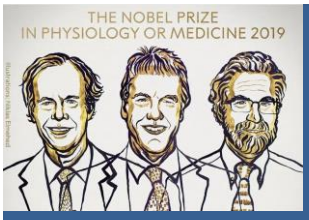


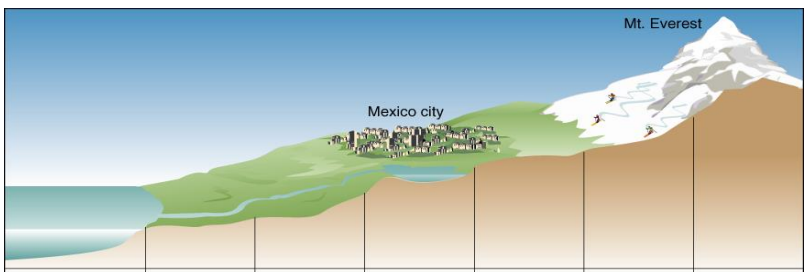
Expédition 5300 :
À la découverte de la ville la plus haute du monde

Dr. Samuel Vergès

Laboratoire Hypoxie-Physiopathologie (HP2)
Chaire Montagne-Altitude-Santé Fondation UGA
Centre d'Expertise sur l'Altitude EXALT
Université Grenoble Alpes - INSERM - CHU Grenoble Alpes

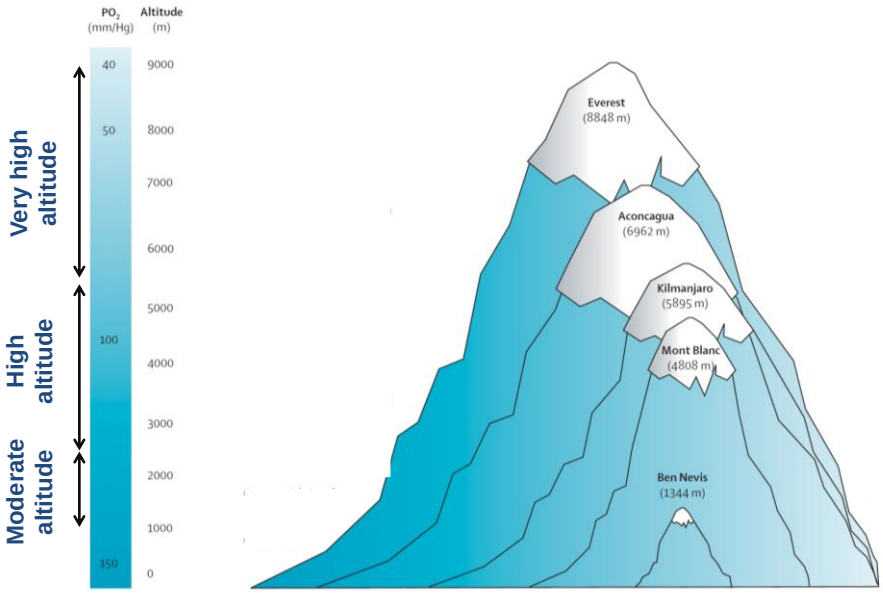
Altitude, pressure & hypoxia

Reduced barometric pressure
=
Reduced inspiratory oxygen pressure

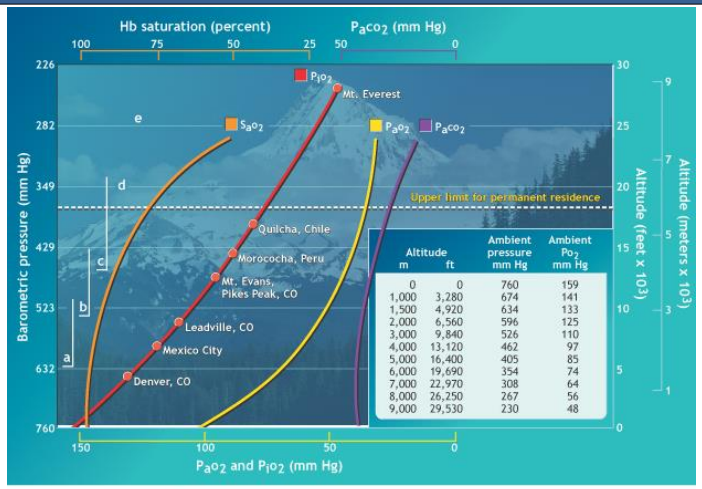


Altitude (ft) (m)	0 (sea level) 0	3,280 1,000	6,560 2,000	9,840 3,000	13,120 4,000	29,520 9,000
P_B (mmHg)	760	674	596	526	462	231
PO_2 (mmHg)	159.1	141.1	124.7	110.0	96.7	48.3

Types of altitude exposure



Changes in blood gases at altitude



Wilmore and Costill 2005

a) Lightheadedness, headache b) Insomnia, nausea, vomiting, pulmonary discomfort
c) Dyspnea, anorexia, GI disturbances d) Lethargy, general weakness e) Impending collapse

Changes in blood gases at altitude

Arterial Blood Gases and Oxygen Content in Climbers on Mount Everest

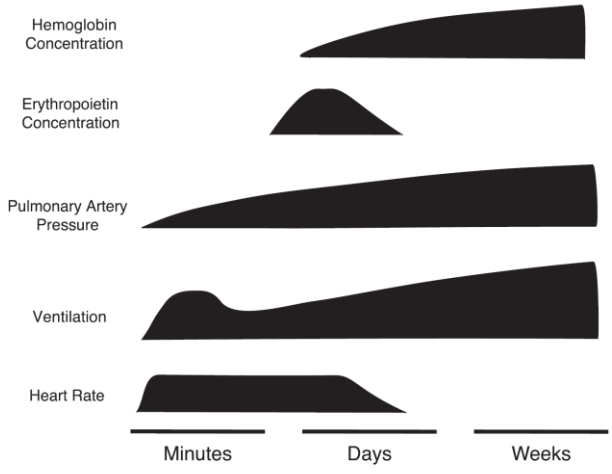
Michael P.W. Grocott, M.B., B.S., Daniel S. Martin, M.B., Ch.B., Denny Z.H. Levett, B.M., B.Ch., Roger McMorrow, M.B., B.Ch., Jeremy Windsor, M.B., Ch.B., and Hugh E. Montgomery, M.B., B.S., M.D., for the Caudwell Xtreme Everest Research Group*

Table 2. Arterial Blood Gas Measurements and Calculated Values for Pulmonary Gas Exchange from Four Subjects at an Altitude of 8400 m, during Descent from the Summit of Mount Everest.*

Variable	Subject No.				Group Mean
	1	2	3	4	
pH	7.55	7.45	7.52	7.60	7.53
PaO_2 (mm Hg)†	29.5	19.1	21.0	28.7	24.6
$PaCO_2$ (mm Hg)†	12.3	15.7	15.0	10.3	13.3
Bicarbonate (mmol/liter)‡	10.5	10.67	11.97	9.87	10.8
Base excess of blood‡	−6.3	−9.16	−6.39	−5.71	−6.9
Lactate concentration (mmol/liter)	2.0	2.0	2.9	1.8	2.2
SaO_2 (%)‡	68.1	34.4	43.7	69.7	54.0
Hemoglobin (g/dl)§	20.2	18.7	18.8	19.4	19.3
Respiratory exchange ratio¶	0.81	0.74	0.72	0.70	0.74
PAO_2 — mm Hg†**	32.4	26.9	27.4	33.2	30.0
Alveolar–arterial oxygen difference — mm Hg†	2.89	7.81	6.44	4.51	5.41

