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RAPID REPORT

Urinary physiology and hypoxia: a pilot study of moderate-altitude trekking effects on urodynamic indexes

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Verratti V, Mrakic-Sposta S, Moriggi M, Tonacci A, Bhandari S, Migliorelli D, Bajracharya A, Bondi D, Agrò EF, Cerretelli P. Urinary physiology and hypoxia: a pilot study of moderate-altitude trekking effects on urodynamic indexes. *Am J Physiol Renal Physiol* 317: F1081–F1086, 2019. First published August 28, 2019; doi: 10.1152/ajprenal.00333.2019.—Exposure to high altitude is one of the most widely used models to study the adaptive response to hypoxia in humans. However, little is known about the related effects on micturition. The present study addresses the adaptive urinary responses in four healthy adult lowlanders, comparing urodynamic indexes at Kathmandu [1,450 m above sea level (a.s.l.); K^{1450}] and during a sojourn in Namche Bazar (3,500 m a.s.l.; NB^{3500}). The urodynamic testing consisted of cistomanometry and bladder pressure/flow measurements. Anthropometrics, electrocardiographic, and peripheral capillary oxygen saturation data were also collected. The main findings consisted of significant reductions in bladder power at maximum urine flow by ~30%, bladder contractility index by 13%, and infused volume both at first (by 57%) and urgency sensation (by 14%) to urinate, indicating a reduced cystometric capacity, at NB^{3500}. In addition to the urinary changes, we found that oxygen saturation, body mass index, body surface area, and median RR time were all significantly reduced at altitude. We submit that the hypoxia-related parasympathetic inhibition could be the underlying mechanism of both urodynamic and heart rate adaptive responses to high-altitude exposure. Moreover, increased diuresis and faster bladder filling at altitude may trigger the anticipation of being able to void, a common cause of urgency. We believe that the present pilot study represents an original approach to the study of urinary physiology at altitude.

altitude hypoxia; autonomic nervous system; trekking; urinary physiology; urodynamics

INTRODUCTION

At high altitude, there is a progressive alveolar P_{O_2} reduction with a concomitant decrease in arterial P_{O_2}. Hypoxia causes a low peripheral oxygen supply and adaptive responses of organ systems. Changes occur in the cardiovascular and ventilatory systems, muscular bioenergetic activity, energy and water homeostasis, oxidative processes, lymphocyte function, and human reproduction (4, 8, 19, 32). Another physiological function, which seems modified by altitude exposure, is micturition (6, 21, 31, 33).

The lower urinary tract has a complex physiological function easily impaired by internal and external factors. The physiological urothelial barrier and detrusor muscle activity are influenced by an adequate blood oxygen supply (21). A reduction in bladder blood flow elicits chronic moderate bladder ischemia and enhanced contractility of bladder smooth muscles in response to stimulation. Chronic severe bladder ischemia, on the other hand, produces oxidative stress and functional detriment of muscle contractility (35). The bladder responds to chronic hypoxia with reduced compliance, detrusor instability, and increased spontaneous contraction, causing interalia nocturia (34). Hence, hypoxia is posed to have an impact on urinary physiology, but the knowledge on this topic is still limited (26). Pioneering studies attributed the reduction in caliber and force of the urinary stream to factors such as vibrations, noise, and temperature rather than altitude per se (6). Hypoxia can induce micturition changes by direct and indirect actions involving different neurological and humoral systems. Neurological control of the bladder-urethral unit is governed by somatic and autonomic neural fibers; in particular, parasympathetic pelvic plexus nerves cause bladder detrusor excitation, stimulating the emptying reflex, while the activation of sympathetic nerves inhibits the detrusor muscle with bladder body relaxation and a simultaneous contraction of the bladder neck and proximal urethra, thus promoting continence (12, 14).

Several works have investigated the autonomic system activity at high altitude, expressed through heart rate (HR) variability (HRV) changes, showing an overall increase in the ratio of low-frequency (LF) to high-frequency (HF) bands (LF/HF) (7, 13). Indeed, high altitude is one of the extrinsic factors decreasing HRV and increasing sympathetic activity, especially when non-native individuals perform a rapid ascent. On the other hand, high-altitude natives experience reduced sympathetic activation when performing the same ascent, which holds true even after sea level acclimatization (1, 5, 18).

