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Influence of renal denervation on blood pressure, sodium and water excretion in acute total obstructive apnea in rats

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Obstructive apnea (OA) can exert significant effects on renal sympathetic nerve activity (RSNA) and hemodynamic parameters. The present study focuses on the modulatory actions of RSNA on OA-induced sodium and water retention. The experiments were performed in renal-denervated rats (D; N = 9), which were compared to sham (S; N = 9) rats. Mean arterial pressure (MAP) and heart rate (HR) were assessed via an intrafemoral catheter. A catheter was inserted into the bladder for urinary measurements. OA episodes were induced via occlusion of the catheter inserted into the trachea. After an equilibration period, OA was induced for 20 s every 2 min and the changes in urine, MAP, HR and RSNA were recorded. Renal denervation did not alter resting MAP (S: 113 ± 4 *vs* D: 115 ± 4 mmHg) or HR (S: 340 ± 12 *vs* D: 368 ± 11 bpm). An OA episode resulted in decreased HR and MAP in both groups, but D rats showed exacerbated hypotension and attenuated bradycardia (S: -12 ± 1 mmHg and -16 ± 2 bpm *vs* D: -16 ± 1 mmHg and 9 ± 2 bpm; $P < 0.01$). The basal urinary parameters did not change during or after OA in S rats. However, D rats showed significant increases both during and after OA. Renal sympathetic nerve activity in S rats increased (34 ± 9%) during apnea episodes. These results indicate that renal denervation induces elevations of sodium content and urine volume and alters bradycardia and hypotension patterns during total OA in unconscious rats.

Key words: Obstructive apnea; Renal nerve; Natriuresis; Diuresis

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Introduction

Obstructive apnea (OA) events during sleep affect normal respiratory and cardiovascular functions (1,2). It is well established that apnea, especially OA, can exert a significant effect on renal sympathetic nerve activity (RSNA) (1,3), which is well known to play a pivotal role in cardiovascular reflexes, including the chemoreflex. This reflex may be activated when airway obstruction produces hypoxemia with oxyhemoglobin desaturation and a significant increase in $PaCO_2$ (3,4). The responses induced by chemoreflex activation are a rise in sympathetic nerve activity to the kidneys and other vascular beds, as well as an increase in the activity of vagal efferents on heart rate (HR) (5). In addition to the chemoreflex, other cardiovascular reflexes such as cardiopulmonary reflexes, and vasoactive hormones could be involved simultaneously in modifications of the kidney's excretory responses to OA, which include a reduced RSNA (6-11).

Although systemic hypoxia has pronounced effects on renal function through RSNA and/or vasoactive hormones, the nature of these effects is still unclear. For example, it has been reported that systemic hypoxia induces antidiuresis and antinatriuresis in anesthetized dogs (12) and fetal lambs (13), conscious rats (14) and rabbits (15), and human subjects (16). In contrast, diuresis and natriuresis have been reported in conscious dogs (17,18), in human subjects (19,20) and in anesthetized rats (21). The wide

variety of responses obtained in these studies can be attributed to differences in animal species, degree of hypoxia and state of anesthesia.

Therefore, the goal of the present study was to investigate the influence of RSNA on sodium and water excretion, and hemodynamic parameters during acute severe OA episodes in anesthetized rats, caused by ineffective inspiratory efforts against total occlusion of the upper airways.

Material and Methods

Experiments were performed on male Wistar rats (240-260 g) obtained from the animal care facilities of the Physiological Sciences Graduate Program of the University Federal of Espírito Santo. All procedures were conducted in accordance with the biomedical research guidelines for the care and use of laboratory animals as stated by the Federation of the Brazilian Societies of Experimental Biology (FeSBE). Rats were housed at recommended levels of temperature and humidity in a room with a 12-h light/dark cycle. Standard rat chow (Na^+ content 163 mEq/kg) and tap water were available *ad libitum*.

Renal denervation

Rats underwent bilateral renal denervation to eliminate the neural influence on renal excretory functions. Under sodium thiopental (50 mg/kg, *ip*) anesthesia, the left kidney was exposed via a flank incision. The adventitia surrounding the renal artery and vein was stripped and all visible renal nerves were cut under a surgical microscope (902DF Vasconcellos, São Paulo, SP, Brazil). The vessels were then treated with 95% alcohol containing 10% phenol. After renal denervation the flank incision was sutured and the procedure was repeated on the opposite side to denervate the right kidney. This surgical procedure was performed 15 days before the experimental protocol because it is known that it prevents the renal vasoconstrictor response to suprarenal lumbar sympathetic nerve stimulation and the antinatriuretic response to environmental stress and reduces renal tissue norepinephrine concentration to <5% of control for up to 15 days post-denervation (22,23).

