Altitude illness is related to low hypoxic chemoresponse and low oxygenation during sleep

By

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Online Data Supplement

E-add 1 Sleep studies in normoxia and hypoxia.

To achieve appropriate level of hypoxic exposure, we used a commercially available altitude tent (Hypoxico®, Colorado). Hypoxic environment was created by a compressor (oxygen extractor, Hypoxico®). The F_iO_2 was continuously monitored using an O_2 sensor (Maxtec OM-25MEI). A continuous flow of hypoxic gas through the tent minimized CO_2 build up.

Two full night polysomnographies were performed. O_2 saturation was monitored continuously and recorded for each subjectovernight throughout the exposure (BlueNight®, SleepInnov Technology, Moirans, France). This allowed real-time monitoring of the exposure by the investigators. Polysomnographies were performed with an ambulatory system (Cidélec, Sainte-Gemmes sur Loire, France), analyzed manually with the added software package (Cidélec, Sainte-Gemmes sur Loire, France). Physiological signals included 2 electroencephalogram channels (CZ-O1 and C3-A2), submental electromyogram, and electro-oculogram. Chest wall and abdominal movements were assessed by non-calibrated inductive plethysmography and oxygen saturation by pulse oximetry. Airflow was monitored with a nasal cannula connected to a pressure transducer..

Sleep stages were analyzed manually using the standard criteria of Rechtschaffen and Kales. Microarousals were scored manually using ASDA criteria. Hypopneas were scored as either central or obstructive according to the following: a central hypopnea was scored when flow exhibited a decrease of more than 30% during at least 10 seconds, with a visually assessed proportional decrease in thoracic and abdominal movement without flow limitation and/or phase decay; if none of the preceding could be applied to the event, an obstructive hypopnea was scored. The obstructive or central nature of respiratory events was according to the occurrence of flow limitation, hypopnoea and/or apnoea on the nasal pressure trace and whether co-existing phase decay or opposite movement on thoracic and abdominal captors was observed or not.

E-table 1. High-altitude illness symptoms in « altitude intolérant » subjects and paired AMS-s.

AMS: Acute Mountain Sickness, HAPE/HACE : High Altitude Pulmonary/Cerebral Edema. AMS severity was estimated with Lake Louise Score.

AMS+ 'altitude-intolerant' subjects or paired AMS- subjects	LLS
AMS- (maximal altitude ever reached = 4810 m)	0
AMS- (maximal altitude ever reached = 6700 m)	0
AMS- (maximal altitude ever reached = 5700 m)	0
AMS- (maximal altitude ever reached = 5000 m)	0
AMS- (maximal altitude ever reached = 4400 m)	0
AMS- (maximal altitude ever reached = 4810 m)	0
AMS- (maximal altitude ever reached = 5400 m)	0
AMS- (maximal altitude ever reached = 5100 m)	0
AMS- (maximal altitude ever reached = 5600 m)	0
AMS- (maximal altitude ever reached = 6800 m)	0
AMS- (maximal altitude ever reached = 4810 m)	1
AMS- (maximal altitude ever reached = 4810 m)	1
AMS+ (recurrent severe Acute Mountain Sickness and one HAPE at 4000m)	12
AMS+ (recurrent severe AMS at 3500m)	10
AMS+ (severe AMS. Three HAPE between 3500 and 4000m)	9
AMS+ (recurrent severe AMS at 3400m)	8
AMS+ (severe AMS. HAPE at 3600m)	12
AMS+ (recurrent severe AMS at 3000m)	9
AMS+ (severe AMS and two HAPE around 4000m)	10
AMS+ (recurrent severe AMS at 3500m)	8
AMS+ (recurrent severe AMS at 3500 m and one HACE at 4800m)	12
AMS+ (recurrent severe AMS at 3000m)	6
AMS+ (recurrent severe AMS at 3500m)	12

AMS+ (recurrent severe AMS at 3600m)	8

E-table 2. Polysomnographic measurements during hypoxic night in both groups.

