

# Association Between Arterial Blood Gas Variation and Intraocular Pressure in Healthy Subjects Exposed to Acute Short-Term Hypobaric Hypoxia

Yuan Xie<sup>1,2</sup>, Yiquan Yang<sup>1,2</sup>, Ying Han<sup>3</sup>, Diya Yang<sup>1,2</sup>, Yunxiao Sun<sup>1,2</sup>, Xinmao Wang<sup>4</sup>, Anh Hong Nguyen<sup>3</sup>, Yihan Chen<sup>1,2</sup>, Jiabin Tian<sup>1,2</sup>, Qing Zhang<sup>2</sup>, Chen Xin<sup>2</sup>, Kai Cao<sup>2</sup>, Huaizhou Wang<sup>1,2</sup>, Xiaofang Liu<sup>4</sup>, Guozhong Wang<sup>5</sup>, and Ningli Wang<sup>1,2</sup>

<sup>1</sup> Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, Beijing Ophthalmology and Visual Sciences Key Laboratory, Beijing, China

<sup>2</sup> Beijing Institute of Ophthalmology, Beijing Tongren Hospital, Capital Medical University, Beijing, China

<sup>3</sup> Department of Ophthalmology, University of California, San Francisco, CA, USA

<sup>4</sup> Department of Pneumology, Beijing Tongren Hospital, Capital Medical University, Beijing, China

<sup>5</sup> Department of Hyperbaric and Hypobaric Chamber, Civil Aviation General Hospital, Beijing, China

**Correspondence:** Ningli Wang, Beijing Institute of Ophthalmology, Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, No. 1 Dongjiaominxiang St, Dongcheng District, Beijing, 100730, China. e-mail: wningli@vip.163.com

**Received:** 7 May 2019

**Accepted:** 10 September 2019

**Published:** 20 November 2019

**Keywords:** high altitude; hypoxia; hypobaric chamber; intraocular pressure; arterial blood gases; bicarbonate ion

**Citation:** Xie Y, Yang Y, Han Y, Yang D, Sun Y, Wang X, Nguyen AH, Chen Y, Tian J, Zhang Q, Xin C, Cao K, Wang H, Liu X, Wang G, Wang N. Association between arterial blood gas variation and intraocular pressure in healthy subjects exposed to acute short-term hypobaric hypoxia. *Trans Vis Sci Tech.* 2019;8(6):22, <https://doi.org/10.1167/tvst.8.6.22> Copyright 2019 The Authors

**Purpose:** To investigate the association between changes in arterial blood gases and intraocular pressure (IOP) after acute, short-term exposure to simulated elevation of 4000 m above sea level.

**Methods:** Twenty-five healthy young lowlanders participated in this prospective study. IOP was measured in both eyes with an Accupen tonometer. Arterial blood gas parameters (partial oxygen pressure [PaO<sub>2</sub>], partial carbon dioxide pressure [PaCO<sub>2</sub>], pH, and bicarbonate ion [HCO<sub>3</sub><sup>-</sup>]) were checked using a blood gas analyzer. Measurements were taken at sea level (T1), at 15-minute (T2) and at 2-hour (T3) exposure times to simulated 4000 m above sea level in a hypobaric chamber, and upon return to sea level (T4). Associations between arterial blood gas parameters and IOP were evaluated using multivariate linear regression.

**Results:** PaO<sub>2</sub> significantly decreased at T2 and T3, resolving at T4 ( $P < 0.001$ ). pH significantly increased at T2 and returned to baseline at T3 ( $P = 0.004$ ). Actual and standard bicarbonate ion both dropped with IOP at T3 and T4. IOP significantly decreased from  $16.4 \pm 3.4$  mm Hg at T1 to  $15.1 \pm 2.1$  mm Hg ( $P = 0.041$ ) at T3 and remained lower ( $14.9 \pm 2.4$  mm Hg;  $P = 0.029$ ) at T4. IOP was not correlated with pH. Multivariate linear regression showed that lower IOP was associated with lower standard bicarbonate ion ( $\beta = -1.061$ ; 95% confidence interval,  $-0.049$  to  $-2.074$ ;  $P = 0.04$ ) when adjusted for actual bicarbonate and diastolic blood pressure.

**Conclusions:** Hypobaric hypoxia triggers plasma bicarbonate ion reduction which, rather than pH, may decrease aqueous humor formation and subsequently cause IOP reduction. These findings may shed light on the mechanism of IOP regulation at high altitude.

**Translational Relevance:** Hypoxia-triggered reduction in plasma bicarbonate ion may decrease aqueous humor production, leading to IOP reduction at high altitude. These findings may provide new insight into a potential mechanism of IOP regulation. Hypobaric hypoxia at high altitude is an environmental factor that can reduce IOP and, therefore, deserves further study.

## Introduction

In 1918, Wilmer and Beren<sup>1</sup> conducted the first study measuring intraocular pressure (IOP) changes in 14 airmen with altitude simulations by using a hypobaric chamber; they found no significant changes. More recently, various studies have reported IOP changes with altitude increases either in a simulated or real settings. However, results have been inconsistent and even conflicting.<sup>2–11</sup>

The exact mechanisms of IOP changes at high elevation remain unknown, with different explanations being suggested. Some investigators speculate that increases in IOP at high altitude could result from altered intracranial pressure<sup>8</sup> or corneal thickness.<sup>2,9</sup> In contrast, other previous studies propose that lower IOP may occur as an effect of hypobaric hypoxia acclimatization,<sup>4,6</sup> retinal vasodilatation,<sup>11</sup> increased aqueous outflow,<sup>3</sup> or impaired oxygen supply to the ciliary body<sup>10</sup> at high altitude. These dissimilar findings from previous studies may be due to different external environments or ascent profiles.

Generally, hypoxia at high altitudes provokes sufficient hyperventilation (hypoxic ventilatory response)<sup>12,13</sup> to cause changes in a series of arterial blood gas parameters. However, whether these changes are correlated with IOP variation is still unknown. Hence, our study aims to evaluate the association between arterial blood gas parameters and IOP under the simulated, controlled environment of hypobaric hypoxia by using young, healthy subjects. Findings from this study may shed light on the mechanism of IOP changes with altitude elevation and potentially provide a new understanding of IOP regulation.

