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Effects of Hyperventilation and Hypocapnic/Normocapnic Hypoxemia on Renal Function and Lithium Clearance in Humans

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Background: Using the renal clearance of lithium as an index of proximal tubular outflow, this study tested the hypothesis that acute hypocapnic hypoxemia decreases proximal tubular reabsorption to the same extent as hypocapnic normoxemia (hyperventilation) and that this response is blunted during normocapnic hypoxemia.

Methods: Eight persons were studied on five occasions: (1) during inhalation of 10% oxygen (hypocapnic hypoxemia), (2) during hyperventilation of room air leading to carbon dioxide values similar to those with hypocapnic hypoxemia, (3) during inhalation of 10% oxygen with the addition of carbon dioxide to produce normocapnia, (4) during normal breathing of room

air through the same tight-fitting face mask as used on the other study days, and (5) during breathing of room air without the face mask.

Results: Hypocapnic and normocapnic hypoxemia and hyperventilation increased cardiac output, respiratory minute volume, and effective renal plasma flow. Glomerular filtration rate remained unchanged on all study days. Calculated proximal tubular reabsorption decreased during hypocapnic hypoxemia and hyperventilation but remained unchanged with normocapnic hypoxemia. Sodium clearance increased slightly during hypocapnic and normocapnic hypoxemia, hyperventilation, and normocapnic normoxemia with but not without the face mask.

Conclusions: The results indicate that (1) respiratory alkalosis with or without hypoxemia decreases proximal tubular reabsorption and that this effect, but not renal vasodilation or natriuresis, can be abolished by adding carbon dioxide to the hypoxic gas; (2) the increases in the effective renal plasma flow were caused by increased ventilation rather than by changes in arterial oxygen and carbon dioxide levels; and (3) the natriuresis may be secondary to increased renal perfusion, but application of a face mask also may increase sodium excretion. (Key words: Renal blood flow; sodium excretion; sympathetic nervous system; ventilation.)

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ACUTE hypoxemia increases sympathetic discharge from the vasomotor center by strongly activating peripheral and central chemoreceptors.^{1,2} Graded levels of hypoxemia have been shown to progressively increase cardiac, pulmonary, muscle, and renal sympathetic nerve activity.³⁻⁷ Within a few minutes, hypoxic chemoreceptor stimulation results in hyperventilation, leading to hypocapnia and respiratory alkalosis.^{1,8} Unopposed, an increase in renal sympathetic nerve activity causes renal vasoconstriction and a decrease in renal sodium excretion.^{9,10} During apnea in diving animals, the overall cardiovascular response to acute hypoxemia consists of marked regional vasoconstriction also in the renal circulation.^{1,11} However, this response to hypoxic chemoreceptor stimulation is greatly attenuated when pulmonary stretch receptors are activated secondary to increased ventilation.^{1,12,13} Studies in spontaneously breathing

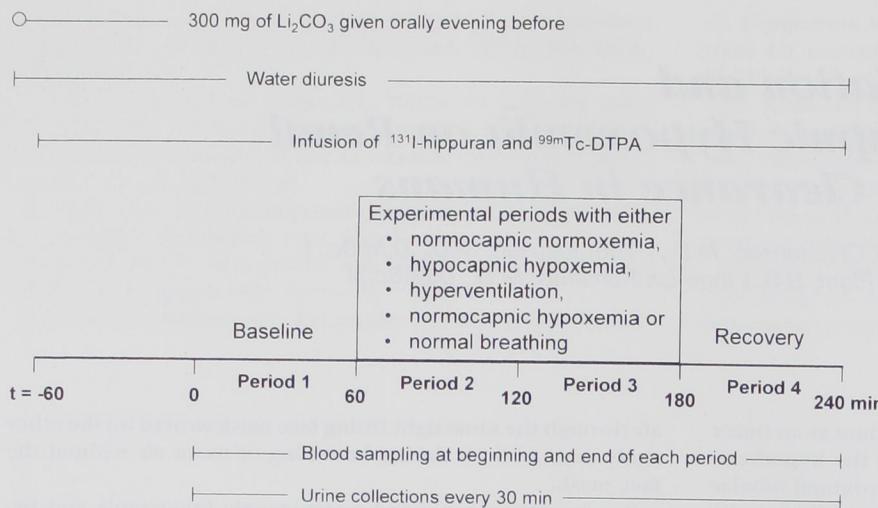


Fig. 1. Experimental protocol.

rats, dogs, and humans indicate that acute hypoxic exposure is associated with an increase in renal perfusion,^{8,12,14-16} and that the renal response may include increased excretion rates of sodium and water.¹⁵⁻²¹

In addition to attenuation of sympathetic vasoconstrictor outflow by activation of afferent pulmonary nerve activity, the hypoxic ventilatory response may affect renal function secondary to the specific effects of the accompanying hypocapnia. In spontaneously breathing dogs^{12,15} and rats,²² the increase in renal perfusion induced by hypocapnic hypoxemia was diminished when carbon dioxide was added to the hypoxic gas. In rats²³ and humans,^{20,24} respiratory alkalosis with or without hypoxemia increased the urine ρH and the excretion rates of sodium and bicarbonate. The natriuretic-diuretic response can be abolished if normocapnic conditions are maintained.^{20,23} These effects of hypocapnia and alkalosis may be attributed to a decrease in peripheral chemoreceptor sensitivity to hypoxemia,^{1,2} to the inhibition of renal proximal tubular reabsorption of bicarbonate and sodium,^{25,26} or to both.

The effects of acute hypoxemia and hyperventilation on proximal tubular reabsorption rates in humans remains unknown. Based on the assumption that lithium in the proximal tubules is reabsorbed to the same extent as sodium and water and that lithium is not reabsorbed or secreted in the distal tubules, renal clearance of lithium (C_{Li}) may be used as an index of proximal tubular outflow and to estimate directional changes in segmental tubular reabsorption rates.^{27,28} The current study tested the hypothesis that acute hypocapnic hypoxemia decreases proximal tubular reabsorption to the same extent as normoxic hyperventilation, and that this re-

sponse is blunted during normocapnic hypoxemia. Furthermore, renal hemodynamic and excretory responses were assessed by renal clearance techniques, and changes in cardiovascular and hormonal status were measured.