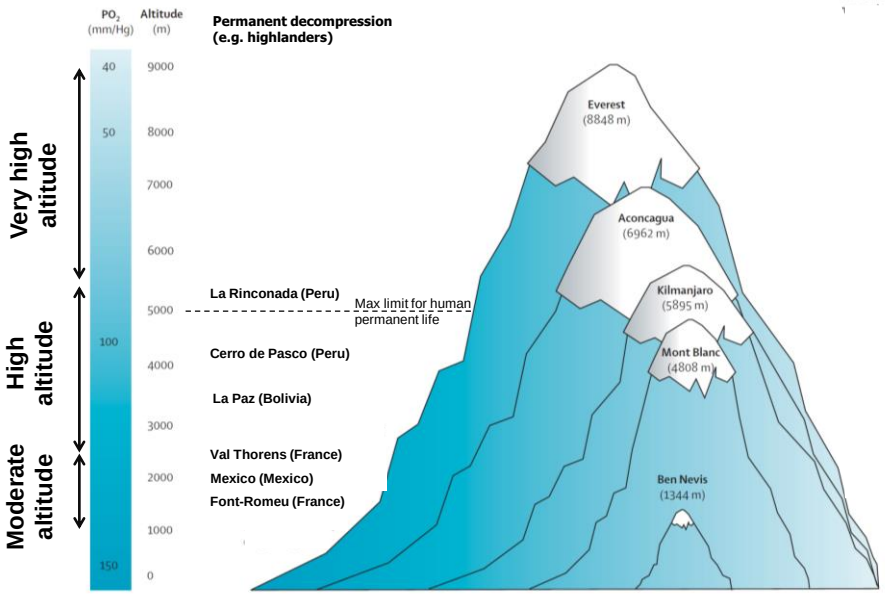
Grocott et al. 2009

Physiological responses to altitude



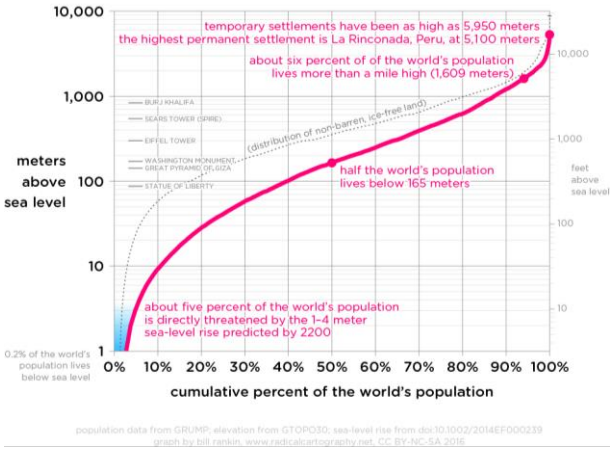
Luks 2015

Types of altitude exposure



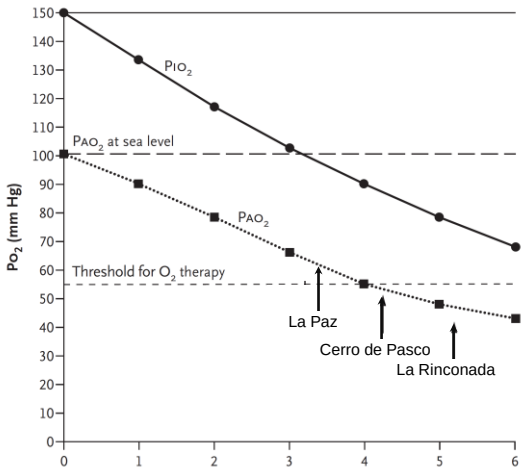
Human populations at high altitude

100 millions habitants in the world living at >2500 m



Human populations at high altitude

Oxygen pressure according to the altitude of residence

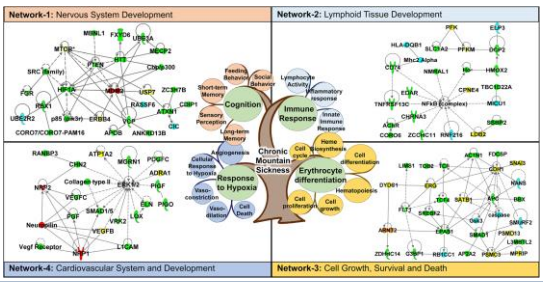


West et al. 2017

Human populations at high altitude

Main physiological consequences of living at high altitude:

- Hypoxemia
- Pulmonary hypoxic vasoconstriction
- Increased hemoglobin concentration
- Genetic specificities



Azad et al. 2017

Highlanders and chronic mountain sickness

- **Chronic mountain sickness syndrom (consensus ISMM, 2005):**
  Excessive erythrocytosis + Symptoms
  (breathlessness/palpitations, sleep disturbances, cyanosis, dilatation of veins, paresthesia, headache, tinnitus)
- **5-20% of high altitude populations (> 2500 m)**
- **Underlying mechanisms ? Inter-individual differences ? Morbi-mortality ?**

From Sahota 2013

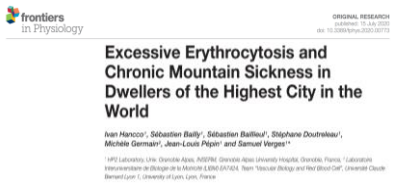
LA RINCONADA: THE HIGHEST CITY IN THE WORLD

TRADITIONAL CONCEPT REGARDING EXCESSIVE ERYTHROCYTOSIS AND CHRONIC MOUNTAIN SICKNESS

Excessive erythrocytosis → Increased blood viscosity → Cardiovascular dysfunction → CMS symptoms

?

EXCESSIVE ERYTHROCYTOSIS AND CHRONIC MOUNTAIN SICKNESS IN THE HIGHEST CITY IN THE WORLD



frontiers in Physiology

ORIGINAL RESEARCH

Excessive Erythrocytosis and Chronic Mountain Sickness in Dwellers of the Highest City in the World

Ivan Hancco, Sébastien Bailly, Sébastien Baillieul, Stéphane Doutreleau, Michèle Germain, Jean-Louis Pépin and Samuel Verges

1600 highlanders from La Rinconada

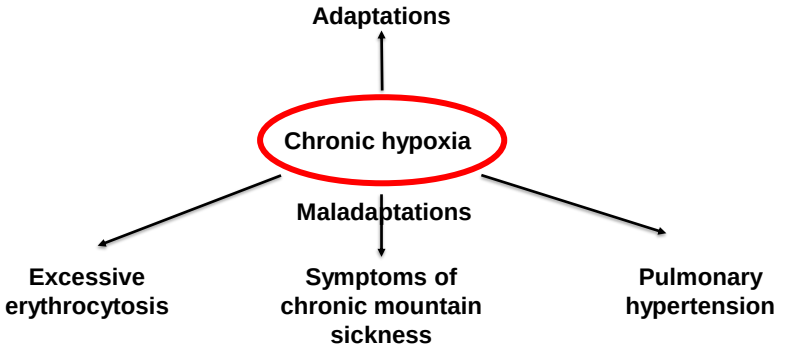
TABLE 1 | Description of subject characteristics for the whole population.

	Median [IQR] or n (%)
Age (years)	32 [23; 39]
Sex	
Female	235 (14.7)
Male	1,359 (85.3)
Ethnic group	
Aymara	75 (4.7)
Quechua	1,519 (95.3)
Residency in La Rinconada (years)	3 [2; 5]
Hematocrit (%)	60 [54; 66]
Heart rate (bpm)	87 [75; 94]
SpO_2 (%)	82 [78; 85]
Diastolic blood pressure (mm Hg)	70 [70; 80]
Systolic blood pressure (mm Hg)	100 [100; 110]
Classification 1 (excessive erythrocytosis, international consensus)	
No excessive erythrocytosis	891 (55.9)
Excessive erythrocytosis	703 (44.1)
Classification 2 (excessive erythrocytosis, calculated threshold)	
No excessive erythrocytosis	1,381 (86.6)
Excessive erythrocytosis	213 (13.4)
Classification 3 (total CMS score, international consensus)	
≤5 (no CMS)	1,373 (86.1)
6–10 (mild total CMS score)	156 (9.8)
11–14 (moderate total CMS score)	52 (3.3)
>14 (severe total CMS score)	13 (0.8)

CMS, chronic mountain sickness; IQR, interquartile range; SpO_2, pulse oxygen saturation. Classifications 1 and 3 were performed according to the current international consensus on CMS (Leon-Velarde et al., 2005), while Classification 2 was performed based on a calculated threshold for excessive erythrocytosis in the population from La Rinconada (see section "Materials and Methods" for further details).

