Am J Physiol Renal Physiol 311: F562–F566, 2016.
First published June 29, 2016; doi:10.1152/ajprenal.00284.2016.

The influence of altitude hypoxia on uroflowmetry parameters in women

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Submitted 5 May 2016; accepted in final form 24 June 2016

Verratti V, Paulesu L, Pietrangelo T, Doria C, Di Giulio C, Aloisi AM. The influence of altitude hypoxia on uroflowmetry parameters in women. *Am J Physiol Renal Physiol* 311: F562–F566, 2016. First published June 29, 2016; doi:10.1152/ajprenal.00284.2016.—There is scientific evidence to suggest a correlation between hypoxia and the physiology of micturition. During a Himalayan Scientific and Mountaineering Expedition, we performed tests to investigate the functional interactions between altitude hypoxia and uroflowmetry parameters in women. The tests were carried out in seven women (36.3 ± 7.1 yr) from normoxic [1,340 meters above sea level (m a.s.l.)] to hypoxic conditions (up to 5,050 m a.s.l.) and during the return descent. The following measures were determined: uroflowmetry parameters and saturation of peripheral oxygen (Sp_{O_2}). As expected, Sp_{O_2} decreased from 97.7 to 77.8% with increasing altitude. Micturition flow time, flow volume, and voiding time increased with altitude ($P < 0.04$ for all), indicating a negative correlation with Sp_{O_2}. In conclusion, in young adult women, micturition physiological parameters were affected during adaptation to hypoxia; the correlation with Sp_{O_2} strongly suggests a role of hypoxia in these changes. These data could help to support the design of new strategies for both prevention and medical treatment. An example of the latter might be hyperbaric oxygen therapy, which in some studies has proved able to reduce the symptoms in patients with hypoxic bladder.

uroflowmetry; hypoxia; altitude; female; micturition

High-Altitude Environment

THERE IS A NEGATIVE CORRELATION between altitude and air density. Hence, during the ascent to high altitude the P_{O_2} in ambient air shows a progressive decrease with a concomitant alveolar P_{O_2} reduction, producing a state of low P_{O_2} (Pa_{O_2}), also called hypoxemia. This condition is followed by a low peripheral oxygen supply and an adaptive physiological response involving the organism as a whole (acclimatization). Indeed, subjects exposed to altitude show several changes in their physiological functions to adapt their body to the new situation and these changes are mostly due to hypoxemia.

Changes caused by hypoxia occur in the cardiovascular and ventilator response, in the bioenergetics of muscular activity, energy, water, and oxidative processes, in lymphocyte functions, and human reproduction (5, 7, 20, 24, 27). Another physiological function that seems to be modified by exposure to high altitude and by hypoxemia is micturition (6).

Physiology of Micturition

Micturition is a complex physiological function easily impaired by internal and external factors, with important consequences for the quality of life, particularly in aged subjects. The function of the lower urinary tract is to collect and store urine at low intravesical pressure and then expel it periodically (urination) by means of a highly coordinated sustained contraction (18).

The roles of oxygen in the physiology and pathophysiology of micturition. Detrusor activity is influenced by blood oxygen supply (22). It has been argued that a reduction in bladder blood flow induces chronic moderate bladder ischemia, detrusor overactivity, and an increase in smooth muscle contractility in response to stimulation, while chronic severe bladder ischemia can produce oxidative stress (29) and functional alterations of detrusor contractility (3). As shown by Koritsiadis et al. (17), the bladder response to chronic hypoxia is limited in time and might depend on the functional status of the detrusor. In addition, the hypoxic state, typical of obstructive sleep apnea, causes ultrastructural and pathophysiological changes, with bladder detrusor instability, bladder noncompliance, nocturia, and an increase in spontaneous contractions (28).