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Apart from the pathological reasons, lower urinary tract symptoms, notably urinary urgency, become prevalent with aging (36). There are reductions in both oxygen tissue demand and oxygen tissue supply, developing with age (3). Thus, natural hypoxia at high altitude constitutes an enticing experimental model for studying urinary alterations. In the present study, we simultaneously investigated adaptive urodynamic and HRV responses in individuals native to sea level during a 7-day-long trek at moderate altitude. The study, which is the first of its kind, to the best of our knowledge, was designed to test the feasibility of a high-altitude hypoxia model in the assessment of physiological urinary regulation and to provide preliminary data on the adaptive urodynamic responses to altitude.

MATERIALS AND METHODS

Participants, altimetric plan, and study protocol. The present study is a subset of the research project "Environmentally-modulated metabolic adaption to hypoxia in altitude natives and sea-level dwellers: from integrative to molecular (proteomics, epigenetics, and ROS) level" approved by the Ethical Review Board of the Nepal Health Research Council. All study procedures were performed in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all study participants.

The study was carried out during a lightweight expedition of four healthy, Caucasian lowlander trekkers (2 women, 39 and 37 yr old, and 2 men, 48 and 46 yr old) living in Italy at sea level. A preliminary assessment of health status, with regard to hypertension, hypercholesterolemia, diabetes, etc., of each participant, was performed. All of them did not have any urological or metabolic dysfunction before the trip. All participants were nonsmokers. The measurements of the indexes assessed in the study were performed twice, each at a distinctly different altitude: *1*) Kathmandu [1,450 m above sea level (a.s.l.); K^{1450}] before the expedition (*day 1*) and *2*) during a sojourn in Namche Bazar (3,500 m a.s.l.; NB^{3500}) on *day 7* (Fig. 1). During the preparations and expedition, participants did not follow an individualized dietary program, but we administered nutritional instructions with a standardized dietary intake of ~65% carbohydrates, 20% lipids, and 15% proteins; the participants avoided any antioxidant supplementation and/or drugs, abstained from alcohol consumption, and drank ~2 liters of mineral water every day.

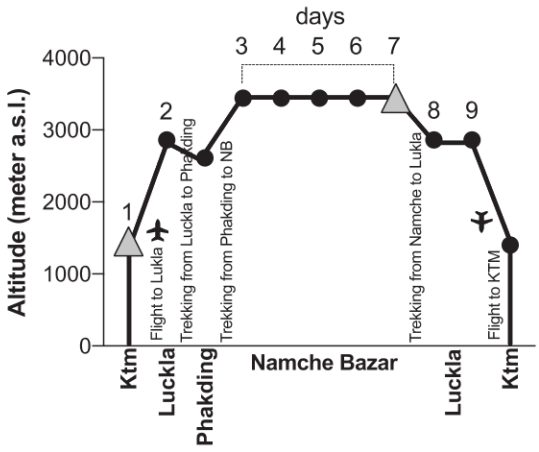

Fig. 1. Timeline and altimetric profile of the expedition. The *y*-axis shows altitude (in m); the *x*-axis shows the day-to-day proceedings with place names. The large gray triangles indicate the times and altitudes of each data collection. KTM, Kathmandu; NB, Namche Bazar.

Measurements and tests. Body mass index and body surface area were calculated on the basis of the participants' height and weight. For body surface area, the Du Bois formula was used: $0.20247 \times \text{height (in m)}^{0.725} \times \text{weight (in kg)}^{0.425}$. Peripheral capillary oxygen saturation was measured with pulse oximetry with the study participant at rest (503 OXY-5 GIMA, Gima, Gessate, Italy).

Standard urinalysis was performed using urine test strips (Combi screen 11sys PLUS, Gima, Gessate, Milan, Italy) to detect red blood cells, white blood cells, and biochemical indexes such as protein, ketones, bilirubin, urobilinogen, and glucose. These tests were performed in triplicate in each study participant.

Urodynamic examinations were performed with an Albyn Smart-Dyn Peristaltic Infusion Pump, a weight subtraction sensor for recording real-infused volume, three pressure channel "bladder, abdominal, and urethral" flow sensor; bladder scanner Caresono HD2 with sectoral probe 3D (Caresono Technology, Dandong, Liaoning, China); bladder double lumen, six catheters (288426, Albyn Medical); and double lumen rectal catheters with balloon, 9 (4114AE, Wiest, Albyn Medical, Navarra, Spain). The urodynamic tests were performed at two different altitudes: K^{1450} and NB^{3500}. They were conducted according to the following paradigm: *1*) verification of the system's calibration, *2*) estimation of bladder volume with a scanner to check for emptying flaws, *3*) execution of uroflowmetry, *4*) evaluation of a postvoid residual, *5*) insertion of a vesical catheter (6 Ch), and *6*) insertion of a rectal catheter. Urodynamic testing involved cistomanometry to assess bladder function during its filling and a pressure/flow investigation to assess bladder function during its emptying, which were performed according to International Continence Society guidelines (25).