## Methods

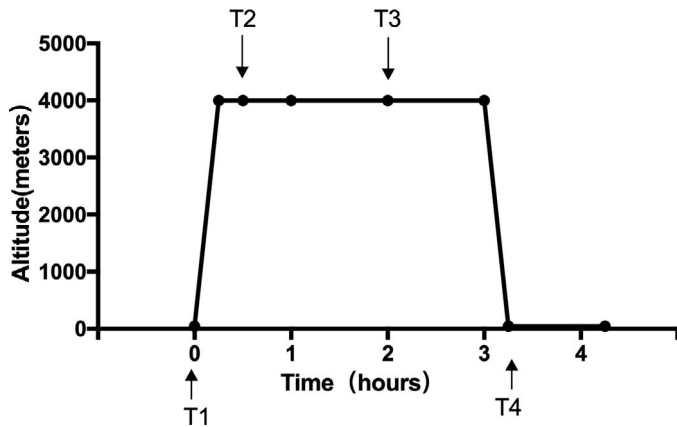
### Subjects

This prospective study had 25 physically fit and healthy volunteers, with 14 men and 11 women recruited through advertisement. The mean age was  $26.6 \pm 3.3$  years (range, 21–33 years), and all individuals were of Han descent living at altitudes between 40 m and 100 m above sea level (ASL). None of the subjects were trained mountaineers or soldiers. Two subjects total, both male, had a history of smoking. We used a Portable Spirometer Pulmonary Function Analyzer (MicroLab<sup>TM</sup>) to measure pulmonary function (forced expiratory volume in one

second [FEV1] and forced vital capacity [FVC]) in participants. All of the subjects demonstrated normal baseline pulmonary function, with a mean FEV1/FVC of  $85.3\% \pm 5.7\%$ . The volunteers also underwent tube tympanometry before they joined the study to exclude those who have Eustachian tube ventilation insufficiency. Exclusion criteria were any type of cardiac or respiratory diseases, a history of renal diseases or urinary abnormalities, and a history of high-altitude pulmonary edema or high-altitude cerebral edema. Ophthalmological exclusion criteria were refractive error of  $\geq 6$  diopters, current or positive history of conditions affecting IOP including glaucoma, narrow anterior chamber angle, history of ocular surgeries, pseudophakia, contact lens wear, and use of any drugs affecting IOP such as acetazolamide, corticosteroids, and beta-blockers. Before baseline recordings and simulated ascent, subjects had to spend  $>14$  days below 2000 m ASL to exclude confounding effects due to previous altitude exposure. We adhered to the tenets of the Declaration of Helsinki and the research was approved by the Beijing Tongren Hospital ethics committee. Written and oral informed consent were obtained from the participants after full explanation of the nature and possible consequences of the study. The study was registered at <http://www.chictr.org.cn> (study number ChiCTR-CPC-17011623).

### Ascent Profile and Measurements

Experiments were safely conducted in a hypobaric chamber (WYC3.2D2622; Anhui Wuhu Diving Equipment Manufacturing Factory, An Hui, China) (size, 8.97 m long; 3.2-m diameter; floor dimension, 60.0 m<sup>2</sup>; accommodation, 16 people) at Civil Aviation General Hospital (Beijing, China) under the constant supervision of two medical doctors. The temperature and humidity inside the chamber were set at 22.0 to 22.8°C and 44% to 58%, respectively, throughout the entire observation time. The study participants sat in comfortable chairs and could breathe and drink freely. Once the control measurements were taken at sea level, the barometric pressure of the chamber was gradually lowered to  $-61.1$  kpa (462 mm Hg, equivalent to 4000 m [15,000 feet] ASL) at a rate of 300 m/min ( $-2$  Torr/min). The participants were maintained at simulated altitude for 3 hours. Measurements were taken at sea level (baseline, T1), at 15-minute (T2) and at 2-hour (T3) exposure to the hypobaric chamber, and upon return to sea level (T4) (Fig. 1). Supplemental O<sub>2</sub> was available if a partici-



**Figure 1.** Ascent profile and examination time point. T1, before ascent (baseline); T2, at 15 minutes during exposure to simulated 4000 m above sea level; T3, at 2 hour during exposure to simulated 4000 m above sea level; T4, upon return to sea level.

patient's arterial blood oxygen level ( $\text{PaO}_2$ ) decreased below 40 mm Hg.

A catheter was inserted in the radial artery to collect arterial blood samples from T1 to T4. Arterial blood samples were collected by a medical doctor who was present in the chamber. The samples were removed through a service hatch and analyzed immediately for  $\text{PaO}_2$ , pulse oxygen saturation ( $\text{SaO}_2$ ), arterial partial pressure of carbon dioxide ( $\text{PaCO}_2$ ), actual bicarbonate ion ( $\text{a}[\text{HCO}_3^-]$ ), standard bicarbonate ion ( $\text{s}[\text{HCO}_3^-]$ ), lactate (LC), and hematocrit by using a blood gas analyzer (IL-1304; Instrumentation Laboratory, Lexington, MA). Venous blood was drawn from another arm while subjects were seated, and the blood was placed in separate tubes. Erythrocyte and hemoglobin concentrations were examined and recorded at T1, T3, and T4. Systolic and diastolic blood pressures were measured by one observer with an electronic sphygmomanometer (HEM-7133; Omron Corporation, Kyoto, Japan), and pulse rate was monitored by a finger pulse oximeter (PC-60NW; Health force, Shanghai, China).

IOP was concurrently measured at all four examination points. IOP was measured in both eyes with a handheld tonometer (24–3000, 12K1031; Accutome, Malvern, PA) by placing the tip of the device onto the central cornea after applying local anesthesia with proparacaine hydrochloride 0.5% (S.A. Alcon-Couvreur N.V., Puurs, Belgium). Three measurements were taken, and the average was calculated and recorded. The tonometer was calibrated according to the manufacturer's guidelines before each examination session and was measured by a

single proficient doctor. Central corneal thickness (CCT) was measured in both eyes with an anterior segment optical coherence tomography (CASIA SS-1000, SP-2000; Tomey, Nagoya, Japan) at T1 and T3 by a single proficient doctor.

