decreased cardiopulmonary baroreflex sensitivity, as seen in other models of NaCl-induced hypertension, develops later in the course of the disease, we studied an older backcross population derived from borderline hypertensive rats and Wistar-Kyoto rats. Anesthetized borderline hypertensive rats fed 1% and 8% NaCl diets were volume-loaded while right atrial pressure, afferent vagal nerve activity, and renal sympathetic nerve activity were recorded. In 28- to 30-week-old backcross rats fed an 8% NaCl diet, renal sympathetic nerve activity, natriuresis, and diuresis were measured before and during volume loading. Renal sympathetic nerve activity was analyzed with the sympathetic peak detection algorithm. Increases in afferent vagal nerve activity and renal sympathomimetic response were similar in borderline hypertensive rats on either diet during a right atrial pressure rise of 25 to 30 mm Hg. Increases in afferent vagal nerve activity and renal sympathomimetic response were similar in borderline hypertensive rats on either diet during a right atrial pressure rise of 25 to 30 mm Hg. In backcross rats, correlations between arterial pressure and renal sympathomimetic response, natriuresis, and diuresis were not found. During volume loading, the peak height of synchronized renal sympathetic nerve discharge decreased while their frequency increased. Afferent vagal nerve activity during acute increases in intravascular volume was not involved in the development or maintenance of NaCl-induced hypertension in borderline hypertensive rats. Renal sympathetic nerve activity decreases because of a reduction in the number of active renal sympathetic nerve fibers (Hypertension. 1997;30[part 2]:464-470.)

Key Words • sympathetic nervous system • vagus nerve • rats, inbred strains • sodium chloride, dietary • baroreflex

In rats, reflex adjustments in the level of RSNA during changes in intravascular volume are mediated by cardiopulmonary baroreceptors located mainly in the heart. Their afferents travel via vagal C-fibers to the brain stem. Since alterations in RSNA have a major influence on renal sodium handling, the role of cardiopulmonary baroreflex regulation of RSNA can be significant in the pathogenesis of various experimental forms of NaCl-induced hypertension. In SHR, NaCl-induced hypertension was found to be associated with blunted renal sympathomimetic response and reduced natriuresis and diuresis in response to intravenous volume loading. In Dahl NaCl-resistant rats, intravenous volume loading induced a more sustained inhibition of RSNA than in Dahl NaCl-sensitive rats, whereas the renal excretory responses did not differ between these rat strains. DIIR, the F0 generation obtained from breeding female SHR and male WKY, responded to acute volume loading with increased natriuresis and diuresis and exaggerated inhibition of RSNA when fed an 8% but not a 1% NaCl diet. Renal denervation experiments showed that the exaggerated diuretic and natriuretic responses in BHR fed an 8% NaCl diet depended on intact renal innervation. Afferent vagal C-fiber stimulation in anesthetized BHR revealed a greater inhibition of RSNA in rats fed an 8% compared with rats fed a 1% NaCl diet for 12 weeks, suggesting that increased central cardiopulmonary baroreflex sensitivity might be involved in the exaggerated inhibition of RSNA in response to volume loading in BHR fed an 8% NaCl diet.

The relationship of enhanced renal sympathomimetic response during volume loading, accompanied by exaggerated natriuresis and diuresis, to NaCl-induced hypertension in BHR is unclear. One possibility is that BHR fed an 8% NaCl diet have a persistently elevated basal RSNA that decreases during volume expansion. This differs from normotensive rats, in which increased dietary NaCl intake decreases baseline RSNA and renal sodium excretion in response to volume loading. Another possibility could be the development of an increased sensitivity of cardiopulmonary baroreflex regulation of RSNA in BHR during the early period of exposure to an 8% NaCl diet, similar to that observed in Dahl NaCl-resistant rats. This might contribute to the relatively slow progression of NaCl-induced hypertension in BHR. After 6 weeks of an 8% NaCl diet, arterial pressure was not elevated in BHR, but after 12 weeks of an 8% NaCl diet (age, 16 weeks), arterial pressure was increased by 25 to 30 mm Hg compared with BHR fed a 1% NaCl diet.

