Low sodium intake does not impair short-term renal compensation of hypoxia-induced respiratory alkalosis in conscious dogs

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ABSTRACT

Acute hypoxia causes hyperventilation and respiratory alkalosis, often combined with increased diuresis, sodium-, potassium- and bicarbonate excretion. On a low sodium intake the excretion of the anion bicarbonate may be limited by the lower excretion rate of the cation sodium through activated sodium retaining mechanisms. This study investigates whether the short-term renal compensation of hypoxia-induced respiratory alkalosis is impaired by a low sodium intake. Nine conscious, tracheotomized dogs were studied twice either on a low sodium diet (LS = 0.5 mmol sodium per kg body weight (body wt) per day), or on a high sodium diet (HS = 7.5 mmol sodium·kg body wt⁻¹·day⁻¹). The dogs were breathing spontaneously via a ventilator circuit during the experiments: first hour, normoxia (F_{iO_2} = 0.21, inspiratory oxygen fraction); second to fourth hour, hypoxia (F_{iO_2} = 0.1). During hypoxia (P_{A0_2} 34.4±2.1 mm Hg), plasma pH increased from 7.37±0.01 to 7.48±0.01 (P<0.05) due to hyperventilation (P_{ACO_2} 25.6±2.4 mm Hg). Urinary pH and urinary bicarbonate excretion increased irrespective of the sodium intake. Sodium excretion increased more during HS than during LS, whereas the increase in potassium excretion was comparable in both groups. In conclusion, the quick onset of bicarbonate excretion within the first hour of hypoxia-induced respiratory alkalosis was not impaired by a low sodium intake. The increased sodium excretion during hypoxia seems to be combined with a decrease in plasma aldosterone and angiotensin II in LS as well as in HS dogs. Other factors, e.g., increased MAP, minute ventilation and renal blood flow may have contributed.

Key words: hypoxia, acid-base balance, hormones, short-term
Humans as well as many mammals acutely exposed to hypoxia, develop respiratory alkalosis due to hyperventilation. Consecutively an increase in diuresis, sodium-, potassium- and bicarbonate excretion is frequently observed (9, 18, 29). The complex renal response to acute hypoxia seems to be beneficial for the adaptation to high altitude, where fluid retention may lead to high altitude sickness (1). In addition, bicarbonate excretion is a renal compensatory reaction following acute respiratory alkalosis. Although many studies exist, the underlying mechanisms responsible for the renal response to hypoxia and/or hypocapnia are not yet fully understood. Studies on humans (9) and on animals (8) describe renal excretion of bicarbonate and sodium as a long-term response to hypocapnia. Other studies suggest that only a weak correlation exists between bicarbonate and sodium excretion during hypoxia (18, 29). Furthermore, it remains unclear if high altitude natriuresis is compromised under conditions in which sodium conserving mechanisms are activated (24). It is well known, that after total body sodium reduction, induced by, e.g., peritoneal dialysis combined with a low sodium diet or repeated mannitol infusion, even strong natriuretic stimuli like osmotic diuresis or inhibition of aldosterone fail to initiate natriuresis (3).

The objective of the current study was to examine the acute physiological reactions towards hypoxia-induced respiratory alkalosis on intact organisms, and to determine whether the renal compensatory response would be impaired by a low sodium intake.
MATERIALS AND METHODS

Animals, Maintenance, and Diets

A total of 18 experiments were performed on nine purebred female Beagle dogs (body wt 12.6 ± 0.9 kg), two experiments on each dog. The dogs were obtained from the Central Animal Facilities of the Humboldt-University in Berlin. They were tested for their social behavior, tolerance to urinary bladder catheterization, and intravascular cannulas. The permission to perform the experiments was obtained from the Governmental Animal Protection Committee (AZ G0183/97).

The dogs were kept under highly standardized conditions: air-conditioned animal room during the day and large individual kennels (5 m²) during the night (21°C, 55% humidity). General status, body temperature, and body weight were checked daily. A permanent tracheotomy was performed four to five weeks prior to the experiments (for details see 14, 18). Thereafter, the dogs were trained to lie quietly on their right side on a padded animal table for at least 5 hours.

Beginning at least 7 days before the experiments, the dogs were fed either one of two standardized diets. The diet consisted of minced beef (12 g), and boiled rice (58 g), and contained 91 ml water, and 3.5 mmol potassium (all values were given per kg body wt per day). In one protocol the sodium intake was low (0.5 mmol Na·kg body wt⁻¹·day⁻¹) and in addition to this, 20 mg furosemide (Furosemid®, ratiopharm, Ulm, Germany) was given intravenously at the seventh and sixth day before the experiments. The low sodium diet and furosemide application was chosen to activate sodium retaining mechanisms. In the other protocol the sodium intake was high (7.5 mmol Na·kg body wt⁻¹·day⁻¹). The calories supplied with these diets (277 kJ·kg body wt⁻¹·day⁻¹) were sufficient to keep the dog’s body weight constant for weeks. The food mash was given once a day at 2 PM and the intake was
finished by all dogs within one hour. No further intake was allowed until feeding on the next day.

