Monte Verita, 2011

Physiological risk factors of Severe Mountain Sickness: a prospective cohort study.

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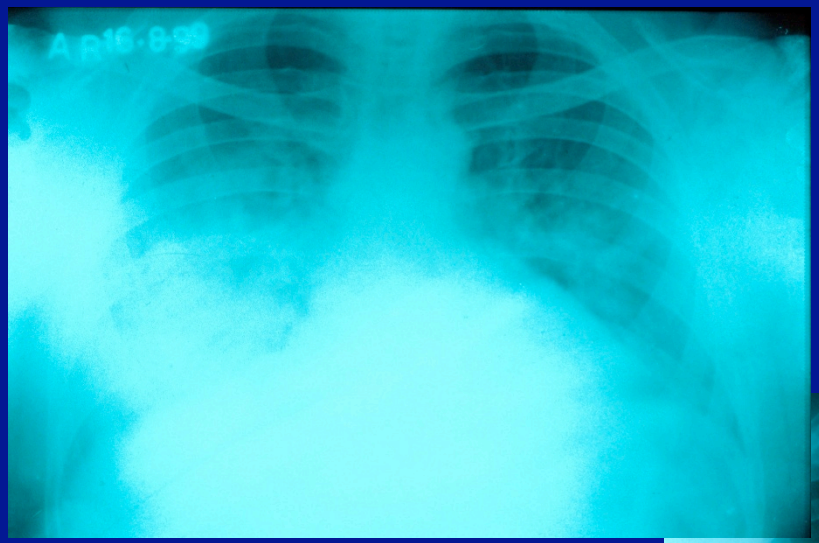
Population concerned

- Trekkers, alpinists
- Tourists (cultural trips)
- Workers
  - Ski resorts, cable cars, etc.
  - Astronomers, engineers (observatories)
  - Mine workers, oil prospecting