We agree that hypoxia influences detrusor activity. However, it is necessary to clarify some aspects. One of the factors underlying the physiopathological mechanisms of lower urinary tract symptoms (LUTS) might be chronic bladder ischemia (29). Furthermore, these studies are focused on pathological conditions, such as obstruction of bladder outflow in males and atherosclerosis in both sexes (29), which present such overall complexity that it becomes difficult to distinguish the role of bladder hypoxia in the development of LUTS. Many studies that attempt to relate bladder function to hypoxia consider bladder wall hypoxia a physiopathological consequence of altered blood flow to the bladder secondary to bladder outflow obstruction (2, 8–10, 19, 26). Although, the normal bladder maintains a high oxygen saturation level during filling (25), some authors have found that bladder obstruction can produce hypoxia of the bladder wall, directly related to physiopathological changes such as increased intravesical pressure (21), mechanical deformation of human bladder smooth muscle, increased bladder smooth muscle mass, increased metabolic requirements of the detrusor muscle, and, above all, bladder overactivity, which causes mechanical compression of the arteries regulating the oxygen supply (8, 21, 25). It seems clear that the hypoxic suffering of the bladder wall is related to these structural and functional modifications, but the exact physiological and physiopathological mechanisms regulating the relationship between these bladder modifications and the low saturation of peripheral oxygen (Sp_{O_2}) levels in the blood are not yet known (25). On the other hand, it has been observed that LUTS are not necessarily related to bladder outlet obstruction (BOO), and it is increasingly clear that pelvic ischemia could be a primary factor in the onset of a nonobstructed,

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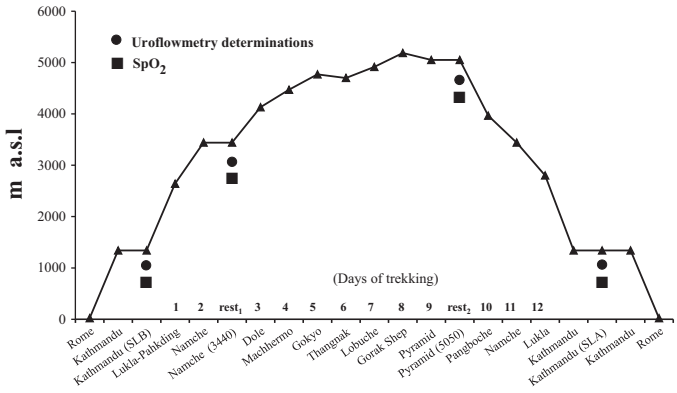

Fig. 1. Altimetric profile of the "Gokyo Khumbu/Ama Dablam Trek 2012" Expedition and experimental determination phases in the expedition timeline. The single altitudes refer to altitudes overnight.

nonneurogenic overactive bladder, which may cause a malfunction of lower urinary tract structures (32).

From a certain point of view, the hypoxic model of our study shows some similarities to bladder wall hypoxia, secondary to bladder blood flow alteration or to a state of bladder overactivity, one of the LUTS increasingly prevalent with aging (19, 30–31).

Unfortunately, the scientific literature includes only one article in which the physiology of micturition was studied in subjects exposed to progressive hypoxic changes. This pioneering study, conducted by Cockett's group on sixteen male Air Force subjects, was carried out in a hypoxic chamber simulating an altitude of 6,000 meters above sea level (m a.s.l). The authors showed a reduction in urodynamic parameters at altitudes above 4,000 m a.s.l; interestingly the changes were attributed to factors such as vibration, noise and temperature rather than altitude per se (6).

Aim

Since the urinary system is affected by hypoxia, we carried out tests at different altitudes during a Himalayan Scientific and Mountaineering Expedition "Gokyo Khumbu/Ama Dablam Trek 2012" to determine the influence of altitude hypoxia on uroflowmetry parameters in women[1].

MATERIALS AND METHODS

Subjects

The study was carried out in seven well-trained, healthy, fertile females (36.3 ± 7.1 yr old) resident at sea level. To participate, each subject signed a "declaration of risk acceptance and assumption of responsibility" and authorized the personal data collection and processing. The study was approved by the Bioethics Committee of "G. d'Annunzio" University of Chieti-Pescara, Italy (protocol no. 773 COET) and was designed in accordance with the recommendations of the Declaration of Helsinki.