After the acute experiments, the kidneys were removed under anesthesia and stored frozen until norepinephrine was measured. The success of the renal denervation procedure was confirmed by the reduction of the quantity of renal tissue norepinephrine to undetectable values in the renal-denervated (D) group compared to 382 ± 25 ng/g wet weight kidney in the sham-operated (S) group.

Experimental protocol

Fifteen days after denervation, on the day of the acute experiment, rats were anesthetized with urethane (1 g/kg, *ip*) and supplemented with the same anesthetic (*iv*) as needed. A polyethylene catheter was placed into the femoral artery and vein to measure mean arterial pressure (MAP) and HR and for infusion of isotonic saline, respectively. The catheter was tunneled subcutaneously to the back of the neck, flushed and plugged. For urinary measurements, a suprapubic incision was made and a polyethylene catheter was inserted and sutured into the bladder. This catheter was then exteriorized and secured by suturing it to the adjacent muscle and skin (23). Rats also underwent tracheal catheterization to induce severe OA episodes via total occlusion of the tracheal polyethylene catheter.

Renal excretory responses

Experiments comparing the natriuretic and diuretic responses induced by OA were performed under anesthesia. Initially, the animals received *iv* infusions of isotonic saline (55 µL/min) to enhance renal excretion of water and sodium (23). After an equilibration period for the stabilization of renal excretory responses the experimental protocol was performed and divided into 3 periods: control (C), apnea (A) and recovery (R). During the control period, two consecutive urine samples (C1 and C2) were collected (10 min each). During the apnea period, urine was collected during five intervals of 10 min (A1, A2, A3, A4, and A5). During each of these periods, five OA episodes were performed (20 s each), with 2-min intervals between them. After the OA episodes, urine was collected five consecutive times (10 min each) during the recovery period (R1, R2, R3, R4, and R5).

Urinary volume and sodium content, MAP and HR were determined at all time. For saline infusion, we used an infusion pump (model 600-900V; Harvard Apparatus, USA). The arterial catheter was connected to a pressure transducer, model P23Db (Statham, USA). Throughout the experiment MAP and HR were recorded continuously using a polygraph (Sensormedics Dynograf Recorder R 711, USA).

Nerve activity

In a separate experimental group, rats were anesthetized with urethane (1 g/kg, *ip*) and the left kidney was exposed via a retroperitoneal approach through a left flank incision. Using a dissecting microscope (M 900 DF, Vasconcellos, São Paulo, SP, Brazil), renal nerves were identified, isolated, and carefully dissected. The renal nerve branch was then placed on a bipolar platinum wire electrode and gelled with silicone. Extracellular action potentials were recorded with an AC amplifier (NL 104, NeuroLog,

Digitimer, England) connected to a high impedance headstage (NL 100). The amplified signals were filtered (NL 126), connected to an audio amplifier (NL 120) and displayed on an oscilloscope (Tektronix 2205, Brazil). The data were processed using a spike trigger (NL 200) and a ratemeter (NL 256) and displayed on a Biopac System (MP100). All data were digitized and stored (Digital MTE 46602 Tape Stream, USA) for further analysis (Acknowledge for Windows; Biopac Inc., USA) (24). After completion of surgical preparation and an equilibration period, RSNA was quantified by measuring the integrated RSNA during a 20-s apnea episode. MAP and HR were monitored simultaneously during the OA. We determined the background noise level of RSNA by observing the neural signal that remained after the animals were euthanized by an overdose of urethane and this value was subtracted from all control and experimental RSNA values.

Examination of excretory system function

The kidneys were removed, rinsed in physiological saline, decapsulated, blotted, and weighed for normalization of renal excretory data. Urine sodium concentration was measured by flame photometry with a model B Micronal apparatus (Brazil).

Statistical analysis

All data are reported as means ± SEM. Data for basal MAP, HR, sodium, and volume excretion and changes in these parameters evoked by OA were subjected to two-way analysis of variance (ANOVA), followed by the *post hoc* Tukey test for multiple comparisons. Statistical significance was set at $P < 0.05$.

Results

Hemodynamic parameters

Renal denervation did not change resting values of MAP (S: 113 ± 4 *vs* D: 115 ± 4 mmHg) or HR (S: 340 ± 12 *vs* D: 368 ± 11 bpm). However, OA induced significant changes in hemodynamic parameters including bradycardia and hypotension. Episodes of 20-s OA were repeated in S and D animals and also caused hypotension followed by bradycardia during the apnea periods (A1 to A5). In the D group, OA caused a stronger hypotension and minor bradycardia. The results of the first apnea period (A1) (S: -12 ± 1 mmHg and -16 ± 2 bpm *vs* D: -16 ± 1 mmHg and 9 ± 2 bpm; $P < 0.01$) did not change during the other apnea events (A2 to A5) in either group.