Eight days before an experiment, 100 ml of the dog’s own blood was collected via puncture of a foreleg vein and stored in a blood bag at 4°C (Biopack® , Biotrans, Dreieich, Germany). The blood served to replace the blood withdrawn for analysis during the experiments. No other fluids were administered during the experiments.

After completion of the studies, the tracheotomy was surgically closed, and the dogs were handed to private persons with the assistance of our university veterinarians.

Procedures during the experiments

Preparation of the dogs started at 7:30 AM. Body weight and temperature were recorded. The urinary bladder was catheterized with a self-retaining Foley catheter. A foreleg vein was punctured and an infusion of creatinine started (priming dose 1.4 g for 30 min, maintenance infusion 4.7 mg/min) for assessment of glomerular filtration rate (GFR) (exogenous creatinine clearance). After local anesthesia (lidocain 1%, Braun Melsungen, Germany), an arterial line (20 G, No. 4235-8, Ohmeda, Erlangen, Germany) was advanced into the abdominal aorta via the femoral artery and a pulmonary artery catheter (5 F, No. 132F5, Baxter, Unterschleissheim, Germany) was inserted via the right external jugular vein. The catheters were used for continuous systemic and pulmonary blood pressure monitoring, cardiac output measurements and blood sampling. After catheter insertion, the dogs were placed on the padded animal table and positioned on their right side. The pressure transducers were adjusted to the level of the right atrium. The distance between transducer and table was recorded and also used for the next experiment on this individual dog. Finally, the tracheal tube was inserted, blocked, and connected to the ventilator set to CPAP mode with 4 cm H₂O continuous airway pressure. Thereafter, the conscious
dogs were given 60 min to adjust to the experimental situation.

Each of the nine dogs was studied twice in randomized order: (1) on the low sodium diet (LS) and (2) on the high sodium diet (HS). The interval between the two experiments on the same dog was at least 14 days.

In both experiments (LS and HS) the dogs breathed room air (21 % O₂, 79 % N₂; normoxia) for one hour, followed by breathing a gas mixture containing 10 % O₂ and 90 % N₂ for three hours (hypoxia).

Mean arterial blood pressure (MAP), heart rate (HR), central venous pressure (CVP), pulmonary artery pressure (PAP), and minute ventilation (using the flow transducer in the ventilator) were measured continuously and the data stored on a computer. Cardiac output was measured using the thermodilution technique (5 ml injection volume at 5 - 10 °C; Vigilance®, Baxter Edwards Critical Care). Five consecutive measurements were performed. The highest and lowest values were rejected. The mean cardiac output was calculated from the remaining three determinations and taken for calculation of systemic (SVR) and pulmonary (PVR) vascular resistance by standard formulas.

At the end of each experimental hour, blood samples were taken to determine arterial blood gases, actual bicarbonate, base excess, plasma electrolytes, lactate, hormones, and creatinine. The blood withdrawn was immediately replaced with an equal amount of the dog’s own stored blood using a blood filter system (TNSB-3, Biotest, Alzenau, Germany).

At hourly intervals, renal sodium, water, potassium, bicarbonate, chloride, phosphate, calcium, and creatinine excretions were measured after complete evacuation of the urinary bladder (air washout). Exogenous creatinine clearance was calculated by the standard formula to assess glomerular filtration rate.
Measurement of urinary and plasma values

Urinary sodium and potassium concentrations were measured by flame photometry (Photometer Eppendorf, Hamburg, Germany). Urinary calcium concentration was determined by photometric reaction, urinary chloride concentration by ion-specific electrodes, urinary phosphate concentration by malachite green reaction, and creatinine with a creatinine analyzer (modified Jaffé reaction; Beckmann Instruments, Brea, USA).

Blood gas analysis, plasma sodium, potassium, calcium, and chloride measurements were performed at hourly intervals (ABL 505, Radiometer, Copenhagen, Denmark). Plasma and urinary bicarbonate concentrations were calculated using the Henderson – Hasselbalch equation. The pK used for blood was 6.1, the pK used for urine was 6.33 – 0.5·B\(^{1/2}\) (where B represents the total cation concentration estimated as the sum of sodium and potassium expressed in equivalents per liter). The solubility coefficients applied for CO\(_2\) were 0.0301 for blood and 0.0309 for urine.

Arterial lactate was determined by the reduction of NAD with lactate dehydrogenase (Abbott ABA100 system).