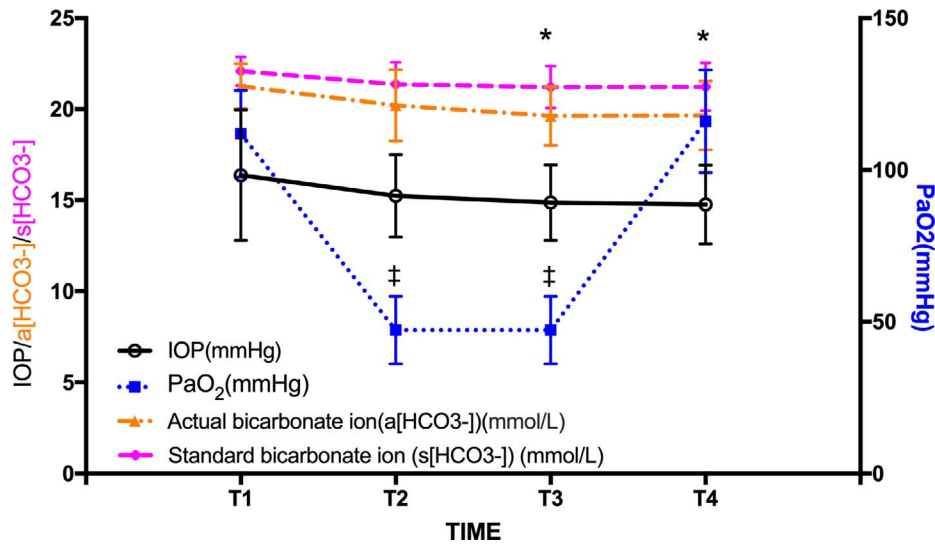
## Statistical Analysis

A test for normal distribution was performed with the Kolmogorov-Smirnov test. Descriptive statistics for all the parameters are presented as means  $\pm$  SD. The linear mixed model was used to compare repeated measurements in IOP and CCT at each time point to adjust for correlation between paired eyes. Repeated-measures analysis of variance was applied to analyze the differences among four exam time point in blood pressure, pulse rate, blood gas parameters, and hemoglobin and erythrocyte concentrations. Bonferroni correction was applied for multiple comparisons. Univariate linear regression was used to detect associations between IOP (mean of paired eyes) and arterial blood gas parameters, hemoglobin and erythrocyte concentrations, as well as systemic parameters. Finally, we used multivariate linear regression analysis to examine the correlation between IOP (dependent variable) and variables with significant results according to univariate linear regression analysis (actual bicarbonate ion, standard bicarbonate ion, and diastolic blood pressure). A  $P$  value of  $<0.05$  is considered significant. All evaluations were done using commercially available statistical software packages (SPSS for Mac, v. 24.0, IBM-SPSS, Chicago, IL).

## Results

All the subjects were able to reach the simulated altitude of 4000 m ASL, and experiments were performed safely. No study participant required supplemental  $\text{O}_2$  inhalation during the study.

IOP significantly decreased from  $16.4 \pm 3.4$  at sea level (T1) to  $15.1 \pm 2.1$  mm Hg at 2-hour exposure to hypobaric hypoxia stimulus (T3), and further decreased to  $14.9 \pm 2.4$  mm Hg upon return to sea level (T4). CCT remained comparable during exposure to hypobaric chamber compared with baseline. We corrected IOP based on CCT variation after 2-hour exposure in the hypobaric chamber according to two different correction factors recommended in the literature ( $0.10$  mm Hg/ $10 \mu\text{m}$  of CCT and  $0.31$  mm Hg/ $10 \mu\text{m}$  of CCT).<sup>14,15</sup> The analysis produced similar results. The corrected IOPs for both corrections were



**Figure 2.** Intraocular pressure, oxygen pressure, and actual and standard bicarbonate ion variation after exposure to hypobaric hypoxic stimulus. Arterial oxygen pressure (PaO<sub>2</sub>) initially decreased at 15-minute exposure to simulated 4000 m (blue line). Intraocular pressure (IOP) (black line), actual bicarbonate, and standard bicarbonate (orange and purple line, respectively) decreased at 2 hours in hypobaric chamber and upon return to sea level. T1, before ascent (baseline); T2, at 15 minutes during exposure to simulated 4000 m above sea level; T3, at 2 hours during exposure to simulated 4000 m above sea level; T4, upon return to sea level; IOP, intraocular pressure; a(HCO<sub>3</sub><sup>-</sup>), actual bicarbonate ion; s(HCO<sub>3</sub><sup>-</sup>), standard bicarbonate ion; PaO<sub>2</sub>, arterial oxygen pressure; \*, significant changes in IOP and actual and standard bicarbonate ion; ‡, significant changes in PaO<sub>2</sub>.

still lower than IOP at sea level; the IOP with the first correction factor was  $14.9 \pm 2.0$  mm Hg ( $P = 0.008$ ), and the IOP with the second correction factor was  $15.0 \pm 2.0$  mm Hg ( $P = 0.012$ ).

PaO<sub>2</sub>, SaO<sub>2</sub>, and PaCO<sub>2</sub> significantly decreased at T2 and remained lower at T3. Upon return to sea level, PaO<sub>2</sub> and SaO<sub>2</sub> immediately resolved, whereas PaCO<sub>2</sub> still remained lower than baseline. pH statistically significantly increased at T2 and resolved at T3. Actual and standard bicarbonate ion significantly decreased at T3 and T4. The bicarbonate ion reduction was parallel, with IOP changes as shown in Figure 2.

As can be seen in Table 1, systolic and diastolic blood pressure significantly decreased, whereas pulse rate significantly increased at T2 and T3. Upon return to sea level, all vital parameters returned to baseline. Hematocrit, hemoglobin, and erythrocyte concentrations did not change throughout the whole observation time (Table 1).