Experimental Study Protocol

During the scientific trek expedition, several parameters were determined in each subject, as reported in Fig. 1. The experimental evaluations were carried out four times. Two normoxic evaluations were carried out, one before (Fig. 1*B*) and one after (Fig. 1*A*) the trek at Kathmandu (1,340 m a.s.l.), which conventionally we consider sea level (SL_B and SL_A). Two hypoxic evaluations were carried out at altitude at Namche Bazaar, 3,440 m a.s.l. ($Namche_{3440}$) and at the EV-K2-CNR Pyramid Laboratory, 5,050 m a.s.l. ($Pyramid_{5050}$) (Fig. 1).

Measurements

Sp_{O_2}. As shown in Fig. 2, Sp_{O_2} was recorded in normoxic conditions at SL_B and SL_A and at altitude at $Namche_{3440}$ and $Pyramid_{5050}$ by means of pulse oximetry from the fingertip with the subject at rest (503 OXY-5 GIMA, Gima S.p.A., Gessate, Italy).

Uroflowmetry. A Microflo II Digital Automatic Uroflowmeter (Life-Tech, Sanford, TX) was used to record the uroflowmetry parameters. To avoid any external influence, the equipment was installed in a quiet, comfortable bathroom (temperature 17–21°C) exclusively dedicated to the experiment during the pauses between stages of the trek (12). Uroflowmetry was carried out twice in normoxic conditions at SL_B and SL_A and twice at altitude: once at $Namche_{3440}$ and once at $Pyramid_{5050}$ (Fig. 1). Data are reported as the mean of two to three

[1] The 21-day "Gokyo Khumbu/Ama Dablam Trek 2012" expedition started in Rome on October 23, 2012, and ended in the same city on November 12, 2012. After the flight from Rome to Kathmandu, Nepal, the expedition group stayed for 2 days in Kathmandu (October 24 and 25) to obtain permits, to carry out experiments, and to define organizational, managerial, and strategic activities for the high-altitude trek. On October 26, the group flew from Kathmandu to Lukla (2,800 m a.s.l) where the altitude trek started on the same day via Phakding. The altitude trek lasted 14 days (from October 26 to November 8), with 12 days of real trekking at moderate and high altitude and 2 days spent at rest at altitude: one for acclimatization in Namche Bazaar (3,440 m a.s.l) (*day 3*) and one at the EV-K2-CNR Pyramid laboratory (5,050 m a.s.l) (*day 11*). The end of the trek coincided with the return to Lukla on November 8 and the return to Kathmandu on November 9, which ended the hypoxic experience for the expedition members (Fig. 1). The total walking distance was 122.4 km. The total ascent was 6,953 m (569 m/day; range: 86–1,875 m/day) and the total descent 6,040 m (503 m/day; range: 37–1,193 m/day). The total walking time was 4,320 ± 125 min, mean 6 h/day, and the average speed was 0.47 m/s. The total number of steps was 181,319 ± 18,440.

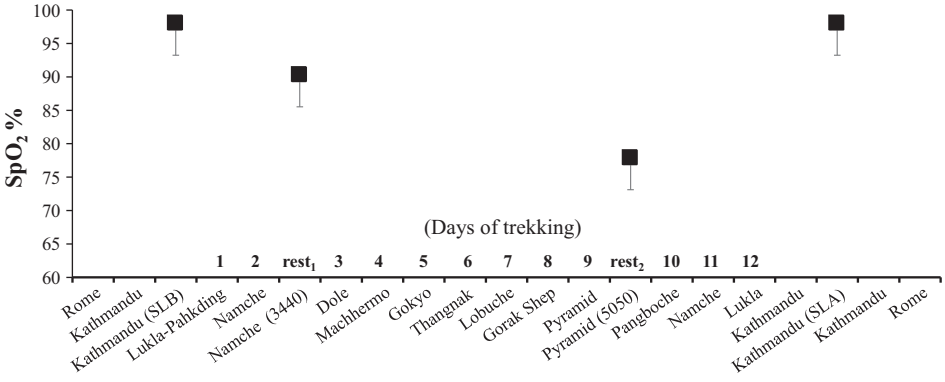

Fig. 2. Saturation of peripheral oxygen (Sp_{O_2}) during the expedition. Shown are normoxic (SL_B and SL_A) and hypoxic ($Namche_{3440}$ and $Pyramid_{5050}$) determinations.