EXPEDITION 5300 – Objectives 2019

Background - Questioning



EXPEDITION 5300 - Scientific project 2019

THEORETICAL FRAMEWORK

Genetic - Epigenetic				
Haematology	Haemorheology	Vascular function: - Microvascular - Systemic - Pulmonary - Cerebral	Cardiac function Respiratory function	Sleep Exercise
Biology: oxidative stress, inflammation, NO, iron and EPO status, vascular biomarkers, etc				

EXPEDITION 5300 – Protocol 2019

Populations

Peruvian lowlanders Lima, 80 m Healthy, n=20	Peruvian highlanders Puno, 3800 m Healthy, n=23	Peruvian highlanders La Rinconada, 5100 m Healthy CMS-, n=17	Peruvian highlanders La Rinconada, 5100 m CMS+, n=38

Caucasian lowlanders, healthy, n=10

CMS, Chronic Mountain Sickness: Essoufflement/palpitations, perturbations sommeil, cyanose, dilatation des veines, paresthésie, céphalée, accouphène, [Hb] ≥21g/dL

	Lowlanders Sea level (n = 20)	Highlanders at 3,800 m (n = 23)	Highlanders without CMS at 5,100m (n = 17)	Highlanders mild CMS at 5,100m (n = 16)	Highlanders moderate-severe CMS at 5,100m (n = 22)
Age (yrs)	29.9 ± 9.1	35.6 ± 12.8	41.4 ± 8.6*	43.0 ± 7.7*	44.5 ± 6.8*
Duration of stay (yrs)	-	32.2 ± 13.9	12.4 ± 8.0$^{\#}$	13.6 ± 9.1$^{\#}$	17.5 ± 8.0$^{\#}$
BMI (kg·m^{-2})	25.0 ± 4.0	25.0 ± 3.8	25.4 ± 2.1	26.3 ± 3.5	26.3 ± 3.0
[Hb] (g·dL^{-1})	14.2 ± 2.2	19.1 ± 2.3*	22.1 ± 2.4$^{*,\#}$	22.4 ± 1.6$^{*,\#}$	24.0 ± 1.6$^{*,\#,\$,£}$
Haematocrit (%)	42.6 ± 5.4	56.1 ± 6.1*	69.4 ± 7.8$^{*,\#}$	70.3 ± 4.8$^{*,\#}$	75.3 ± 4.8$^{*,\#,\$,£}$
SpO_2 (%)	97.7 ± 0.9	91.6 ± 3.5*	83.7 ± 5.0$^{*,\#}$	83.1 ± 4.2$^{*,\#}$	78.0 ± 6.5$^{*,\#}$
CMS score	-	2.9 ± 3.6	4.0 ± 1.5$^{\#}$	8.1 ± 1.1$^{\#,\$}$	12.7 ± 2.0$^{\#,\$,£}$

Mean ± SD, * different from Lowlanders, $^{\#}$ different from Highlanders 3800m, $^{\$}$ different from Highlanders 5100m without CMS, $^{£}$ different from Highlanders 5100m with mild CMS ($p<0.05$)

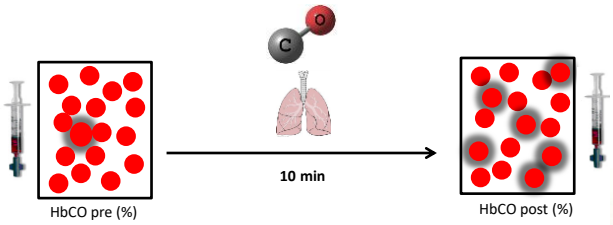
EXPEDITION 5300 – Protocol 2019

Evaluations

Génétique Epigénétique	Biologie (statut oxidative, inflammatoire, métabolisme du fer, EPO …)	Hématologie Hémorheologie	Fonction vasculaire (microvasculaire, systemique, pulmonaire, cérébrovasculaire)	Fonction cardiaque et respiratoire	Test d'effort Evaluation du sommeil

EXPEDITION 5300 – Hematology

Carbon monoxide (CO) rebreathing



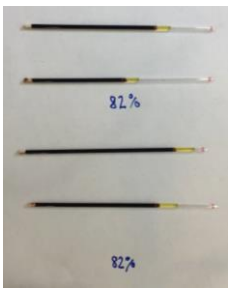
HbCO pre (%)

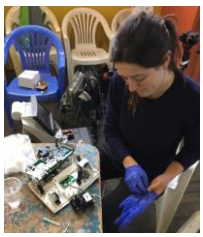
HbCO post (%)

ABL80

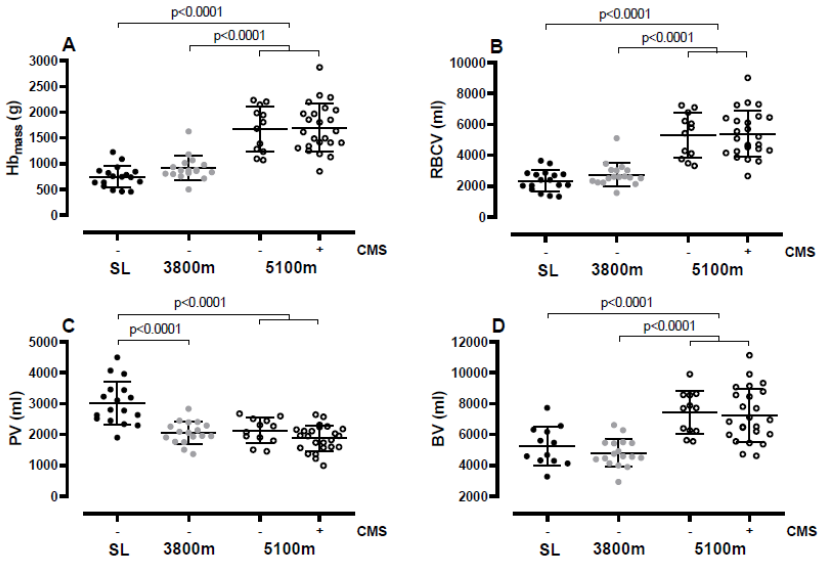
EXPEDITION 5300 – Hematology

Carbon monoxide (CO) rebreathing





EXPEDITION 5300 – Hematology



EXPEDITION 5300 – Hematology

blood

American Society of Hematology
2021 L Street NW, Suite 900,
Washington, DC 20036
Phone: 202-776-0544 | Fax 202-776-0545
editorial@hematology.org

Re-evaluation of excessive erythrocytosis in diagnosing chronic mountain sickness in men from the world's highest city

Tracking no: BLD-2019-004508R2

Laura Oberholzer (Centre for Physical Activity Research, University Hospital Copenhagen, Denmark) Carsten Lundby (Innland Norway University of Applied Sciences, Lillehammer, Norway) Emeric Stauffer (Centre de Médecine du Sommeil et des Maladies Respiratoires, Hôpital Croix Rousse, Hospices Civils de Lyon, France) Mathilde Ulliel-Roche (Grenoble Alpes University INSERM, France) Ivan Hancco (Grenoble Alpes University INSERM, France) Aurélien Pichon (Université de Poitiers, France) Anne-Kristine Lundby (Copenhagen University Hospital, Denmark) Francisco Villafuerte (Universidad Peruana Cayetano Heredia, Peru) Samuel Verges (Grenoble Alpes University INSERM, France) Paul Robach (Ecole Nationale de Ski et d'Alpinisme, France)

EXPEDITION 5300 – Hemorheology

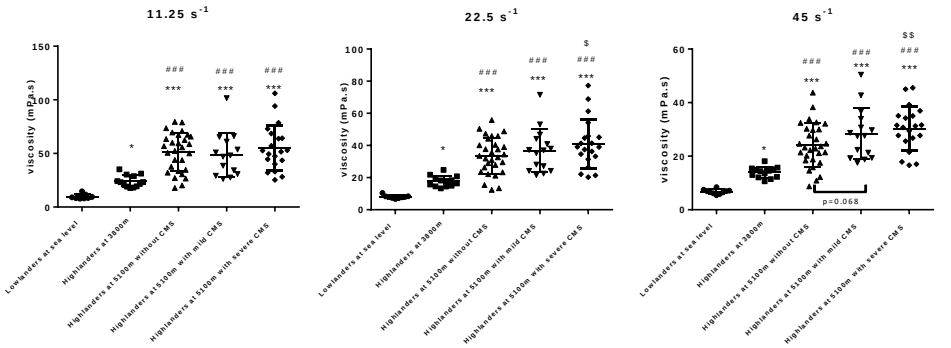
Hemorheology measurements

- Blood viscosity:
  - Measured with a cone plan viscometers
  - A different shear rates
  - At native hematocrit and corrected hematocrit (40%)