Procedures for analysis of plasma renin activity (PRA), angiotensin II concentration (Ang II), plasma aldosterone concentration and atrial natriuretic peptide (ANP) have been described previously (14).

Statistical Analysis

All values are given as means ± SE (n = 9). Inter-group comparison, i.e., LS vs. HS during the respective normoxia and hypoxia period, was performed using Student’s \(t\)-test. For intra-group
comparisons (time course) a general linear model of analysis of variance (GLM ANOVA) for repeated measures was applied (SPSS 9.0, Chicago, IL, USA). Post-hoc testing of the means was performed with Student’s $t$-test with Bonferroni correction for multiple comparisons. Regression analysis was used to determine the correlation between minute ventilation and urine volume, and between renal bicarbonate excretion and renal sodium and potassium excretion, respectively. Statistical significance was considered at $P < 0.05$ (*).
RESULTS

Minute Ventilation, Arterial Blood Gases, plasma pH

With hypoxia, arterial O₂ tension (PaO₂) decreased from about 98 mm Hg to 35 - 38 mm Hg in both groups (P < 0.05) (Tab. 1). Minute ventilation increased by 1.3 – 1.6 l/min on both diets (Tab. 1). Due to the increase in minute ventilation (P < 0.05) the arterial carbon dioxide tension (PaCO₂) decreased similarly in both groups from 34 ± 1 during normoxia to 27 ± 1 mm Hg during hypoxia (P < 0.05) (Tab. 1). Plasma pH increased during hypoxia (P < 0.05) (Tab. 1). Base excess was slightly negative in both groups and increased during hypoxia (P < 0.05) (Tab. 1).

Plasma values, plasma hormones

Plasma actual bicarbonate concentration (18.1 – 19.5 mmol/l) (Tab. 1), plasma sodium concentration (143 – 147 mmol/l) and plasma osmolality (295 – 300 mosmol/l) were similar in both groups and remained unchanged during hypoxia. Plasma potassium concentration decreased during hypoxia in LS as well as in HS experiments (P < 0.05) (Tab. 2). Plasma calcium concentration decreased slightly in the LS dogs (1.35 ± 0.01 to 1.33 ± 0.01 mmol/l) as well as in the HS dogs (1.38 ± 0.01 to 1.33 ± 0.02 mmol/l) (P < 0.05); plasma chloride concentration decreased from 110 ± 0.8 (LS and HS) to 108 ± 0.7 mmol/l (LS and HS) during hypoxia (P < 0.05). Plasma lactate concentration (2.7 – 3.1 mmol/l) was similar in both groups and remained unchanged during hypoxia. Plasma renin activity (Tab. 2), angiotensin II (Tab. 2) and plasma aldosterone concentrations (Fig. 2) were always lower in the HS dogs (P < 0.05) and decreased during hypoxia in both protocols. The decrease was more pronounced
in LS than in HS dogs (P < 0.05). Plasma concentrations of atrial natriuretic peptide (42 – 53 pg/ml) were similar in both protocols and did not change during hypoxia in either protocol (Tab. 2).

Renal function data

Urine volume, and urinary potassium excretion increased similarly during hypoxia, in LS as well as in HS dogs (P < 0.05) (Tab. 3). Minute ventilation correlated with urine excretion in LS (r = 0.72, P = 0.03) but not in HS dogs (r = 0.66, P = 0.052) (Fig. 5). Urinary sodium excretion (Fig. 1) and fractional excretion of sodium (Tab. 3) during hypoxia was much greater in HS dogs than in LS dogs (P < 0.05). For comparison, the individual values of plasma aldosterone, sodium excretion, and urine volume on both diets are given in Table 5. No correlation of delta PAC/U\text{Na}_V or delta PAC/UV was found (P > 0.05). Urinary chloride excretion was also greater in HS (1.6 ± 0.3 µmol·kg body wt\textsuperscript{-1}·min\textsuperscript{-1}) than in LS dogs (0.8 ± 0.2 µmol·kg body wt\textsuperscript{-1}·min\textsuperscript{-1}) (P < 0.05) but did not change during hypoxia. Urinary bicarbonate excretion increased during hypoxia in both groups (P < 0.05) (Fig. 1). Bicarbonate excretion correlated with urinary potassium excretion in both groups (LS: r = 0.75, P = 0.01; HS: r = 0.85, P = 0.04) (Fig. 3), whereas it correlated with urinary sodium excretion in HS dogs only (HS: r = 0.85, P = 0.01; LS: r = 0.28, P = 0.5) (Fig. 4). Urinary calcium (12 – 30 nmol·kg body wt\textsuperscript{-1}·min\textsuperscript{-1}), phosphate (0.05 – 0.3 µmol·kg body wt\textsuperscript{-1}·min\textsuperscript{-1}), and osmolal excretion (12 – 16 µosm·kg body wt\textsuperscript{-1}·min\textsuperscript{-1}) were similar in both groups and did not change during hypoxia. Urinary pH increased in both groups during hypoxia (P < 0.05) (Tab. 3). Glomerular filtration rate (3.5 – 3.9 ml·kg body wt\textsuperscript{-1}·min\textsuperscript{-1}) did not change during hypoxia in either protocol.
Hemodynamics