Materials and Methods

Participants and Experimental Protocol

Eight healthy, well-trained male volunteers with a mean age of 24 yr (range, 22–29 yr), a mean weight of 73 kg (range, 64–80 kg), and a mean height of 179 cm (range, 172–188 cm) gave informed consent. The study was approved by the regional scientific ethical committee of Copenhagen, Denmark. Each participant was observed on five different days, separated by intervals of at least 7 days. Figure 1 shows the experimental protocol for each of the five study days. The participants were instructed to maintain the same diet with a sodium intake of 140–150 mm/day and to avoid strenuous physical activity for 3 days before each study. A test dose of lithium carbonate (300 mg) for measurements of exogenous C_{Li} was administered orally on the evening before each investigation. After an overnight fast, water diuresis was induced by oral administration of water at a fixed rate of 400 ml every 30 min to facilitate urine collections (fig. 1). A radial arterial catheter and a venous catheter into an antecubital vein were inserted for blood sampling and infusion, respectively. The volunteers were confined to a resting supine position except for briefly standing when voiding every 30 min. Steady state was considered to be achieved when urine flow rates ap-

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proximately equaled the water intake. On each of the 5 study days, the protocol then included four consecutive 1-h clearance periods (fig. 1). After a 1-h baseline period (period 1), the volunteers were equipped with a tight-fitting face mask and investigated in two 1-h periods (periods 2 and 3) during spontaneous breathing of either of the following gas mixtures: (1) room air (normocapnic normoxemia), (2) 10% oxygen in nitrogen (hypocapnic hypoxemia), (3) hyperventilation of room air to carbon dioxide values similar to hypocapnic hypoxemia (hypocapnic normoxemia), (4) 10% oxygen supplemented with carbon dioxide to produce normocapnia (normocapnic hypoxemia), and (5) room air without the use of the face mask. Finally, a 1-h recovery period (period 4) was allowed with the participants breathing spontaneously without the face mask. The hypoxic gas mixtures (10% oxygen in nitrogen with and without additional carbon dioxide) were led from upright cylinders through gas mixer rotameters, flexible tubings, and a 5-l reservoir bag, connected with a three-way tap to the face mask. The respiratory effort during hyperventilation and the addition of carbon dioxide during normocapnic hypoxemia were adjusted according to the values of end-tidal carbon dioxide partial pressure monitored continuously on a capnograph (CPX; Medical Graphics, St. Paul, MN). During hyperventilation, each volunteer was instructed to adjust his ventilation so end-tidal carbon dioxide values were similar to those monitored during the preceding study day with hypocapnic (poikilocapnic) hypoxemia.

The investigations with hypocapnic hypoxemia and normocapnic normoxemia were performed in random order on the first or the second study day. Hyperventilation and normocapnic hypoxemia were applied in random order on the following days. The study with normocapnic normoxemia without the face mask was performed on the last day.

Hemodynamic Measurements

Intraarterial blood pressure was monitored continuously (model 9050; Athena, Copenhagen, Denmark) and recorded in 2-min periods with the participant in the supine position before voiding at the end of each clearance period. Heart rate was recorded continuously. Packed cell volume was measured in periods 1, 3, and 4 using capillary tubes spun for 5 min. Cardiac output was measured by a carbon dioxide rebreathing method^{29,30} using a cardiopulmonary gas exchange monitoring device (CPX, Medical Graphics) according to the principles described previously.³¹ Cardiac output was determined

in the second half of periods 1, 3, and 4 as the mean of at least two measurements. Before the measurements in period 3, the volunteers were disconnected from the face mask for 2 or 3 s while shifting to a mouthpiece (and a nose clip) with a dead space of 150 ml. Administration of the gas mixtures was then continued during the measurements. The carbon dioxide rebreathing method includes rebreathing for 10–15 s from a bag containing a volume of 1.5 times the tidal volume and with a carbon dioxide fraction that is 2–3% higher than end-tidal carbon dioxide fraction.³¹ Thus, both rebreathing and the administration of carbon dioxide may influence the results. However, the intervention is short lasting and was applied on all study days. The method has been found to provide values that correspond well with those obtained by the direct Fick method in the same participants.³⁰

Ventilation, Arterial Blood Gases, and pH

Respiratory minute volume (V_E), respiratory rate, and end-tidal carbon dioxide partial pressure were recorded continuously in periods 2 and 3 using the CPX system. Arterial oxygen saturation was monitored continuously by a pulse oximeter with the sensor attached to the participants' index fingers. Based on arterial blood samples drawn in duplicate, the partial pressures of oxygen and carbon dioxide in arterial blood (Pa_{O_2} and Pa_{CO_2} , respectively), and pH were measured in each period using an ABL 500 blood gas analyzer (Radiometer, Copenhagen, Denmark).

Renal Measurements

Effective renal plasma flow (ERPF) and glomerular filtration rate (GFR) were measured by a constant infusion technique with urine collections using ^{131}I -hippuran (priming dose, 0.33 megabecquerels (MBq); infusion rate, 0.011 MBq/min) and ^{99m}Tc -DTPA (priming dose, 4.81 MBq; infusion rate, 0.037 MBq/min), respectively. After an equilibration time of at least 1 h, renal clearances of ^{131}I -hippuran, ^{99m}Tc -DTPA, lithium, and sodium (C_{Na}) were determined in periods 1, 2, 3, and 4, respectively. Each 1-h clearance was calculated from the urinary excretion rates and plasma values from arterial blood samples drawn at the beginning and the end of each 1-h period (fig. 1).

Hormones

Plasma concentration of active renin, and plasma concentrations of aldosterone, atrial natriuretic peptide, norepinephrine, and epinephrine were measured from arte-

trial blood drawn at the end of periods 1, 3, and 4, respectively. Urinary concentrations of dopamine were measured in the same periods.