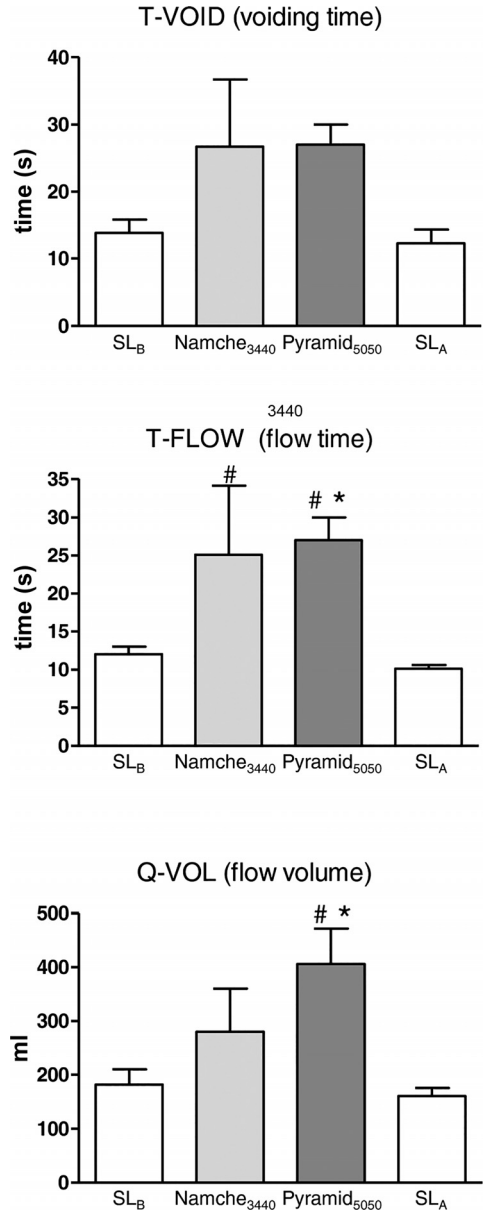

Fig. 3. Variation of uroflowmetry parameters (T_{Void}, T_{Flow}, Q_{Vol}) recorded at different altitudes: SL_B, SL_A, $Namche_{3440}$, and $Pyramid_{5050}$. Values are means ± SE. *$P < 0.04$ vs. SL_B. §$P < 0.04$ vs. SL_A. #$P < 0.04$ vs. $Namche_{3440}$.

repeated determinations on the same testing day. The following uroflowmetry parameters were considered: maximal flow $rate_{ml/sec}$ (Q_{Max}); average flow $rate_{ml/s}$ (Q_{Avg}); time to maximal $flow_s$ (T_{toMax}); flow $time_s$ (T_{Flow}); voiding $time_s$ (T_{Void}) and flow $volume_{ml}$ (Q_{Vol}). To record postvoid residual volume, we used the ultrasound device Voyager Ardent Sound (Ardent Sound, Mesa, AZ).

Statistical Analysis

Nonparametric analyses were carried out (Friedman ANOVA followed by a Wilcoxon Matched Pairs Test when appropriate) to evaluate the effect of altitude on the parameters (details reported in RESULTS). The Spearman rank correlation test was used to identify correlations. The data are expressed as means ± SE in the figures and tables.

RESULTS

Weather conditions were perfect throughout the trek, with dry sunny days and moderate cold. No significant health problems were recorded in any of the subjects.

Capillary Sp_{O_2}

Four measurements of capillary Sp_{O_2} were carried out (Fig. 2). As expected, Sp_{O_2} was significantly affected by altitude [Friedman ANOVA ($N = 7$, df $= 13$) $= 82.19$, $P < 0.001$], with levels already decreased at $Namche_{3440}$ and even lower levels recorded during the ascent from $Namche_{3440}$ to $Pyramid_{5050}$ with a saturation of ~77%. The values returned to basal levels when measurements were once made back in Kathmandu (SL_A).