During hypoxia, heart rate, cardiac output, mean arterial pressure, mean pulmonary artery pressure, and pulmonary vascular resistance increased to a similar extent in HS as well as in LS dogs (P < 0.05) (Tab. 4), whereas central venous pressure (1.2 – 1.8 cm H$_2$O) and systemic vascular resistance (3739 – 3903 dyn·s$^{-1}·$cm$^{-5}$) remained stable in both protocols.
DISCUSSION

The aim of the present study was to determine whether short-term renal compensation following acute hypoxia-induced respiratory alkalosis is impaired by a low sodium intake. Experiments were performed on nine trained, conscious Beagle dogs, each of whom was studied on both a low and high sodium diet. In the four hour protocol, the dogs were breathing room air for one hour and thereafter a hypoxic gas mixture for three hours. The results demonstrated that during three hours of hypoxia neither the time course nor the extent of acute respiratory alkalosis were affected by the dietary salt intake. Acute renal bicarbonate excretion was observed on both diets but could not compensate for the respiratory alkalosis within the observation period.

Urinary bicarbonate excretion. Acute hypoxia induces an increase in alveolar ventilation and results - through hyperventilation - in respiratory alkalosis. One of our aims was to determine whether a low sodium intake would deteriorate respiratory alkalosis by impairing renal compensatory mechanisms. An organism with all its regulatory mechanisms intact will strive to bring back plasma pH from alkalotic to normal in this situation. There are several ways by which this can be accomplished, e.g., by decreasing \( \text{NH}_4^+ \) and titratable acid excretion, and reducing the rate of \( \text{H}^+ \) secretion. Most importantly, however, the kidney responses to hypocapnia with an increase in bicarbonate excretion (5, 6). In our dogs, the onset of bicarbonate excretion starts within the first hour of hypoxia and increases throughout the three hour observation period (Fig. 1). This did not prevent plasma pH from increasing during hypoxia, however, and there was no difference in the magnitude of respiratory alkalosis between the LS and HS dogs (Tab. 1). This is not what we had expected. We assumed that after seven days on a low sodium intake and two times furosemide - on days 6 and 7 before the study - the “need” to save sodium would
restrict its excretion as an accompanying cation for the anion bicarbonate. We presumed that on the LS
diet the dogs would be in a conflicting situation during hypoxia: bringing back plasma pH to normal by,
e.g. sodium bicarbonate excretion on the one hand, and preventing sodium loss on the other. In our
short-term experiments on a low sodium intake, the dogs increased sodium excretion more than twofold
and seem to excrete sodium partly as sodium bicarbonate despite the presumed need to conserve
sodium, because of the low sodium intake. The prime bicarbonate compound in LS dogs seems to be
potassium bicarbonate, however. This was also shown to happen in healthy humans exposed to chronic
hypocapnia (8). In the present study potassium excretion increased about threefold during hypoxia in
both groups (Tab. 3) which is in agreement with Gledhill et al. (9) in humans. We found a strong
correlation between bicarbonate and potassium excretion in both groups (Fig. 3), whereas bicarbonate
correlated with sodium excretion in the HS dogs only (Fig. 4). This indicates that during a low sodium
intake, bicarbonate excretion is more related to potassium than to sodium excretion.

*Urinary sodium excretion.* Despite a great number of studies, the literature about natriuresis during
hypoxia is quite conflicting. In humans, Swenson et al. (29) found natriuresis after six hours of hypoxia,
whereas others - after two hours of hypoxia - found no natriuresis in humans (13) as well as in rats (12).
It is known that a standardized sodium and water intake - as in our and in Swenson et al.’s study (29) -
has a great impact on the rate of renal electrolyte excretion, with and without hypoxia. This could be one
of the reasons for the conflicting results between these and the other studies. Otherwise it has to be
assumed that the renal response towards hypoxia or respiratory alkalosis is faster in dogs than in other
mammals.