AMS – peripheral edema

High Altitude Pulmonary Edema

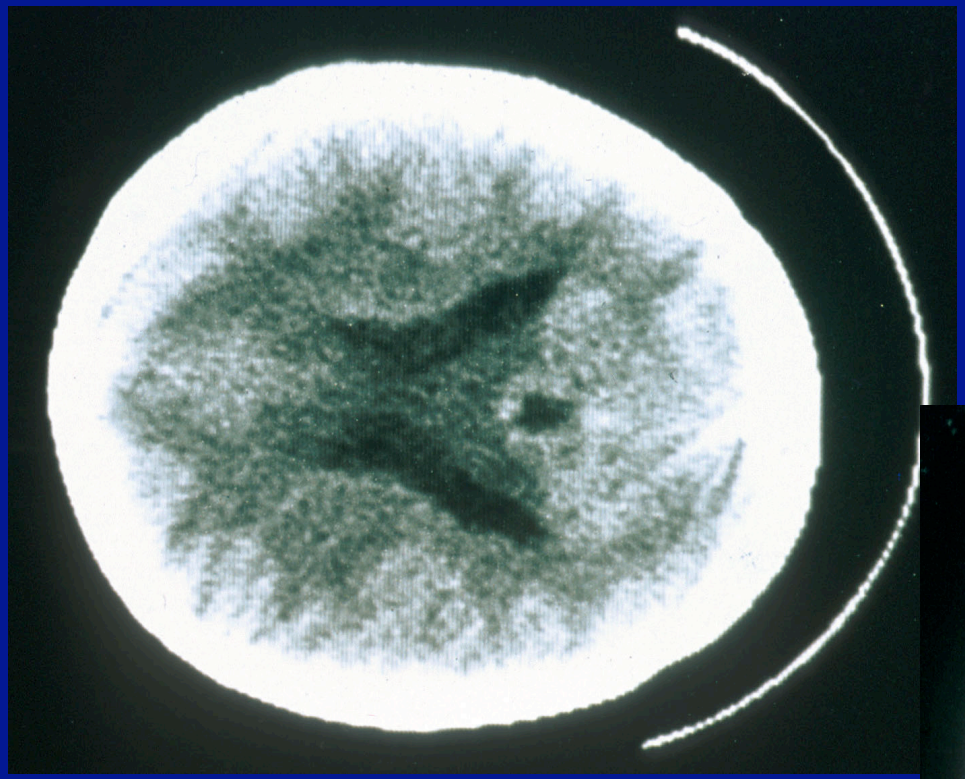


Ladakh. D+0

Ladakh. D+2

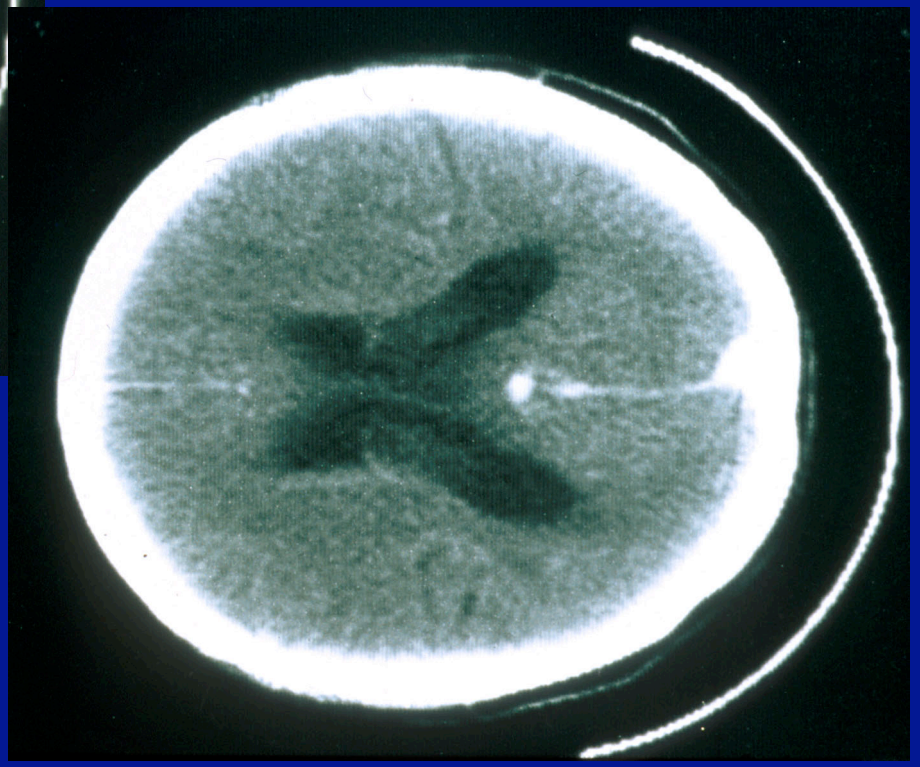
Ladakh. D+4

High Altitude Cerebral Edema

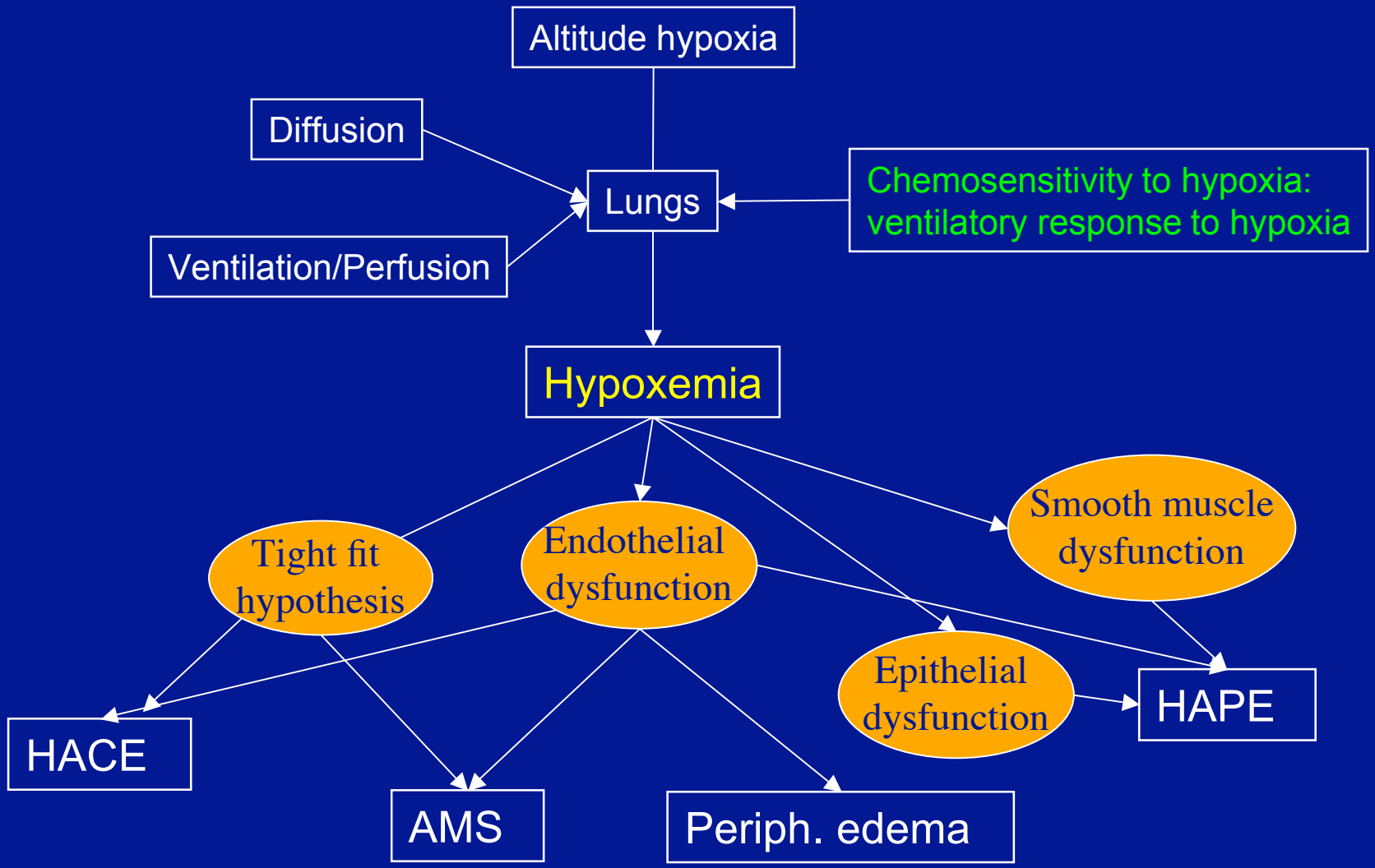


