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Prediction of Periodic Breathing at Altitude

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1 Background

Periodic breathing at high altitude has been known to occur for perhaps hundreds of years, but was first described in the medical literature by Mosso in 1898 (Mosso 1898). Lahiri *et al*. (1983) published an examination of the relationship between ventilatory response to hypoxia measured at high altitude (5,300 m) and prevalence of periodic breathing during sleep at that altitude in a group of acclimatized mountaineers and high altitude sherpas as part of the American Medical Expedition to Mount Everest (Lahiri, Maret and Sherpa 1983). They showed a strong correlation between high ventilatory response to hypoxaemia at altitude in awake subjects who were acclimatized for a month and the prevalence of central sleep apnea. When we studied the relationship between ventilatory response to hypoxia and hypercapnia at sea level, and the subsequent prevalence of periodic breathing at high altitude, we found no such relationship (Burgess 2001; Burgess Johnson and Edwards 2004), probably because ventilatory responses change due to acclimatization.

These studies were undertaken to investigate the possible relationship between ventilatory response and periodic breathing during sleep, in a group of normal volunteers, at a low altitude and high altitude. Although there are too few subjects to generate a new model after the style of Topor *et al*. (2004), we hoped there would be sufficient data to test his current model.

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2 Methods

The studies were approved by the Human Research and Ethics Committee of the University of Calgary, the Northern Sydney Area Health Service and the Nepal Health Medical Research Council. Each subject gave informed written consent.

Five healthy individuals [aged 32 ± 10 (mean ± SD) years; body mass index 22.8 ± 1.6 $kg.m^2$] were studied. Subjects were studied within 48 hr of arrival in Kathmandu from sea level abode. Subjects then flew to Lukla and hiked initially to Mount Everest Basecamp at 5,340 m over 6 days. They remained at Basecamp for 4 days and then descended over 2 days to Kunde, where the repeat experiments were conducted over the succeeding 3 days. The repeat experiments were initially intended for Mount Everest Basecamp, however the ventilatory response equipment would not function at that altitude. Subjects were studied in the afternoon fasting, having avoided alcohol and caffeine for at least 18 hr prior to the test. They then underwent ventilatory response testing in the awake sitting position. Subjects wore eyeshades and headphones playing relaxing music of their choice, to minimise distraction during the ventilatory response testing. Two runs were performed of each of the hypoxic and hypercapnic ventilatory tests. In addition, subjects also underwent arterial blood gas collection after 10 minutes rest in the sitting position at each altitude. Finally each subject underwent 13-channel polysomnography during overnight sleep.

The ventilatory responses were tested using combined rebreathing techniques developed by Duffin and McEvoy (1988). In the hypercapnic ventilatory responses, subjects rebreathed a mixture of 7% CO_2 in 93% oxygen from an 8 litre reservoir bag, after hyperventilating down to a end tidal CO_2 of approximately 17 mmHg for 5 min. Ventilation was measured by a turbine system, and end tidal CO_2 was measured by a portable high-speed infrared CO_2 analyser (Jaeger Oxycon mobile system, Rietzens, Keizer and Kuipers 2000).

The hypoxic ventilatory responses were measured using the same system, except that subjects rebreathed from an 8 litre bag containing 4 litres of 9% oxygen in 7% CO_2, with the balance nitrogen (Duffin *et al.* 1988). Supplemental oxygen was added to the bag to try to maintain an end tidal oxygen between 45 and 55 mmHg (SaO_2, 80–90%). The results of the two separate runs are shown in Table 3.

The arterial blood gas samples were analysed using an i-STAT machine (Jacobs, Vadasdi, Sarkozi and Colman 1993; Sediame, Zerah-Lancer, d'Ortho Arnet and Harf 1999) that was electronically calibrated before each blood gas analysis. The blood gases were collected either in the afternoon before the sleep study or the following morning.

The sleep studies were performed using the Compumedics PS2 portable polysomnogram equipment (Compumedics, Melbourne, Australia), (Burgess, Cooper, Rice, Wong, Kinsman and Hahn 2006). The recorded data included: EKG, 2 channels EEG, 2 channels EOG, leg movement, oxygen saturation, nasal flow by pressure transducer attached to nasal cannulae, thoracic and abdomen effort by piezo-electric band system, snoring, body position and lights on/off.

The results were tested for normality. In those results where the results appeared to be normally distributed, paired t-tests were used for comparison between the two altitudes (Bland 1996; Lang and Secic 1997). In those results where the data appeared not to be normally distributed, the Wilcoxin sign rank test (Aabel for the Macintosh, Gigawiz Ltd. Co., USA) was used. In the HVR runs, data points where the SaO_2 was < 80% or > 90% were excluded. The intersection of the regression lines was determined in an interactive process that maximised the r values for the intersecting linear regression lines.

3 Results

Results are represented in Tables 1 to 5.