Electrocardiographic recordings. Electrocardiography (ECG) was acquired during 5 min of rest in a supine position. The acquisition system consisted of a lightweight (≈50 g) chest strap developed by the National Research Council of Italy (Shimmer Research, Cambridge, MA), with a sampling frequency of 100 Hz and an algorithm of interpolation to refine R peaks (2, 20). ECG signals were processed in MATLAB (MathWorks, Natick, MA) in a stepwise process: Kalman filter, IIR filter (order 29 and bandwidth: 25–35 Hz), and parabolic interpolation. The Pan-Tompkins method for the detection of the QRS complex and the parametric autoregressive Yule-Walker model (order 9) for the calculation of power spectrum density were then applied. The median RR time and standard deviation of RR intervals (SDRR) were calculated. LF (0.03–0.15 Hz) and HF (0.15–0.40 Hz) power bands were estimated and turned into the LF-to-HF power ratio.

Statistical elaboration. Data are presented as means ± SD. Data distribution was checked with the Shapiro-Wilk test. Statistical differences were assessed with a two-tailed paired *t*-test. Percent changes, defined as [(post NB^{3500} − pre K^{1450})/pre K^{1450}] were used to assess the effects of hypoxia. Analysis was performed using the commercial GraphPad Prism v8.0 package (GraphPad Software, San Diego, CA), G*Power software version 3.1.9.3 (http://www.gpower.hhu.de), and the R-based open-source software Jamovi (https://www.jamovi.org).

RESULTS

No significant health problems were recorded during the trek in any of the study participants. In particular, there were no changes in bowel pattern or constipation. None of them required medications such as nonsteroidal anti-inflammatory drugs or altitude sickness treatments. Weather conditions were perfect, with dry sunny days and moderate cold throughout the whole period. As expected, oxygen saturation significantly dropped at the higher altitude of NB^{3500} ($P = 0.007$, Cohen's $d = 3.395$, $1\text{-}\beta = 0.620$) (Table 1). Body mass index and body surface area were also significantly reduced by altitude ($P =$

Table 1. *Anthropometric and physiological parameters of study participants at lower and higher altitudes*

	Kathmandu (1,450 m above sea level)				Namche Bazar (3,500 m above sea level)			
	M (I)	M (II)	F (I)	F (II)	M (I)	M (II)	F (I)	F (II)
Weight, kg	90	94	55	65	87	90	53	63
Body mass index, kg/m^2	27.8	28.1	20.5	23.9	26.9	26.9	19.7	23.2
Body surface area, m^2	2.1	2.2	1.6	1.7	2.1	2.1	1.6	1.7
Oxygen saturation, %	96	99	97	92	94	95	94	88

M, male; F, female.

0.004, Cohen's $d = 4.147$, 1-β = 0.628, and $P = 0.005$, Cohen's $d = 3.674$, 1-β = 0.588, respectively) (see Table 1).

Standard urinalysis failed to disclose any signs of inflammatory state in the urinary tract (Table 2). Regarding the urodynamic parameters, we found reductions in bladder power at maximum flow ($P = 0.045$, Cohen's $d = 1.668$, 1-β = 0.583) and in the bladder contractility index at NB^{3500} ($P = 0.026$, Cohen's $d = 2.070$, 1-β = 0.592). Furthermore, we found a reduction in cystometric capacity, manifesting as a smaller urine volume, causing the sensation to void, both at first sensation ($P = 0.047$, Cohen's $d = 1.628$, 1-β = 0.577) and at urgency (maximal cystometric capacity; $P = 0.044$, Cohen's $d = 1.682$, 1-β = 0.582) (Fig. 2). In addition, we found a significantly lower median RR interval in ECG recordings ($P = 0.025$, Cohen's $d = 2.088$, 1-β = 0.587) at NB^{3500}, with appreciable changes in SDRR or the LF-to-HF ratio.

DISCUSSION

The ascent to NB^{3500}, despite being relatively low in distance and altitude, provoked typical effects of exposure to high altitude, such as weight loss, expressed by body mass index and body surface area reduction, urine specific gravity increment, and peripheral oxygen desaturation (8, 17). Concomitantly, urinary pH increased, which reflected a renal compensatory response conducive to altitude acclimatization (37). As expected, we found an increase in resting HR at NB^{3500}. Siebenmann et al. (27) have shown that inhibition of parasympathetic activity is the main mechanism to increase resting HR at a similar altitude in adult lowlanders. An analysis of HRV seemed to predominantly define the parasympathetic rather than sympathetic influence on rate (28). The absence of significant and uniform alterations in SDRR and the LF-to-HF ratio from K^{1450} to NB^{3500} may reflects the nonunique correspondence between psychophysiological state and LF and HF spectral power, which should be further explored with alternative approaches to HRV investigation (24).