Nepal. D+3

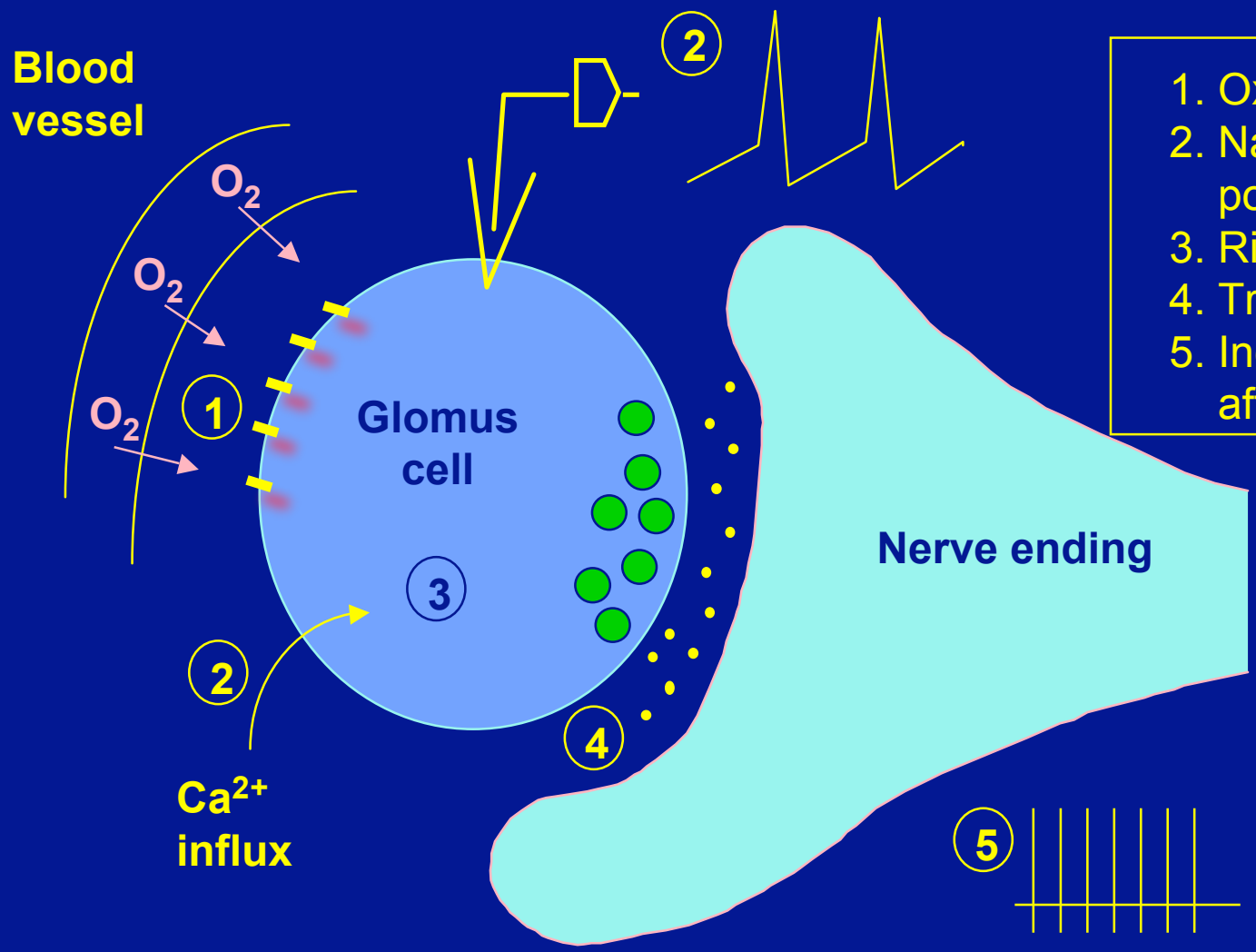
Nepal. D+24



Pathophysiology of High Altitude related diseases



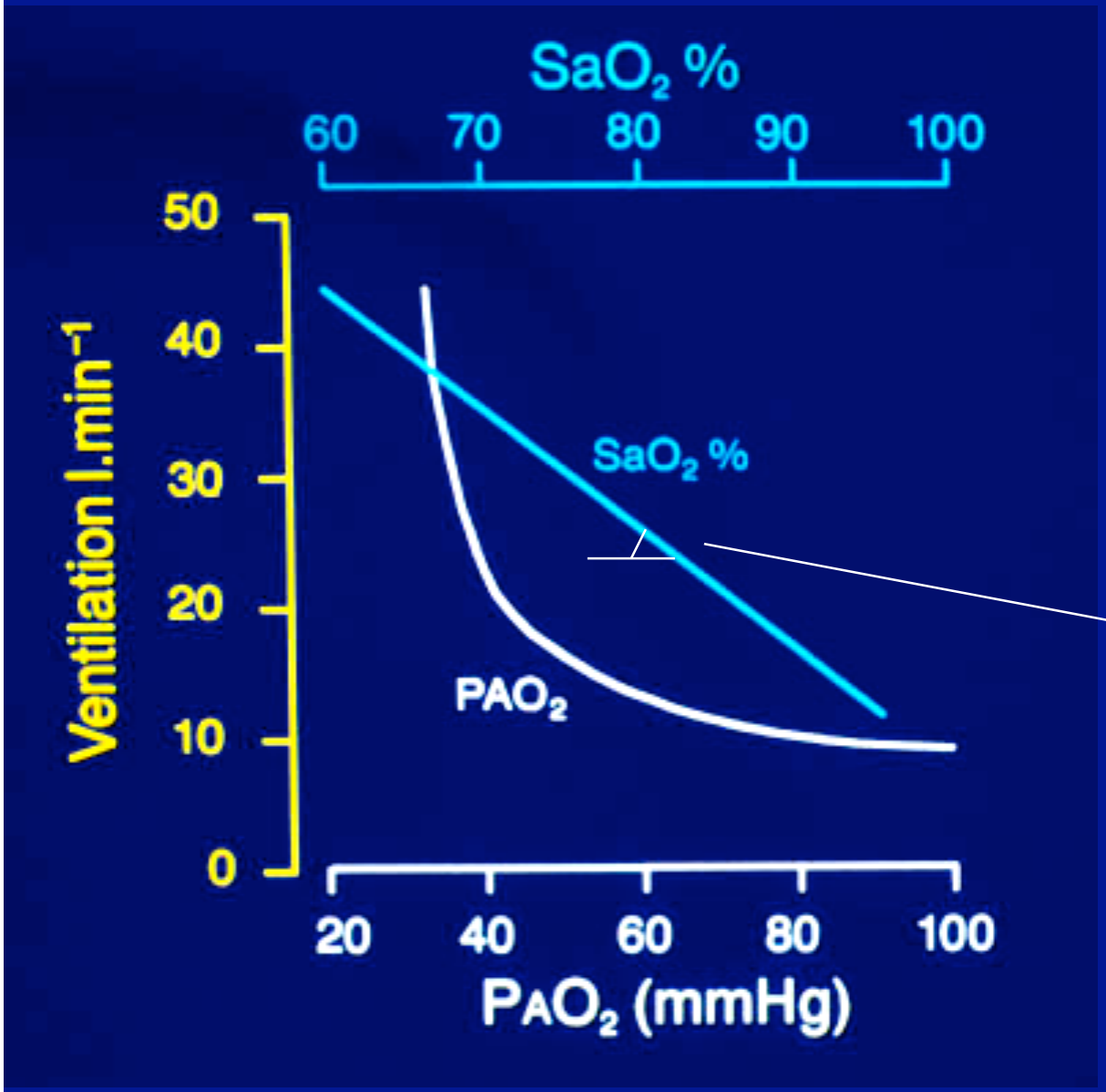
Chemoreceptors and ventilatory response to hypoxia: the principle of the hypoxia exercise test