Univariate linear regression showed a correlation between lower IOP and lower actual bicarbonate ion (beta = -0.29; 95% confidence interval [CI], -0.009 to -0.572;  $P = 0.044$ ), lower standard bicarbonate ion (beta = -0.613; 95% CI, -0.187 to -1.039;  $P = 0.005$ ), and lower diastolic blood pressure (beta = -0.053; 95% CI, -0.007 to -0.099;  $P = 0.025$ ). There were no

associations between IOP and PaO<sub>2</sub>, SaO<sub>2</sub>, PaCO<sub>2</sub>, pH, and lactate and pulse rate. We performed multivariate linear regression analysis with lower IOP as the dependent variable and actual bicarbonate, standard bicarbonate, and diastolic blood pressure as the independent variables. It revealed a partial correlation coefficient of beta = -1.061 (95% CI, -0.049 to -2.704;  $P = 0.04$ ) for lower standard bicarbonate, beta = 0.365 (95% CI, -0.289 to 1.02;  $P = 0.27$ ) for lower actual bicarbonate, and beta = -0.044 (95% CI, -0.092 to 0.003;  $P = 0.067$ ) for lower diastolic blood pressure (Table 2).

## Discussion

This is the first study to simultaneously monitor IOP and arterial blood gas parameters by using a simulated hypobaric chamber to exclude several confounding factors. Our results indicate that hypobaric hypoxia leads to lower PaO<sub>2</sub>, lower PaCO<sub>2</sub>, and higher pH immediately after exposure to simulated high altitude. Afterward, IOP, actual bicarbonate, and standard bicarbonate ion all decreased in parallel at T3 (2-hour exposure) and T4 (upon return to sea level). Yet, pH returned to baseline at T3 and PaO<sub>2</sub> returned at T4. Lower IOP is associated with lower standard bicarbonate ion but not with pH. This



**Table 1.** Parameters Changes After Acute, Short-Term Exposure to Simulated High Altitude in Hypobaric Chamber (mean  $\pm$  SD)

Variable	Baseline (T1)	4000 m, 15 minutes (T2)	4000 m, 2 hours (T3)	Upon Return to Sea Level (T4)
Intraocular pressure (mm Hg)	16.4 $\pm$ 3.4	15.2 $\pm$ 2.2	15.1 $\pm$ 2.1	14.9 $\pm$ 2.4
Central corneal thickness (um)	540.9 $\pm$ 37.5		536.4 $\pm$ 38.8	
PaO <sub>2</sub> (mm Hg)	111.9 $\pm$ 13.99	44.05 $\pm$ 7.45	47.21 $\pm$ 10.87	107.39 $\pm$ 9.49
SaO <sub>2</sub> (%)	97.61 $\pm$ 0.48	80.98 $\pm$ 6.68	82.6 $\pm$ 6.1	97.8 $\pm$ 0.41
PaCO <sub>2</sub> (mm Hg)	35.1 $\pm$ 2.82	31.74 $\pm$ 3.86	31.62 $\pm$ 3.25	31.66 $\pm$ 3.54
Actual bicarbonate (mmol/L)	21.27 $\pm$ 1.23	20.22 $\pm$ 1.97	19.63 $\pm$ 1.61	19.65 $\pm$ 1.9
Standard bicarbonate (mmol/L)	22.08 $\pm$ 0.79	21.38 $\pm$ 1.2	21.21 $\pm$ 1.16	21.23 $\pm$ 1.3
pH	7.4 $\pm$ 0.02	7.42 $\pm$ 0.03	7.41 $\pm$ 0.02	7.41 $\pm$ 0.02
Lactate (mmol/L)	1.78 $\pm$ 0.42	1.74 $\pm$ 0.34	1.54 $\pm$ 0.36	1.3 $\pm$ 0.27
Hemoglobin (g/L)	138.1 $\pm$ 12.9		139.6 $\pm$ 12	140.9 $\pm$ 11.7
Hematocrit (%)	0.41 $\pm$ 0.03	0.42 $\pm$ 0.05	0.41 $\pm$ 0.05	0.4 $\pm$ 0.03
Erythrocyte (10 <sup>12</sup> /L)	4.67 $\pm$ 0.36		4.72 $\pm$ 0.33	4.98 $\pm$ 0.69
Systolic pressure (mm Hg)	115.2 $\pm$ 10.1	104.9 $\pm$ 11.9	105.8 $\pm$ 17.5	109.5 $\pm$ 9.8
Diastolic pressure (mm Hg)	75.8 $\pm$ 7.8	70.2 $\pm$ 11.2	67.3 $\pm$ 9.6	75.5 $\pm$ 9.9
Pulse rate (bpm)	77.3 $\pm$ 11.9	89.5 $\pm$ 14.7	90.0 $\pm$ 11.4	81.4 $\pm$ 15.3

<sup>a</sup> *P* value calculated based on mixed linear model and repeated-measures analysis of variance for eye-specific data and individual-level data, respectively.

<sup>b</sup> Paired comparisons were shown as T1&T2, T1&T3, and T1&T4.

**Table 1.** Extended

Variable	<i>P</i> Value <sup>a</sup>	T1&T2 <sup>b</sup>	T1&T3 <sup>b</sup>	T1&T4 <sup>b</sup>
Intraocular pressure (mm Hg)	0.028	0.314	0.041	0.029
Central corneal thickness (um)	0.833			
PaO <sub>2</sub> (mm Hg)	<0.001	<0.001	<0.001	1
SaO <sub>2</sub> (%)	<0.001	<0.001	<0.001	1
PaCO <sub>2</sub> (mm Hg)	<0.001	0.008	0.001	0.003
Actual bicarbonate (mmol/L)	<0.001	0.195	0.002	0.007
Standard bicarbonate (mmol/L)	0.005	0.123	0.024	0.053
pH	0.004	0.004	0.281	0.274
Lactate (mmol/L)	<0.001	1	0.246	<0.001
Hemoglobin (g/L)	0.725		1	1
Hematocrit (%)	0.222	0.399	1	1
Erythrocyte (10 <sup>12</sup> /L)	0.129		1	0.141
Systolic pressure (mm Hg)	0.01	0.012	0.178	0.307
Diastolic pressure (mm Hg)	0.003	0.165	0.005	1
Pulse rate (bpm)	0.001	0.014	0.002	1

preliminary study indicates that hypobaric hypoxia-triggered standard bicarbonate ion reduction, rather than pH, is correlated to IOP reduction at high altitude. These findings shed light on the potential mechanism of IOP regulation at high altitude.