Several factors have been proposed to initiate natriuresis during hypoxia, e.g., respiratory alkalosis
(15, 19, 22, 30) or hypoxia per se. Whatever the cause may be, sodium excretion during acute hypoxia
seems to be a tubular process, since we found an increased fractional sodium excretion, but no change in glomerular filtration rate. The markedly decreased PRA, angiotensin II- and plasma aldosterone concentrations during hypoxia may partly account for this finding and the natriuresis observed (Tab. 2 and 5). However, when delta values (delta = normoxia minus hypoxia values) of urine sodium or volume excretion were correlated with delta aldosterone values, no good correlation was found. Indicating that there must be additional factors involved that increase sodium and volume excretion during hypoxia. Irrespective of this poor correlation, the decrease of sodium retaining hormones during hypoxia is in accordance with both previous studies from our laboratory (14, 18) and studies from other authors (23, 31). The decrease was more pronounced in the LS than in the HS dogs due to the pre-experimental stimulation of the renin-angiotensin-aldosterone system (RAAS) through the low sodium intake (Fig. 2, Tab. 2 and 5).

The reasons for the decrease in PRA during hypoxia are manifold, e.g.:

1. The increase in arterial blood pressure and thus renal perfusion pressure during hypoxia (MAP was ~98 mmHg during normoxia and ~109 mm Hg during hypoxia) may have reduced PRA via the renal baroreceptor mechanism (Tab. 4). However, an MAP increase of ~10 mmHg in this pressure range is usually not followed by such a striking decrease in PRA, at least not in normoxic dogs (7, 27).

2. A recent study of ours suggests that the decrease in PRA during hypoxia may be mediated by adenosine (14).

3. In addition, endothelins were shown to suppress renin secretion in vitro (20) and in vivo (26), possibly via ET_{A} receptor dependent mechanisms.
Finally, nitric oxide (NO) may be involved, since NO synthase inhibition was shown to reduce PRA levels in conscious normoxic dogs (28).

The decrease in plasma aldosterone during hypoxia, which was observed on both diets, is generally assumed to be due to the reduced conversion from cortisol to aldosterone by 18-hydroxylase during hypoxia (4) and occurs independent from the decrease in PRA and Ang II (14). In addition, the slight decrease in plasma potassium concentration (-0.2 mmol/l) may have contributed to the decrease of aldosterone (Tab. 2). This decrease in plasma potassium concentration is most probably a result of hypoxia-induced respiratory alkalosis shifting potassium from the extracellular to the intracellular space (5).

In addition to hormonal and/or neuronal factors (14, 15, 16), the increase in MAP during hypoxia possibly contributed to sodium and water excretion via the pressure natriuresis/diuresis mechanism (10, 11, 21, 25). Furthermore, an increase in renal blood flow during hypoxia may have contributed to sodium and water excretion (21).

Although sodium excretion increased on the high as well as on the low sodium diet, the percent increase in sodium excretion during hypoxia was blunted during the low sodium intake (Fig. 1). This could be due to the presence of sodium conserving mechanisms, e.g., by the overall higher aldosterone, angiotensin II, and PRA levels on the LS diet. In how far different activities of the NO system on a low and a high sodium intake are involved remains to be determined (2).

**Urine volume during hypoxia.** Compared with sodium excretion, the increase in urine volume was more pronounced during the first hour of hypoxia, and continued to increase at a lower pace during the following two hours (Tab. 3). Our findings are in line with studies in rats (12) and humans (13)
demonstrating that the onset of increased urine volume can be observed within the first two hours of hypoxia. However, it is still unknown which specific mechanisms are responsible for hypoxic diuresis.

Honig (15) postulates a direct link between peripheral chemoreceptor stimulation and renal water and sodium excretion from studies on hypoxic, isolated perfused carotid bodies. Swenson et al. (29) speculate that a high hypoxic ventilatory responsiveness might predict the magnitude of hypoxia induced diuresis and natriuresis. In the present study, minute ventilation increased quickly in both groups (Tab. 1), but only in the LS dogs the correlation between minute ventilation and urinary volume excretion was found significant (Fig. 5).

**Hemodynamics:** Despite signs of general sympathetic stimulation (increase in heart rate, mean arterial pressure, cardiac output, and minute ventilation) (Tab. 1 and 4), the increase in renal sympathetic nerve activity (RSNA) was not powerful enough to induce an increase in PRA levels and sodium and/or water retention during hypoxia (Fig. 1, Tab. 4).

Pulmonary artery pressure and pulmonary vascular resistance increased on both diets as a sign of hypoxic pulmonary vasoconstriction (Tab. 4).

In summary, we have shown that the increase in diuresis and natriuresis during hypoxia corresponded mainly with a decrease in angiotensin II and plasma aldosterone concentration in our conscious resting dogs. Other factors, such as increased MAP (10, 11, 25) increased minute ventilation (29) and possibly renal blood flow (21) have probably contributed to the renal response. Renal bicarbonate excretion after hypoxia-induced respiratory alkalosis was not influenced by the amount of sodium intake during three hours of hypoxia. It cannot be excluded, however, that three hours of hypoxia were too short a period to show advantages or disadvantages of either one diet. Looking at Fig. 1, one gets the impression that
bicarbonate excretion in the HS dogs starts to gain over the LS dogs after 3 hours. Because of the practical relevance, e.g., for mountaineers, well controlled long-term experiments with respect to compensation of respiratory alkalosis on different sodium intakes are recommended.
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LEGENDS TO FIGURES

Fig. 1. Urinary sodium and bicarbonate excretion during one hour of normoxia (21% inspiratory O$_2$ concentration) and three hours of hypoxia (10% inspiratory O$_2$ concentration). Values are means ± SE (n = 9). *P < 0.05 vs. normoxia, § P < 0.05 vs. LS.