1. Oxygen detection
2. Na and Ca action potential (Ca influx)
3. Rise in cytosolic Ca
4. Transmitter release
5. Increase of firing in afferent fibers

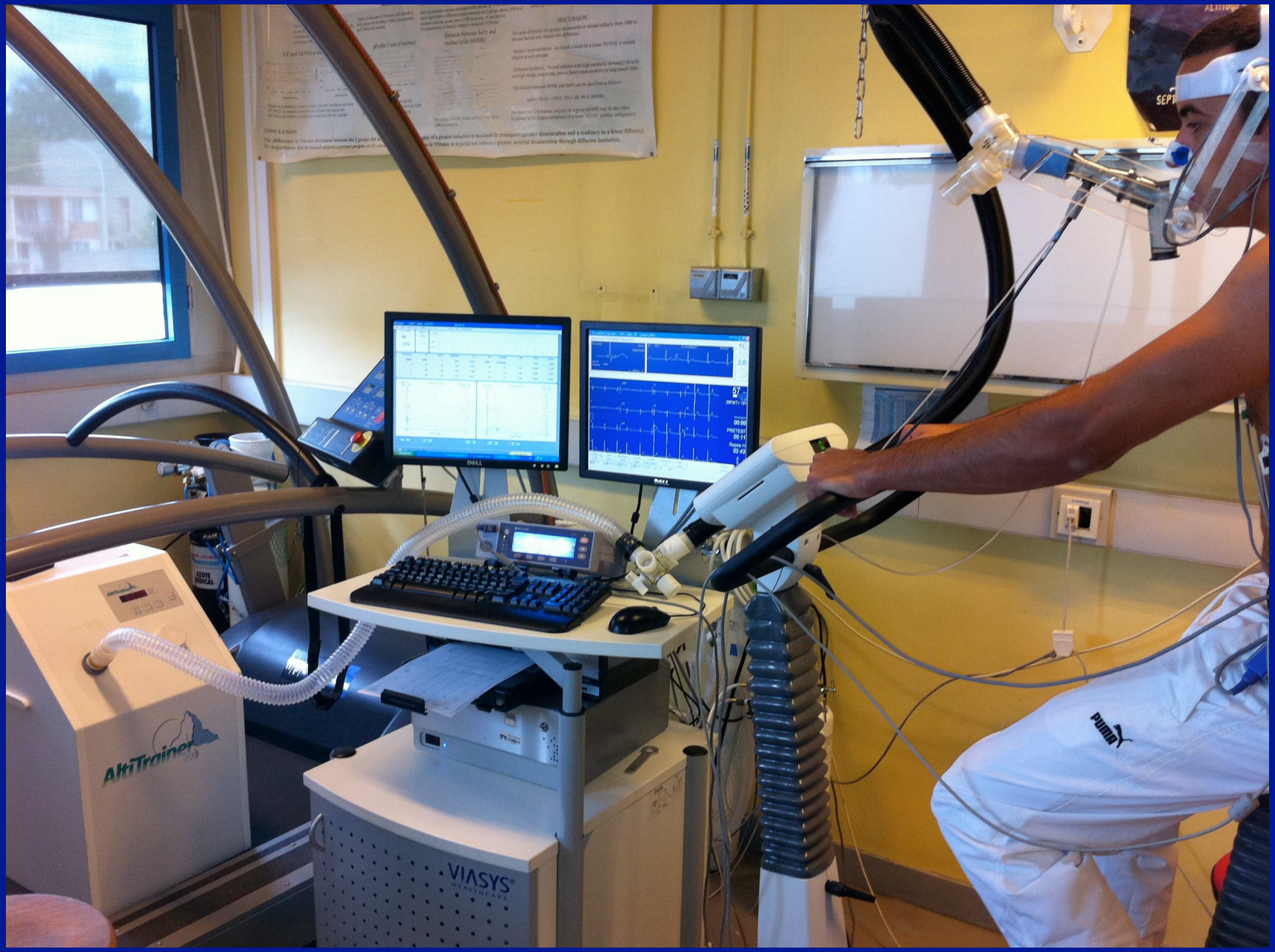
From Lopez-Barneo et al.. NIPS. 1993

Ventilatory response to hypoxia

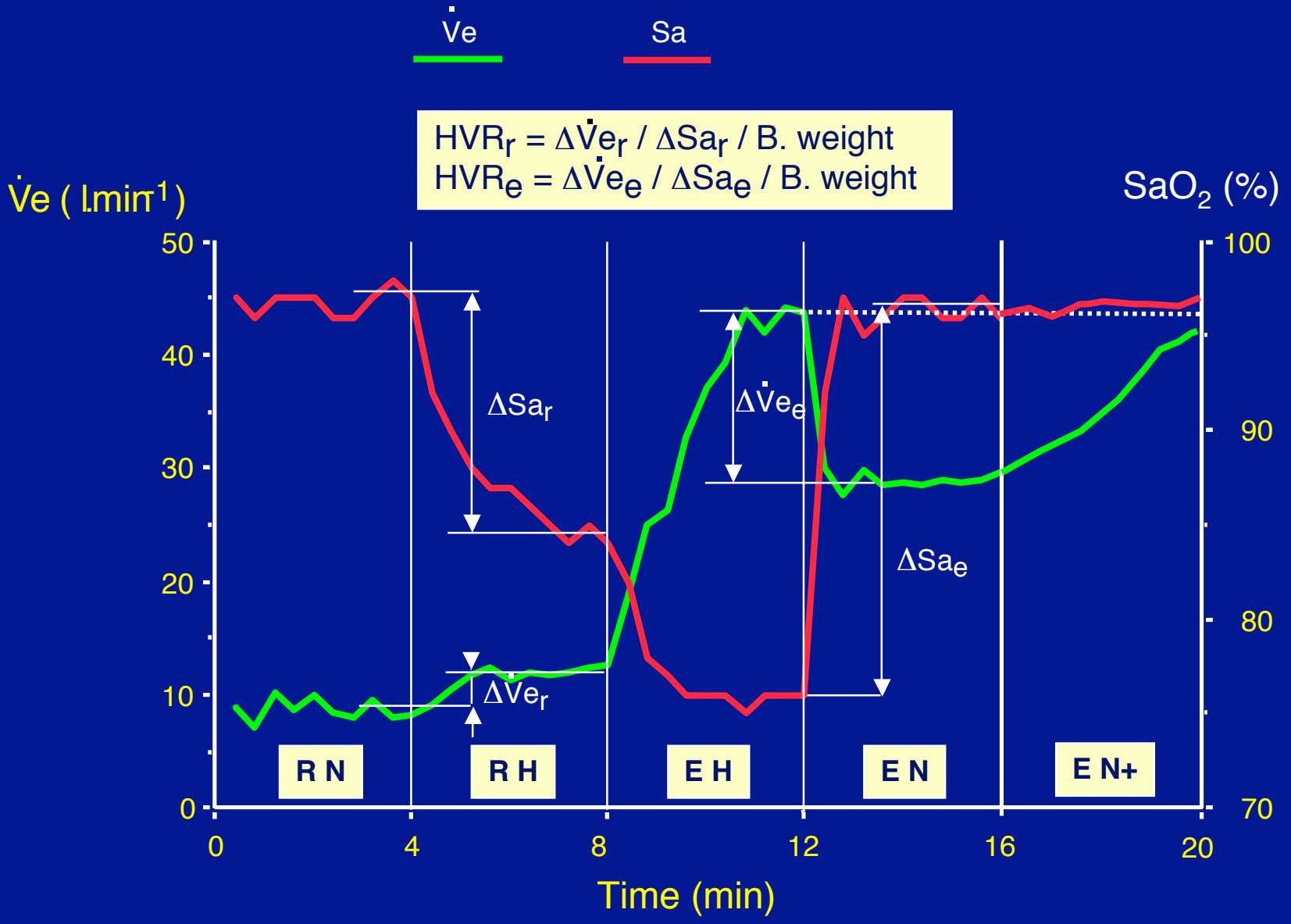


HVR= $\Delta \dot{V}e/\Delta Sa$

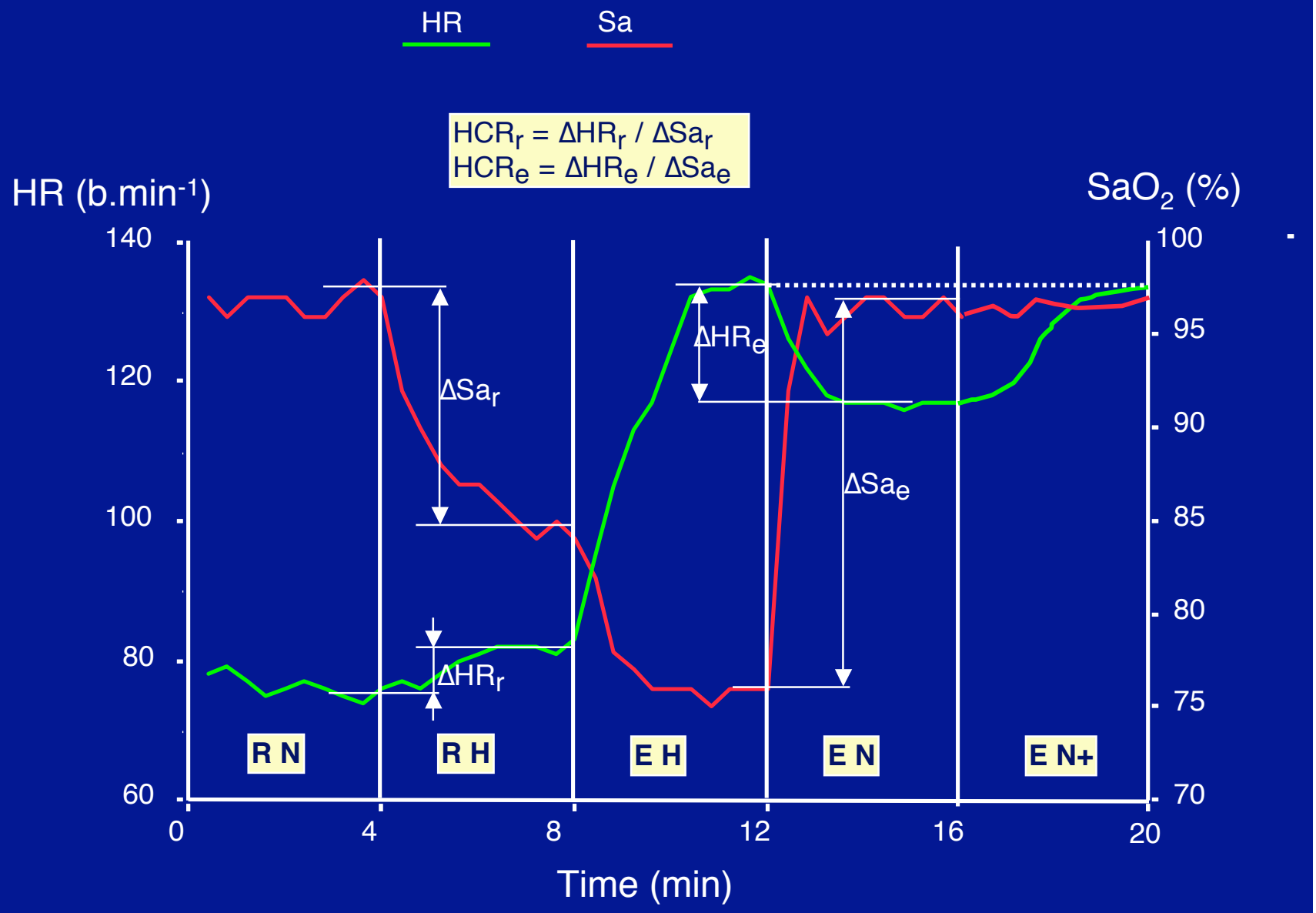
Hypoxia exercise test: FIO_2=11.5%. power output ≈ 30% VO_2max SL



