A Meta-Analysis of Exhaled Nitric Oxide in Acute Normobaric Hypoxia

Martin J. MacInnis; Eric A. Carter; Joseph Donnelly; Michael S. Koehle

BACKGROUND: The effect of hypoxia on the exhaled nitric oxide (NO) of humans is unresolved. Many studies have measured the fraction of exhaled NO (FE_{NO}) or the partial pressure of exhaled NO (PE_{NO}) in normobaric and hypobaric hypoxia, with differing results.

METHODS: To better understand NO physiology and altitude acclimatization, we employed a random effects meta-analysis to determine the effect of acute normobaric hypoxia on the PE_{NO} of humans. A total of 93 subjects from 7 published studies (with 9 groups) were included. The median duration of exposure was 30 min and the mean hypoxic P_IO_2 was 95 (SD = 10) mmHg.

RESULTS: The weighted standardized mean difference (SMD) in PE_{NO} measured at baseline and during an acute exposure to normobaric hypoxia was not significantly different from zero (SMD = 0.09; 95% CI = −0.17, 0.34; z = 0.65).

CONCLUSION: Based on this meta-analysis, acute normobaric hypoxia does not affect the PE_{NO} measured from the mouths of humans. This result should be considered for interpretations of high-altitude (and hypobaric) measurements of exhaled NO. As the PE_{NO} is a potential biomarker for altitude-illness susceptibility, recognizing that normobaric hypoxia does not affect the PE_{NO} will be important for understanding previous associations between low exhaled NO and poor acclimatization to hypoxia.

KEYWORDS: altitude, FE_{NO}, PE_{NO}, high-altitude pulmonary edema, acute mountain sickness.

MacInnis MJ, Carter EA, Donnelly J, Koehle MS. *A meta-analysis of exhaled nitric oxide in acute normobaric hypoxia*. Aerosp Med Hum Perform. 2015; 86(8):693–697.

Nitric oxide (NO) is a gaseous signaling molecule with a diverse set of functions in the human body, including airway and vascular smooth muscle relaxation, ventilation-perfusion matching, neurotransmission, and host defense (reviewed in Conkin and Wessel[7] and Dweik[12]). The main sites of NO production are the endothelium of the vasculature and the epithelium of the lungs and conducting airways.[18,22] Some of this endogenous NO is exhaled in the breath of humans and it can be measured at the mouth or nose.[1,11] Exhaled NO is typically measured as a fraction of exhaled NO (FE_{NO}, often measured in parts per billion, ppb) or as a partial pressure of exhaled NO (PE_{NO}, often measured in nmHg). The concentration of NO in exhaled breath summarizes the production, transfer, and consumption of NO in the lungs.[4,15]

Exhaled NO is usually measured at or near sea level; however, there is much interest in the role that exhaled NO might have in hypoxia adaptation[3] and hypoxia acclimatization.[12,19] Furthermore, hypoxia at high altitude (hypobaric hypoxia) results from a lower barometric pressure (P_B), which decreases the ambient partial pressure of oxygen (Po_2). In contrast, normobaric hypoxia can be generated in a laboratory by lowering the fraction of inspired oxygen (F_IO_2) and maintaining the ambient P_B. While not necessarily eliciting equivalent physiological responses,[7,18,22] equivalent inspired partial pressures of oxygen (P_IO_2) are obtainable from the two modes of hypoxia. Because oxygen is a substrate in the production of NO via the L-arginine pathway, cellular oxygen concentrations are thought to regulate the enzymatic production of NO.[4,11] Consequently, if hypoxia limits the endogenous production of NO, exposure to either mode of hypoxia could be expected to result in lower rates of NO production and lower values of PE_{NO}.

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This manuscript was received for review in October 2014. It was accepted for publication in May 2015.