Uroflowmetry

Friedman ANOVA applied to the uroflowmetry determinations in normoxic conditions at SL_B and SL_A and in hypoxic states at $Namche_{3440}$ and $Pyramid_{5050}$ revealed significant hypoxia-related effects (results shown in detail in Fig. 3 and Table 1). T_{Void}, T_{Flow}, and Q_{Vol} were higher at $Pyramid_{5050}$ than at SL_B ($P < 0.04$ for all); As shown in Table 1, all these values were affected already at $Namche_{3440}$ after 3 days of trekking. The changes became significant at $Pyramid_{5050}$, probably due to the lower variability present in this third determination. The values returned to basal levels at SL_A (Fig. 3), while Q_{Max}, Q_{Avg}, and T_{toMax} did not show any significant change (Table 1). The postvoid residual volume in all the determinations was in line with the physiological values of emptying.

Correlations

Spearman correlations revealed that T_{Flow}, T_{Void}, T_{toMax}, and Q_{Vol} were negatively correlated with Sp_{O_2}(Table 2).

DISCUSSION

The main result of the present study is the ability of high-altitude hypoxia to modify the uroflowmetry parameters in

Table 1. *Uroflowmetry parameters recorded at SL_{B-A}, $Namche_{3440}$, and $Pyramid_{5050}$*

Uroflowmetry Parameters	SL_B	Namche Bazaar (3,440 m)	Pyramid (5,050 m)	SL_A	Friedman ANOVA (P)
Q_{Max}, ml/s	24.00 ± 5.57	24.00 ± 3.91	28.28 ± 4.24	25.57 ± 3.52	0.856
Q_{Avg}, ml/s	14.28 ± 2.43	14.00 ± 2.27	15.71 ± 1.99	15.71 ± 2.02	0.776
Q_{Vol}, ml	182.14 ± 27.50	280.57 ± 85.64	389.00 ± 62.02*§	160.28 ± 17.04	0.013
T_{Flow}, s	12.00 ± 0.87	25.14 ± 9.46§	24.28 ± 2.32*§	10.14 ± 0.34	0.002
T_{Void}, s	13.86 ± 2.05	26.71 ± 11.01	24.28 ± 2.32*§	12.28 ± 2.31	0.034
T_{toMax}, s	6.43 ± 0.72	11.00 ± 4.45	7.43 ± 1.13	4.86 ± 0.70	0.190

Values are means ± SE. Q_{Max}, maximal flow rate; Q_{Avg}, average flow rate; Q_{Vol}, flow volume; T_{Flow}, flow time; T_{Void}, voiding time; and T_{toMax}, time to maximal flow recorded at SL_B, SL_A, $Namche_{3440}$, and $Pyramid_{5050}$. Significance in Friedman ANOVA was $P < 0.05$. Post hoc: *$P < 0.05$ vs. SL_B. §$P < 0.05$ vs. SL_A.

Table 2. *Significant correlations among T_{Flow}, T_{Void}, T_{Max}, Q_{Vol}, and Sp_{O_2}*

Correlation	Valid *N*	Spearman *R*	*P* Value
T_{Flow} vs. Sp_{O_2}	28	−5.268	0.001
T_{Void} vs. Sp_{O_2}	28	−3.616	0.001
T_{Max} vs. Sp_{O_2}	28	−2.343	0.027
Q_{Vol} vs. Sp_{O_2}	28	−3.698	0.001

Sp_{O_2}, saturation of peripheral oxygen. A *P* value <0.05 was considered significant.

young adult women, as shown by some changes occurring within a few days from sea level to 5,050 m a.s.l. and in the return to sea level. High-altitude hypoxia increased T_{Flow} (from 12 to 27 s) and Q_{Vol} (from 182 to 389 ml). These changes can be related to chronic states of hypoxic stress, since T_{Flow} and Q_{Vol} were found to be negatively correlated with Sp_{O_2}; i.e., the decrease in Sp_{O_2} was related to the longer T_{Flow} and higher Q_{Vol}. The strong negative correlation supports a direct and/or indirect dependence of bladder functionality on oxygen availability.