The increased sensitivity of the central portion of the cardiopulmonary baroreflex observed in BHR fed an 8% NaCl diet did not completely account for the differences in overall cardiopulmonary baroreflex sensitivity observed in previous experiments. Therefore, we undertook an analysis of the entire cardiopulmonary baroreflex arc in BHR fed 1% and 8% NaCl diets; to obtain additional information concerning the afferent limb, we recorded AVNA. Since NaCl-induced hypertension in BHR progresses slowly, we sought to determine whether attenuated car-
diopulmonary baroreflex function is associated with hypertension in a BHR×WKY backcross population exposed to an 8% NaCl diet over a prolonged period. As the backcross population exhibits a wide range of MAP in response to this feeding regimen, this approach allowed the control of diet effects unrelated to NaCl-induced hypertension. In addition to the measurement of the mean integrated voltage of RSNA, RSNA was analyzed with the sympathetic peak detection algorithm [4-16]. This method facilitates comparison of sympathetic nerve activity between rats that is complicated when conventional voltage-averaging techniques are used because of the variation in nerve recording conditions between rats [18]. We tested the hypothesis that analysis of peak height and periodicity of synchronized renal sympathetic nerve discharges would reveal a correlation between RSNA and arterial pressure. Furthermore, we analyzed changes in the characteristics of synchronized RSNA in response to volume loading.

Methods

Rats

Female SHR (IBU-3 colony) and male WKY were purchased from Taconic Farms (Germantown, NY) and bred to obtain BHR. BHR were weaned at 4 weeks of age, housed two to three per cage, and randomly placed on a 1% NaCl diet (Teklad) or 8% NaCl diet (ICN Pharmaceuticals) with free access to tap water. BHR fed the 1% NaCl diet of either sex were bred with WKY to obtain the backcross population. Backcross rats were weaned at 4 weeks of age, housed two to three per cage, and fed the 8% NaCl diet. BHR were studied at 16 weeks of age, and the backcross population was studied between 28 and 30 weeks of age. Rats of both sexes were used because previous experiments did not reveal sex differences in terms of NaCl sensitivity [13,14]. All animal procedures were in accordance with the guidelines of the University of Iowa Animal Care and Use Committee.

Catheterization and Arterial Pressure Recording

Arterial and venous catheters (medical-grade Tygon tubing) were placed in the right femoral and ear vein with rats under methohexitol anesthesia (50 mg/kg IP) [Dorminal, Eli Lilly & Co] 1 (BHR) or 2 (backcross rats) days before the experiment. The catheters were exteriorized at the back of the neck, filled with 30% dextrose containing 500 IU/mL heparin, and plugged. Rats were kept in the laboratory until the day of study and housed singly with free access to food and water.

On the day of the experiment, arterial and venous catheters were connected with extension lines covered with spring wire. The rats remained unrestrained in their home cage. MAP was measured with a pressure transducer (Statham P23Db, Gould Instruments) coupled to a polygraph (model 7, Grass Instruments) HR was determined with a Grass 7P4 tachograph driven by the pulsatile arterial pressure wave form. Thirty minutes after the lines were connected, MAP and HR were recorded over a 15-minute period between 9 and 10 AM.

Cardiopulmonary Baroreflex Function in BHR

After MAP recording with rats in the conscious state, BHR were reanesthetized with methohexitol and placed on a heating pad to maintain body temperature between 37°C and 38°C. After insertion of a tracheal cannula via a midline neck incision, mechanical ventilation was instituted according to ventilation standards for small laboratory animals [20]. Anesthesia was maintained with alphadalone/salbutamolxone acetate (Staffan, Pitman Moore) (6 to 9 mg/kg per hour of total steroids), and pancuronium bromide (Genxia Pharmaceuticals) (1 mg/kg per hour) diluted in isotonic saline and infused at 0.05 mL/min. A PE-50 catheter was inserted into the inferior vena cava via the left femoral vein for administration of drugs and intravenous volume loading. To allow for free urine flow, a PE-190 catheter was inserted into the urinary bladder via a suprapubic incision.

Arterial baroreceptors were denervated according to the method of Kreger [21]. A medical-grade Tygon catheter was inserted into the right atrium via the right jugular vein and connected to a Statham P23Db pressure transducer positioned at the level of the rat's thorax for measurement of MRAP.