The main finding of the present study was a modification of uroflowmetry by high-altitude hypoxia in healthy adult sojourners. Hypoxia can lead to bladder obstruction that increases intravesical pressure and causes bladder deformation and can impair metabolism of bladder smooth muscles. Using an automatic digital uroflowmeter, we have previously shown in young adult native lowlander women, that micturition is altered by an increase in flow time, flow volume, and voiding time during adaptation to hypoxia (33). In this study, high altitude provoked a reduction in bladder power at maximum flow and bladder contraction index. Among the various methods for assessing detrusor function, the bladder contraction index is considered highly practical and clinically informative; our results demonstrated a reduction in the index already taking place at a moderately high altitude, which is compatible with a mitigation of detrusor activity (23). The detrusor muscle plays a fundamental role in urinary function. The muscle is under the control of the autonomic nervous system, with sympathetic-driven relaxation and parasympathetic-driven contractility. Thus, it is a reasonable presumption that hypoxia-related downregulation of detrusor activity may be due to a detriment in neural input to the muscular bladder compartment, which discoordinates the delivery, collection, and expulsion of urine (10). On the other hand, a reduction in bladder power at maximum flow can likely be considered a consequence of lower parasympathetic tone. A small reduction in bladder capacity, leading to a small reduction in voided volume, was also noted in all study participants: although bladder voiding may impact flow, the observed reduction in voided volumes does not seem to be adequate to cause a significant reduction in maximal urinary flow rate and should have no impact on detrusor pressure. Thus, the reduction in bladder contraction

Table 2. *Urinalysis performed with a test strip at lower and higher altitudes*

	Kathmandu (1,450 m above sea level)				Namche Bazar (3,500 m above sea level)			
	M (I)	M (II)	F (I)	F (II)	M (I)	M (II)	F (I)	F (II)
Bilirubin, μmol/l	0	0	0	0	0	0	0	0
Urobilinogen, μmol/l	1	1	1	1	1	1	1	1
Ketones, mmol/l	6	5	5	5	7	7	7	6
Protein, mg/dl	0	0	0	0	0	0	0	0
Erythrocytes, μl	0	0	0	0	0	0	0	0
pH	7	6	5	5	7.5	6.5	5.5	7
Leukocytes, μl	0	0	0	0	0	0	0	0
Nitrite	0	0	0	0	0	0	0	0
Glucose	0	0	0	0	0	0	0	0
Specific gravity	1.025	1.020	1.020	1.025	1.025	1.025	1.025	1.030