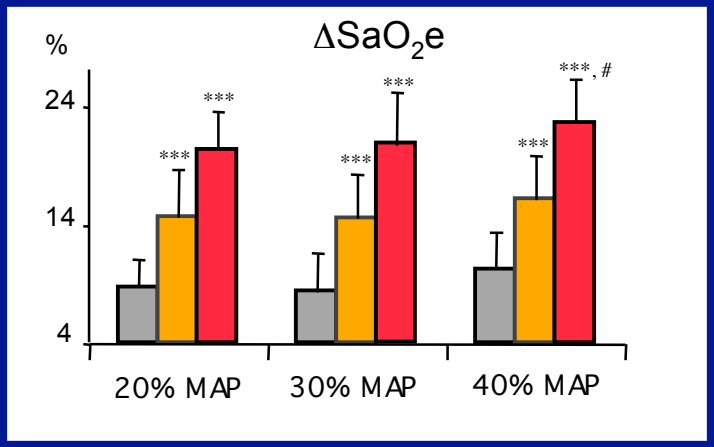
Hypoxia exercise test

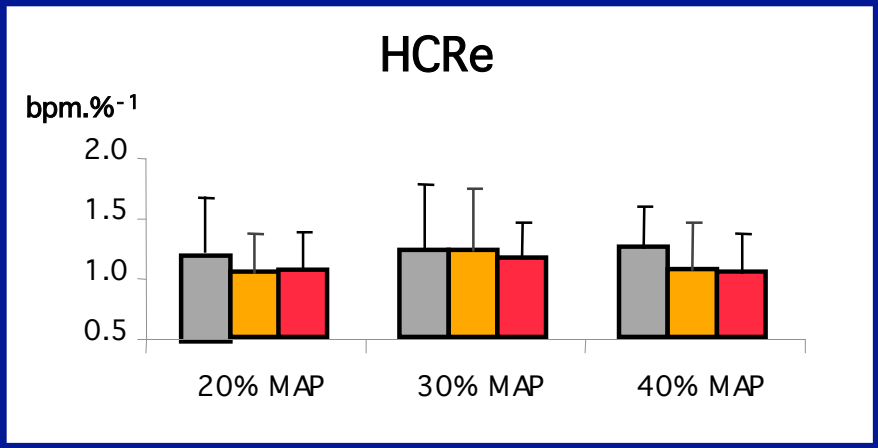


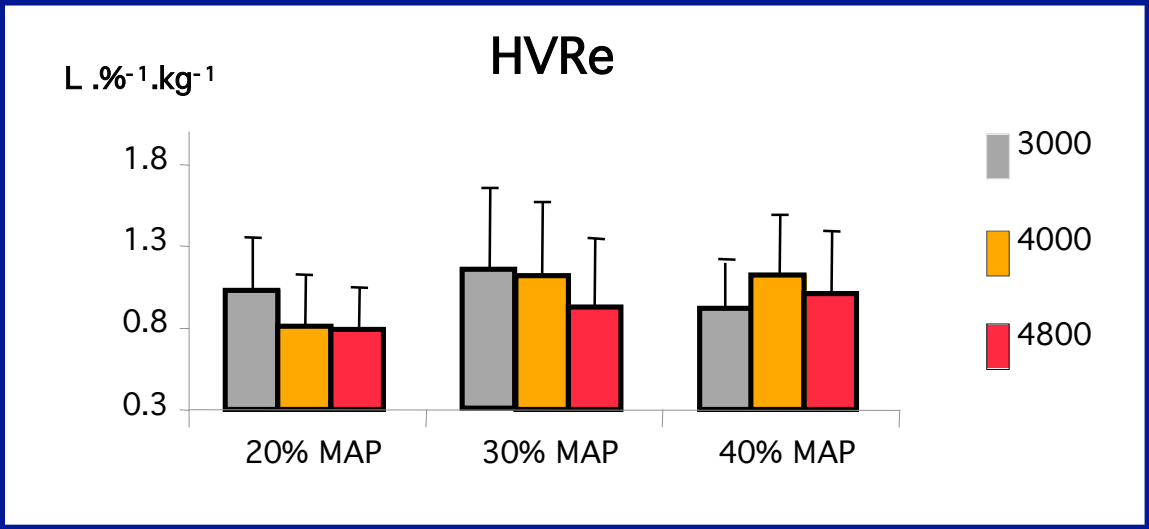
Hypoxia exercise test



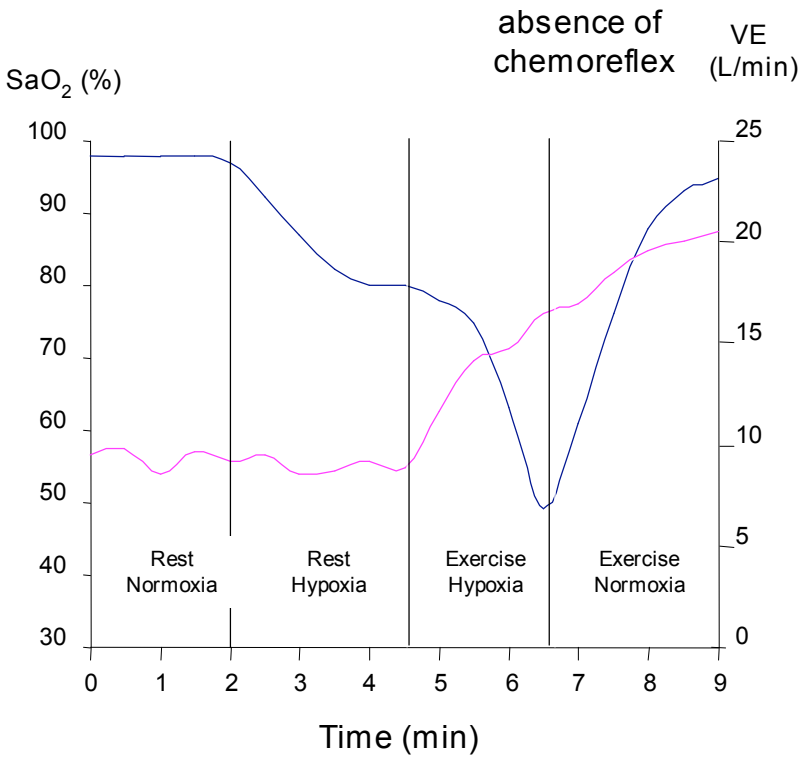
Response to hypoxia at exercise is insensitive to altitude (3000 - 4800m) and power output (20 - 40% MAP)



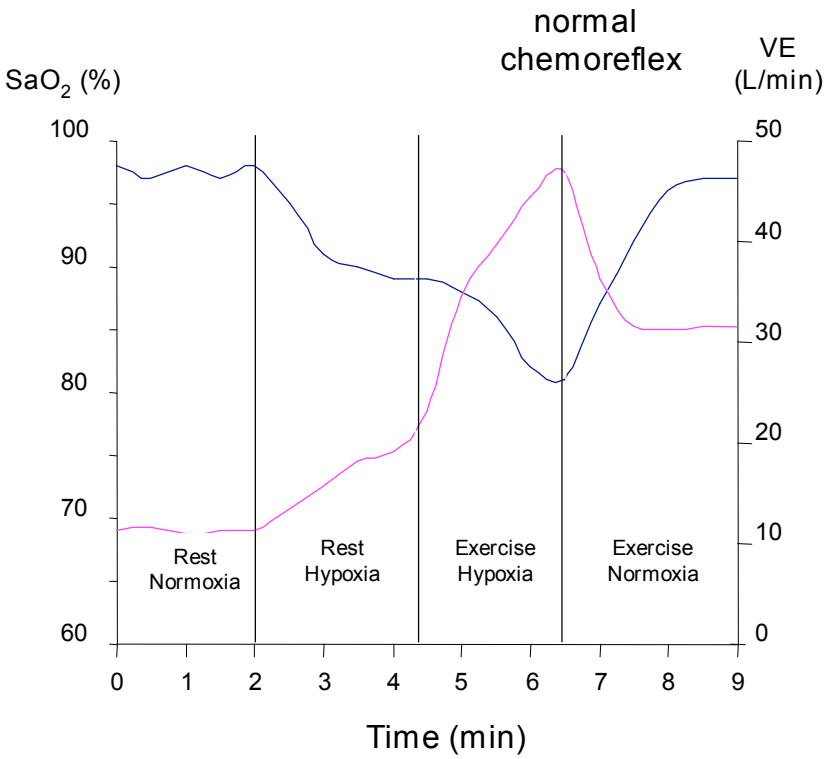




Patient with Holmes-Adie syndrome



Normal subject



Richalet et al. Clin Auton Res, 2010

Population studied

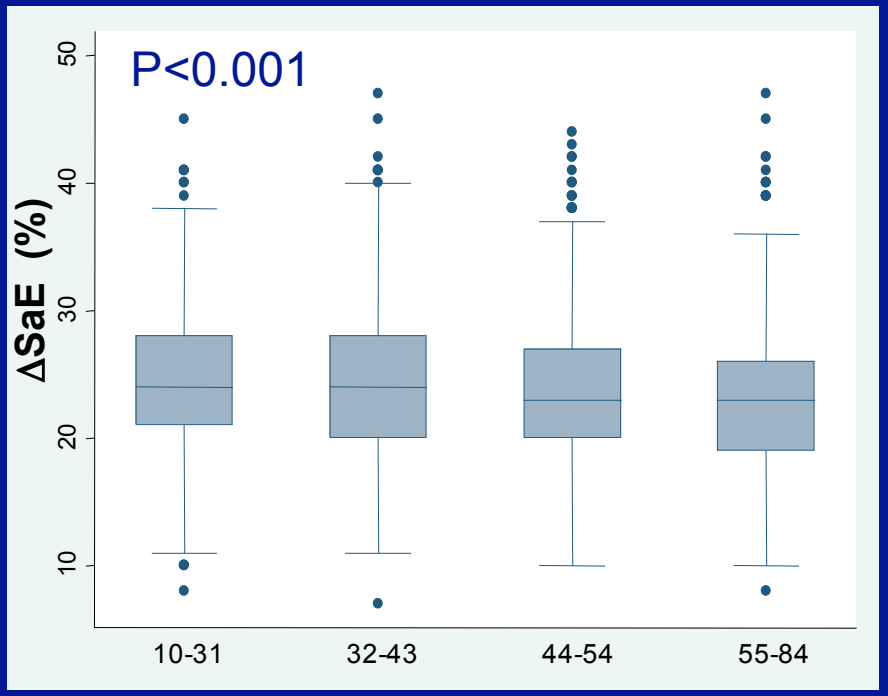
3994 subjects (60% M. 40% F) from 1992 to 2008
Before a stay at high altitude > 4000m
with overnight > 3500m