Previous studies have investigated IOP changes after ascent to high altitude and found that several

environmental factors (i.e., temperature,<sup>16</sup> humidity, wind, and exercise<sup>17</sup>) may cause inconsistent results. The current study examined the relationship between IOP and high altitude by controlling those confounding factors by using a hypobaric chamber. Thick CCT due to hypoxia was also thought to be a factor that can artificially inflate IOP changes at high altitude.<sup>9</sup>

**Table 2.** Linear Regression Analyses on the Association Between Arterial Blood Gas Parameters and Intraocular Pressure<sup>a</sup>

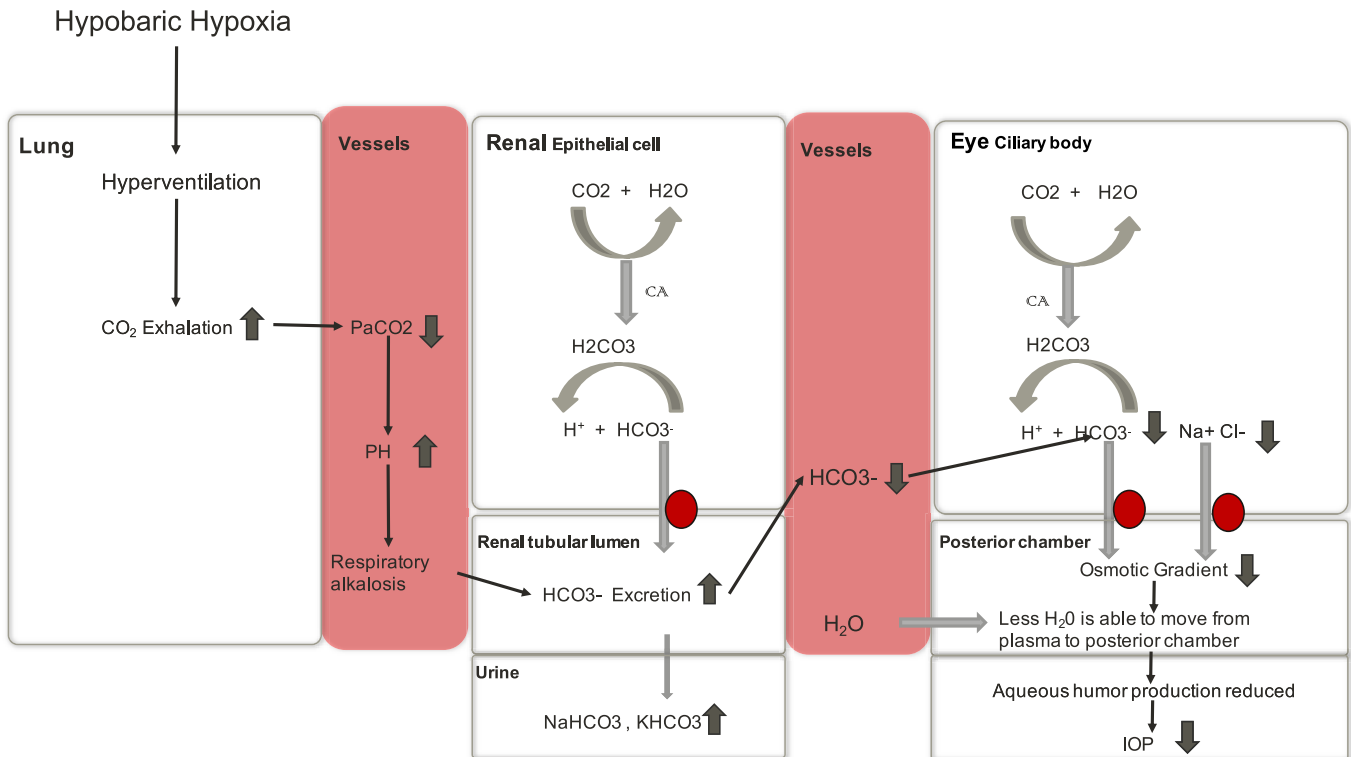
Arterial Blood Gas Parameters	Univariate Linear Regression		Multivariate Linear Regression	
	Beta (95% CI)	P Value	Beta (95% CI)	P Value
PaO <sub>2</sub> , per 1 mm Hg decrease	-0.002 (0.013 to -0.016)	0.822		
SaO <sub>2</sub> , per 1 mm Hg decrease	-2.581 (-8.21 to 3.047)	0.365		
PaCO <sub>2</sub> , per 1 mm Hg decrease	-0.071 (-0.213 to 0.070)	0.318		
pH, per 0.1 unit	-0.167 (-3.613 to 3.28)	0.924		
Lactate, per 1 mmol/L	0.988 (-0.312 to 2.287)	0.135		
Actual bicarbonate, per 1 mmol/L decrease	-0.29 (-0.009 to -0.572)	0.044	0.365 (-0.289 to 1.020)	0.27
Standard bicarbonate, per 1 mmol/L decrease	-0.613 (-0.187 to -1.039)	0.005	-1.061 (-0.049 to -2.074)	0.04
Pulse rate, per 1 bpm	-0.007 (-0.043 to 0.028)	0.677		
Diastolic blood pressure, per 1 mm Hg decrease	-0.053 (-0.007 to -0.099)	0.025	-0.044 (-0.092 to 0.003)	0.067
Systolic blood pressure, per 1 mm Hg decrease	-0.031 (-0.066 to 0.005)	0.088		

<sup>a</sup> Univariate linear regression is depicted (values on coefficient of correlation [beta] and *P* value). Multivariate linear regression is depicted (values on coefficient of correlation [beta] and *P* value). PaO<sub>2</sub>, arterial oxygen pressure; SaO<sub>2</sub>, pulse oxygen saturation; PaCO<sub>2</sub>, arterial partial pressure of carbon dioxide.