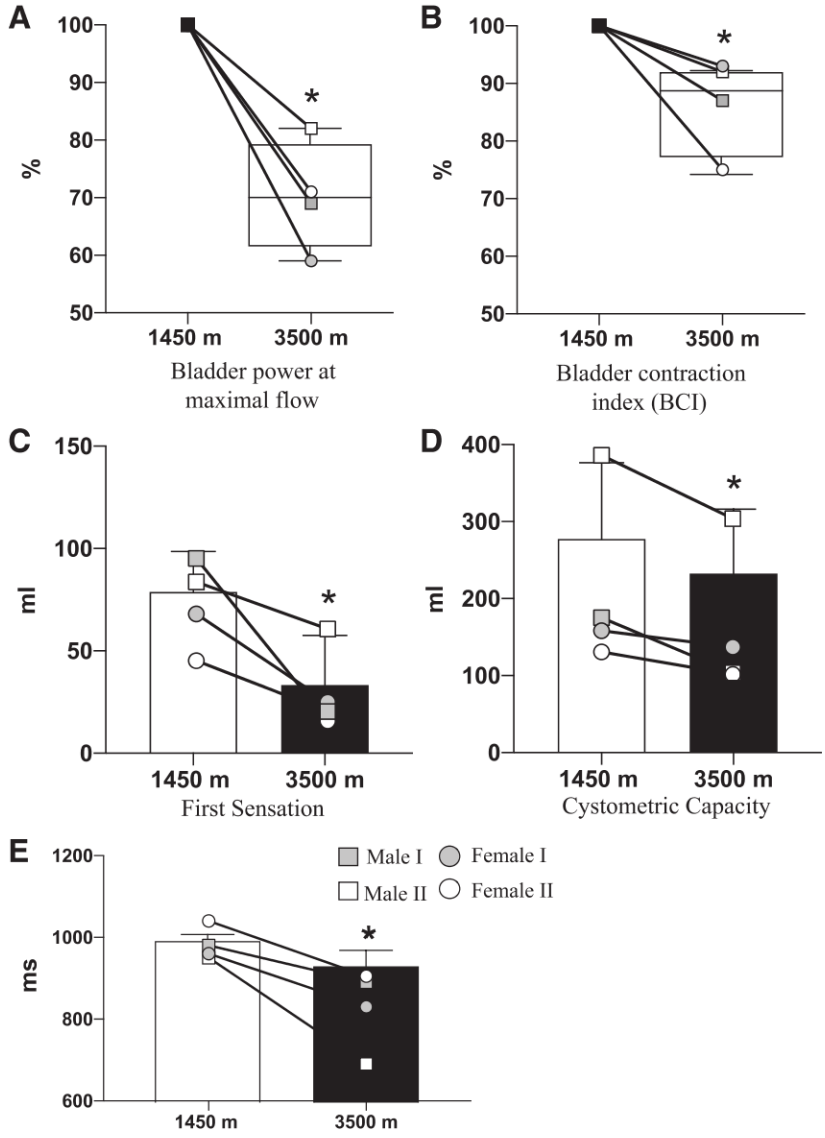

Fig. 2. *A* and *B*: individual values of bladder power at maximal flow and bladder contraction index (BCI) at 1,450 and at 3,500 m above sea level (a.s.l.). *C* and *D*: histograms (means ± SD) and individual values of infused volume of the first sensation to void and urgency (maximal cystometric capacity) at 1,450 and at 3,500 m a.s.l. *E*: histogram (means ± SD) and individual values of median RR time at 1,450 and at 3,500 m a.s.l.. $*P < 0.05$.

index and bladder power at maximum urine flow seems related to an intrinsic reduction of contractility, more than to the reduction in voided volume.

Regarding bladder sensitivity during the filling phase, high altitude reduces the ability to anticipate both the first sensation and cystometric capacity, suggesting that the activity of sensory fibers engaged in stretching of the bladder walls may be downregulated.

A second interpretative hypothesis on the appearance of the sensation to void has to do with an increase in the glomerular filtration rate and diuresis at altitude (9). Rapid filling due to an increased glomerular filtration rate enhances bladder pressure at a relatively low volume of the voiding stimulus (15). Bladder mechanoreceptors, which transduce bladder wall tension, are essential for micturition (30). Morrison (22) has described that rat bladder mechanoreceptors respond to distension, but not to contraction, and defined them as "volume" receptors. Thus, increased diuresis and faster filling at altitude may alter the volumetric stimulus of muscle-mucosal mechanoreceptors of the bladder wall, promoting the anticipation of a filling sensation. Like other visceral organs, the bladder has sensory innervation that can be altered by periodic exposure to hypoxia. There seems to be a biological plausibility that hypoxia-related parasympathetic inhibition could underlie both HR and urodynamic adaptations noticed in the present study.

In conclusion, to our knowledge, there has not yet been a study that has examined urodynamic responses in high-altitude sojourns. The understanding of urinary tract physiology at high altitude should be integrated by the evaluation of other organ systems, such as the nutritional, hormonal, immunological, and neurological systems (11, 16, 29), and should be complemented by long-term exposure to discriminate the effects of acclimatization. We believe that the preliminary findings of this study, notably reductions in bladder urodynamic function and cystometric capacity during exposure to higher altitude, are of interest to the physiology of mountaineering. These findings also could help with an understanding of the intertwined neural and myogenic signaling pathways related to bladder dysfunction in clinical hypoxic pathologies and in the process of aging that is conducive to chronic hypoxia as well.

An integrative approach to investigate the regulation of urinary function, with the emphasis on the effect of hypoxia on it, should be further explored with alternative study designs.

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GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

V.V. and P.C. conceived and designed research; V.V., S.M.-S., M.M., S.B., D.M., and A.B. performed experiments; V.V., S.M.-S., A.T., D.M., and D.B. analyzed data; V.V., S.M.-S., A.T., S.B., D.M., and D.B. interpreted results of experiments; S.M.-S. and D.B. prepared figures; V.V., S.M.-S., A.T., S.B., D.M., A.B., and D.B. drafted manuscript; V.V., S.M.-S., M.M., A.T., S.B., D.M., A.B., D.B., E.F.A., and P.C. edited and revised manuscript; V.V., S.M.-S., M.M., A.T., S.B., D.M., A.B., D.B., E.F.A., and P.C. approved final version of manuscript;

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