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DOI: 10.3357/AMHP.4172.2015

That hypobaric hypoxia decreases the FE_{NO} is a common finding among many studies;[3,4,15] however, studies of FE_{NO} in response to normobaric hypoxia have produced varied results.[9,24] Thus, the factors responsible for the decreased PE_{NO} observed in hypobaric hypoxia [i.e., hypoxia, hypobaria, an interaction of the two conditions, or some other factor(s)] are unclear. To date, there has been no systematic review of the literature pertaining to the effect of acute normobaric hypoxia on the FE_{NO} measured from humans. To investigate this aspect of NO physiology, we employed a random effects meta-analysis using the summary data from the available published studies.

METHODS

Collection of Data

We investigated available published studies examining the effects of acute normobaric hypoxia on oral exhaled NO from healthy conscious humans (**Tables I** and **II**). Studies were identified through searches of PubMed and Google Scholar using combinations of the following terms as queries: "normobaric," "hypoxia," and "exhaled nitric oxide." Additional studies were obtained from the references of identified papers. All identified studies published in English before March 2014 were reviewed. To be included in the meta-analysis, each study needed to report the effect sizes (or the means and standard deviations) for comparisons of groups measured at baseline (normoxia) and during normobaric hypoxia. As the techniques for measuring exhaled NO varied between the studies, we limited our analysis to those studies with consistent protocols across conditions: we excluded studies that measured exhaled NO during tidal breathing or without controlling for changes in ventilation, as exhaled NO varies greatly depending on the exhaled flow rate[17] and ventilation is greater in hypoxia than normoxia.

Conversion of Data to PE_{NO}

Exhaled NO is typically measured as a FE_{NO} or a PE_{NO}. To better allow for comparisons across studies, we converted all FE_{NO} values to PE_{NO} values using the provided P_B and the following equation:

$$PE_{NO}\ (nmHg) = FE_{NO}\ (ppb)^*[P_B\ (mmHg) - 47\ (mmHg)]/1000$$

If P_B was not stated and the study took place at or near sea level, a value of 760 mmHg was assumed. As this value was used for the calculation of baseline and hypoxic PE_{NO} measurements, it did not affect the relative difference between the two measurements.

Analysis of Summary Data

A random-effects meta-analysis was used to determine whether acute normobaric hypoxia affected the PE_{NO}. The duration of exposure to hypoxia was less than 30 min for six of the nine studies. For the studies with a longer duration, the mean PE_{NO} values from the first hours of a 6-h exposure[19] and a 24-h exposure[13] were used in the analysis. The mean PE_{NO} from hour 12 was used from the ninth study,[20] as intermediate measures of exhaled NO were not collected. If exhaled NO was measured at multiple P_IO_2, the lowest P_IO_2 was chosen to maximize the potential effect of hypoxia.

Using the random-effects model[8] from RevMan 5.0 (Review Manager, Copenhagen, Denmark), the standardized mean differences (SMD; Hedges' adjusted G), the 95% confidence intervals of the SMD, and the weight of each study were calculated (see Higgens and Green[16]). A *P*-value less than 0.05 was considered statistically significant. The I^2 index was used to quantify heterogeneity. Data are presented as means (SD) unless otherwise stated.

RESULTS

A total of 11 studies reporting the effects of acute normobaric hypoxia on exhaled NO from conscious humans were identified. Seven of these studies were included in the meta-analysis. Two of the included studies had two groups, resulting in the inclusion of nine groups. Three studies[5,11,28] were excluded because exhaled NO was measured during tidal breathing. One additional study[24] was excluded because it used a breath-hold maneuver and was difficult to interpret: the FE_{NO} was similarly low for subjects breathing 10% and 20% oxygen relative to baseline (21% oxygen); however, 20% oxygen should not affect FE_{NO}. Removing this one study from the analysis greatly reduced heterogeneity among the studies. Details of the protocols of each of the seven included studies are provided in **Table I**.