- Red blood cell aggregation:
  - Measured with an aggregometer (Myrenne)
  - At corrected hematocrit (40%)

EXPEDITION 5300 – Hemorheology

BLOOD VISCOSITY AT NATIVE HEMATOCRIT



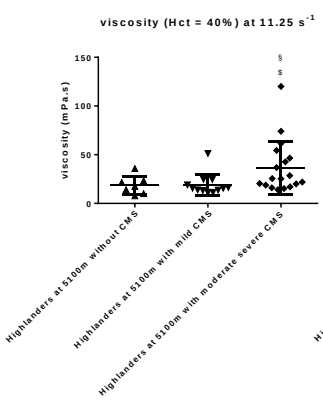
Different from Lowlanders (*p < 0.05; ***p < 0.001)
Different from Highlanders 3800m (###p < 0.001)

Different from Lowlanders (*p < 0.05; ***p < 0.001)
Different from Highlanders 3800m (###p < 0.001)
Different from Highlanders 5100m without CMS ($p < 0.05)

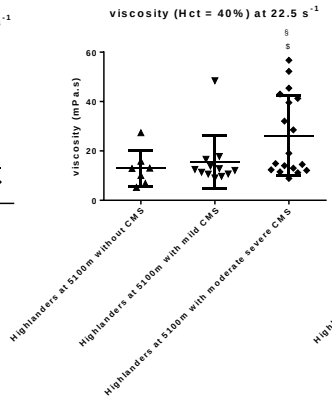
Different from Lowlanders (*p < 0.05; ***p < 0.001)
Different from Highlanders 5100m (###p < 0.001)
Different from Highlanders 5100m without CMS ($$p < 0.01)

EXPEDITION 5300 – Hemorheology

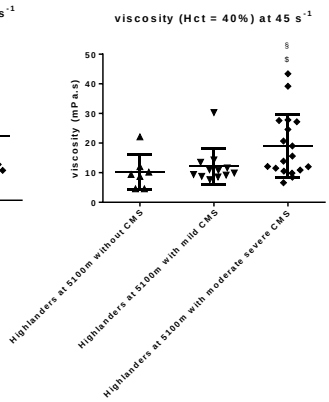
BLOOD VISCOSITY AT NORMALIZED HEMATOCRIT (40%)



Different from Highlanders 5100 m without CMS ($^{\S}p < 0.05$)
Different from Highlanders 5100 m with mild CMS ($^{\S}p < 0.05$)



Different from Highlanders 5100 m without CMS ($^{\S}p < 0.05$)
Different from Highlanders 5100 m with mild CMS ($^{\S}p < 0.05$)



Different from Highlanders 5100 m without CMS ($^{\S}p < 0.05$)
Different from Highlanders 5100 m with mild CMS ($^{\S}p < 0.05$)

EXPEDITION 5300 – Hemorheology

Blood viscosity and its determinants

Increased viscosity with altitude of residency and CMS severity

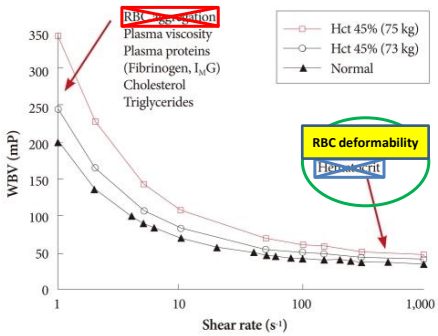
Slight effect of CMS on red blood cell aggregation

Larger differences in blood viscosity at higher shear rates

Higher blood viscosity in CMS patients even at corrected haematocrit (40%)

Increase in blood viscosity with the altitude of residency mostly due to increased haematocrit

Increase in blood viscosity with CMS severity possibly due to reduced red blood cell deformability



Korean Circ J. 2011 Jun; 41(6): 287–295.

EXPEDITION 5300 – Hemorheology

Blood viscosity and its determinants

J Physiol 598.18 (2020) pp 4121–4130

Blood viscosity and its determinants in the highest city in the world

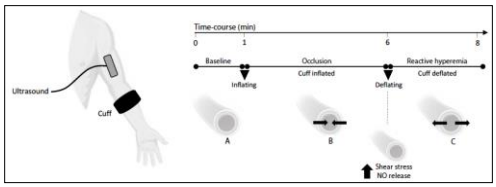
Emeric Stauffer[1,2,3], Emmanuelle Loyrion[4], Ivan Hancco[4], Xavier Waltz[4], Mathilde Ulliel-Roche[4], Laura Oberholzer[5], Paul Robach[4,6], Aurélien Pichon[7], Julien V. Brugniaux[4], Pierre Bouzat[4], Stéphane Doutreleau[4], Philippe Connes[1,2,8] and Samuel Verges[4]

[1]*Laboratoire Interuniversitaire de Biologie de la Motricité (LIBM) EA7424, Team 'Biologie vasculaire et du globule rouge', Université Claude Bernard Lyon 1, Université de Lyon, France*
[2]*Laboratoire d'Excellence du Globule Rouge (Labex GR-Ex), PRES Sorbonne, Paris, France*
[3]*Centre de Médecine du Sommeil et des Maladies Respiratoires, Hospices Civils de Lyon, Hôpital Croix Rousse, Lyon, France*
[4]*HP2 laboratory, Université Grenoble Alpes, Inserm, CHU Grenoble Alpes, Faculté de Médecine, Grenoble, 38000, France*
[5]*The Centre of Inflammation and Metabolism and the Centre for Physical Activity Research, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark*
[6]*National School for Mountain Sports, Site of the National School for Skiing and Mountaineering (ENSA), Chamonix, France*
[7]*Laboratoire MOVE, Université de Poitiers, Poitiers, France*
[8]*Institut Universitaire de France, Paris, France*

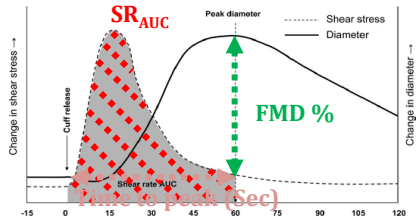
EXPEDITION 5300 – Vascular function

Systemic vascular reactivity

- **Flow mediated dilation (FMD)** = Measurement of increased brachial artery diameter during post-ischemia hyperemia by ultrasonography
- Shear stress on vessel walls induced by increased blood flow induces vasodilation (especially due to nitric oxide (NO) production).
- Reduced endothelial function increases cardiovascular risks (*e.g.* atherosclerosis, arterial hypertension, cardiac insufficiency)



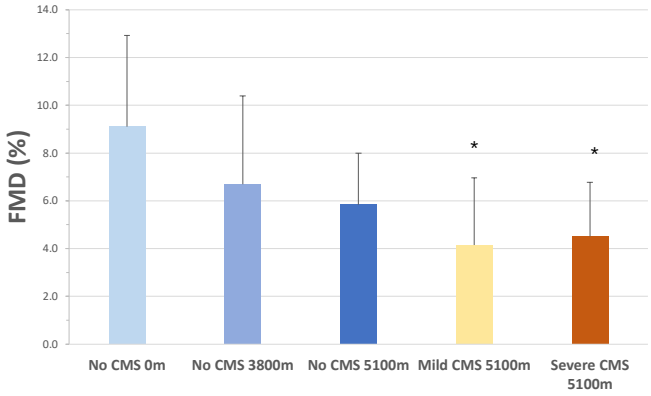
Jarrete et al. *Motriz Rio Claro*, 2016



Thijssen et al. *Am J Physiol Heart Circ Physiol*, 2011

EXPEDITION 5300 – Vascular function

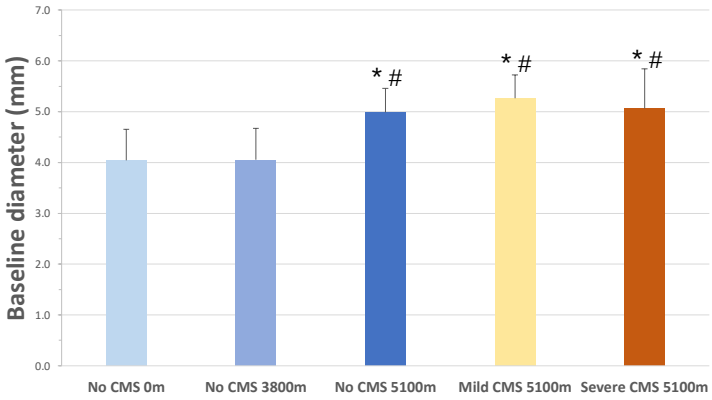
FMD : Flow mediated dilation



* p<0,05 vs No CMS 0m
Test : Kruskal Wallis (+ correction Bonferroni)