Fig. 2. Plasma aldosterone concentration during one hour of normoxia (21% inspiratory O$_2$ concentration) and three hours of hypoxia (10% inspiratory O$_2$ concentration). Values are means ± SE (n = 9). *P < 0.05 vs. normoxia, § P < 0.05 vs. LS.

Fig. 3. Mean urinary potassium excretion of each dog on a low sodium (LS) (n = 9) and high sodium (HS) (n = 9) diet during hypoxia (3$^{rd}$ hour) plotted against urinary bicarbonate excretion at the same time period.

Fig. 4. Mean urinary sodium excretion of each dog on a high sodium diet (HS) (n = 9) during hypoxia (3$^{rd}$ hour) plotted against urinary bicarbonate excretion at the same time period.

Fig. 5. Minute Ventilation of each dog on a low sodium (LS) (n = 9) and high sodium (HS) (n = 9) diet during hypoxia (3$^{rd}$ hour) plotted against urine excretion at the same time period.
Table 1. *Arterial blood gases, pH, actual bicarbonate concentration, base excess, and minute ventilation in LS and HS group*

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HS, high sodium intake; LS, low sodium intake; PaO₂, arterial oxygen tension; PaCO₂, arterial carbon dioxide tension; aHCO₃, actual bicarbonate concentration; BE, base excess; Vₑ, minute ventilation.

Values measured during one hour of normoxia (21 % inspiratory oxygen concentration) and three hours of hypoxia (10 % inspiratory oxygen concentration). Means ± SE, n = 9; * P < 0.05 vs. normoxia.
Table 2. Plasma hormones, and plasma potassium concentration in LS and HS group

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<th>Normoxia</th>
<th>Hypoxia</th>
<th>Hypoxia</th>
<th>Hypoxia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1&lt;sup&gt;st&lt;/sup&gt; h</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; h</td>
<td>3&lt;sup&gt;rd&lt;/sup&gt; h</td>
<td>4&lt;sup&gt;th&lt;/sup&gt; h</td>
</tr>
<tr>
<td>PRA, ng AngI·ml&lt;sup&gt;-1&lt;/sup&gt;·h&lt;sup&gt;-1&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LS</td>
<td>8.0 ± 0.8</td>
<td>5.4 ± 0.6*</td>
<td>4.8 ± 0.8*</td>
<td>3.6 ± 0.4*</td>
</tr>
<tr>
<td>HS</td>
<td>4.7 ± 0.7§</td>
<td>2.3 ± 0.5*§</td>
<td>2.3 ± 0.5*§</td>
<td>2.4 ± 0.6*§</td>
</tr>
<tr>
<td>Ang II, pg/ml</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LS</td>
<td>13.0 ± 2.1</td>
<td>8.8 ± 1.5*</td>
<td>6.4 ± 0.8*</td>
<td>6.2 ± 0.8*</td>
</tr>
<tr>
<td>HS</td>
<td>6.7 ± 1.0§</td>
<td>4.2 ± 0.8*§</td>
<td>3.9 ± 0.6*§</td>
<td>3.6 ± 0.6*§</td>
</tr>
<tr>
<td>ANP, pg/ml</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LS</td>
<td>45 ± 7</td>
<td>49 ± 7</td>
<td>47 ± 7</td>
<td>44 ± 4</td>
</tr>
<tr>
<td>HS</td>
<td>45 ± 4</td>
<td>53 ± 5</td>
<td>51 ± 3</td>
<td>56 ± 5</td>
</tr>
<tr>
<td>P&lt;sub&gt;K&lt;/sub&gt;, mmol/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LS</td>
<td>3.9 ± 0.1</td>
<td>3.5 ± 0.1*</td>
<td>3.5 ± 0.1*</td>
<td>3.6 ± 0.1</td>
</tr>
<tr>
<td>HS</td>
<td>3.5 ± 0.1§</td>
<td>3.3 ± 0.1</td>
<td>3.3 ± 0.1*</td>
<td>3.2 ± 0.1*§</td>
</tr>
</tbody>
</table>