The left kidney was exposed via a left flank incision, and a renal nerve bundle was dissected in the angle between the abdominal aorta and renal artery. The nerve bundle was placed on a bipolar platinum electrode (Cooner Wire) for RSNA recording. When an optimal signal with clear pulse synchronous rhythm was obtained, the electrode was fixed to the nerve bundle with silicone cement (Wacker Sil-Gel 601, Wacker Chemie). The sheath from the left vagal nerve was removed, and an strand containing about 25% of the total fibers was placed on a bipolar platinum electrode, fixed with silicone cement, and cut centrally. The remaining fibers from the left vagus nerve remained intact. The afferent signal was evaluated by its respiratory synchronous discharge and its marked increase in response to 50 μg/kg 2-methyl-serotonin IV (Research Biochemicals Inc) [22].

The nerve signals were amplified ×20,000 and filtered (100 Hz low and 3000 Hz high) with Grass P511 band-pass amplifiers. The amplified and filtered signals were displayed on an oscilloscope (Tektronix 5113), an audio monitor (Grass model AM 8), and a polygraph (Grass model 7). Both AVNA and RSNA signals were full wave rectified and integrated with rectifying voltage integrators (Grass model 7P3) at time constants of 20 milliseconds.

After completion of surgery, arterial baroreceptor denervation was verified by complete absence of inhibition of RSNA in response to an increase in MAP of 40 mm Hg produced by 3 μg/kg phenylephrine IV (Elkins-Sinn, Inc.). Inhibition of RSNA due to afferent vagal nerve stimulation was again tested with 50 μg/kg 2-methyl-serotonin IV. This produced a transient increase in AVNA of 70% to 150% and a decrease in RSNA of 70% to 100%, accompanied by a fall in MAP and bradycardia.

Experimental Protocol

After a 45-minute postsurgical equilibration period, continuous measurements of MAP, HR, MRAP, AVNA, and RSNA were begun, and a 10-minute control period was made. After the control period, isotonic saline was infused rapidly (125 mL/kg per minute) to produce an increase in MRAP of 3 mm Hg within 100 to 120 seconds. Measurements were continued for another 5-minute period beyond the end of acute volume loading. The rats were then killed by an overdose of intravenous methohexitol AVNA and RSNA recorded 30 minutes after death were subtracted from the experimental values to correct for background noise. The hearts were excised and drained, and the wet weight of the left ventricle including the interventricular septum and of the remaining right ventricular wall were measured separately.

Conscious Backcross Rats

After MAP and HR were recorded with rats in the conscious state, rats were reanesthetized with 30 mg/kg meth-
Obexital IV Supplemental anesthetic was given as needed (10 mg/kg). Through a small suprapubic incision, the dome of the urinary bladder was exposed, and a short piece of PE-190 tubing was inserted into the bladder and sutured tightly to the bladder wall. Thereafter, the suprapubic incision was closed, with the catheter being exteriorized. A renal nerve recording electrode was implanted as described above, sutured to the trunk muscles, and exteriorized at the back. The flank incision was closed in layers.

**Experimental Protocol**

After completion of surgery, rats were placed in rat holders that permitted forward and backward movement but did not allow the rats to turn around. The bladder catheter exited the bottom of the rat holder, and arterial and venous catheters and renal nerve recording electrodes were connected to their extensions and an intravenous infusion of isotonic saline at 100 μL/kg per minute was started. After 5 to 6 hours so rats could recover from surgery, continuous recordings of MAP, HR, and RSNA were made during a 15-minute control urine collection period. This was followed by another 15-minute recording—urine collection period during which the rats were infused with a volume of isotonic saline equal to 5% of body weight. Thereafter, the rats were killed with an overdose of methohexitol, and the postmortem signal was recorded 30 minutes later as a correction for background noise signal. The kidneys and hearts were removed, drained, and weighed.

**Data Analysis**

Analogue data (MAP, HR, MRAP, AVNA, and RSNA) were recorded on videotape with a recording adapter (4000 PCM, Vetco) The tape-recorded data were sampled at 1 Hz with an analogue-to-digital converter (DT9801, Data Translation) using Labtech Notebook 4.2 software (Laboratory Technologies) and an IBM PC computer. For MAP and HR in conscious unrestrained rats, the average data for the 15-minute recording period are reported. For correlations in the backcross population, MAP data obtained under conscious unrestrained conditions were used.