EXPEDITION 5300 – Vascular function

FMD : Basal diameter (before occlusion)



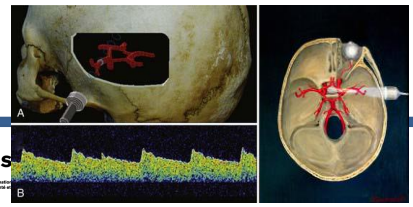
* p<0,05 vs No CMS 0m
# p<0,05 vs No CMS 3800m
Test : Kruskal Wallis (+ correction Bonferroni)

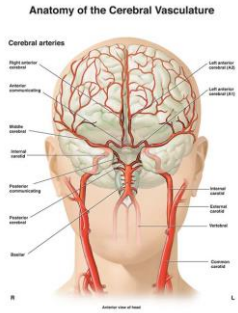
EXPEDITION 5300 – Vascular function

Cerebral perfusion

- **Index of cerebral blood flow:**
  blood flow velocity within the middle cerebral artery (MCAv)

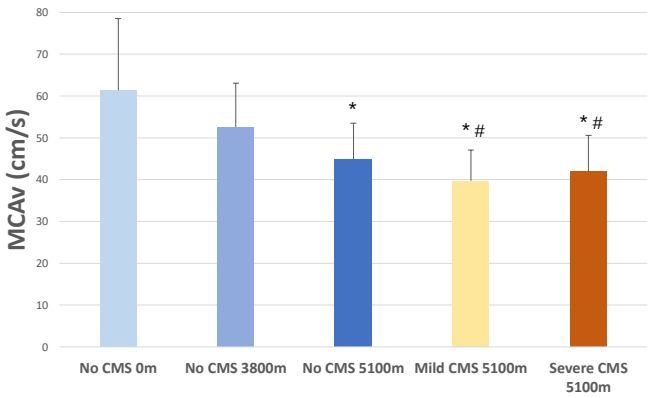
- Measurement performed within the temporal window by echo-Doppler





EXPEDITION 5300 – Vascular function

Cerebral perfusion:
Blood flow velocity within the middle cerebral artery (MCAv)



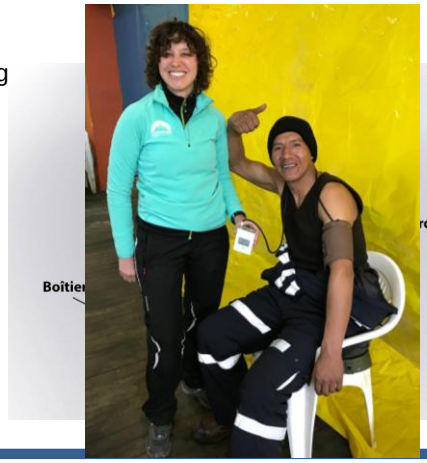
* p<0,05 vs No CMS 0m
# p<0,05 vs No CMS 3800m
Test : Kruskal Wallis (+ correction Bonferroni)

EXPEDITION 5300 – Arterial pressure

Ambulatory blood pressure measurement (ABPM)

Arterial blood pressure measurement during 24 hours:
- Evaluation during diurnal activity
- Evaluation during sleep

Automatic measurements:
- every 15 min during the day
- every 20 min during the night

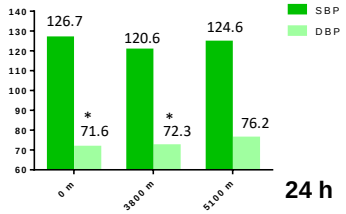


EXPEDITION 5300 – Arterial pressure

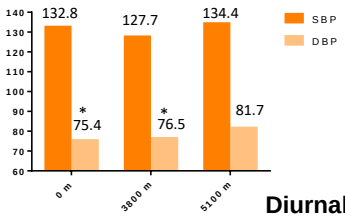
Results: effect of altitude of residency

*: p<0.05 5100 vs 3800 m or 0 m

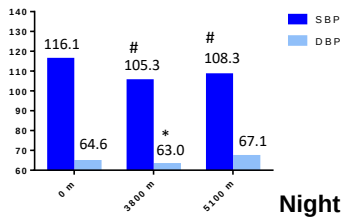
#: p<0.05 0 m vs 5100 m or 3800 m



24 h



Diurnal

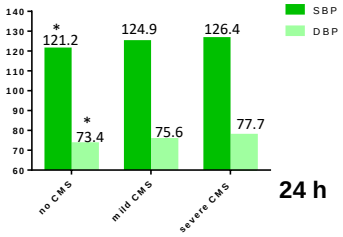


Night

EXPEDITION 5300 – Arterial pressure

Results: Effect of CMS in highlanders at 5100 m

*: p<0.05 No CMS vs Severe CMS



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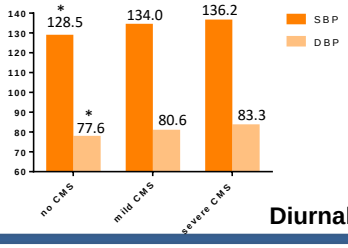

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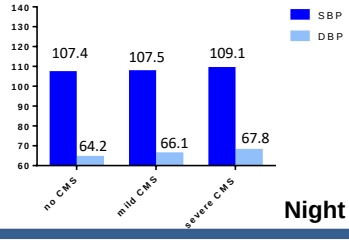


Night

EXPEDITION 5300 – The heart

Resting echocardiography

EXPEDITION 5300 – The heart

Resting echocardiography: Right heart remodeling

	Lowlanders Sea level (n = 20)	Highlanders at 3,800 m (n = 23)	Highlanders without CMS at 5,100 m (n = 17)	Highlanders with mild CMS at 5,100 m (n = 14)	Highlanders with moderate-severe CMS at 5,100 m (n = 24)
RV S' ($cm.s^{-1}$)	12.3 ± 1.7	11.6 ± 1.5	11.0 ± 1.6	11.1 ± 1.1	11.8 ± 1.6
Tricuspid E/A	1.7 ± 0.4	1.7 ± 0.4	1.4 ± 0.4*#	1.2 ± 0.4*#	1.2 ± 0.4*#
Peak Et ($cm.s^{-1}$)	50.2 ± 7.5	45.7 ± 103	39.0 ± 7.4*	34.5 ± 6.2*	37.2 ± 7.1*
Peak At ($cm.s^{-1}$)	31.0 ± 6.7	28.0 ± 7.3	29.8 ± 6.0	31.2 ± 7.9	34.1 ± 8.7
Pulmonary acceleration time (ms)	148 ± 20	128 ± 18	113 ± 14	107 ± 17	108 ± 22
RV/RA gradient (mmHg)	24 ± 4	34 ± 6*	38 ± 9*	39 ± 11*	41 ± 8*
Systolic PAP (mmHg)	29 ± 4	39 ± 6*	43 ± 9*	44 ± 11*	46 ± 8*
Mean PAP (mmHg)	19 ± 2.5	26 ± 4*	28 ± 5*	29 ± 7*	30 ± 5*
RA end-diastolic volume ($ml.m^{-2}$)	27.6 ± 6.4	34.2 ± 10.9*	41.5 ± 12.7*	50.6 ± 16.2*#	54.9 ± 15.7*#
RV end-diastolic area (cm^2)	18.3 ± 3.9	17.2 ± 3.8	19.6 ± 2.6	21.6 ± 3.4#	23.6 ± 5.0*#
RV end-systolic area (cm^2)	9.3 ± 2.3	9.5 ± 2.4	10.2 ± 1.7	11.7 ± 2.8	12.7 ± 3.2*#
RV FAC (%)	49.4 ± 7.4	44.7 ± 7.4	47.9 ± 5.6	45.9 ± 6.3	46.1 ± 5.7
PVR (mmHg.min.l)	2.7 ± 0.9	4.5 ± 1.4	4.5 ± 1.7	4.4 ± 1.5	4.8 ± 1.5
RV strain (%)	- 27 ± 1	- 25 ± 1	- 22 ± 1*	21 ± 1	21 ± 1