HS, high sodium intake; LS, low sodium intake; PRA, plasma renin activity; Ang II, plasma angiotensin II concentration; ANP, atrial natriuretic peptide; P<sub>K</sub>, plasma potassium concentration. Values measured during one hour of normoxia (21% inspiratory oxygen concentration) and three hours of hypoxia (10% inspiratory oxygen concentration). Means ± SE, n = 9; * P < 0.05 vs. normoxia; § P < 0.05 vs. LS.
Table 3. *Renal excretion parameters in LS and HS group*

<table>
<thead>
<tr>
<th></th>
<th>Normoxia</th>
<th>Hypoxia</th>
<th>Hypoxia</th>
<th>Hypoxia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1st h</td>
<td>2nd h</td>
<td>3rd h</td>
<td>4th h</td>
</tr>
<tr>
<td>UV, µl·min⁻¹·kg⁻¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LS</td>
<td>22.8 ± 3.7</td>
<td>72.4 ± 14.3*</td>
<td>85.9 ± 15.4*</td>
<td>95.7 ± 16.5*</td>
</tr>
<tr>
<td>HS</td>
<td>23.2 ± 3.1</td>
<td>79.9 ± 10.4*</td>
<td>75.0 ± 15.4*</td>
<td>77.8 ± 13.9*</td>
</tr>
<tr>
<td>U_kV, µmol·min⁻¹·kg⁻¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LS</td>
<td>0.34 ± 0.12</td>
<td>0.47 ± 0.1</td>
<td>0.82 ± 0.23*</td>
<td>0.81 ± 0.23*</td>
</tr>
<tr>
<td>HS</td>
<td>0.36 ± 0.04</td>
<td>0.53 ± 0.06*</td>
<td>0.78 ± 0.14*</td>
<td>0.95 ± 0.3</td>
</tr>
<tr>
<td>pH_U</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LS</td>
<td>6.11 ± 0.16</td>
<td>6.30 ± 0.16</td>
<td>6.62 ± 0.21*</td>
<td>6.83 ± 0.23*</td>
</tr>
<tr>
<td>HS</td>
<td>5.77 ± 0.19</td>
<td>6.14 ± 0.22*</td>
<td>6.66 ± 0.26*</td>
<td>6.99 ± 0.25*</td>
</tr>
<tr>
<td>FE_{Na}, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LS</td>
<td>0.02 ± 0.003</td>
<td>0.03 ± 0.003</td>
<td>0.08 ± 0.04</td>
<td>0.11 ± 0.05*</td>
</tr>
<tr>
<td>HS</td>
<td>0.04 ± 0.008</td>
<td>0.11 ± 0.05*</td>
<td>0.37 ± 0.1*</td>
<td>0.41 ± 0.09*</td>
</tr>
</tbody>
</table>

HS, high sodium intake; LS, low sodium intake; UV, urine volume; U_kV, urinary potassium concentration; pH_U, urinary pH; FE_{Na}, fractional sodium excretion. Values measured during one hour of normoxia (21 % inspiratory oxygen concentration) and three hours of hypoxia (10 % inspiratory oxygen concentration). Means ± SE, n = 9; * P < 0.05 vs. normoxia, § P < 0.05 vs. LS.
Table 4. Hemodynamic parameters in LS and HS group

<table>
<thead>
<tr>
<th></th>
<th>Normoxia 1st h</th>
<th>Hypoxia 2nd h</th>
<th>Hypoxia 3rd h</th>
<th>Hypoxia 4th h</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, b/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LS</td>
<td>80 ± 3</td>
<td>99 ± 5*</td>
<td>98 ± 4*</td>
<td>100 ± 4*</td>
</tr>
<tr>
<td>HS</td>
<td>82 ± 2</td>
<td>100 ± 4*</td>
<td>104 ± 4*</td>
<td>99 ± 5*</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LS</td>
<td>98 ± 2</td>
<td>106 ± 2*</td>
<td>108 ± 3*</td>
<td>107 ± 3*</td>
</tr>
<tr>
<td>HS</td>
<td>98 ± 2</td>
<td>106 ± 2*</td>
<td>109 ± 3*</td>
<td>108 ± 3*</td>
</tr>
<tr>
<td>CO, l/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LS</td>
<td>2.0 ± 0.1</td>
<td>2.3 ± 0.2*</td>
<td>2.3 ± 0.1*</td>
<td>2.3 ± 0.1*</td>
</tr>
<tr>
<td>HS</td>
<td>2.0 ± 0.1</td>
<td>2.4 ± 0.1*</td>
<td>2.6 ± 0.1*</td>
<td>2.3 ± 0.1*</td>
</tr>
<tr>
<td>PAP mean, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LS</td>
<td>13 ± 1</td>
<td>21 ± 1*</td>
<td>21 ± 1*</td>
<td>22 ± 1*</td>
</tr>
<tr>
<td>HS</td>
<td>14 ± 1</td>
<td>21 ± 1*</td>
<td>22 ± 1*</td>
<td>22 ± 1*</td>
</tr>
<tr>
<td>PVR, dyn·s(^{-1})·cm(^{-5})</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LS</td>
<td>359 ± 27</td>
<td>650 ± 73*</td>
<td>644 ± 59*</td>
<td>642 ± 57*</td>
</tr>
<tr>
<td>HS</td>
<td>397 ± 26</td>
<td>593 ± 35*</td>
<td>625 ± 51*</td>
<td>632 ± 37*</td>
</tr>
</tbody>
</table>