However, our data showed comparable CCT during exposure to simulated 4000 m ASL and at sea level. This finding is in accordance with a recent meta-analysis that found that the unoperated corneas of healthy lowlanders take over 10 days to change to a point of clinical significance at high altitude.<sup>18</sup> Moreover, IOP corrected for CCT changes also showed a similar reduction during hypobaric hypoxic stimulus. Our findings are in accordance with previously published data; they reported an IOP reduction at various altitudes in a hypobaric chamber (4300 m and 5486 m ASL)<sup>3,6</sup> and in real high-altitude settings (2234 m, 3740 m, 4300 m, 4559 m, 5050 m, and 5200 m ASL).<sup>2,4-7,9,19</sup> The reported IOP reduction ranges were between 1.2 and 4 mm Hg. Our earlier study found that IOP (measured by Accupen tonometer) in lowlanders decreased from 18.4 ± 2.4 mm Hg at sea level to 11.9 ± 2.5 mm Hg at the sixth hour after ascent to 3750 m ASL by plane (unpublished data). Studies with greater recorded IOP changes involved trekking in real high altitude<sup>4</sup> or relatively long-term exposure. In contrast, some scholars found an increased IOP at simulated altitudes of 9144 m and 6250 m ASL<sup>3,20,21</sup> in the hypobaric or normobaric hypoxic chamber<sup>22</sup> and when hiking in the real setting of 6265 m ASL.<sup>10</sup> The

reported mean IOP increases were mostly below 2 mm Hg except Ersanli et al.,<sup>19</sup> who showed an increase in IOP from a baseline of 12.3 ± 3.0 mm Hg to 14.4 ± 3.4 mm Hg during 1 to 3 minutes in a hypobaric chamber (equivalent to 9000 m ASL). A recent study also reported an IOP increase of 1.2 ± 1.9 mm Hg at 4 minutes and 0.9 ± 2.3 mm Hg at 10 minutes during normobaric hypoxia challenges (equivalent to 6250 m ASL).<sup>22</sup> Studies with increased IOP involved extreme high altitude (>5500 m ASL) or IOP measurements within 10 minutes of exposure. Our results may differ because we measured IOP changes at a more often frequented and moderate altitude (4000 m ASL) and after 15 minutes of rest to exclude the effect of mental stress.<sup>23</sup> The different altitudes reached and measured time points may explain the inconsistent results.

Changes in blood gas parameters in this study were consistent with previous reports.<sup>12</sup> Barometric pressure decreases exponentially as altitude rises, resulting in a lower total oxygen content in the inspired air and subsequent hypoxemia (lower PaO<sub>2</sub> and SaO<sub>2</sub>), as shown in our study. Meanwhile, a decreased PaCO<sub>2</sub> and increased pH during exposure to hypobaric hypoxia indicate a well-documented hypoxia ventilatory response.<sup>13,24,25</sup> Hypoxemia is detected by the carotid bodies that release neurotransmitters to cause



**Figure 3.** The underlying mechanism of how hypobaric hypoxia induces intraocular pressure reduction at simulated high altitude. Hypoxia triggers hyperventilation at high altitude. Excess exhalation decreases plasma  $\text{CO}_2$ , causing pH to rise. This respiratory alkalosis provokes renal compensation by increasing the excretion of bicarbonate ion ( $\text{HCO}_3^-$ ). Reduction of plasma bicarbonate shifts the balance toward increase  $\text{H}^+$  ion production, acidifying and correcting blood pH toward pH at sea level. In the eye, lower bicarbonate ion in the nonpigment ciliary epithelial (NPE) cells results in decreased  $\text{Na}^+$ ,  $\text{Cl}^-$ , and bicarbonate transport from NPE cells to posterior chamber. The lower osmotic gradient insufficiently drives water to the posterior chamber, resulting in less aqueous humor production and lower IOP.

a subsequent rise in ventilation characterized by deep and fast breathing. This augmentation of ventilation lowers arterial and tissue  $\text{PCO}_2$ , subsequently increasing pH and inducing respiratory alkalosis. The kidney rectifies elevated body pH by excreting bicarbonate ions in the form of sodium and potassium bicarbonate. The fact that the actual and standard bicarbonate ion decreased in our study while pH returned to sea level at the second hour (T3) indicates a kidney acid-base compensation. This renal compensation (a compensatory metabolic acidosis) has the important effect of decreasing pH back toward the value at sea level.

To the best of our knowledge, this is the first study to find a correlation between IOP reduction and decreased arterial  $\text{HCO}_3^-$  after hyperventilation triggered by hypobaric hypoxic stimulus. Specifically, we proposed a mechanism based on the known physiology about aqueous humor (AH) production.  $\text{HCO}_3^-$  production in the nonpigmented ciliary epithelium is a key step in AH formation in the eye. The active process of AH secretion is mediated by two enzymes present in the nonpigmented epithelium:

$\text{Na}^+\text{-K}^+\text{-ATPase}$  and carbonic anhydrase (CA). CA is a ubiquitous metalloenzyme that catalyzes the reversible hydration of  $\text{CO}_2$  into  $\text{HCO}_3^-$  and protons ( $\text{CO}_2 + \text{H}_2\text{O} \leftrightarrow \text{HCO}_3^- + \text{H}^+$ ). Newly formed  $\text{HCO}_3^-$  passes into the posterior chamber, along with  $\text{Na}^+$  and  $\text{Cl}^-$ . The osmotic gradient established by the transfer and accumulation of these ions facilitates the passive flow of water into the posterior chamber, forming AH.<sup>26</sup> This mechanism is supported by the effectiveness of carbonic anhydrase inhibitor (CAI), which decreases IOP by blocking CA from producing bicarbonate ions.<sup>27,28</sup> The mechanism we propose of how high altitude causes a decrease in IOP is similar to how CAI works: decreasing bicarbonate ions. We propose that at high altitudes, hyperventilation activates renal compensation to excrete bicarbonate ions. With lower plasma and tissue bicarbonate concentrations, fewer ions enter the posterior chamber of the eye, resulting in less AH production and, hence, decreased IOP. The detailed mechanism is summarized in Figure 3. Our data support this hypothesis in that plasma bicar-

bonate ion and IOP decrease in parallel and are correlated after exposure to high altitude.