« Alteration » in RV diastolic function

mPAP increases with altitude

Enlargement of the right cavities
RV and RA+++

Decrease in RV longitudinal strain

EXPEDITION 5300 – The heart

Resting echocardiography: Right heart remodeling

	Lowlanders Sea level (n = 20)	Highlanders at 3,800 m (n = 23)	Highlanders without CMS at 5,100 m (n = 17)	Highlanders with mild CMS at 5,100 m (n = 14)	Highlanders with moderate-severe CMS at 5,100 m (n = 24)
RV S' ($cm.s^{-1}$)	12.3 ± 1.7	11.6 ± 1.5	11.0 ± 1.6	11.1 ± 1.1	11.8 ± 1.6
Tricuspid E/A	1.7 ± 0.4	1.7 ± 0.4	1.4 ± 0.4*#	1.2 ± 0.4*#	1.2 ± 0.4*#
Peak Et ($cm.s^{-1}$)	50.2 ± 7.5	45.7 ± 103	39.0 ± 7.4*	34.5 ± 6.2*	37.2 ± 7.1*
Peak At ($cm.s^{-1}$)	31.0 ± 6.7	28.0 ± 7.3	29.8 ± 6.0	31.2 ± 7.9	34.1 ± 8.7
Pulmonary acceleration time (ms)	148 ± 20	128 ± 18	113 ± 14	107 ± 17	108 ± 22
RV/RA gradient (mmHg)	24 ± 4	34 ± 6*	38 ± 9*	39 ± 11*	41 ± 8*
Systolic PAP (mmHg)	29 ± 4	39 ± 6*	43 ± 9*	44 ± 11*	46 ± 8*
Mean PAP (mmHg)	19 ± 2.5	26 ± 4*	28 ± 5*	29 ± 7*	30 ± 5*
RA end-diastolic volume ($ml.m^{-2}$)	27.6 ± 6.4	34.2 ± 10.9*	41.5 ± 12.7*	50.6 ± 16.2*#	54.9 ± 15.7*#
RV end-diastolic area (cm^2)	18.3 ± 3.9	17.2 ± 3.8	19.6 ± 2.6	21.6 ± 3.4#	23.6 ± 5.0*#
RV end-systolic area (cm^2)	9.3 ± 2.3	9.5 ± 2.4	10.2 ± 1.7	11.7 ± 2.8	12.7 ± 3.2*#
RV FAC (%)	49.4 ± 7.4	44.7 ± 7.4	47.9 ± 5.6	45.9 ± 6.3	46.1 ± 5.7
PVR (mmHg.min.l)	2.7 ± 0.9	4.5 ± 1.4	4.5 ± 1.7	4.4 ± 1.5	4.8 ± 1.5
RV strain (%)	- 27 ± 1	- 25 ± 1	- 22 ± 1*	21 ± 1	21 ± 1

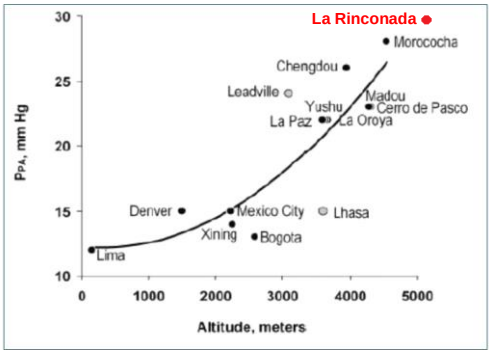
RV less compliant

No difference in mPAP

Larger dilatation of right cavities

EXPEDITION 5300 – The heart

Resting echocardiography: Right heart remodeling



Level of altitude as related to mean value of PAP (P_{PA}).
(Penaloza and Arias-Stella, 2007)

EXPEDITION 5300 – The heart

Resting echocardiography: Left heart remodeling

No difference in resting blood pressure (same afterload)

No important modification
A thicker and smaller LV

No variation in LV EF

A decrease in E/A ratio
Greater proportion of diastolic dysfunction

A decrease in LV longitudinal strain

	Lowlanders Sea level (n = 20)	Highlanders at 3,800 m (n = 23)	Highlanders without CMS at 5,100 m (n = 17)	Highlanders with mild CMS at 5,100 m (n = 14)	Highlanders with moderate-severe CMS at 5,100 m (n = 24)
Septum thickness (mm)	9.6 ± 1.2	10.2 ± 2.0	11.1 ± 1.4	10.9 ± 0.9	12.1 ± 1.3*#
LV end-diastolic diameter (mm)	47.9 ± 3.6	44.1 ± 3.7*	45.1 ± 3.2	46.9 ± 3.3	44.7 ± 3.9
Posterior wall thickness (mm)	9.5 ± 1.2	9.3 ± 1.7	9.7 ± 1.4	9.9 ± 1.5	11.7 ± 7.0
LV end-systolic diameter (mm)	29.2 ± 3.3	28.0 ± 3.3*	29.2 ± 3.7	31.4 ± 3.2	29.5 ± 3.5
Indexed left atrial volume (ml.m^2)	30.4 ± 8.9	26.3 ± 7.3	29.4 ± 5.0	29.9 ± 6.1	30.7 ± 8.0
EF (Teichholz) (%)	69 ± 7	66 ± 6	65 ± 7	62 ± 5*	63 ± 7
LV mass indexed (g.m^2)	89.2 ± 12.5	80.0 ± 22.9	92.6 ± 25.6	96.8 ± 20.9	100.2 ± 23.4#
Cardiac index (L.min^{-1}.m^{-2})	3.3 ± 0.6	2.8 ± 0.5	3.0 ± 0.7	3.1 ± 0.9	3.1 ± 0.5
Mitral E/A ratio	1.6 ± 0.3	1.4 ± 0.5	1.1 ± 0.3*	1.1 ± 0.4*	1.1 ± 0.3*
Peak E (cm.s^{-1})	79.6 ± 14.1	65.7 ± 143	54.6 ± 10.4*	53.5 ± 11.8*	55.6 ± 11.8*
Peak A (cm.s^{-1})	49.6 ± 8.1	48.3 ± 10.3	53.9 ± 14.7	50.9 ± 10.8	50.8 ± 11.1
Mitral E/E' ratio	5.1 ± 1.0	5.1 ± 1.0	4.8 ± 0.9	5.2 ± 1.1	5.0 ± 1.0
SVR (mmHg.min.l)	14.1 ± 3.6	19.0 ± 5.0	18.0 ± 5.0	17.3 ± 4.4	16.7 ± 3.1
LV long strain (%)	- 19.5 ± 0.4	- 19.4 ± 0.4	- 17.8 ± 0.3*	17.4 ± 0.4	17.3 ± 0.4

EXPEDITION 5300 – The heart

Resting echocardiography: Left heart remodeling

No difference in resting blood pressure (same afterload)