Analytical Methods

Activities of ^{131}I -hippuran and $^{99\text{m}}\text{Tc}$ -DTPA in plasma and urine were determined in a well counter. Plasma and urinary lithium concentrations were measured by atomic absorption spectrophotometry (model 403; Perkin-Elmer, Norwalk, CT). Plasma sodium was measured by a Technicon SMAC III instrument and urinary sodium was measured with a Technicon RA-XT instrument (Tarrytown, NY). The plasma renin concentration was measured by a two-site, two-monoclonal-antibody immuno-radiometric assay with plastic beads for the solid phase (Nichols Institute, San Juan Capistrano, CA). One milli-International unit per liter (mIU/l) obtained by the active renin assay is equivalent to 0.6 $\mu\text{g}/\text{l}$ of World Health Organization "2nd IRP (68/356)" for active renin.³² The detection limit was 2 mIU/l. Intra- and interassay coefficients of variation were 4% and 5%, respectively. Aldosterone was measured by radioimmunoassay in unextracted serum (Diagnostic Products Corporation, Los Angeles, CA). The detection limit was 41 pm. Intra- and interassay coefficients of variation were 10% and 15%, respectively. α -Atrial natriuretic peptide was measured with an ^{131}I radioimmunoassay system (Biotrak, Amersham International, Inc., Buckinghamshire, UK). The minimal detectable concentration was 1 pm, and the intra- and interassay coefficients of variation were 5% and 15%, respectively. Plasma concentrations of norepinephrine and epinephrine and urine concentrations of dopamine were measured using a radioenzymatic method with separation by high-performance liquid chromatography with electrochemical detection. Intra- and interassay coefficients of variation (calculated by measurements on a plasma pool [$n = 35$], where concentrations of norepinephrine, epinephrine, and dopamine [mean \pm SD] were $2.01 \pm 0.13 \text{ nm}$, $0.34 \pm 0.03 \text{ nm}$, and $0.84 \pm 0.11 \text{ nm}$, respectively) were 5.5% and 5% for norepinephrine, 7.6% and 7.4% for epinephrine, and 13% and 13% for dopamine, respectively. The limits of detection were 0.03 nm and 0.02 nm for norepinephrine and epinephrine, respectively, and 0.4 nm for dopamine.

Calculations

Effective renal plasma flow, GFR, C_{Li} , and C_{Na} were calculated using standard formulas (clearance = rate of excretion/plasma concentration). Renal proximal tubular reabsorption rates of sodium and water were calcu-

lated based on the assumption that C_{Li} provides an accurate measurement of the end-proximal delivery of fluid to the thin descending loop of Henle: the absolute proximal reabsorption rate = GFR - C_{Li} ; fractional proximal reabsorption = $(\text{GFR} - C_{\text{Li}})/\text{GFR}$. The fractional excretion of sodium and lithium were calculated as C_{Na}/GFR and C_{Li}/GFR , respectively.

Statistical Analysis

Differences within and between study days were analyzed by analysis of variance for repeated measures. If variances showed significant differences ($P < 0.05$), paired Student's *t* tests corrected for multiple comparisons were used to analyze differences between the baseline period (period 1) and periods 2, 3, and 4 and to analyze differences between corresponding periods on different study days. Normocapnic normoxemia with the face mask served as the control day. Unless otherwise indicated, values are presented as the mean \pm SD.

Results

Hemodynamic Effects

Compared with normocapnic normoxemia, heart rate increased during hypocapnic hypoxemia (table 1). Compared with the baseline, heart rate increased during normocapnic hypoxemia as well. The mean arterial blood pressure remained unchanged during hypocapnic hypoxemia but was higher during normocapnic hypoxemia compared with the control day (table 1); however, baseline and recovery values were increased as well. During hyperventilation, the mean arterial blood pressure decreased compared with baseline. Hypocapnic and normocapnic hypoxemia and hyperventilation increased cardiac output (table 1). Packed cell volume remained unchanged within and between study days (data not shown).

Ventilatory Effects

Respiratory minute volume increased during hypocapnic and normocapnic hypoxemia, but values were higher during normocapnic hypoxemia ($P < 0.001$; table 2). Respiratory minute volume increased during hyperventilation compared with baseline. Respiratory rate only increased during normocapnic hypoxemia and hyperventilation (table 2).

Blood Gases and pH

With hypocapnic hypoxemia, Pa_{O_2} in periods 2 and 3 averaged 38.4 mmHg (table 3). During normocapnic

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Table 1. Hemodynamic Effects

		Experimental Periods		
	Baseline 1	2	3	Recovery 4
Heart rate (beats/min)				
Normocapnic normoxemia	50 ± 9	50 ± 9	49 ± 6	48 ± 6
Hypocapnic hypoxemia	50 ± 5	63 ± 8†§	61 ± 11*§	49 ± 5
Hyperventilation	48 ± 6	49 ± 6	48 ± 6	47 ± 5
Normocapnic hypoxemia	47 ± 3	55 ± 9¶	52 ± 6§	48 ± 3
Normal breathing	48 ± 9	47 ± 9	48 ± 9	47 ± 9
MABP (mmHg)				
Normocapnic normoxemia	93 ± 6	94 ± 9	94 ± 6	95 ± 6
Hypocapnic hypoxemia	99 ± 13	94 ± 8	93 ± 8	94 ± 11
Hyperventilation	96 ± 6	91 ± 3§	92 ± 6	96 ± 8
Normocapnic hypoxemia	99 ± 9*	103 ± 9†	104 ± 9‡§	104 ± 9†§
Normal breathing	99 ± 11	99 ± 11	101 ± 11	100 ± 11
Cardiac output (l/min)				
Normocapnic normoxemia	3.7 ± 1.1	—	3.7 ± 0.6	4.0 ± 0.9
Hypocapnic hypoxemia	4.2 ± 1.3	—	6.2 ± 1.6¶	4.2 ± 1.4
Hyperventilation	3.7 ± 0.9	—	4.5 ± 0.9*	3.6 ± 0.5
Normocapnic hypoxemia	3.8 ± 1.1	—	5.1 ± 1.4*	4.0 ± 0.9
Normal breathing	4.0 ± 1.1	—	4.0 ± 1.1	3.8 ± 1.1

Values are mean ± SD; n = 8, except during hypocapnic hypoxemia (n = 7) and during hyperventilation in period 4 (n = 7).