Actual and standard bicarbonate ion differ.<sup>29</sup> Actual bicarbonate ion represents the concentration of hydrogen carbonate in the plasma. Actual bicarbonate ion changes with both respiratory and metabolic acid-base disturbances. By contrast, standard bicarbonate is the concentration of hydrogen carbonate in whole blood that has been equilibrated at 37°C at a PaCO<sub>2</sub> of 40 mm Hg with oxygen to fully saturate hemoglobin. As a result, changes in standard bicarbonate occur only as a result of the effects of metabolic factors and regulation by the kidney, not altered respiration. Multivariate linear regression in this study showed that lower IOP was associated with lower standard bicarbonate ion, but association was lost with actual bicarbonate ion. These findings imply that the decreased plasma bicarbonate ion caused by renal compensation is relevant to IOP reduction. In accordance with our results, a previous study showed a marked, rapid decrease in IOP when inspired CO<sub>2</sub> was suddenly decreased.<sup>30</sup> During general anesthesia, hypercapnia elevates IOP, whereas hyperventilation lowers it.<sup>31</sup> The mechanism we propose may also complement the underlying mechanism of IOP reduction in conditions that cause hyperventilation or decreased inspired CO<sub>2</sub> at sea level, such as exercise<sup>17,32</sup> and anesthesia.<sup>33–35</sup> IOP may be correlated with respiratory patterns; this potential association deserves further study.

Results from our study partially agree with Pavlidis' proposed mechanism of how high altitude affects IOP.<sup>4</sup> They suspected but did not find evidence that hypoxia-induced respiratory alkalosis (pH increase) was responsible for IOP reduction during ascent phase from 2286 m to 5050 m ASL. Renal compensation of respiratory alkalosis can lead to IOP normalization after acclimatization by changing the activity of carbonic anhydrase (CA) in both renal and ciliary nonpigmented epithelium cells. Pavlidis hypothesized that pH may play a large role in IOP reduction. Another study also found that respiratory alkalosis could reduce both intracranial and IOP.<sup>35</sup> CA was thought to reduce IOP by causing an acidosis that decreases AH production.<sup>36</sup> In the current study, the increased pH indicates a respiratory alkalosis, whereas the decreased bicarbonate indicates a compensatory metabolic acidosis. The combination of those two processes results in a shifting of pH at 2-hour exposure back to baseline. Yet, IOP remained significantly lower than at sea level. Hence, we infer from these results that hypoxia-triggered pH changes

are not involved in IOP reduction at high altitude. Whether CA activation is the cause of IOP changes in the acclimatization phase at high altitude is still unknown. However, our results suggest that a lower bicarbonate ion leads to IOP reduction using a similar mechanism as the CA inhibitor. Because renal compensation is a factor in early acclimatization to high altitude, both decreased bicarbonate ion and IOP may be the factors associated with acclimatization.

It has been proposed that lower systolic and diastolic blood pressure cause hypoxic vasodilatation that subsequently decreases episcleral venous pressure.<sup>37</sup> Low episcleral venous pressure increases outflow of the AH into the venous system, thus causing a decrease in IOP. Univariate linear regression analysis showed a correlation between IOP and diastolic blood pressure, but we were not able to find the same correlation by using multivariate linear regression analysis. However, our results cannot exclude vasodilatation as a potential player in IOP changes.

Our study had limitations. First, exposure time was relatively short due to safety considerations. Second, all volunteers in the present study were young healthy adults. Hence, it is unclear whether similar effects of hypobaric hypoxia would be observed in elderly subjects or those with ocular hypertension. Third, baseline IOP diurnal changes<sup>38</sup> and respiratory rate variations should be taken into consideration in future studies.

In conclusion, this well-controlled, prospective study indicates that acute, effortless, short-term exposure to hypobaric hypoxia at simulated 4000 m ASL results in statistically significant IOP reduction independent of CCT changes. Systemic hypoxia is the trigger factor; reduced HCO<sub>3</sub><sup>-</sup> rather than increased pH is associated with IOP reduction. Our results shed light on one of the mechanisms of reducing IOP with elevated altitude and may provide new insight into a potential mechanism of IOP regulation.

## Acknowledgments

This study was supported by National Natural Science Foundation of China (81271005 and 81300767), Beijing Natural Science Foundation (7122038), and The Capital Health Research and Development of Special Foundation (ZYLX201501).

Disclosure: **Y. Xie**, None; **Y. Yang**, None; **Y. Han**,



None; **D. Yang**, None; **Y. Sun**, None; **X. Wang**, None; **A.H. Nguyen**, None; **Y. Chen**, None; **J. Tian**, None; **Q. Zhang**, None; **C. Xin**, None; **K. Cao**, None; **H. Wang**, None; **X. Liu**, None; **G. Wang**, None; **N. Wang**, None