Table 1 ABG Data

	1,400 m					3,840 m				
SUB	pH	$PaCO_2$	PaO_2	HCO_3	BE	pH	$PaCO_2$	PaO_2	HCO_3	BE
01	7.38	37.5	76	22.2	–3	7.456	26.2	50	18.5	–5
02	7.393	36	74	22	–3	7.459	28.1	58	19.9	–4
03	7.472	36.2	75	26.5	+3	7.439	29.7	56	20.1	–4
04	7.468	31.9	78	23.1	–1	7.440	27.3	55	18.5	–6
08	7.416	35.9	69	23.1	–1	7.453	28	53	19.6	–4
Mean ± SD	7.426	35.5	74	23.4	–1	7.449	27.9	54	17.1	–5
	0.042	2.1	3	1.8	2	.009	1.3	3	5.5	1

Statistical comparison between low and high altitude. pH: p = .36 $PaCO_2$: p = 0.002; PaO_2: p = 0.001; HCO_3: p = 0.005; BE: p = 0.029 (Paired t-test)

Table 2 Key Sleep Variable Data

	1,400 m					3,840 m				
SUBJ	AI	OAHI	CAHI	Min Sat%	Mean Sat%	AI	OAHI	CAHI	Min Sat%	Mean Sat%
01	7.0	1.4	0	85	93	9.2	0.3	22.4	77	86
02	7.4	6.6	0	89	95	13.7	0	50.7	83	91
03	8.4	0	0	93	96	8.5	2.3	48	79	86
04	6.7	0	0	90	95	8.7	0	1.2	84	89
08	9.7	0	0	90	95	9.9	0	2.0	82	86
Mean ± SD	7.8	1.6	0	89	91	10.0	0.5	24.9	81	88
	1.2	2.0	0	3	1	2.1	1.0	23.9	3	2

AI = Arousal Index; OAHI = Obstructive Apnea – Hypopnea Index; CAHI = Central Apnea – Hypopnea Index; Min Sat = Minimum Saturation; Mean Sat = Mean Saturation; NS = Not Significant. Results of comparison between low and high altitude by paired t-test:- AI = NS OAHI = NS CAHI = p = 0.08 Min Sat = p = 0.005 Mean Sat = p = 0.003

Table 3 Sleep Architecture Data

SUBJ	1,400 m				3,840 m			
	1	2	3&4	REM	1	2	3&4	REM
01	3.9	55.9	20.4	19.8	5	60.4	12	22.7
02	3.8	47.7	18.4	30	11.7	60.9	10.5	16.9
03	2.9	50.1	24.5	19.3	2	46.9	15.6	35.4
04	1.3	54.2	39.6	4.9	1.8	66.1	22.5	9.5
08	3.2	43.4	30.8	22.5	7.6%	60.6%	9.8%	22
Mean ± SD	3.0	50.3	26.7	19.3	5.6	59.0	14.1	21.3
	1.0	5.0	8.6	9.1	4.2	7.2	5.2	9.5

Results of statistical comparison between low and high altitude (paired t-test)
Stage 1: NS Stage 2: $p = 0.07$ Stages 3&4: $p = 0.009$ REM: NS

Table 4 Ventilatory Response Data

	1,400 m		3,840 m	
SUBJECT	HVR	HCVR	HVR	HCVR
01	5.1	8.1	5.8	26.9
	4.1	8.7	4.1	29.6
02	0.5	1.4	2.1	1.9
	0.7	2.1	2.7	1.9
03	0.4	10.8	3.2	6.6
	0.4	6.8	5.1	7.8
04		2.1		8.6
	0.5	1.2	3.7	8.3
08	0.7	0.8	0.8	1.5
		1.3	0.9	2.1
Mean	1.6	4.3	3.2*	9.5+
SD	1.9	3.8	1.7	10.3

The ventilatory response data shown here are the values of the slopes of the linear portions of the relationships between ventilation and end tidal PCO_2. * $p = 0.02$ high altitude compared to low altitude.+ $p < 0.05$ high altitude compared to low altitude (Wilcoxin sign rank test).

Table 5 Regressions of VRs Against CSA Index at 3,840 m

HVR at 1,400 m Vs. CSAI at 3,840 m	r = −0.26
HVR at 3,840 m Vs. CSAI at 3,840 m	r = 0.29
HCVR at 1,400 m Vs. CSAI at 3,840 m	r = 0.43
HCVR at 3,840 m Vs. CSAI at 3,840 m	r = −0.09
Delta HVR Vs. CSAI at 3,840 m	r = 0.42
Delta HCVR Vs. CSAI at 3,840 m	r = −0.32

Results of linear regressions of VR data shown in Table 4 against CSA Index of the same subjects at 3,840 m.

4 Conclusion

These are pilot data, with too few subjects to allow us to draw convincing conclusions. However, we can say that ventilatory responses do increase with acclimatization to altitude. The trends in change in the ventilatory response at altitude and the development of CSA suggest that it is the change in hypoxic ventilatory response moving to high altitude that is more important in the development of central sleep apnea, than the hypercapnic ventilatory response. Indeed, the general pattern suggests that (and this fits with Topor's model) it is the disproportionate increase in one ventilatory response relative to the other ventilatory response, that predicts or predisposes to the development of CSA at high altitude.

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