In total, the seven included studies assessed the effect of acute normobaric hypoxia on the PE_{NO} of 93 different subjects (the same 24 subjects were assessed twice by MacInnis et al.[20]). The average baseline and hypoxic P_IO_2 values were 149 (SD 3) mmHg and 95 (SD 10) mmHg, respectively (**Table II**). The median duration of exposure was 30 min (Table II).

The included studies did not report effect sizes; therefore, all calculations are based on summary data. For all nine groups, the SMD in the PE_{NO} between baseline and normobaric hypoxia were not significantly different from zero (Table II; **Fig. 1**). The overall SMD for the nine groups was 0.09 (95% CI = −0.17, 0.34; Fig. 1), which was also not significantly different from an SMD of zero ($z = 0.65$; $P = 0.51$). The I^2 value was 0%, suggesting that the effect of normobaric hypoxia was consistent across studies.

DISCUSSION

According to this meta-analysis, acute normobaric hypoxia did not affect the PE_{NO} measured at the mouth from humans. This finding is supported by the individual results of the included studies: acute normobaric hypoxia did not significantly affect the PE_{NO} relative to baseline measures in any of the seven studies (or nine groups). Our results should be considered in the interpretation of past and future studies that measure exhaled NO in hypobaric and normobaric hypoxia.

Table I. Summary of the Protocols Used in the Included Studies.

	DESCRIPTION OF TECHNIQUE AND ANALYSIS					
STUDY	BREATHING PATTERN	FLOW RATE ($ml \cdot s^{-1}$)	ON-LINE/OFF-LINE?	DURATION (MIN)	REPORTED ADHERENCE TO ATS/ERS GUIDELINES?	NITRIC OXIDE ANALYZER
Donnelly et al. 2011[9]	SB	50	On	25	Yes*	NIOX MINO
Faiss et al. 2013[13]	SB	50	On	60	No	NIOX MINO
Hemmingsson and Linnarsson 2009[15]	SB	50	On	10	Yes*	NIOX MINO
MacInnis et al. 2012[19]	SB	50	On	60	Yes*	Bedfont NObreath
MacInnis et al. 2014[20]	SB	50	On	720	Yes*	NIOX MINO
St. Croix et al. 1999[26]	SB	46	On	5	No	Sievers Model 280 NOA
Verges et al. 2005[29]	SB	170	On	30	Yes**	Cosma analyzer

SB, single breath.
* ATS/ERS 2005; **ATS 1999.

That the PE_{NO} is reduced in hypobaric hypoxia relative to sea level is a common finding at high[4] and moderate[6] altitudes. The decreased PE_{NO} in hypobaric hypoxia is often attributed to the hypoxia (i.e., the low P_IO_2); however, the present meta-analysis (and the majority of individual studies) demonstrated that acute normobaric hypoxia does not affect the PE_{NO}. Extrapolating this finding to hypobaric hypoxia, a causal relationship between the P_IO_2 and the PE_{NO}, independent of an effect of P_B, would be unexpected. It is more likely that the decreased PE_{NO} observed in hypobaric hypoxia is caused by a relatively low P_B, an interaction between a low P_B and a low P_IO_2, or some other factor(s). The possibility that P_B and not P_IO_2 affects the PE_{NO} is further supported by three repeated-measures studies that reported decreased PE_{NO} in hypobaric hypoxia, but a similar PE_{NO} in an equivalent normobaric hypoxia.[9,13,15] While studies of hypobaric hypoxia typically use greater durations of hypoxic exposure than studies of normobaric hypoxia (e.g., ~3 wk of hypobaric hypoxia and 25 min of normobaric hypoxia[9]), Hemmingsson and Linnarsson[15] and Faiss et al.[13] exposed subjects to equal durations of normobaric and hypobaric hypoxia, controlling for this potential confounding factor. Both of these studies reported no effect of normobaric hypoxia on exhaled NO. It is outside the scope of this study to discuss the possible explanations for a role of P_B on the PE_{NO}; however, that the two modes of hypoxia could elicit different physiological responses is not unprecedented.[14,21]

Exhaled NO has been investigated as a factor in the development of high altitude pulmonary edema (HAPE) and acute

Table II. The Summary Data Collected from Each Study and the Random Effects Meta-Analysis Data That Were Generated for Each Study.