OA-induced changes in sodium and water excretion

Basal sodium and water excretion (C1 and C2) did not differ between groups. However, urinary sodium and volume excretion during the periods from A1 to A5 and at the beginning of the recovery phase differed between S and D rats (Table 1). S rats displayed the same excretory pattern during the basal phase (resting values) and during the experimental (from A1 to A5) and recovery phases (from R1 to R5). However, in D rats, these levels increased during A1 and remained elevated through the A5 period and during the recovery phase (Table 1).

Renal sympathetic nerve activity

RSNA increased by 34 ± 9% during the 20-s OA episodes in S rats (N = 7). After the apnea events, the RSNA values always returned to basal levels.

Discussion

In the present study, we reproduced conditions close to those observed during sleep apnea under total airway blockage via tracheal occlusion (25), even though in our experiments we observed only acute effects. We demonstrated that acute total obstructive apneic events resulted in an increase in diuresis and natriuresis in D rats. Basal values of urinary sodium excretion and urine volume were

Table 1. Sodium excretion and urinary volume in renal-denervated rats during the control (C1 and C2), experimental (A1 to A5), and recovery (R1 to R5) phases.

Experimental protocol	Sodium excretion ($\mu Eq \cdot min^{-1} \cdot g^{-1}$)		Urine volume ($\mu L \cdot min^{-1} \cdot g^{-1}$)	
	Sham	Renal-denervated	Sham	Renal-denervated
C1	2.1 ± 0.5	2.3 ± 0.6	16.9 ± 3.9	17.3 ± 3.0
C2	2.2 ± 1.3	2.5 ± 1.7	19.4 ± 5.1	18.1 ± 3.1
A1	4.2 ± 1.0	6.8 ± 0.5*+	24.2 ± 5.4	35.1 ± 4.3*+
A2	3.0 ± 1.0	5.8 ± 1.5*+	19.0 ± 4.2	27.8 ± 3.9*+
A3	3.4 ± 1.0	6.8 ± 1.2*+	20.7 ± 3.4	32.9 ± 4.3*+
A4	3.8 ± 0.9	6.4 ± 1.0*+	21.8 ± 2.2	30.8 ± 3.3*+
A5	3.9 ± 1.0	7.7 ± 1.2*+	22.5 ± 2.1	37.6 ± 2.2*+
R1	3.9 ± 1.0	7.3 ± 1.0*+	22.6 ± 5.8	36.8 ± 6.6*
R2	4.9 ± 1.6	6.6 ± 1.1*	23.3 ± 5.9	42.2 ± 9.2*
R3	4.0 ± 1.2	6.0 ± 1.0*	22.7 ± 7.9	34.5 ± 8.3*
R4	4.6 ± 1.6	6.6 ± 1.2*	24.8 ± 8.1	36.9 ± 7.7*
R5	4.6 ± 1.5	7.3 ± 1.4*	24.6 ± 7.7	39.8 ± 7.5*

Data are reported as means ± SEM for N = 9 animals per group. *$P < 0.05$ within group comparisons. +$P < 0.05$ *vs* sham rats (ANOVA followed by the *post hoc* Tukey test for multiple comparisons).

not affected by OA episodes in S animals, but these episodes elicited falls in HR and MAP. These hemodynamic and renal alterations occurred despite an increase in RSNA. However, in D rats, OA episodes caused a significant increase in renal parameters compared to basal values. Denervation induced a higher decrease in MAP and a smaller reduction in HR.

In the case of OA, sympathetic activity has been reported to be regulated by the chemoreflex. O'Donnell et al. (3) showed that OA led to a significant decrease in PaO_2 levels and an elevation of sympathetic activity, which was attenuated when the animals breathed 100% oxygen. As the peripheral chemoreflex is first stimulated by hypoxia (5), the airway obstruction in the rats was probably sufficient to activate the peripheral chemoreceptors and, as a consequence, to increase the RSNA (5,15). This could result in reduction of urinary sodium excretion and urine volume (7). Therefore, the rise in natriuresis and diuresis in renal-denervated animals during the OA sequences could directly result from renal denervation and from the consequent reduction of the chemoreflex influence on the renal excretory parameters (3,26).