The increase in T_{Flow}, T_{Void}, and Q_{Vol} can be explained by other neural hypotheses. Indeed, these changes can be related to higher bladder filling due to a lesser need to contract, perhaps linked to the fact that the threshold volume for the urination activation mechanism would be increased. Since our subjects were asked to undergo the test following a physiological stimulus, it is possible that a lower sensitivity to distension during bladder filling (13) would occur later due to desensitization of the bladder mechanoreceptors. Moreover, hyperstimulation of the sympathetic nervous system, as occurs during ascent (11), would increase inhibition of bladder emptying (11), with increasing continence and time to flow (16). Thus the chronic states of hypoxia and the possible hypoxia-related sympathetic hyperexcitability would have induced the observed changes.

At first glance, our results may contrast with those reported by other studies. In recent years, much attention has been given to the effects of bladder ischemia from iliac artery injury with occlusion, and the physiopathological consequences of these ischemic processes have been linked to increased voiding frequency, reduced voiding volume (23), and overactivity with increased reactive oxygen species and nitrosative stress (1). Clearly, a reduction in voiding volume is a discrepancy with respect to our results. However, we consider it essential to underline some points that illustrate the reasons for which we, absolutely, cannot talk about discrepancies. First, the ischemic model cannot be compared with the hypoxic model because it is characterized by a different physiopathological mechanism. Second, it has been demonstrated that alterations of the functional metabolism of the bladder only occur with a certain degree of ischemia (4), and also that the amount of bladder dysfunction in chronic bladder ischemia could be dependent on the severity and duration of ischemia (29). The latter concept recalls an old axiom of physiology that the intensity and time of exposure are two key variables that can radically alter processes, even reversing the results.

In contrast to the pathological models used in research in this field, in our study the investigation of healthy subjects seeks to find purely physiological responses concerning the selective role of oxygen in the functional mechanisms of the bladder. Indeed, the study of physiological responses and adaptation to high-altitude hypoxia has always been a valid research possibility for a better understanding of the physiological and physiopathological mechanisms present in hypoxia-induced pathological conditions, e.g., in obstructive sleep apnea syndrome, diabetes, and aging, where one of the primary complications is bladder dysfunction (4, 14, 15, 19, 28).

The results of our study show some changes in uroflowmetry parameters that reflect an integrated systemic response to the various stimuli to which the subjects were exposed, including high altitude, type of food, and physical exercise. Of course, many variables that can affect urination must be considered, e.g., hypoxia, hormonal response, inflammatory reaction, nervous response, and oxidative stress. Although many questions remain to be clarified, these data could help in our understanding the changes observed in micturition in several clinical conditions, quite often involving aged subjects and mainly women.

We believe that it is important to provide new knowledge of the physiological and physiopathological mechanisms underlying the adaptive-functional response of the bladder to hypobaric hypoxia and LUTS and to support the design of new strategies for both prevention and treatment. An example of the latter might be hyperbaric oxygen therapy, which in some studies was able to reduce the symptoms in patients with obstructed-hypoxic bladder (19).

Clearly, the results of our, preliminary study must be confirmed and enriched by further urodynamic studies, taking into account the differences between the high-altitude hypobaric hypoxia model and the ischemic/hypoxic model related to physiopathological and pathological alterations.

ACKNOWLEDGMENTS

Thanks go to all the Nepalese porters and Sherpas whose role was essential to the scientific expedition. We thank Danilo Migliorelli (Compumed-Europe-srl) and Prof. Luigi Menghini for free instrumental support and Gaetano di Blasio for hormonal determinations. Special thanks go to all participants in the "Gokyo Khumbu/Ama Dablam Trek 2012," both researchers and experimental subjects who volunteered to participate in the study. We thank Dr. Peter Christie for the English language revision.

DISCLOSURES

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

AUTHOR CONTRIBUTIONS

V.V., L.P., C.D.G., and A.M.A. provided conception and design of research; V.V., C.D., and A.M.A. performed experiments; V.V. and A.M.A. analyzed data; V.V., L.P., T.P., C.D., and A.M.A. interpreted results of experiments; V.V. prepared figures; V.V., L.P., C.D.G., and A.M.A. drafted manuscript; V.V., L.P., T.P., C.D., C.D.G., and A.M.A. edited and revised manuscript; V.V., L.P., T.P., C.D., C.D.G., and A.M.A. approved final version of manuscript.

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