Measurements		**Mean ± SD**	**Statistical comparisons** **P value**
Number of intra-sleep arousal (>30s)	AMS+	29.8 ± 10.0	0.25
	AMS-	26.7 ± 12.4	
Total duration of intra-sleep wake time (min)	AMS+	70.4 ± 45.1	0.03
	AMS-	44.9 ± 31.1	
Number of micro-arousals (/h)	AMS+	31.3 ± 17.3	0.1
	AMS-	39.1 ± 15.9	
Number of legs periodic movements	AMS+	26.2 ± 65.3	0.44
	AMS-	30.5 ± 68.9	
Number of micro-arousal related to legs periodic movements	AMS+	19.8 ± 54.2	0.5
	AMS-	20.3 ± 50.5	
Number of micro-arousal related to legs periodic movements /h	AMS+	3.4 ± 9.6	0.5
	AMS-	3.4 ± 8.4	

Measurements		**Mean ± SD**	**Statistical comparisons** **P value**
AHI (events.h^{-1})	AMS+	18.2 ± 18.1	0.038
	AMS-	33.4 ± 24.8	
Apnea index (/h)	AMS+	3.5 ± 9.4	0.037
	AMS-	12.3 ± 13.7	
Stage 1 Apneas index /h	AMS+	8.2 ± 14.3	0.008
	AMS-	75.2 ± 82.3	
Stage II Apneas index /h	AMS+	15.7 ± 40.4	0.049
	AMS-	59.8 ± 76.9	
Stage III/IV Apneas index /h	AMS+	8.3 ± 27.2	0.16
	AMS-	0.1 ± 0.4	
REM Sleep Apneas index /h	AMS+	0.4 ± 0.9	0.003
	AMS+	16.2 ± 15.9	
Number of apneas (/TST)	AMS+	20.8 ± 51.4	0.026
	AMS-	78.9 ± 86.8	
Cumulated duration of	AMS+	1.1 ± 3.2	0.028

apneas (%TST)	AMS-	5.0 ± 5.9	
Apneas mean duration (s)	AMS+	11.3 ± 5.6	0.16
	AMS-	13.8 ± 4.6	
Apneas longest duration (s)	AMS+	13.8 ± 7.1	0.04
	AMS-	20.6 ± 7.6	
Number of obstructive sleep apneas	AMS+	0.5 ± 1.4	0.028
	AMS-	2.4 ± 2.3	
Number of mixed sleep apneas	AMS+	0.4 ± 1.4	0.17
	AMS-	1.6 ± 3.6	
Number of central sleep apneas	AMS+	19.8 ± 49.5	0.03
	AMS-	74.8 ± 85.5	
Hypopneas index /h	AMS+	14.7 ± 11.6	0.1
	AMS-	21.1 ± 14.2	
Stage 1 Hypopneas index /h	AMS+	27.2 ± 21.5	0.03
	AMS-	68.4 ± 66.5	
Stage II Hypopneas index /h	AMS+	67.2 ± 60.7	0.14
	AMS-	95.4 ± 84.8	
Stage III/IV Hypopneas index /h	AMS+	2.1 ± 3.4	0.097
	AMS-	10.6 ± 20.9	
REM Sleep Hypopneas index /h	AMS+	53.2 ± 49.6	0.097
	AMS-	88.5 ± 70.4	
Total number of hypopneas	AMS+	87.2 ± 68.5	0.07
	AMS-	135.2 ± 92.5	
Number of central hypopneas	AMS+	49.8 ± 53.2	0.09
	AMS-	80.9 ± 90.7	
Number of obstructives hypopneas	AMS+	34.1 ± 63.4	0.2
	AMS-	52.3 ± 61.8	
Limitation index /h	AMS+	1.5 ± 1.5	0.3
	AMS-	1.9 ± 1.9	
AHI + flow limitation (events.h^{-1})	AMS+	19.7 ± 36.4	0.03
	AMS-	35.3 ± 42.9	
AHI + nasal flow limitation (events.h^{-1})	AMS+	19.5 ± 18.0	0.03
	AMS-	35.4 ± 24.9	
Total number of limitations	AMS+	9.2 ± 6.6	0.09
	AMS-	14.3 ± 8.5	
Snoring /h	AMS+	67.0 ± 103.7	0.4
	AMS-	74.7 ± 114.3	