HR, heart rate; MAP, mean arterial pressure; CO, Cardiac output; PAP mean, pulmonary arterial pressure; PVR, pulmonary vascular resistance. Values measured during one hour of normoxia (21 % inspiratory oxygen concentration) and three hours of hypoxia (10 % inspiratory oxygen concentration).

Means ± SE, n = 9; * P < 0.05 vs. normoxia.
Table 5. Plasma aldosterone concentration, urinary sodium and volume excretion of each individual dog during normoxia and after 4 hours of hypoxia.

<table>
<thead>
<tr>
<th></th>
<th>Low sodium intake</th>
<th></th>
<th>High sodium intake</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PAC pg/ml</td>
<td>U&lt;sub&gt;Na,V&lt;/sub&gt; µmol·min&lt;sup&gt;-1&lt;/sup&gt;·kg&lt;sup&gt;-1&lt;/sup&gt;</td>
<td>UV µmol·min&lt;sup&gt;-1&lt;/sup&gt;·kg&lt;sup&gt;-1&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Normoxia Hypoxia 4&lt;sup&gt;th&lt;/sup&gt; hour</td>
<td>Normoxia Hypoxia 4&lt;sup&gt;th&lt;/sup&gt; hour</td>
<td>Normoxia Hypoxia 4&lt;sup&gt;th&lt;/sup&gt; hour</td>
</tr>
<tr>
<td>dog 1</td>
<td>116</td>
<td>0.09</td>
<td>79</td>
</tr>
<tr>
<td>dog 2</td>
<td>683</td>
<td>0.11</td>
<td>125</td>
</tr>
<tr>
<td>dog 3</td>
<td>762</td>
<td>0.06</td>
<td>402</td>
</tr>
<tr>
<td>dog 4</td>
<td>308</td>
<td>0.19</td>
<td>119</td>
</tr>
<tr>
<td>dog 5</td>
<td>615</td>
<td>0.13</td>
<td>70</td>
</tr>
<tr>
<td>dog 6</td>
<td>348</td>
<td>0.12</td>
<td>88</td>
</tr>
<tr>
<td>dog 7</td>
<td>372</td>
<td>0.08</td>
<td>66</td>
</tr>
<tr>
<td>dog 8</td>
<td>1018</td>
<td>0.14</td>
<td>107</td>
</tr>
<tr>
<td>dog 9</td>
<td>601</td>
<td>0.14</td>
<td>99</td>
</tr>
<tr>
<td>Mean ± SE</td>
<td>536 ± 102</td>
<td>0.11 ± 0.01</td>
<td>128 ± 38 *</td>
</tr>
</tbody>
</table>

Values measured after one hour of normoxia (21 % inspiratory oxygen concentration) and after the fourth hour of hypoxia (10 % inspiratory oxygen concentration). The individual dog number is the same in LS and HS protocols. * P < 0.05 vs. normoxia; § P < 0.05 vs. LS.
(Figure 1)

- Urinary bicarbonate excretion
  - Normoxia
  - Hypoxia

- Urinary sodium excretion
  - LS
  - HS

Time:
1 h 2 h 3 h 4 h
Figure 2

Plasma aldosterone concentration [pg/ml]

- LS
- HS

Time:
- 1 h
- 2 h
- 3 h
- 4 h

Normoxia Hypoxia
(Figure 3)

Urinary bicarbonate excretion

\[ \text{[µmol · kg body wt}^{-1} \cdot \text{min}^{-1}] \]

Urinary potassium excretion

\[ \text{[µmol · kg body wt}^{-1} \cdot \text{min}^{-1}] \]

LS group
\[ r = 0.75, P = 0.01 \]

HS group
\[ r = 0.85, P = 0.04 \]
Urinary sodium excretion
\[
\text{[\text{\mu mol} \cdot \text{kg body wt}^{-1} \cdot \text{min}^{-1}]}
\]
HS group
\[
r = 0.85, P = 0.01
\]
Urinary bicarbonate excretion
\[
\text{[\text{\mu mol} \cdot \text{kg body wt}^{-1} \cdot \text{min}^{-1}]}
\]
(Figure 5)

![Graph showing the relationship between minute ventilation and urine volume for two groups (LS and HS)].

- **LS group**: $r = 0.72$, $P = 0.03$
- **HS group**: $r = 0.66$, $P = 0.052$