MABP = mean arterial blood pressure; period 1 = baseline; periods 2 and 3 = experimental periods with normocapnic normoxemia, hypocapnic hypoxemia, hyperventilation, normocapnic hypoxemia, or normal breathing without the face mask; period 4 = recovery.

* P < 0.05, † P < 0.01, ‡ P < 0.001, versus normocapnic normoxemia.

§ P < 0.05, ¶ P < 0.01, ** P < 0.001 versus baseline.

hypoxemia, the mean of Pa_{O_2} in periods 2 and 3 was 61.7 mmHg, which was significantly higher than with hypocapnic hypoxemia ($P < 0.001$). Pa_{CO_2} did not differ between hypocapnic hypoxemia and hyperventilation. Hypocapnic hypoxemia and hyperventilation induced an equal increase in pH (table 3).

Renal Hemodynamics

Effective renal plasma flow increased during hypocapnic hypoxemia, hyperventilation, and normocapnic hypoxemia (fig. 2). The percentage increases did not differ between study days. None of the experiments induced significant changes in the GFR (fig. 2).

Lithium Clearance and Renal Proximal Tubular Function

Hypocapnic and normocapnic hypoxemia both caused small but significant increases in C_{Li} (fig. 3). In addition, hyperventilation slightly increased C_{Li} ($P = 0.058$). The fractional excretion of lithium increased during hypocapnic hypoxemia ($P < 0.05$) and hyperventilation ($P < 0.05$) but remained unchanged during normocapnic hypoxemia (data not shown). During normocapnic hypox-

emia, the fractional excretion of lithium was lower than that of hypocapnic hypoxemia ($P < 0.05$). The calculated absolute proximal reabsorption rate was lower during hypocapnic hypoxemia (period 3) than with normocapnic normoxemia (fig. 3). When compared with normocapnic hypoxemia, the absolute proximal reabsorption rate was also decreased ($P < 0.001$). Fractional proximal reabsorption decreased during hypocapnic hypoxemia and hyperventilation but remained unchanged during normocapnic hypoxemia (fig. 3). The fractional proximal reabsorption was lower during hypocapnic hypoxemia than with normocapnic hypoxemia ($P < 0.05$).

Sodium and Water Excretion

Plasma sodium concentration remained unchanged within and between study days (data not shown). Compared with baseline, C_{Na} increased during hypocapnic hypoxemia, normocapnic hypoxemia, and hyperventilation (fig. 4). However, C_{Na} also increased on the study day with normocapnic normoxemia with the face mask but not without the face mask. Changes in the urinary excretion rate of sodium and the fractional excretion of

Table 2. Ventilatory Effects

	Baseline 1	Experimental Period 3	Recovery 4
V_E (l/min)			
Normocapnic normoxemia	8.2 ± 2.0	8.9 ± 2.0	8.1 ± 1.4
Hypocapnic hypoxemia	8.2 ± 2.6	14.7 ± 3.4*§	10.6 ± 5.1†‡
Hyperventilation	7.4 ± 0.6	11.6 ± 3.7†‡	8.5 ± 0.9†‡
Normocapnic hypoxemia	8.0 ± 0.8	23.4 ± 2.4†§	8.6 ± 1.6
Normal breathing	7.8 ± 1.0	7.7 ± 1.0	8.0 ± 0.5
Respiratory rate (min^{-1})			
Normocapnic normoxemia	13 ± 6	14 ± 3	13 ± 3
Hypocapnic hypoxemia	12 ± 3	15 ± 3	14 ± 3
Hyperventilation	13 ± 3	15 ± 3†‡	14 ± 3
Normocapnic hypoxemia	14 ± 3	16 ± 3§	14 ± 3
Normal breathing	14 ± 3	14 ± 3	14 ± 3

Values are mean ± SD; n = 8, except during normal breathing (n = 6) and normocapnic hypoxemia (n = 7).

V_E = respiratory minute volume; period 1 = baseline; period 3 = last experimental 1-h period with normocapnic normoxemia, hypocapnic hypoxemia, hyperventilation, normocapnic hypoxemia or normal breathing without the face mask; period 4 = recovery.

* $P < 0.05$, † $P < 0.001$ versus normocapnic normoxemia.

‡ $P < 0.05$, § $P < 0.001$ versus baseline.

sodium followed the same trend (data not shown). In four volunteers in whom the arterial Pa_{O_2} levels were particularly low, an antidiuretic response was observed during hypocapnic hypoxemia in periods 3 and 4. Two of these men had nausea, one with vomiting. Compared with normocapnic normoxemia, the mean value of the urine flow rate increased during normocapnic hypoxemia in period 3. Otherwise, there were no significant differences within or between study days (fig. 4).

Catecholamines

Compared with baseline, the plasma norepinephrine concentration increased during normocapnic hypoxemia (table 4). Plasma epinephrine increased slightly during hypocapnic and normocapnic hypoxemia. Urinary excretion rates of dopamine did not differ between study days or periods.

Renin, Aldosterone, and Atrial Natriuretic Peptide

Small but significant decreases in the plasma renin concentration were observed on all study days (table 5). Compared with baseline, plasma concentrations of aldosterone decreased during normocapnic hypoxemia and, compared with the control day, also during hyperventilation. Atrial natriuretic peptide increased during hypocapnic and normocapnic hypoxemia.

Discussion

The main findings of the current study are that cardiac output and ERPF increased with hypocapnic hypoxemia

and normocapnic hypoxemia and hyperventilation, but GFR remained unchanged. Respiratory alkalosis with and without hypoxemia decreased calculated proximal tubular reabsorption, but with normocapnic hypoxemia it remained unchanged. Hypocapnic hypoxemia and hyperventilation and normocapnic hypoxemia and breathing of room air through a face mask slightly increased C_{Na} .