	SUMMARY DATA						META-ANALYSIS DATA		
					PE_{NO} (nmHg)				
AUTHORS	*N*	F_IO_2	P_IO_2 (mmHg)*	EQUIVALENT ALTITUDE (M)	MEAN	SD	SMD	95% CI OF SMD	WEIGHT (%)
Donnelly et al. 2011[9]	11	0.21	150	0	18.8	11.4	0.09	−0.75, 0.92	9.4
	11	NR**	NR**	NR**	21.0††	12.4††			
	11	NR†	NR†	NR†	19.9	12.8			
Faiss et al. 2013[13]	10	0.21	140	485	15.2	8.5	−0.03	−0.91, 0.84	8.6
	10	0.15	99	~3000	14.9	9.2			
Hemmingsson and Linnarsson 2009[15]	8	0.21	149	0	18.2	2.2	−0.34	−1.33, 0.65	6.7
	8	0.15	104	~2700	17.6††	2.6††			
	8	0.11	80	~5000	17.4	2.3			
MacInnis et al. 2012[19]	15	0.21	150	0	8.8	5.6	0.08	−0.64, 0.79	12.9
	15	0.12	86	~4500	9.3	6.9			
MacInnis et al. 2014[20]	24	0.21	150	0	15.4	7.7	0.04	−0.52, 0.61	20.6
	24	0.13	90	~4000	15.7	6.2			
	24	0.21	150	0	15.8	6.4	0.17	−0.40, 0.73	20.5
	24	0.13	90	~4000	16.9	6.5			
St. Croix et al. 1999[26]	5	0.21	150	0	22.4	17.3	0.10	−1.14, 1.34	4.3
	5	0.14	100	~3200	24.5	19.7			
Verges et al. 2005[29]	11	0.21	150	0	8.9	4.8	0.36	−0.48, 1.20	9.3
	11	0.15	107	~2700	11.1	6.8			
	9‡	0.21	150	0	14.0	12.4	0.16	−0.77, 1.09	7.7
	9‡	0.15	107	~2700	16.0	11.5			

* If P_B was not reported, P_IO_2 was calculated from an assumed P_B of 760 mmHg; **subjects' pulse oxygen saturations were maintained at ~90% (P_IO_2 was not provided); †subjects' pulse oxygen saturations were maintained at ~80% (P_IO_2 was not provided); ††these data were not used in the meta-analysis; ‡subjects were diagnosed with exercise induced arterial hypoxemia, but this diagnosis was independent of the concentration of exhaled NO measured under resting conditions.
N, sample size; SD, standard deviation; SMD, standardized mean difference of the PE_{NO} between baseline and hypoxia; CI, confidence interval of the SMD; NR, not reported.

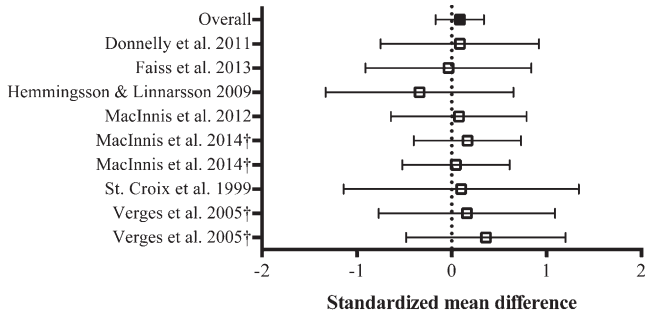

Fig. 1. A forest plot of the standardized mean differences (SMD) of the PE_{NO} between baseline and acute exposure to normobaric hypoxia. Lines represent 95% confidence intervals of the SMD. The black box represents the average SMD for all included studies (see Table II for each study's weight in the calculation of the overall SMD). A positive SMD indicates that mean PE_{NO} increased during exposure to acute normobaric hypoxia and vice versa. The † indicates studies with more than one group/exposure.