**Cardiopulmonary Baroreflex Sensitivity**

Changes in AVNA and RSNA are expressed as percentage of the control period value. As a measure of the sensitivity of the total cardiopulmonary baroreflex (total gain), the slope of the regression of decreases in RSNA on increases in MRAP was calculated for each rat. As a measure of the sensitivity of the afferent limb (afferent gain), the slope of the regression of increases in AVNA on increases in MRAP was calculated for each rat. To evaluate the central sensitivity (central gain), we calculated the slope of the regression of decreases in RSNA on increases in AVNA for each rat.

**Inhibition of RSNA During Volume Expansion in Conscious Rats**

Mean RSNA during the 15-minute control and 15-minute volume expansion periods was expressed as integrated voltage over time (μV s) by calculating the area under the curve (mean voltage versus time) with Sigma Plot software (Jandel Scientific). RSNA inhibition during volume expansion is given as percent decrease from control. Urine volume was estimated gravimetrically, and urinary sodium concentration was determined with a flame photometer (IL 943, Instrumentation Laboratories). Anuric rats and diuretics were normalized to wet kidney weight.

**Sympathetic Peak Detection Algorithm**

For analysis of RSNA with the sympathetic peak detection algorithm in backcross rats, integrated RSNA was filtered at 33 Hz. This gives a pulsatile voltage signal where individual bursts in the neurogram are smoothed 14 RSNA, together with the pulsatile arterial pressure signal, was acquired off-line from video-tape at 200 Hz using LabView 3.11 (National Instruments). The characteristics of sympathetically recorded renal nerve discharges were analyzed with the Sympathetic Peak Detection Program Version 3 kindly provided by S.C. Malpas, Baker Medical Research Institute, Prahran, Australia. This program is based on the cluster analysis algorithm developed for investigation of pulsatile hormone release 14 23. Based on a 5×4 cluster configuration and a +1 t-statistic, the pulsatile voltage signal is scanned for significant increases and decreases in a small cluster of values (cluster width, 20 milliseconds) 14 14 After all significant increases (peaks) and decreases (nadir) of sympathetically recorded nerve activity are marked, the peaks (in microseconds) and peak-to-peak intervals (in milliseconds) are calculated. The peak height is a measure of the number of active nerve fibers, 15 and the peak interval is a measure of the periodicity (reciprocal of frequency) of the sympathetically recorded discharges.

To allow for comparisons of peak heights between rats, the 95th percentile of the absolute values obtained in each rat during control conditions was set equal to 100%, and all peak heights were expressed as a percentage of this value and are presented as relative peak heights.

**Statistical Analysis**

Statistical analysis was performed with two-way ANOVA for repeated measurements with sex and time as main factors, followed by Duncan’s multiple range test. Single comparisons between BHR fed 1% and 8% NaCl diets were performed with the unpaired t test. To examine correlations between MAP and renal sympathetic nerve discharge characteristics as well as relations between MAP and renal excretory responses to volume loading, we calculated Pearson correlation coefficients because data were normally distributed. The significance level was set at a value of P < 0.05. All data in text, tables, and figures are presented as mean ± SE.

**Results**

**Cardiopulmonary Baroreflex Sensitivity in BHR**

With rats in the conscious unrestrained state, MAP was 124±3 and 162±7 mm Hg in BHR fed 1% and 8% NaCl diet, respectively (P < 0.001, n=10 per group). Similarly, HR was 350±6 and 361±8 beats per minute (bpm), and body weight was 310±22 and 346±25 g, respectively. Left ventricular weight was significantly higher in BHR fed an 8% NaCl (0.23±0.01 g/100 g body weight) than in those fed a 1% NaCl (0.23±0.01 g/100 g body weight).

Before volume loading, MAP, with rats under anesthesia and after sinoaortic denervation, was 111±3 and 104±5 mm Hg in BHR fed 1% and 8% NaCl, respectively. HR was 435±5 and 427±8 bpm, and MRAP was -1±2.0 and -0.9±0.3 mm Hg, respectively. These measurements did not differ significantly between diet groups.