## References

1. Wilmer WH, Berens C, Jr. Medical studies in aviation: V. The effect of altitude on ocular functions. 1918. *Aviat Space Environ Med.* 1989; 60:1018–1023.
2. Willmann G, Schommer K, Schultheiss M, et al. Effect of high altitude exposure on intraocular pressure using Goldmann applanation tonometry. *High Alt Med Biol.* 2017;18:114–120.
3. Nebbioso M, Fazio S, Di Blasio D, Pescosolido N. Hypobaric hypoxia: effects on intraocular pressure and corneal thickness. *ScientificWorld-Journal.* 2014;2014:585218.
4. Pavlidis M, Stupp T, Georgalas I, Georgiadou E, Moschos M, Thanos S. Intraocular pressure changes during high-altitude acclimatization. *Graefes Arch Clin Exp Ophthalmol.* 2006;244: 298–304.
5. Nazari H, Nilforushan N, Sedaghat A, et al. Intraocular pressure after exposure to moderate altitude. *Graefes Arch Clin Exp Ophthalmol.* 2013; 251:123–127.
6. Cymerman A, Rock PB, Muza SR, et al. Intraocular pressure and acclimatization to 4300 M altitude. *Aviat Space Environ Med.* 2000;71: 1045–1050.
7. Bayer A, Mutlu FM, Akay F, Bayraktar MZ. An assessment of intraocular pressure change in healthy subjects during air flight. *Curr Eye Res.* 2008;33:345–349.
8. Hackett PH, Roach RC. High-altitude illness. *N Engl J Med.* 2001;345:107–114.
9. Somner JE, Morris DS, Scott KM, MacCormick IJ, Aspinall P, Dhillon B. What happens to intraocular pressure at high altitude? *Invest Ophthalmol Vis Sci.* 2007;48:1622–1626.
10. Bosch MM, Barthelmes D, Merz TM, et al. Intraocular pressure during a very high altitude climb. *Invest Ophthalmol Vis Sci.* 2010;51:1609–1613.
11. Brinchmann-Hansen O, Myhre K. Blood pressure, intraocular pressure, and retinal vessels after high altitude mountain exposure. *Aviat Space Environ Med.* 1989;60:970–976.
12. Grocott MP, Martin DS, Levett DZ, et al. Arterial blood gases and oxygen content in climbers on Mount Everest. *N Engl J Med.* 2009;360:140–149.
13. West JB. High-altitude medicine. *Am J Respir Crit Care Med.* 2012;186:1229–1237.
14. Bhan A, Browning AC, Shah S, Hamilton R, Dave D, Dua HS. Effect of corneal thickness on intraocular pressure measurements with the pneumotonometer, Goldmann applanation tonometer, and Tono-Pen. *Invest Ophthalmol Vis Sci.* 2002;43:1389–1392.
15. Tonnu PA, Ho T, Newson T, et al. The influence of central corneal thickness and age on intraocular pressure measured by pneumotometry, non-contact tonometry, the Tono-Pen XL, and Goldmann applanation tonometry. *Br J Ophthalmol.* 2005;89:851–854.
16. Ortiz GJ, Cook DJ, Yablonski ME, Masonson H, Harmon G. Effect of cold air on aqueous humor dynamics in humans. *Invest Ophthalmol Vis Sci.* 1988;29:138–140.
17. Read SA, Collins MJ. The short-term influence of exercise on axial length and intraocular pressure. *Eye (Lond).* 2011;25:767–774.
18. Liu HM, Bai CH, Liou CM, Chiou HY, Chen C. Central corneal thickness of healthy lowlanders at high altitude: a systematic review and meta-analysis. *Curr Eye Res.* 2018;43:460–465.
19. Ersanli D, Yildiz S, Sonmez M, Akin A, Sen A, Uzun G. Intraocular pressure at a simulated altitude of 9000 m with and without 100% oxygen. *Aviat Space Environ Med.* 2006;77:704–706.
20. Karadag R, Sen A, Golemez H, et al. The effect of short-term hypobaric hypoxic exposure on intraocular pressure. *Curr Eye Res.* 2008;33:864–867.
21. Karadag R, Sen A, Yildirim N, et al. The relation between intraocular pressure change and plasma natriuretic peptide under simulated hypobaric conditions. *Indian J Ophthalmol.* 2010;58:195–198.
22. Najmanova E, Pluhacek F, Botek M, Krejci J, Jarosova J. Intraocular pressure response to short-term extreme normobaric hypoxia exposure. *Front Endocrinol (Lausanne).* 2018;9:785.
23. Jimenez R, Vera J. Effect of examination stress on intraocular pressure in university students. *Appl Ergon.* 2018;67:252–258.
24. Krapf R, Beeler I, Hertner D, Hulter HN. Chronic respiratory alkalosis. The effect of sustained hyperventilation on renal regulation of

- acid-base equilibrium. *N Engl J Med.* 1991;324: 1394–1401.
25. Teppema LJ, Dahan A. The ventilatory response to hypoxia in mammals: mechanisms, measurement, and analysis. *Physiol Rev.* 2010;90:675–754.
  26. Kiel JW, Hollingsworth M, Rao R, Chen M, Reitsamer HA. Ciliary blood flow and aqueous humor production. *Prog Retin Eye Res.* 2011;30: 1–17.
  27. Lichter PR, Musch DC, Medzihradsky F, Standardi CL. Intraocular pressure effects of carbonic anhydrase inhibitors in primary open-angle glaucoma. *Am J Ophthalmol.* 1989;107:11–17.
  28. Maslanka T. A review of the pharmacology of carbonic anhydrase inhibitors for the treatment of glaucoma in dogs and cats. *Vet J.* 2015;203: 278–284.
  29. Lawrie A, Golda BP. Actual or standard bicarbonate. *Lancet.* 1979;2:201–202.
  30. Kiehar RA, Teraslinna P, Kearney JT, Barker D. Effect of changes in Pco<sub>2</sub> on intraocular tension. *Invest Ophthalmol Vis Sci.* 1977;16:534–537.
  31. Hvidberg A, Kessing SV, Fernandes A. Effect of changes in PCO<sub>2</sub> and body positions on intraocular pressure during general anaesthesia. *Acta Ophthalmol (Copenh).* 1981;59:465–475.
  32. Wylegala A. The effects of physical exercises on ocular physiology: a review. *J Glaucoma.* 2016;25: e843–e849.
  33. Zhou C, Zhu Y, Liu Z, Ruan L. The effects of intravenous dexmedetomidine injections on IOP in general anesthesia intubation: a meta-analysis. *Biomed Res Int.* 2017;2017:6186832.
  34. Mikhail M, Sabri K, Levin AV. Effect of anesthesia on intraocular pressure measurement in children. *Surv Ophthalmol.* 2017;62:648–658.
  35. Smith RB, Aass AA, Nemoto EM. Intraocular and intracranial pressure during respiratory alkalosis and acidosis. *Br J Anaesth.* 1981;53: 967–972.
  36. Bietti G, Virno M, Pecori-Giraldi J. Acetazolamide, metabolic acidosis, and intraocular pressure. *Am J Ophthalmol.* 1975;80:360–369.
  37. Klein BE, Klein R, Knudtson MD. Intraocular pressure and systemic blood pressure: longitudinal perspective: the Beaver Dam Eye Study. *Br J Ophthalmol.* 2005;89:284–287.
  38. Kotecha A, Crabb DP, Spratt A, Garway-Heath DF. The relationship between diurnal variations in intraocular pressure measurements and central corneal thickness and corneal hysteresis. *Invest Ophthalmol Vis Sci.* 2009;50:4229–4236.