mountain sickness (AMS). After a rapid ascent to 14,957 ft (4559 m), subjects who developed HAPE exhaled less NO compared to HAPE-resistant subjects at the same altitude.[10] Additional subjects with a history of HAPE (but without signs of HAPE on that particular ascent) also had a significantly lower mean exhaled NO compared to HAPE-resistant subjects. Similarly, male subjects who developed AMS during a brief normobaric hypoxia exposure had a lower FE_{NO} than subjects who did not develop AMS.[19] In a longer overnight exposure to normobaric hypoxia (12 h), a lower, albeit not statistically significant, FE_{NO} was reported in those individuals who developed AMS.[20] There was no association between FE_{NO} and AMS upon exposure to hypobaric hypoxia,[4] but the duration of exposure (3 h) was relatively short and the incidence of AMS was relatively low.

The physiological mechanisms linking NO production in the lungs and conducting airways with susceptibility to altitude illness have yet to be fully elucidated and verified. One possibility is that variation in exhaled NO production is related to differences in blood oxygenation.[27] To support this hypothesis, the inhalation of NO increased the blood oxygen saturation of patients with HAPE and also reduced the severity of HAPE.[2,23] Similarly, the inhalation of NO reduced the severity of AMS, although subjects' oxygen saturations were not measured before and after NO inhalation.[30] More research is needed to understand the physiological significance of differences in exhaled NO with respect to altitude illness susceptibility.

As exercise is routinely performed at altitude, the effects of hypoxia on exhaled NO are also relevant to exercise physiology, particularly with respect to exercise-induced asthma. For example, with the purpose of improving the monitoring of asthmatic athletes at altitude, Caspersen et al.[6] and Stang et al.[25] both assessed exhaled NO in subjects exposed to moderate altitude under resting and, in the case of Stang et al., exercising conditions. The effects of altitude (and the lack of effect for hypoxia per se) must be considered when interpreting measurements of exhaled NO collected at altitude.

There are several limitations to our analysis. Firstly, slightly different methods were used to measure exhaled NO across studies, and we could not control for all of this variation; however, excluding those studies that measured exhaled NO during tidal breathing eliminated the most significant differences in measurement technique. Secondly, the data included in the meta-analysis were from studies of different durations; therefore, we cannot speculate on the effect of prolonged exposure to normobaric hypoxia on the PE_{NO} relative to baseline. Studies of 12 h[20] and 24 h[13] suggest that there is no effect of normobaric hypoxia on the PE_{NO} in at least the first 24 h of exposure. Thirdly, our results are likely specific to the range of F_IO_2 corresponding to the included studies; therefore, our results cannot be extrapolated to more extreme hypoxic exposures (e.g., an F_IO_2 of 0.05). Finally, although we attempted to conduct a comprehensive search of the literature, we limited our search to English manuscripts accessible through PubMed and Google Scholar. Although we did not identify any additional studies from the reference lists of the studies we examined, it is possible that some data were missed, especially those manuscripts not published in English.

In conclusion, this meta-analysis indicates that acute exposure to normobaric hypoxia does not affect the PE_{NO} measured orally from humans. As several studies have reported decreased PE_{NO} in hypobaric hypoxia, our analysis suggests that a factor other than hypoxia (presumably hypobaria) might mediate the decrease in PE_{NO} at altitude. Further studies of the PE_{NO} in hypobaric hypoxia and hypobaric normoxia are necessary to understand the effects of P_B on the PE_{NO}. The results of this study will aid in the interpretation of the association between altitude-illness susceptibility and exhaled NO, but more research is needed to elucidate this potential relationship.

ACKNOWLEDGMENTS

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