Values of baseline sodium excretion rates before each experimental intervention confirm that the volunteers were investigated while in a normal, sodium-repleted condition. Spontaneous breathing of 10% oxygen for 2 h resulted in mean Pa_{O_2} levels of 37–40 mmHg. Two participants with a marked decrease in Pa_{O_2} to values less than 36 mmHg during hypocapnic hypoxemia had headache, dizziness, nausea, and vomiting followed by decreased urine flow rates. Such a response also has been observed by other investigators,^{19,20} suggesting that inspired oxygen fractions near 10% in some volunteers may activate stimuli that cause nausea, increased circulating levels of antidiuretic hormone, and antidiuresis.¹⁹ The natriuretic response to hypocapnic hypoxemia that we found was smaller than that of some studies in which inspired oxygen fractions of 11–14% were used,^{20,21} but it was of comparable magnitude to the response found with a similar level of hypoxia.¹⁹ The results of Swenson *et al.*²¹ suggest an inverse correlation between the increase in sodium excretion and the arterial oxygen saturation when measured in a range of 82–92%. More severe hypoxemia leads to marked decreases in renal function,³³ and the current results most likely reflect the

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Table 3. Arterial Blood Gases and pH

	Experimental Periods			
	Baseline 1	2	3	Recovery 4
Pa_{O₂} (mmHg)				
Normocapnic normoxemia	107 ± 6	100 ± 6	104 ± 3	105 ± 3
Hypocapnic hypoxemia	104 ± 9	40 ± 6†**	37 ± 11‡**	102 ± 6
Hyperventilation	104 ± 6	118 ± 11†¶	115 ± 11†§	100 ± 5
Normocapnic hypoxemia	100 ± 9	62 ± 9‡**	62 ± 6‡**	103 ± 6
Normal breathing	102 ± 9	101 ± 6	103 ± 9	100 ± 6
Pa_{CO₂} (mmHg)				
Normocapnic normoxemia	40 ± 3	40 ± 3	42 ± 3	40 ± 3
Hypocapnic hypoxemia	41 ± 3	35 ± 6†¶	33 ± 6‡¶	38 ± 3¶
Hyperventilation	41 ± 3	32 ± 9‡¶	31 ± 9‡¶	38 ± 3
Normocapnic hypoxemia	40 ± 3	43 ± 3***	41 ± 3	39 ± 3
Normal breathing	41 ± 3	41 ± 3	40 ± 3	41 ± 3
pH				
Normocapnic normoxemia	7.40 ± 0.03	7.40 ± 0.03	7.39 ± 0.03	7.40 ± 0.03
Hypocapnic hypoxemia	7.40 ± 0.03	7.46 ± 0.03‡¶	7.48 ± 0.06†¶	7.43 ± 0.03§
Hyperventilation	7.39 ± 0.03	7.48 ± 0.09†¶	7.50 ± 0.09†¶	7.42 ± 0.03¶
Normocapnic hypoxemia	7.40 ± 0.03	7.38 ± 0.03	7.40 ± 0.03	7.42 ± 0.03
Normal breathing	7.40 ± 0.03	7.40 ± 0.03	7.40 ± 0.03	7.40 ± 0.03

Values are mean ± SD; n = 8, except during hyperventilation in period 4 (n = 7).

Pa_{O₂} = arterial oxygen tension; Pa_{CO₂} = arterial carbon dioxide tension; period 1 = baseline; periods 2 and 3 = experimental periods with normocapnic normoxemia, hypocapnic hypoxemia, hyperventilation, normocapnic hypoxemia, or normal breathing without the face mask; period 4 = recovery.

*P < 0.05, †P < 0.01, ‡P < 0.001, versus normocapnic normoxemia.

§P < 0.05, ¶P < 0.01, **P < 0.001 versus baseline.

response to a level of hypoxemia close to where a transition in renal functional changes may occur. The mean Pa_{O₂} was higher during normocapnic hypoxemia when compared with hypocapnic hypoxemia, despite identical inspiratory oxygen fractions. More than likely this was caused by the effects of inspired carbon dioxide, which is known to improve overall respiratory gas exchange by reducing dead space and ventilation-perfusion heterogeneity³⁴ and by the higher increase in ventilation on the study day with carbon dioxide supplement. Compared with the other study days, both the higher ventilation and the lesser degree of hypoxemia may have reduced renal sympathetic nerve activity because of more extended stimulation of inhibitory pulmonary mechanoreceptors^{1,10} and less hypoxic chemoreceptor stimulation. Both mechanisms would tend to promote renal perfusion and the excretion of sodium and water, so comparisons between the study day with normocapnia and study days with hypocapnia should be interpreted cautiously.

In the first hours during moderate hypoxemia (F_iO₂ ~10–14%), an increase in the renal excretion of sodium and water has been observed in humans,^{16,19–21} dogs,^{15,18} cats,³⁵ and rats.¹⁷ Studies of humans and rats

have shown that respiratory alkalosis with or without hypoxemia may increase the excretion of sodium, water, and chloride and that this response is associated with an increase in urine pH and excretion rates of bicarbonate and potassium.^{20,23,24} The natriuretic response could be blunted by the addition of carbon dioxide.^{20,23} In conscious rats breathing 10% oxygen, respiratory alkalosis was associated with a decrease in renal tubular H⁺-ATPase, Na⁺-K⁺-ATPase, and H⁺-K⁺-ATPase activity.²⁵ In contrast to hypercapnia, which causes a marked increase in renal sympathetic nervous activity by stimulation of central chemoreceptors, normoxic hypocapnia only exerts minor changes in renal sympathetic nervous activity.³ These results suggest that during hyperventilation, the hypocapnia and the ensuing alkalosis may by themselves contribute to the natriuresis by decreasing the reabsorption of bicarbonate and sodium in the proximal tubule. Current lithium clearance studies show that hypocapnic alkalosis with or without hypoxemia decreases fractional proximal tubular reabsorption in healthy, sodium-repleted humans and that this effect within the proximal tubule is abolished when carbon dioxide is added to the hypoxic gas. In agreement with a specific effect of the respiratory alkalosis, the effect of