We cannot exclude the possible participation of other cardiovascular reflexes in the modulation of renal excretory responses during OA, such as cardiopulmonary reflexes. This neural reflex could be similar to the Müller maneuver, as a result of the great inspiratory effort required to overcome airway obstruction. This obstruction would result in a negative intrathoracic pressure, which could cause low pressure levels and affect the intrathoracic hemodynamics (27), increasing the central venous pressure (28). These OA-induced hemodynamic alterations could stimulate the mechanical cardiopulmonary receptors as a consequence of the enhancement of the central venous pressure, probably resulting in a reduction of RSNA (24). Therefore, a balance between the chemoreflex and cardiopulmonary reflex during OA could result in the maintenance of urinary excretion at basal values, as observed in this study in S rats. Our data show that renal nerve denervation is a critical factor in modifying diuresis during severe OA via tracheal occlusion in anesthetized rats.

In this study, the OA periods caused decreases in MAP and HR when compared to basal values (i.e., before the airway obstruction). This is consistent with studies showing a marked decrease in MAP after OA events (4,29). However, studies have also shown that hypoxia does not affect MAP (15,30) or that it increases due to sympathoexcitation (17,31). Fukuda et al. (32) have suggested that the decrease in HR could be due to a direct effect of CO_2 on cardiac pacemaker cells, but is not due to the baroreflex response. In contrast, Walker and Brizzee (33) have suggested that the baroreflex response plays an important role in the bradycardic response to hypercapnia. This discrepancy may be due to different levels of hypoxia, among other factors.

As stated above, renal denervation affects the fall in MAP and HR induced by the obstruction of the airways, demonstrating that renal nerves participate in these hemodynamic parameters. It is possible that the hypoxia-induced reflex increases the RSNA and consequently the renin overflow and norepinephrine spillover, including the vascular effect of these hormones, could increase the vascular resistance and reduce the MAP fall in S rats. Following renal denervation, the release of these hormones could be reduced, with this reduction contributing to an exacerbated fall of MAP in D rats. This point of view is supported by the findings of Bao et al. (34) showing that the circulating epinephrine (adrenal) may be an important regulator of arterial pressure in the setting of chronic episodes of hypoxia. Also, after acute renal denervation, Evans et al. (35) observed a reduction in renal plasma renin activity overflow and norepinephrine spillover in rabbits.

MAP falls during systemic hypoxia in the rat could be due to a fall in renal perfusion pressure and may influence renal function directly (36) or indirectly by stimulating the release of renin and generation of angiotensin II (37). However, in the present study, the fall of MAP during OA was observed in S animals with intact renal nerve activity and without changes in sodium excretion or urine volume. These parameters were increased only in renal-denervated animals, despite an exacerbated fall of MAP. These data demonstrate that OA produces diuresis and natriuresis only after removal of the renal nerve, and is not dependent on the hypoxia-induced fall in MAP, as observed in our study.

Many studies have demonstrated that patients with obstructive sleep apnea have an abnormal nocturnal level of some vasoactive hormones (6,8-10), such as atrial natriuretic peptide (ANP). The rise of plasma ANP concentration could result from increased transmural pressure (and thus atrial stretching) resulting from the obstruction-induced decrease in intrathoracic pressure at the peak of inspiration (38) and from the increased right atrial transmural pressure resulting from hypoxia-induced pulmonary vasoconstriction (39,40).

Krieger (8) showed that apneic patients have nighttime increases in urine volume and its sodium content. These patients also exhibited increased urinary excretion of cyclic guanosine monophosphate, an intracellular messenger that mediates ANP actions, as well as increased plasma levels of ANP. This suggests that the respiratory efforts due to airway obstruction may influence the secretion of

ANP and that this hormone may play an important role in the regulation of sodium urinary excretion during OA. An increase in urinary cyclic guanosine monophosphate concentration was also observed in rats with enhanced plasma ANP during OA. According to this study, 30 min after the recovery from OA, the urinary excretion volume and sodium content were still elevated when compared to basal values (4). These data are consistent with our study showing that the renal excretory parameters of renal-denervated rats remained elevated during the recovery period, which could be attributed to a direct effect of ANP on renal function.

The data reported here obtained in anesthetized acute animals demonstrate a substantial participation of the RSNA in the control of renal function, HR and MAP during severe OA events in rats. We speculate that RSNA during OA is probably modulated by the balance of chemo- and cardiopulmonary reflexes since it is known that these reflexes are stimulated by OA episodes. Renal denervation-induced elevation of urine volume and sodium excretion suggests that the increase of the RSNA during OA does prevent the elevation of renal excretory function in S animals.

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