**BHR×WKY Backcross Rats**

Fifty-one (27 males and 24 females) BHR×WKY backcross rats were investigated. Body weight was 538±10 g in males and 312±6 g in females. In conscious unrestrained rats, MAP ranged between 109 and 183 mm Hg (mean value, 133±2). MAP was 135±3 mm Hg in males and 131±3 mm Hg in females. HR was significantly (P < 0.001) lower in males (319±7 bpm) than females (370±7 bpm). After rats had recovered from anesthesia...
and surgery, MAP in restrained rats during the control nerve recording and urine collection period (136 ± 2 mm Hg) rats did not differ significantly from that obtained in unrestrained rats.

Integrated RSNA during control conditions was 342 ± 19 μV·s for the entire population, with 315 ± 27 μV·s in males and 372 ± 25 μV·s in females. During volume loading, RSNA fell by 26 ± 2%. In males, the decrease in RSNA was 30 ± 20% versus 21 ± 2% in females (P < 0.01). MAP did not change during volume loading and did not differ significantly between male and female rats. In the control period, HR was lower in males than in females, and during volume loading, HR increased significantly in males and remained unchanged in females (Fig 2).

The degree of RSNA inhibition during volume loading did not correlate with MAP (r = 0.15). When analyzed by sex, correlation coefficients were −0.4 in males and 0.3 in females (Fig 3).

Natriuresis during the control period was 1.4 ± 0.1 μmol/min per gram kidney weight and increased to 12.5 ± 0.6 μmol/min during volume loading. Diuresis increased from 7.3 ± 0.6 mL/min per gram kidney weight during the control period to 97.6 ± 5.5 mL/min during volume loading. Natriuretic and diuretic responses did not differ between males and females. Neither the increase in natriuresis (r = −0.09) nor the increase in diuresis (r = 0.26) in response to volume loading correlated with MAP.

Control period data on the relative peak height and periodicity of synchronized renal nerve discharges were obtained from the last 300 seconds of the control period in each rat. Relative peak height was unmodally distributed (Figs 4A and 5A) and slightly lower in male than female rats (76 ± 1% versus 80 ± 1%, P < 0.05). The periodicity of synchronized discharges was 158 ± 2 milliseconds (mode 156 milliseconds), unmodally distributed, and similar in males and females (Figs 4B and 5B).

Previous experiments showed that the periodicity of synchronized RSNA is bimodally distributed (modes 130 and 210 milliseconds) in 8% NaCl BHR but not 1% NaCl BHR.16 During control conditions, the proportion of synchronized discharges with a periodicity greater than 200 milliseconds was 6% in the entire population, with no sex difference. There was no correlation between the proportion of periodicities greater than 200 milliseconds and MAP (r = −0.21). Mean relative peak height and mean periodicity of synchronized RSNA during control conditions did not correlate with MAP (r = −0.22 and −0.26, respectively).

The volume loading period was divided into six 150-second intervals for analysis of RSNA with the sympathetic peak detection algorithm (Table 2). The periodicity of synchronized RSNA decreased slightly during volume expansion. The decrease in RSNA during this intervention was due to a gradual reduction of peak height, which was more pronounced in males than females (Table 2; Figs 4A and 5A).

**Discussion**

Analysis of the cardiopulmonary baroreflex regulation of RSNA during rapid volume loading showed similar values for gain at all portions of the reflex arc in 1% and 8% NaCl BHR. These findings differ from those previously observed wherein greater decreases in RSNA were found in 8% NaCl BHR than in 1% NaCl BHR during volume loading.20 Furthermore, in those previous experiments, RSNA was more profoundly inhibited in both 1% and 8% NaCl BHR than in the present study. The increases in AVNA observed here are similar to those previously observed in normotensive Sprague-Dawley rats with the use of a similar experimental protocol.20

We chose a rapid-infusion protocol to limit the confounding effects of adaptation of cardiopulmonary baroreceptors to increased central venous and atrial pressures on AVNA. Resetting of low-pressure receptors in the superior vena cava has been demonstrated to occur within seconds in the rat.21 In the previous experiments, an amount of isotonic saline equal to 10% body weight was infused at a rate of 2 mL/min. This larger volume load administered over a longer time likely contributed to the more profound renal sympathoinhibition and may have represented a maximal or supraphysiological stimulus. Furthermore, instead of the previously used pentobarbital anesthesia, we chose alphadalone/alphaxalone anesthesia in the present study as circulatory function has been reported to be relatively well maintained in rats with this type of anesthetic.
esthesis. In addition, in the previous experiments, measurements were made only of the total or overall gain of cardiopulmonary baroreflex regulation of RSNA (ie, no afferent or central measurements).