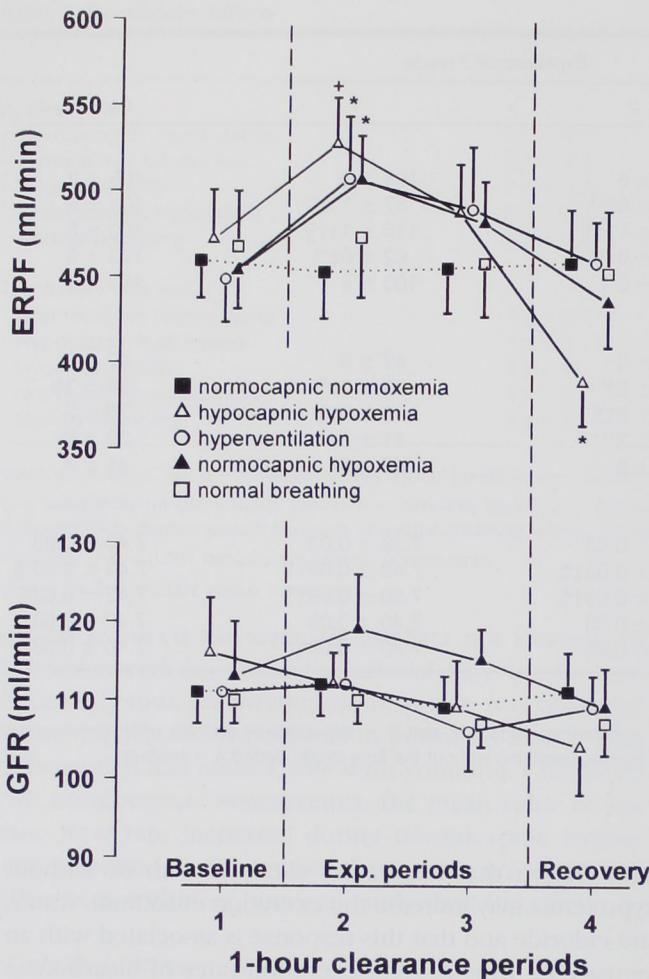


Fig. 2. Effects of normocapnic normoxemia, hypocapnic hypoxemia, hyperventilation, normocapnic hypoxemia, and normal breathing without the face mask on effective renal plasma flow and glomerular filtration rate. Values are the mean \pm SEM; $n = 8$. $^+P < 0.05$ compared with baseline and normocapnic normoxemia, $*P < 0.05$ compared with baseline.

carbon dioxide supplement occurred despite increased ventilation and less pronounced hypoxemia on this study day.

However, the decreases in proximal tubular reabsorption induced by hypocapnia were small, and the functional significance remains doubtful. Hypoxic natriuresis may occur during normocapnic conditions in conscious dogs,¹⁵ and also it has been shown that the sodium excretion exceeds bicarbonate excretion during respiratory alkalosis in hypoxic humans.^{24,36} In humans, voluntary hyperventilation produced natriuresis even when hypocapnia was prevented by the addition of carbon dioxide.³⁷ Furthermore, it was shown recently that the hypoxia-induced increase in sodium excretion in hu-

mans correlated positively with the magnitude of the hypoxic ventilatory response but not with bicarbonate excretion, as would have been expected if the natriuresis was caused primarily by inhibition of proximal tubular bicarbonate reabsorption.²¹ The current finding of a maintained hypoxia-induced natriuresis despite carbon dioxide supplement is in accordance with those studies, indicating that inhibition of proximal tubular reabsorption is not essential to produce the net natriuresis.

The sensitivity of peripheral chemoreceptors to hypoxemia depends on the arterial carbon dioxide level so

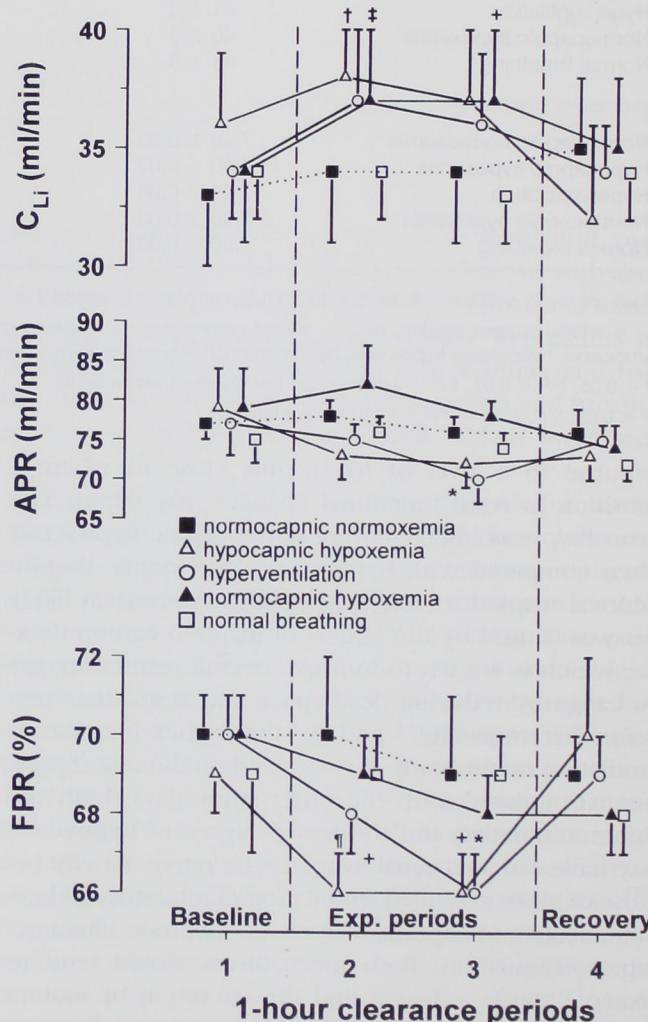


Fig. 3. Effects of normocapnic normoxemia, hypocapnic hypoxemia, hyperventilation, normocapnic hypoxemia, and normal breathing without the face mask on renal lithium clearance (C_{Li}), absolute proximal reabsorption (APR), and fractional proximal reabsorption (FPR). Values are the mean \pm SEM; $n = 8$. $^+P < 0.05$, $^{\dagger}P < 0.001$ compared with normocapnic normoxemia and baseline, $*P < 0.05$, $\#P < 0.01$ compared with normocapnic normoxemia, $\ddagger P < 0.01$ compared with baseline.