A thicker LV in severe CMS

No other significant modification In CMS patient

	Lowlanders Sea level (n = 20)	Highlanders at 3,800 m (n = 23)	Highlanders without CMS at 5,100 m (n = 17)	Highlanders with mild CMS at 5,100 m (n = 14)	Highlanders with moderate-severe CMS at 5,100 m (n = 24)
Septum thickness (mm)	9.6 ± 1.2	10.2 ± 2.0	11.1 ± 1.4	10.9 ± 0.9	12.1 ± 1.3*#
LV end-diastolic diameter (mm)	47.9 ± 3.6	44.1 ± 3.7*	45.1 ± 3.2	46.9 ± 3.3	44.7 ± 3.9
Posterior wall thickness (mm)	9.5 ± 1.2	9.3 ± 1.7	9.7 ± 1.4	9.9 ± 1.5	11.7 ± 7.0
LV end-systolic diameter (mm)	29.2 ± 3.3	28.0 ± 3.3*	29.2 ± 3.7	31.4 ± 3.2	29.5 ± 3.5
Indexed left atrial volume (ml.m^{-2})	30.4 ± 8.9	26.3 ± 7.3	29.4 ± 5.0	29.9 ± 6.1	30.7 ± 8.0
EF (Teichholz) (%)	69 ± 7	66 ± 6	65 ± 7	62 ± 5*	63 ± 7
LV mass indexed (g.m^{-2})	89.2 ± 12.5	80.0 ± 22.9	92.6 ± 25.6	96.8 ± 20.9	100.2 ± 23.4#
Cardiac index (L.min^{-1}.m^{-2})	3.3 ± 0.6	2.8 ± 0.5	3.0 ± 0.7	3.1 ± 0.9	3.1 ± 0.5
Mitral E/A ratio	1.6 ± 0.3	1.4 ± 0.5	1.1 ± 0.3*	1.1 ± 0.4*	1.1 ± 0.3*
Peak E (cm.s^{-1})	79.6 ± 14.1	65.7 ± 143	54.6 ± 10.4*	53.5 ± 11.8*	55.6 ± 11.8*
Peak A (cm.s^{-1})	49.6 ± 8.1	48.3 ± 10.3	53.9 ± 14.7	50.9 ± 10.8	50.8 ± 11.1
Mitral E/E' ratio	5.1 ± 1.0	5.1 ± 1.0	4.8 ± 0.9	5.2 ± 1.1	5.0 ± 1.0
SVR (mmHg.min.l)	14.1 ± 3.6	19.0 ± 5.0	18.0 ± 5.0	17.3 ± 4.4	16.7 ± 3.1
LV long strain (%)	- 19.5 ± 0.4	- 19.4 ± 0.4	- 17.8 ± 0.3*	17.4 ± 0.4	17.3 ± 0.4

EXPEDITION 5300 – The heart

Echocardiography during exercise: Methods

Echocardiography during submaximal exercise:
Cardiac output (Qc) and pulmonary arterial pressures (PAPs)

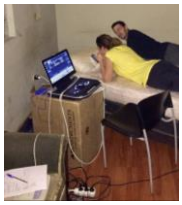
- Rest sitting on the bicycle
- 5 min at 55% maximal theoretical heart rate
- 5 min at 70% maximal theoretical heart rate

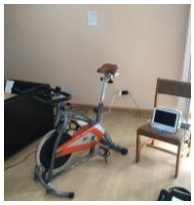
Maximal theoretical heart rate at sea level (FMT_{NM}) :

$FMT_{NM} = 210 – 0.65 \times age$

Maximal theoretical heart rate at altitude (FMT_A) :

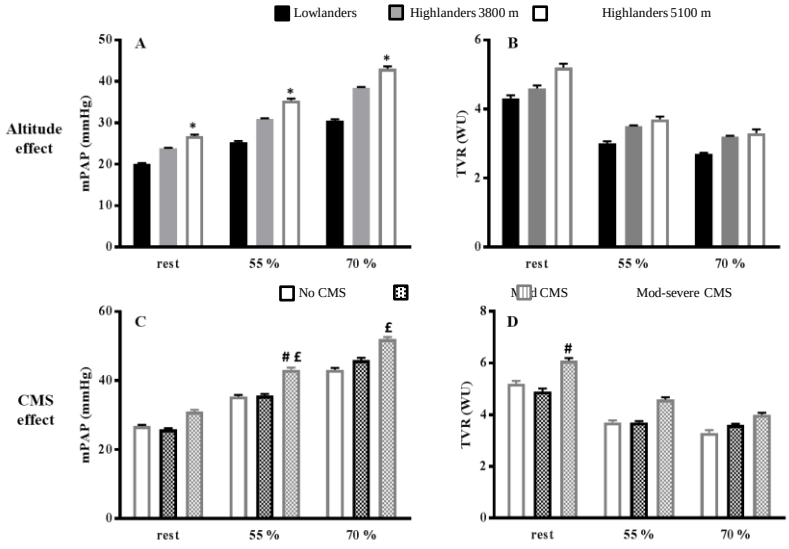
$FMT_A = FMT_{NM} - 0.0024 \times altitude\ (m) + 0.73$





EXPEDITION 5300 – The heart

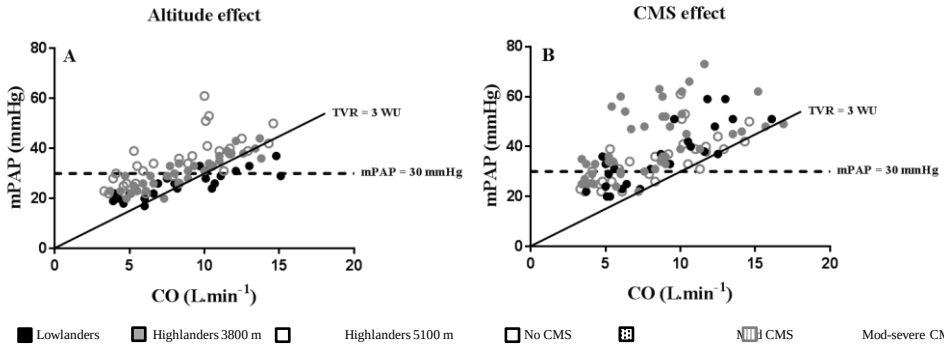
Echocardiography during exercise: Results



EXPEDITION 5300 – The heart

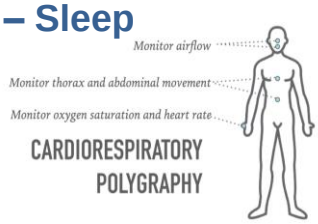
Echocardiography during exercise: Results

Pulmonary hypertension ?



EXPEDITION 5300 – Sleep

Polygraphy



	Lowlanders Sea level (n = 12)	Highlanders at 3,800 m (n = 21)	Highlanders without CMS at 5,100 m (n = 12)	Highlanders with mild CMS at 5,100 m (n = 11)	Highlanders with moderate-severe CMS at 5,100 m (n = 17)
Apnoea-hypopnea index (events·h^{-1})	8.4 ± 10.9	17.3 ± 19.9	13.6 ± 10.8	12.0 ± 10.3	13.7 ± 13.2
Apnoea-hypopnea index obstructive (events·h^{-1})	7.2 ± 10.5	10.9 ± 11.4	7.9 ± 9.0	7.9 ± 7.4	9.7 ± 9.8
Apnoea-hypopnea index central (events·h^{-1})	1.0 ± 0.7	6.7 ± 16.2	5.5 ± 6.1*	3.2 ± 2.6*	3.3 ± 3.3*
Oxygen desaturation index (events·h^{-1})	7.0 ± 11.2	19.3 ± 19.6	25.7 ± 16.4*	30.3 ± 14.1*	40.8 ± 27.6*
Mean nocturnal SpO_2 (%)	95.3 ± 1.4	83.8 ± 2.8*	76.5 ± 5.2*	78.2 ± 6.6*	75.2 ± 7.6*
Mean desaturation (%)	3.7 ± 1.4	4.2 ± 0.5	6.0 ± 2.5*	6.9 ± 2.6*	8.0 ± 3.2*

Data are mean ± SD; * Different from lowlanders

EXPEDITION 5300 – Sleep

Questionnaires

MOCA = Montreal Cognitive Assessment
ISI = Insomnia Severity Index
PSQI = Pittsburgh Sleep Quality Index
SF36 = Medical Outcomes Study Short Form-36 (Quality of life)

	Lowlanders Sea level (n = 20)	Highlanders at 3,800 m (n = 23)	Highlanders without CMS at 5,100 m (n = 17)	Highlanders with mild CMS at 5,100 m (n = 14)	Highlanders with moderate-severe CMS at 5,100 m (n = 24)
MOCA	25.7 ± 2.7	26.1 ± 2.7	19.7 ± 5.3*#	21.4 ± 4.3*#	20.8 ± 3.9*#
ISI	6.8 ± 4.9	6.9 ± 4.9	6.8 ± 5.8	7.3 ± 4.8	9.8 ± 4.6
PSQI	5.2 ± 3.2	4.7 ± 2.5	7.2 ± 3.4	6.4 ± 2.5	7.0 ± 2.6
SF36 - physical	80.9 ± 14.6	76.8 ± 15.4	58.9 ± 21.1*	57.1 ± 17.0*#	49.0 ± 17.3*#
SF36 - mental	78.8 ± 14.3	75.7 ± 15.1	61.0 ± 23.0	65.0 ± 13.2	55.7 ± 17.5*#