Measurements		Mean ± SD	Statistical comparisons P value
Sleep mean SpO_2 (%)	AMS+	81.6 ± 2.6	0.005
	AMS-	85.5 ± 2.4	
Sleep min SpO_2 (%)	AMS+	73.6 ± 3.1	0.005
	AMS-	78.0 ± 2.6	
Number of desaturations of more than 3%	AMS+	106.3 ± 101.9	0.03
	AMS-	194.3 ± 133.4	
Number of desaturation /h	AMS+	17.9 ± 16.9	0.048
	AMS-	30.7 ±19.9	
Duration spent under 90% SpO_2 (% du TST)	AMS+	98.7 ± 1.8	0.003
	AMS-	91.0 ± 8.1	
Mean SpO_2 in stage I (%)	AMS+	83.2 ± 2.7	0.009
	AMS-	86.4 ± 2.6	
Mean SpO_2 in stage II (%)	AMS+	82.4 ± 2.7	0.006
	AMS-	85.9 ± 2.5	
Mean SpO_2 in stage III (%)	AMS+	82.2 ± 2.3	0.07
	AMS-	84.3 ± 3.1	
Mean SpO_2 in REM sleep (%)	AMS+	80.3 ± 3.0	0.001
	AMS-	85.8 ± 2.6	
Min SpO_2 in stage I (%)	AMS+	76.2 ± 4.6	0.048
	AMS-	79.9 ± 3.7	
Min SpO_2 in stage II (%)	AMS+	75.3 ± 3.6	0.01
	AMS-	79.5 ± 3.2	
Min SpO_2 in stage III (%)	AMS+	78.2 ± 3.1	0.007
	AMS-	82.8 ± 3.9	
Min SpO_2 in REM sleep (%)	AMS+	74.5 ± 3.1	0.002
	AMS-	79.3 ± 2.1	

E-table 3. Transthoracic echocardiography measurement in both groups during normoxic and hypoxic exposure at rest.

Measurement	Group	Normoxia	Hypoxia	p
LVEF (Left ventricular ejection fraction) visual method	AMS+	61.58 ± 6.96	67.44 ± 9.79	0.10
	AMS-	70.17 ± 5.97	71.50 ± 8.65	0.34
	p	0.003	0.04	
LVEF (Teicholtz method)	AMS+	60.75 ± 8.70		
	AMS-	66.82 ± 6.10		
	p	0.04		
LVSF (Left Ventricular Shortening Fraction)	AMS+	0.34 ± 0.08	0.38 ± 0.08	0.18
	AMS-	0.37 ± 0.05	0.40 ± 0.06	0.01
	p	0.18	0.35	
St Systolic myocardial peak velocity of the tricuspid annulus in pulse doppler tissue imaging	AMS+	16.99 ± 3.82	16.53 ± 3.21	0.33
	AMS-	15.71 ± 2.73	15.60 ± 1.22	0.44
	p	0.15	0.29	
E/A Pulse wave-doppler measurements of the early (E) and late (A) mitral inflow velocity)	AMS+	1.34 ± 0.57	0.97 ± 0.41	0.04
	AMS-	1.44 ± 0.50	1.05 ± 0.25	0.003
	p	0.39	0.29	
E/Ea Ea: early diastolic velocity of the medial mitral annulus in pulse doppler tissue imaging	AMS+	4.77 ± 1.02	4.58 ± 1.29	0.40
	AMS-	5.81 ± 1.62	4.54 ± 0.54	0.02
	p	0.01	0.50	