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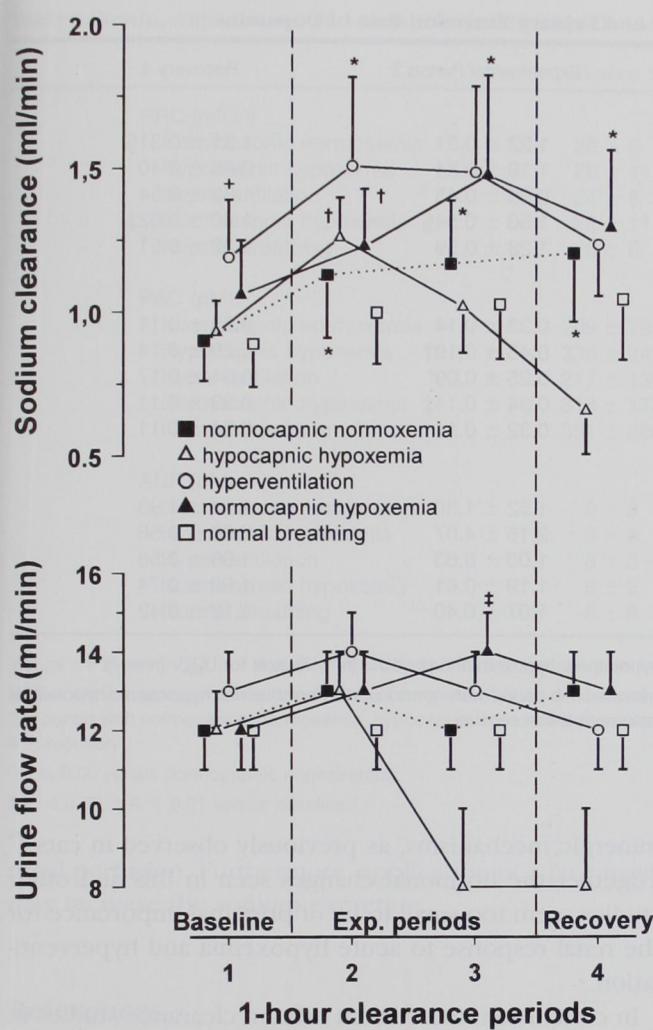


Fig. 4. Effects of normocapnic normoxemia, hypocapnic hypoxemia, hyperventilation, normocapnic hypoxemia, and normal breathing without the face mask on sodium clearance and urine flow rate. Values are the mean \pm SEM; $n = 8$. * $P < 0.05$, † $P < 0.01$ compared with normocapnic normoxemia, * $P < 0.05$, † $P < 0.01$ compared with baseline.

that hypocapnia decreases the firing rate of chemoreceptor fibers in response to a particular level of hypoxemia.¹ Therefore, in hypoxic conditions, hypocapnia may improve renal function by decreasing sympathetic vasoconstrictor outflow and in turn renal sympathetic nervous activity. In conscious dogs, combined hypoxemia and hypercapnia decreased renal blood flow.^{12,38} However, during hypocapnic hypoxemia, renal blood flow increased but remained unchanged when normocapnia was achieved by the addition of carbon dioxide to the hypoxic gas.^{12,15} A similar effect of carbon dioxide supplement has been observed in rats.²² In line with this, other studies in unanesthetized, spontaneously breath-

ing rats,^{8,39} dogs,¹⁴ and humans¹⁶ showed that hypocapnic hypoxemia may increase renal perfusion. In addition, it has been shown that hypocapnic hypoxemia elicits vasodilation in cerebral, coronary, splanchnic, and skeletal muscle circulations.^{1,39-41}

The current renal clearance studies confirm that acute hypocapnic hypoxemia increases renal perfusion but also clearly show that this response may be produced by normoxic hyperventilation alone. In contrast to previous findings in dogs and rats,^{12,15,22} an equal increase in ERPF occurred during normocapnic hypoxemia. Although this may argue against a significant role of hypocapnia as a contributing factor in producing the renal vasodilation, it cannot be excluded that renal vascular effects of the more pronounced ventilation on the study day with normocapnia counteracted the effect of the carbon dioxide supplement. It is well known that activation of intrathoracic stretch receptors inhibits renal sympathetic nervous activity¹⁰ and that the vasoconstrictor response to chemoreceptor stimulation can be abolished by hyperventilation.^{1,12,42,43} Local vascular effects of hypoxia mediated by the release of adenosine seem to be less expressed in the kidneys than in other organ systems³⁹; the current finding of a similar increase in ERPF during normoxic and hypoxic hyperventilation indicates that locally induced vasodilating effects of hypoxia on the renal vessels did not play a major role. Together, the current results suggest that increased ventilation rather than hypocapnia and hypoxemia caused the increases in ERPF. Even small changes in renal blood flow can greatly influence sodium excretion with or without concomitant changes in GFR.⁴⁴ Similar to drug-induced renal vasodilation, it is possible that the natriuretic responses were caused, in part, by alterations in medullary hemodynamics, renal interstitial pressure secondary to an increase in medullary blood flow, or both.^{45,46} Such an effect may decrease fluid and solute reabsorption in the loop of Henle,⁴⁵ but more studies are needed to clarify this issue.

Acute hypoxemia increases cardiac output mainly by an increase in heart rate.⁴⁷ The current study confirms that short-term hypocapnic hypoxemia in persons at rest does not increase plasma norepinephrine concentrations.⁴⁰ The increase in heart rate may be secondary to stimulation of central chemoreceptors.^{3,7} The absence of a chronotropic response to normoxic hyperventilation does not confirm a role in hypoxemia of reduced vagal activity secondary to stimulation of pulmonary mechanoreceptors, as previously proposed.¹ Circulating levels of catecholamines slightly increased on the study

Table 4. Plasma Concentrations of Norepinephrine and Epinephrine and Urinary Excretion Rate of Dopamine