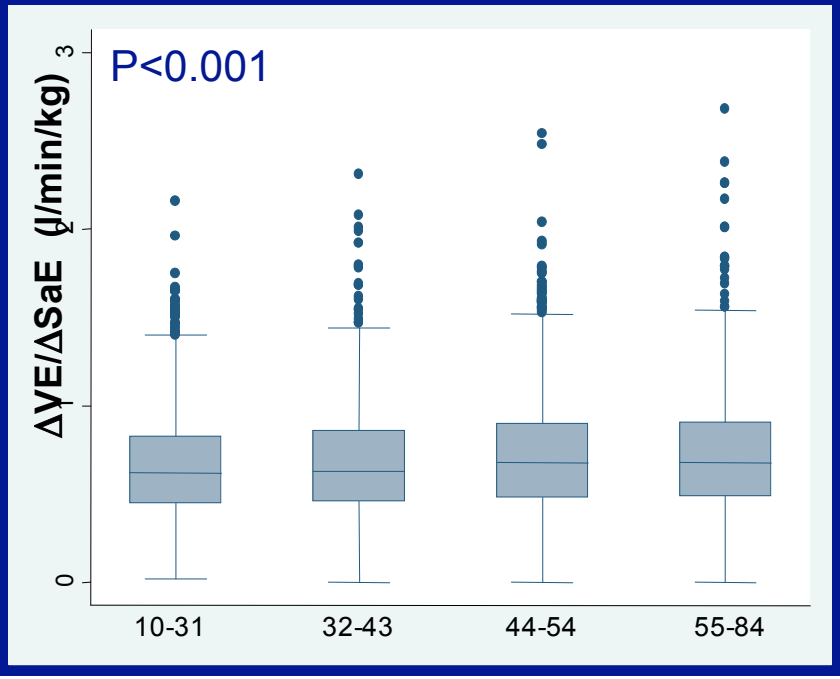
Alpinists	n = 395
Trekkers	n = 2534
Tourists	n = 457
Workers	n = 607

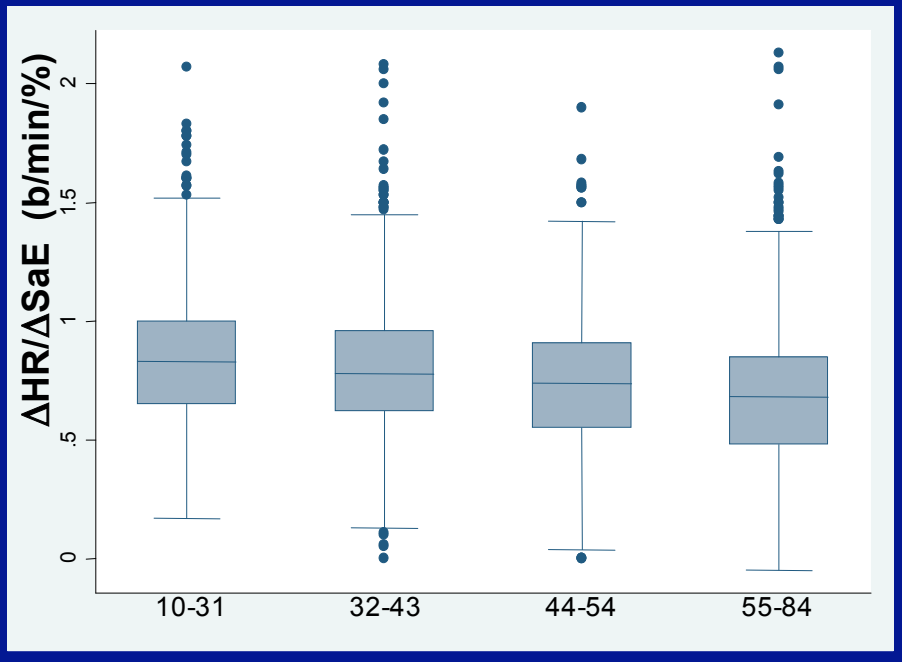
Among them, the feed back information about the events that occurred during their stay at high altitude was obtained in 1326 subjects (mean response rate of 33.2%)

Variation of response to hypoxia with age

(n=3994)

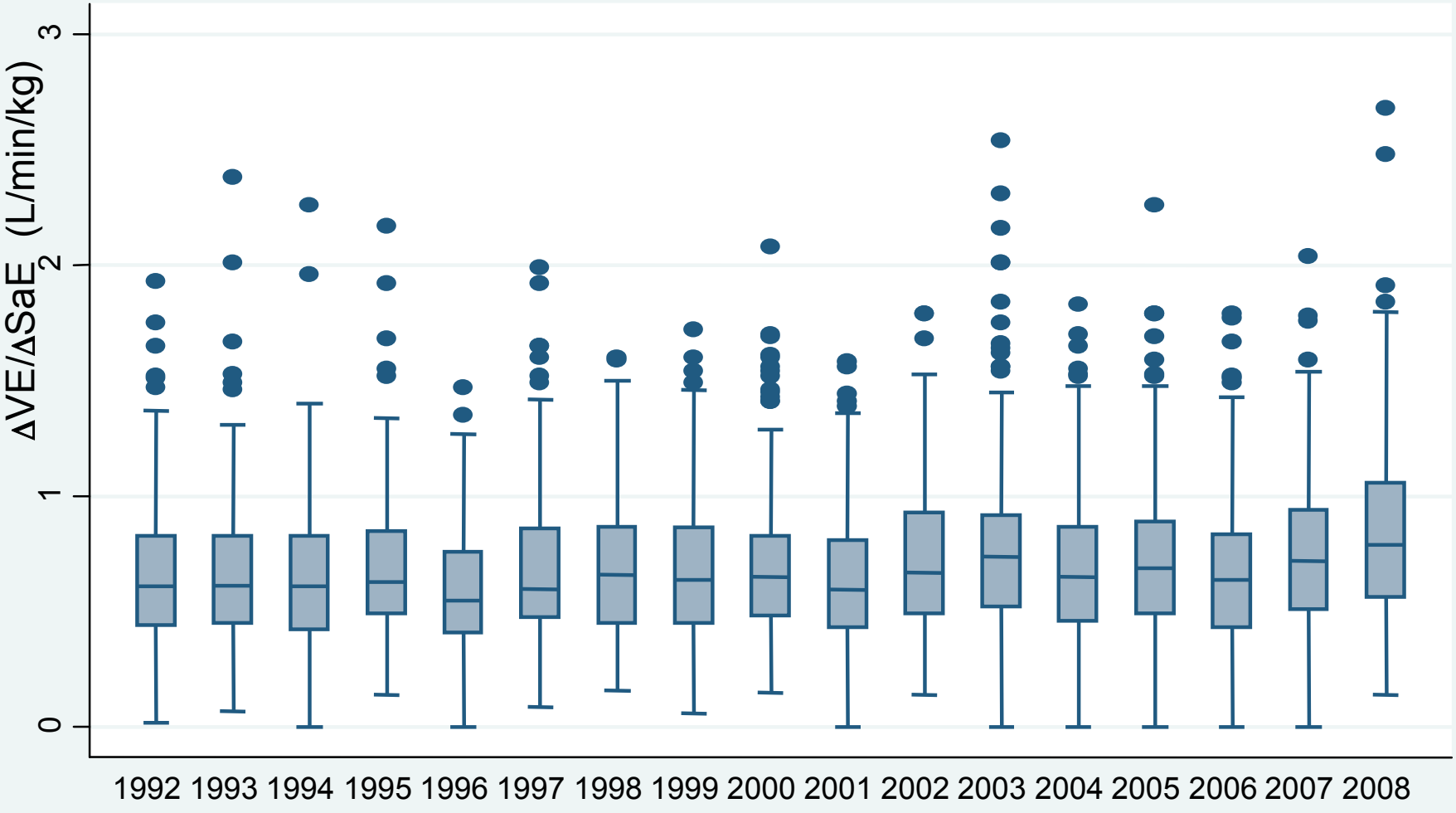






Stability of parameters with time, from 1992 to 2008

(n=3994)



Statistical analysis

- Subjects are classified into two categories following the occurrence or not of Severe High Altitude Related Disease (SHARD):
  - Severe, incapacitating AMS / HAPE / HACE = SHARD +
  - No or moderate AMS = SHARD -

- Comparison between the two groups SHARD+ / SHARD-:
  - t-test / Wilcoxon-Mann-Whitney / Pearson Chi2 / Fisher
  - Odds Ratio associated to each risk factor estimated by logistic regression
  - Variables with $p<0.15$ in univariate analysis are included in a model of multivariate logistic regression
  - Significant interaction between ΔSae and acetazolamide use therefore stratified analysis for acetazolamide

Prevalence of High Altitude diseases

Among the 1326 respondents to the questionnaire,

- 318 suffered from a severe manifestation (SHARD +), i.e. 24%

- 1008 did not suffer from major symptoms (SHARD -). i.e. 76%

Multivariate analysis

Variable	SHARD +	SHARD -	P	OR
Age	42.6 (12.8)	45.3 (14.1)	0.30	0.91 (0.75-1.09)
Sex (F)	47.5 %	38.8 %	0.24	1.24 (0.87-1.77)
Hist. SHARD	41.5 %	10.2 %	<0.001	7.36 (4.55 - 11.89)
Migraine	19.2 %	11.0 %	0.043	1.62 (1.02-2.57)
Trained	39 %	29.9 %	0.036	1.73 (1.04-2.88)
Altitude gain > 400m/night	49.4 %	29.6 %	0.035	2.24 (1.06-4.76)
Δ SaE. %	26.8 (5.5)	22.2 (5.0)	<0.001	1.86 (1.50-2.30)
HCRE. b/min/%	0.72 (0.26)	0.80 (0.30)	0.012	0.77 (0.63-0.94)
HVRE. l/min/kg	0.49 (0.24)	0.78 (0.34)	<0.001	0.30 (0.23-0.40)