Data are mean ± SD; * Different from Lowlanders; # Different from Highlanders at 3800 m; $ Different from Highlanders without CMS at 5100 m; £ Different from Highlanders with mild CMS at 5100 m

EXPEDITION 5300 – Biology

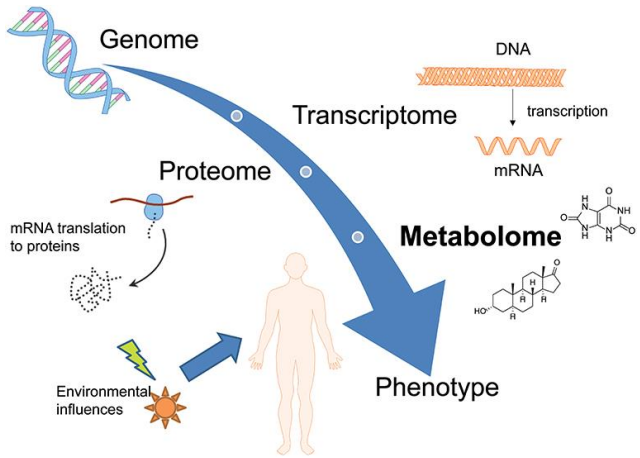
Inflammation, oxidative status, NO metabolism and markers of endothelial function

	Lowlanders Sea level (n = 11)	Highlanders at 3,800 m (n = 10)	Highlanders without CMS at 5,100 m (n = 13)	Highlanders with mild CMS at 5,100 m (n = 11)	Highlanders with moderate-severe CMS at 5,100 m (n = 10)
IL6 (pg·mL^{-1})	1.7 ± 1.2	1.5 ± 1.2	1.4 ± 0.8	1.8 ± 1.4	2.4 ± 1.6^{+}
IL7 (pg·mL^{-1})	1.0 ± 0.7	1.1 ± 0.4	2.2 ± 1.5*‡	2.8 ± 2.2*‡	3.1 ± 1.8*‡
IL8 (pg·mL^{-1})	3.5 ± 1.7	4.3 ± 3.5	11.1 ± 12.7*‡	12.8 ± 10.1*‡	25.0 ± 23.1$^{*‡+}$
IL17 (pg·mL^{-1})	0.2 ± 0.3	0.3 ± 0.3	0.8 ± 0.4*‡	0.8 ± 0.4*‡	0.8 ± 0.5*‡
IFN-g (pg·mL^{-1})	1.4 ± 0.7	2.1 ± 0.8*	3.5 ± 1.4*‡	4.9 ± 4.5*‡	15.8 ± 33.2*‡
MCP1 (pg·mL^{-1})	15.0 ± 6.7	15.5 ± 7.1	33.4 ± 29.7*‡	40.1 ± 29.8*‡	72.2 ± 47.1$^{*‡+}$
MIP-1b (pg·mL^{-1})	4.0 ± 2.3	5.1 ± 9.2	14.9 ± 22.4	14.9 ± 16.4*‡	58.5 ± 82.4$^{*‡+}$
TNFα (pg·mL^{-1})	4.8 ± 1.6	4.8 ± 1.3	7.9 ± 3.2*‡	8.9 ± 3.4*‡	12.0 ± 7.9*‡
SOD (μmol·L^{-1}·min^{-1})	9.4 ± 2.1	12.6 ± 3.6*	15.8 ± 5.8*	10.7 ± 4.6	14.6 ± 6.5*
NOx (μmol·L^{-1})	34.3 ± 26.8	65.8 ± 49.5*	103.0 ± 66.2*	86.2 ± 51.2*	81.6 ± 44.8*
Nitrite (μmol·L^{-1})	9.7 ± 8.7	23.0 ± 16.9*	39.5 ± 21.8*‡	32.6 ± 22.1*	31.0 ± 18.3*
E selectin (MFI)	29334 ± 2073	30269 ± 1184	31638 ± 5478	30178 ± 3082	33436 ± 5346
ICAM-1 (MFI)	108537 ± 12472	145140 ± 20301*	107529 ± 7783	113942 ± 22482	110846 ± 15079

Data are mean ± SD; * Different from Lowlanders; ‡ Different from Highlanders at 3800 m; + Different from Highlanders without CMS at 5100 m

EXPEDITION 5300 – Biology

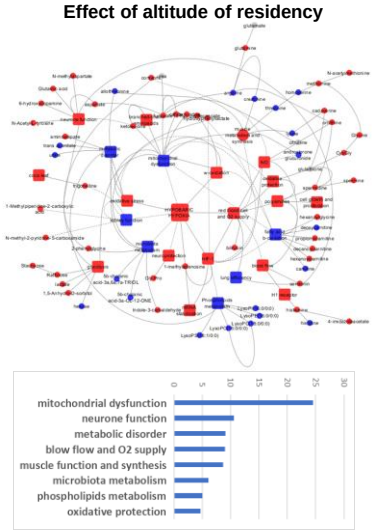
Omics



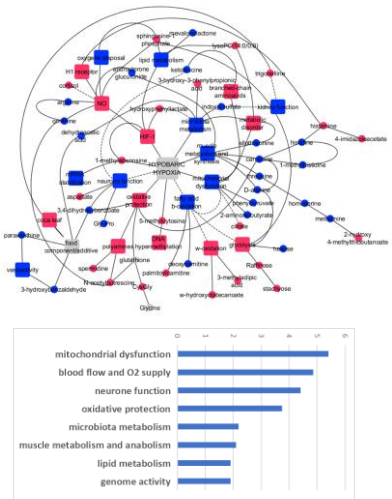
EXPEDITION 5300 – Biology

Metabolomics

Effect of altitude of residency



Effect of CMS in highlander at 5100 m



EXPEDITION 5300 – Project 2020

Clinical trial in highlanders from La Rinconada with chronic mountain sickness

60 patients, 3-weeks and 9-month treatment

- Acetazolamide, 250 mg/day
- Atorvastatine, 40 mg/day
- Placebo

Primary outcome:
Hemoglobin concentration

Secondary outcomes:
Hemoglobin mass, blood viscosity, vascular reactivity, cardiac function, blood pressure, biology…

EXPEDITION 5300 – Perspectives

Centre de Santé et de Recherche sur l'Altitude – La Rinconada

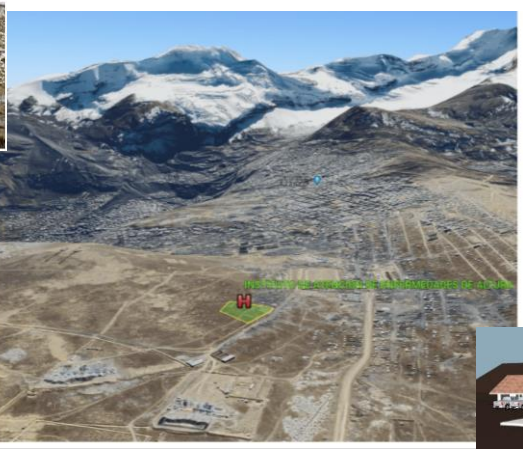
Axe Médical:
Participation à l'offre de soins auprès de la population de La Rinconada

Axe Recherche:
Programme de recherche multidisciplinaire en lien avec la montagne et les peuples d'altitude: Sciences de la vie, Sciences humaines et sociales, Technologie

Axe Formation:
Actions de formation auprès des étudiants péruviens et français (médecine, biologie, géologie, environnement, anthropologie, etc)

EXPEDITION 5300 – Perspectives

Centre de Santé et de Recherche sur l'Altitude – La Rinconada



Chaire *Montagne Altitude Santé*
Fondation Université Grenoble Alpes

Bien-être

Performance

Santé

Formation

Coopération

Communication

Thanks to all !

STÉPHANE DOUTRELEAU
IVAN HANCCO
JULIEN BRUGNIAUX
MATHILDE ULLIEL-ROCHE
EMMANUELLE LOYRION
BLANDINE DESCHAMPS
YANN SAVINA
BENOIT CHAMPIGNEULLE
SEBASTIEN BAILLIEUL
SEBASTIEN BAILLY
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Merci pour votre soutien !

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