	Baseline 1	Experimental Period 3	Recovery 4
Norepinephrine (nM)			
Normocapnic normoxemia	1.06 ± 0.31	1.22 ± 0.31	1.31 ± 0.31§
Hypocapnic hypoxemia	1.28 ± 0.37	1.19 ± 0.34	0.96 ± 0.40
Hyperventilation	1.17 ± 0.45	0.95 ± 0.45	1.32 ± 0.54
Normocapnic hypoxemia	1.15 ± 0.42	1.50 ± 0.54§	1.40 ± 0.62‡
Normal breathing	1.28 ± 0.82	1.28 ± 0.59	1.32 ± 0.51
Epinephrine (nM)			
Normocapnic normoxemia	0.29 ± 0.14	0.33 ± 0.14	0.33 ± 0.11
Hypocapnic hypoxemia	0.34 ± 0.14	0.48 ± 0.19†	0.29 ± 0.14
Hyperventilation	0.26 ± 0.11	0.25 ± 0.09*	0.34 ± 0.17
Normocapnic hypoxemia	0.28 ± 0.11	0.34 ± 0.14‡	0.33 ± 0.11
Normal breathing	0.28 ± 0.14	0.32 ± 0.14	0.34 ± 0.11
$U_{DA}V$ ($\mu\text{mol}/\text{min}$)			
Normocapnic normoxemia	1.62 ± 1.38	1.52 ± 1.30	1.74 ± 1.93
Hypocapnic hypoxemia	1.75 ± 2.14	2.15 ± 4.07	0.96 ± 0.56
Hyperventilation	0.97 ± 0.64	1.00 ± 0.63	1.08 ± 0.58
Normocapnic hypoxemia	0.98 ± 0.53	1.19 ± 0.61	1.08 ± 0.74
Normal breathing	0.99 ± 0.40	1.07 ± 0.40	1.12 ± 0.42

Values are mean ± SD; n = 8, except for norepinephrine and epinephrine during hypocapnic hypoxemia in period 3 (n = 7), and for $U_{DA}V$ (n = 7).

$U_{DA}V$ = renal excretion rate of dopamine; period 1 = baseline; period 3 = last experimental 1-h period with normocapnic normoxemia, hypocapnic hypoxemia, hyperventilation, normocapnic hypoxemia, or normal breathing without the face mask; period 4 = recovery.

*P < 0.05, †P < 0.01, versus normocapnic normoxemia.

‡P < 0.05, §P < 0.001 versus baseline.

day with normocapnic hypoxemia, but concentrations were well below the threshold values previously reported as necessary to produce significant cardiovascular effects.⁴⁸ Nonetheless, it cannot be excluded that the observed increases in cardiac output on the study days with hypoxemia and hyperventilation contributed to the increases in ERPF and sodium excretion.

The increase in C_{Na} seen during normocapnic normoxia with but not without the face mask indicates that application of a face mask may increase sodium excretion without changing renal hemodynamics. In a previous study in humans, spontaneous breathing of room air through a low external airway resistance (a thin valve) led to an increase in the urine flow rate.³⁷ A possible mechanism could be pulmonary and atrial stretch receptor stimulation secondary to an increased airway pressure and an increase in central venous pressure during valve breathing.³⁷ However, the associated intrarenal functional changes remain unknown.

The small changes in plasma renin and aldosterone concentrations found in this study correspond with previous data.^{19,21,49–52} The increase in atrial natriuretic peptide during the two study days with hypoxemia supports previous findings.^{51,53} Our results provide no evidence of hypoxia-induced activation of intrarenal dopa-

minergic mechanisms, as previously observed in cats.³⁵ Together the hormonal changes seen in this and other studies seem too small to be of principal importance for the renal response to acute hypoxemia and hyperventilation.

In conclusion, the current lithium clearance studies in humans indicate that normoxic and hypoxic hypocapnia both decrease renal proximal tubular reabsorption and that this effect can be abolished by the addition of carbon dioxide to produce normocapnic hypoxemia. However, hypoxia-induced natriuresis occurred despite carbon dioxide supplement, indicating that mechanisms other than inhibition of proximal tubular reabsorption contribute to the natriuresis. The current renal clearance studies revealed that acute hypocapnic and normocapnic hypoxemia both increase renal perfusion, but also showed that this response may also be produced by normoxic hyperventilation. This suggests that increased ventilation rather than changes in arterial oxygen and carbon dioxide levels caused the increases in ERPF. Changes in renal blood flow often are associated with changes in medullary hemodynamics and distal tubular sodium reabsorption,^{44,45} and the observed natriuresis may, at least in part, be secondary to the increases in

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Table 5. Renin, Aldosterone, and Atrial Natriuretic Peptide (ANP)

	Baseline 1	Experimental Period 3	Recovery 4
PRC (mIU/l)			
Normocapnic normoxemia	28 ± 6	26 ± 5†	24 ± 5†
Hypocapnic hypoxemia	28 ± 11	24 ± 11	22 ± 11†
Hyperventilation	24 ± 8	20 ± 8‡	19 ± 5‡
Normocapnic hypoxemia	26 ± 11	19 ± 8‡	19 ± 5†
Normal breathing	26 ± 8	24 ± 8‡	24 ± 8†
PAC (pM)			
Normocapnic normoxemia	209 ± 79	200 ± 74	236 ± 138
Hypocapnic hypoxemia	335 ± 249	213 ± 108	150 ± 66
Hyperventilation	217 ± 130	109 ± 34*	117 ± 32
Normocapnic hypoxemia	313 ± 178	145 ± 40†	127 ± 29†
Normal breathing	351 ± 280	349 ± 320	288 ± 225
ANP (pM)			
Normocapnic normoxemia	9 ± 3	8 ± 3	7 ± 3
Hypocapnic hypoxemia	9 ± 6	12 ± 6*†	9 ± 3
Hyperventilation	8 ± 3	10 ± 6	7 ± 3
Normocapnic hypoxemia	8 ± 3	12 ± 6*†	9 ± 3
Normal breathing	8 ± 6	7 ± 3	7 ± 3

Values are mean ± SD; n = 8, except for PRC and PAC in periods 3 and 4 (n = 7), and for ANP during hypocapnic hypoxemia in period 4 (n = 7).

PRC = plasma renin concentration; PAC = plasma aldosterone concentration; ANP = atrial natriuretic peptide; period 1 = baseline; period 3 = last experimental 1-h period with normocapnic normoxemia, hypocapnic hypoxemia, hyperventilation, normocapnic hypoxemia, or normal breathing without the face mask; period 4 = recovery.

* P < 0.05 versus normocapnic normoxemia.

† P < 0.05, ‡ P < 0.01 versus baseline.

renal perfusion. Furthermore, application of a face mask may increase the sodium excretion.

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