Interactions with treatments

Treatment	OD (95% CI)	P
Paracetamol (curative)	3.18 (2.03-4.98)	< 0.001
Aspirin (curative)	3.18 (2.14-4.72)	<0.001
Acetazolamide (preventive)	0.27 (0.19-0.43)	<0.001

Multivariate analysis

Influence of training status on responses to hypoxia

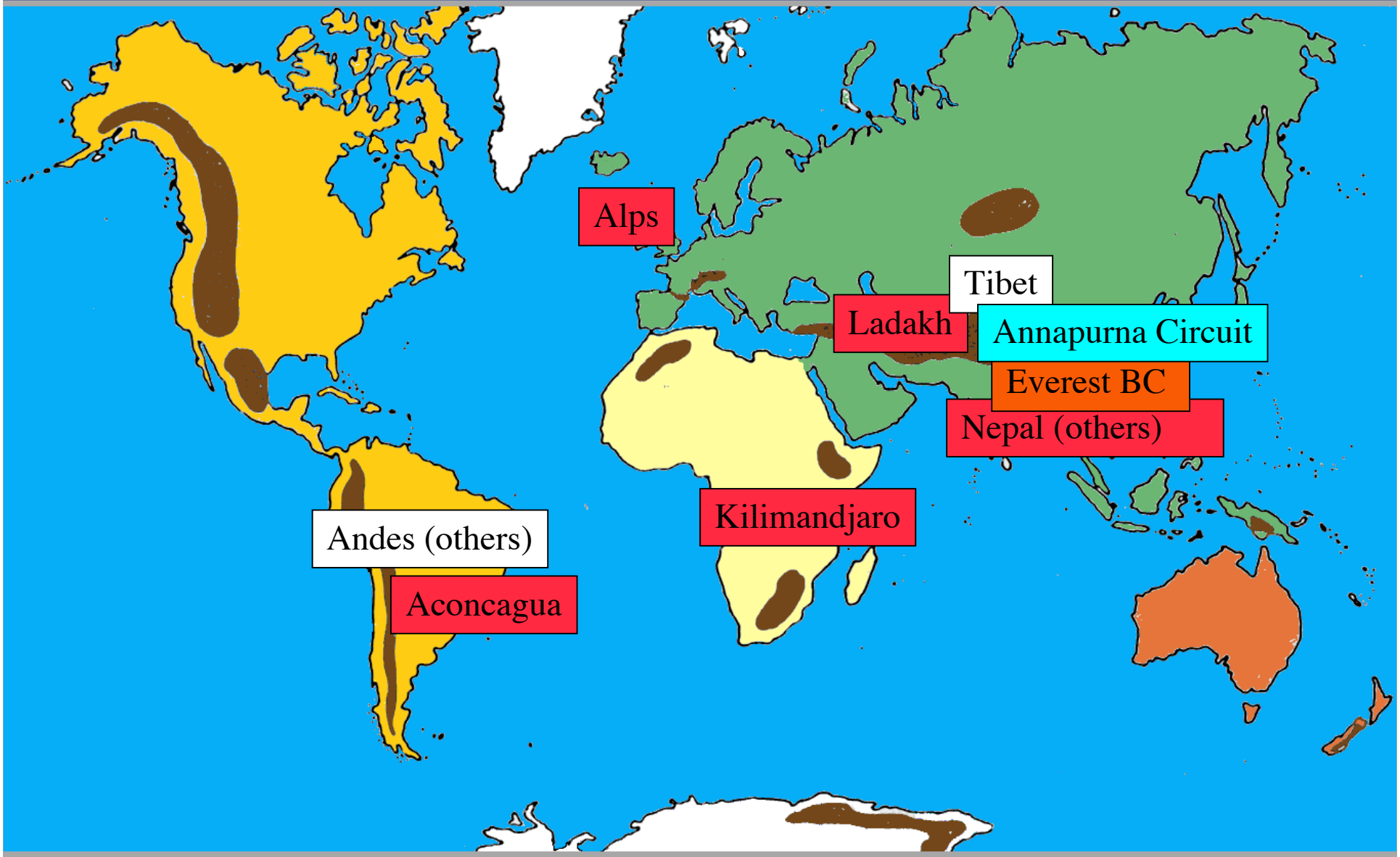
variable	Untrained n=2700	Endurance Trained n=1300	P
Age	45.1± 14.3	40.4± 12.6	<0.001
BMI	23.1±3.1	22.6±2.4	<0.001
Systolic AP	129.8±15.0	129.4±12.8	ns
Diastolic AP	81.6±9.8	80.9±9.1	0.038
VO2max	41.8±9.0	52.2±10.5	<0.001
SaO_2 exerc. hypoxia	73.2±5.5	70.8±5.9	<0.001
HR exerc. hypoxia	133.4±13.7	129.8±11.5	<0.001
VE exerc. hypoxia	38.6±9.0	41.0±10.1	<0.001
ΔSaO_2 rest	11.1±3.5	11.6±3.6	<0.001
ΔSaO_2 exercise	23.1±5.2	25.3±5.8	<0.001
HCR exercise	0.74±0.30	0.82±0.27	<0.001
HVR exercise	0.68±0.32	0.73±0.32	<0.001

Multivariate analysis: characteristics of subjects according to SHARD and acetazolamide use

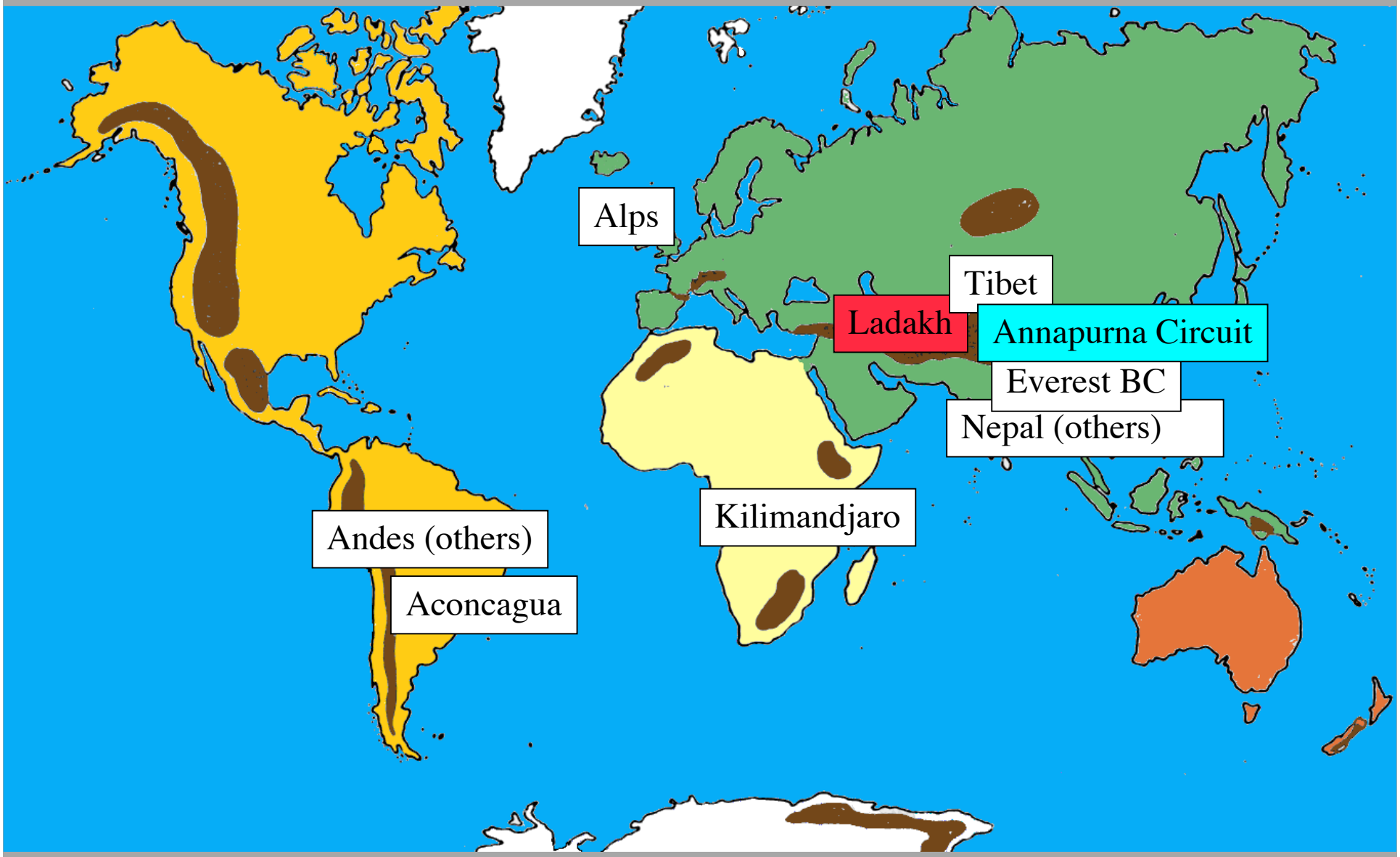
	No acetazolamide use		Acetazolamide use	
	multivariate OR (95% CI)*	p	multivariate OR (95% CI)*	p
Previous migraine	2.28 (1.28-4.07)	<0.001	1.23 (0.62-2.45)	0.64
Previous SHARD	12.82 (6.95-23.66)	<0.001	5.02 (2.41-10.44)	<0.001
Regular endurance activity	1.57 (1.00-2.46)	0.016	1.38 (0.78-2.43)	0.21
Rapid ascent (>400m/day)	5.89 (3.78-9.16)	<0.001	2.26 (1.35-3.81)	0.001
ΔSae, OR for 1 SD increase	2.50 (1.52-4.11)	<0.001	1.63 (0.81-3.27)	0.024
HVRe, OR for 1 SD decrease	6.68 (3.83-11.63)	<0.001	3.89 (1.74-8.73)	0.024