Apart from these differences in anesthesia and experimental protocol, it seems clear from the present experiments that the afferent vagal limb of the cardiopulmonary baroreflex is not altered in 8% NaCl BHR compared with 1% NaCl BHR. Indirect support for an unaltered central portion of the cardiopulmonary baroreflex in 8% NaCl BHR comes from experiments carried out in the parental strains, in which afferent vagal C-fiber stimulation produced identical decreases in RSNA in WKY and SHR fed either 1% or 8% NaCl.

Under anesthesia and after completion of surgery, the difference in arterial pressure between 1% and 8% NaCl BHR noted in the conscious unrestrained state was no longer present. Acute arterial baroreceptor denervation activates and chronic NaCl loading inhibits the renin-angiotensin system. A reduced ability to activate the renin-angiotensin system after sinoaortic denervation in 8% NaCl BHR may have contributed to their lower MAP and the absence of a difference in MAP between 1% and 8% NaCl BHR after anesthesia and surgery.

To investigate whether prolonged exposure to a high NaCl diet would lead to the development of attenuated cardiopulmonary baroreflex function in association with progressive NaCl-induced hypertension, we studied an older (28 to 30 weeks) BHR×WKY backcross population fed 8% NaCl diet. MAP values were similar to those previously obtained in a BHR×WKY backcross population fed 8% NaCl for 12 weeks (age, 16 weeks), indicating no further progression of hypertension.

No correlations between MAP and the degree of renal sympato-inhibition, natriuresis, and diuresis in response to volume loading were found. This suggests, within the limitations of the number of rats studied, that the sensitivity of the cardiopulmonary baroreflex is unrelated to NaCl-induced hypertension in these rats. The periodicity of synchronized renal sympathetic nerve discharges was unimodally distributed, with only a small percentage greater than 200 milliseconds, resembling the pattern previously observed in WKY and BHR fed a 1% NaCl diet.

The degree of activation of renal sympathetic nerve fibers, in terms of numbers of active fibers and discharge frequency, was similar in backcross rats that were NaCl sen-
loading are most likely a result of the higher level of baseline sympathetic tone observed in females. Both the degree of sympathoinhibition and the likelihood of eliciting the Bambidge reflex during volume loading are reduced in the presence of increased baseline sympathetic neural activity.

In conclusion, attenuated renal sympathoinhibition in response to acute changes in intravascular volume is not involved in the development or maintenance of NaCl-induced hypertension in BHR. This contrasts with the situation in other models of NaCl-sensitive hypertension (e.g., the Dahl NaCl-sensitive rat) in which such an association is more clearly defined. This heterogeneity among rat models of NaCl-sensitive hypertension may have implications for further defining groups of individuals with borderline hypertension in whom varying degrees of NaCl sensitivity have been observed, i.e., into those with normal or abnormal renal sympathoinhibitory responses to acute volume loading.

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References

Table 2. Periodicity and Relative Peak Height of Synchronized Renal Sympathetic Neural Discharges During Control and Volume Loading in Backcross Rat Population

<table>
<thead>
<tr>
<th>Time, s</th>
<th>Periodicity, ms</th>
<th>Relative Peak Height, %</th>
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<tbody>
<tr>
<td>Male</td>
<td>Female</td>
<td>Male</td>
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<tr>
<td></td>
<td></td>
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</tr>
<tr>
<td>Control</td>
<td>159±3</td>
<td>158±3</td>
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<tr>
<td>0-150</td>
<td>151±4</td>
<td>153±3</td>
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<tr>
<td>150-300</td>
<td>148±4*</td>
<td>150±3*</td>
</tr>
<tr>
<td>450-600</td>
<td>150±4*</td>
<td>147±3*</td>
</tr>
<tr>
<td>600-750</td>
<td>150±3*</td>
<td>151±3*</td>
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</tbody>
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*P < 0.05, †P < 0.01 vs control, ††P < 0.05 vs males.
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