Heart Rate (HR)	AMS+	60.33 ± 11.40	68.56 ± 5.66	0.01
	AMS-	56.27 ± 12.31	66.50 ± 14.78	0.04
	p	0.17	0.46	
LV-TVI left ventricular outflow time-velocity integral	AMS+	18.95 ± 2.14	19.47 ± 2.57	0.44
	AMS-	19.89 ± 3.26	19.64 ± 2.36	0.43
	p	0.30	0.41	
Stroke volume	AMS+	3.76 ± 1.02	4.16 ± 0.88	0.09
	AMS-	3.82 ± 0.99	4.46 ± 1.05	0.13
	p	0.39	0.40	
TVR (Maximal Tricuspid regurgitation peak velocity)	AMS+	2.01 ± 0.28	2.28 ± 0.56	0.02
	AMS-	2.20 ± 0.24	2.37 ± 0.21	0.02
	p	0.07	0.43	
RV-RA gradient (right ventricle - right atrium)	AMS+	16.75 ± 5.14	21.82 ± 12.43	0.04
	AMS-	20.33 ± 4.50	22.22 ± 4.29	0.13
	p	0.09	0.44	
PASP (pulmonary artery systolic pressure)	AMS+	22.00 ± 7.04	27.82 ± 11.83	0.03
	AMS-	27.25 ± 6.63	27.22 ± 5.78	0.47
	p	0.20	0.49	
Right ventricular outflow time-velocity integral	AMS+	16.49 ± 2.57	14.69 ± 2.26	0.07
	AMS-	19.33 ± 3.16	17.01 ± 2.86	0.06
	p	0.04	0.03	

Pulmonary vascular resistances (PVR)	AMS+	1.40 ± 0.14	1.71 ± 0.46	0.09
	AMS-	1.24 ± 0.13	1.57 ± 0.33	0.01
	p	0.01	0.16	

TAPSE (Tricuspid annular plane systolic excursion)	AMS+	26.88 ± 3.27	26.81 ± 2.24	0.49
	AMS-	28.11 ± 7.51	26.00 ± 3.67	0.23
	p	0.26	0.44	

E-table 4. Results of univariate conditional logistic regression.

Significativity is considered when low and high limits values did not cross 1 and p-value < 0.05.

Variables (medians)	Odds Ratio	Low limit	High Limit	p-value
Eupneic $P_{ET}CO_2$ (>=38/<38)	7	0.861	56.895	0.0687
HCVR Threshold (>=46.8/<46.8)	4	0.849	18.836	0.0795
${}_{i}hvr_{5}$ (>=0.58/<0.58)	0.125	0.016	0.999	0.0499 *
${}_{i}hvr_{20}$ (>=0.37/<0.37)	1.5	0.251	8.977	0.6569
Vc (>=96/<96)	0.333	0.067	1.652	0.1785
PVR in normoxia (>=0.115/<0.115)	5	0.584	42.797	0.1418
PASP in normoxia (>=23/<23)	0.25	0.028	2.237	0.215
ET-1 after normoxic night (>=0.415/<0.415)	1	0.141	7.099	0.99
LVEF in normoxia (>=65/<65)	0.143	0.018	1.161	0.0687
HCVR slope (>=3.25/<3.25)	0.429	0.111	1.657	0.2195

Statistical reference: selection of important variables and determination of fonctional form for continus predictors in multivariable model building. 2007 Statistics in medecine. Willy Sauerbrei. In each analysis, the variable of interest is significantly related with altitude illness, if the odds ratio of the variable in AMS + and – group respectively is (i) either above the higher limit of (positive correlation) and the lower limit of the confidence interval does not cross one or (ii) below the lower limit with a confidence interval above one. Each variable is a distinct and independent variable. A single analysis is performed for correlated variables.

E-table 5. Technical details for biological analysis.

Variable	Kit name	Brand.
Endothelin-1	Endothelin (1-21) ®, BI-20052	Biomedica Gruppe
Big-endothelin	Big endothelin®, BI-20082	Biomedica Gruppe
Aldosterone	DSL-8600 ACTIVE® Aldosterone Coated Tube RIA Kit	Diagnostic Systems Laboratories
Vasopressin	Vasopressin125I RIA Kit®	DiaSorin
Renin	Renin III Generation®	IBL-America