*Logistic regression model adjusted for all the variables listed in the table

Geography = risk factor ? (Univariate analysis)



Geography = risk factor ? (Multivariate analysis)



Discrimination ability of hypoxic exercise test (ΔSae and HVRe)

Comparison between c-statistic indices of multivariable models predicting SHARD.

	No acetazolamide use		Acetazolamide use	
	c-statistic	p-value *	c-statistic	p-value *
Multivariable model adjusted for sex, migraine, history of SHARD, trained and rapid ascent = M1	0.7923	-	0.7006	-
M1+ ΔSae = M2	0.8654	<0.001*	0.7632	0.001*
M1+ HVRe = M3	0.8924	<0.001	0.7926	<0.001
M1 + ΔSae + HVRe = M4	0.9043	<0.001	0.7995	0.33

C-statistic indices were derived from logistic regression model.
The c-statistic indices were compared using the Delong test (DeLong et al., Biometrics, 1988) .

To summarize

Factors *favoring* the occurrence of SHARD (multivariate analysis):

- History of migraine
- History of severe AMS or HAPE / HACE during preceding altitude exposures
- Rapid ascent (> 400 m mean altitude gain / night)
- Regular endurance training
- Large desaturation at exercise during the hypoxia exercise test (ΔSaE)

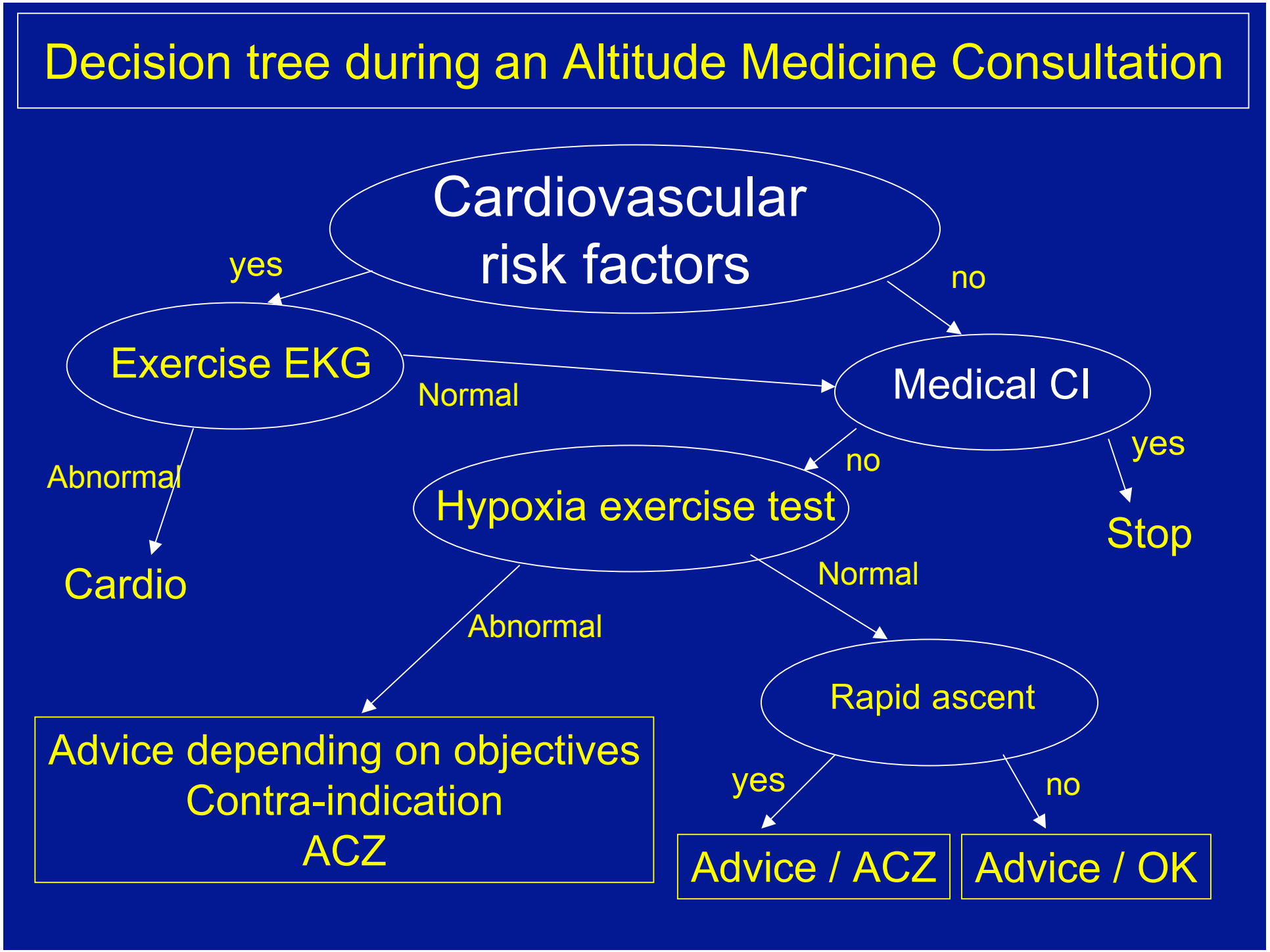
Factors *protecting* against the occurrence of SHARD (multivariate analysis):

- High ventilatory response to hypoxia at exercise
- High cardiac response to hypoxia at exercise
- Prevention by acetazolamide

Factors *not related* to the occurrence of SHARD (multivariate analysis):

- Sex, age, height, body weight, BMI
- Tobacco, atopia, snoring
- Familial history of thrombo-embolic, cardiac, pulmonary events
- Mountaineering experience
- Hypothyroidism, depression, cranial trauma with lack of consciousness
- Systemic hypertension

Decision tree during an Altitude Medicine Consultation



Conclusions

1. There is an individual susceptibility to severe high altitude related diseases AMS / HAPE / HACE
2. Speed of altitude gain is a crucial factor
3. Measurement of HVR **at rest** has no predictive value
4. Evaluation of response to hypoxia at exercise is useful to determine individual risk factors.
5. Prevention through adequate information is an essential part of the Altitude Medicine Consultation.

Perspectives

1. Search for specific risk factors of HAPE / HACE (however, large number of subjects difficult to obtain)
2. Search for genetic determinants : several studies done and on progress but large numbers are necessary
3. Develop this test for other diseases: coronaropathies. lung disorders, flight and O_2 , etc.