

# Ventilatory response to hypoxia and tolerance to high altitude in women.

## Influence of menstrual cycle, oral contraception and menopause



Jean-Paul Richalet<sup>1,3</sup> , François Lhuissier<sup>1,2</sup> and Dominique Jean<sup>4</sup>

<sup>1</sup>Université Paris 13. EA2363 “Hypoxie et Poumon”, Bobigny, France

<sup>2</sup>Assistance Publique Hôpitaux de Paris, Hôpital Avicenne, Bobigny, France

<sup>3</sup>Institut National de l'Expertise et de la Performance, Département Médical,  
Paris, France

<sup>4</sup>CHU Grenoble-Alpes, Centre Pluridisciplinaire de Diagnostic Prénatal,  
Grenoble, France

# Context

- Tolerance to high altitude in women might be influenced by hormonal status since female hormones are known to modulate ventilation
- Ventilatory response to hypoxia might be modulated by the phase of the menstrual cycle
- Menopause is known to influence ventilatory response to hypoxia
- Chronic mountain sickness is present in post-menopausal women

# Objectives of the study

Explore the influence on ventilatory (HVRe) and cardiac (HCRE) responses to hypoxia at exercise of

1. the phase of menstrual cycle,
2. oral contraception,
3. menopause with or without hormonal treatment,

in women prior to a sojourn at high altitude.

Evaluate the tolerance to high altitude, as a function of age, hormonal status and treatments

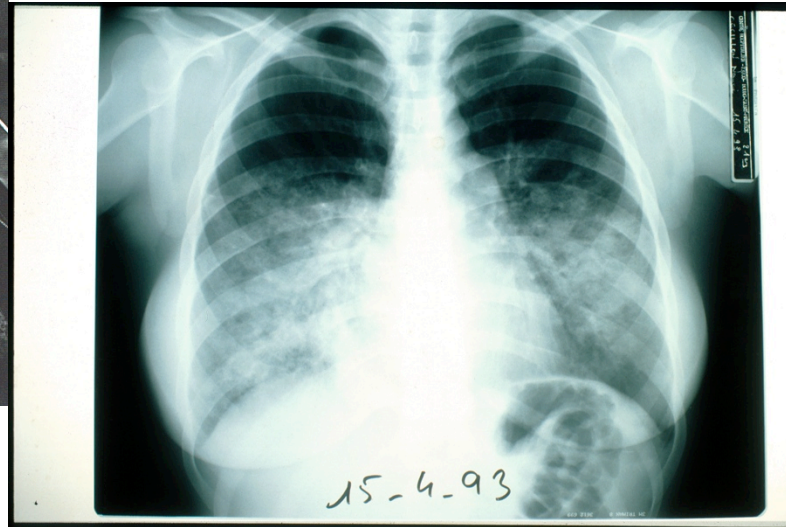
# Subjects and methods

- 1060 women prior to a sojourn at high altitude performed a standard Hypoxia Exercise Test
- Prevalence of SHAI (Severe High Altitude Illness) was assessed in a subgroup of 260.
- Four groups were studied:
  - group A, non-menopausal without oral contraception;
  - group B, non-menopausal with oral contraception;
  - group C, menopausal without hormonal treatment;
  - group D, menopausal with hormonal treatment.
- Within group A, results were compared between the luteal and follicular phases

# The Hypoxia Exercise Test

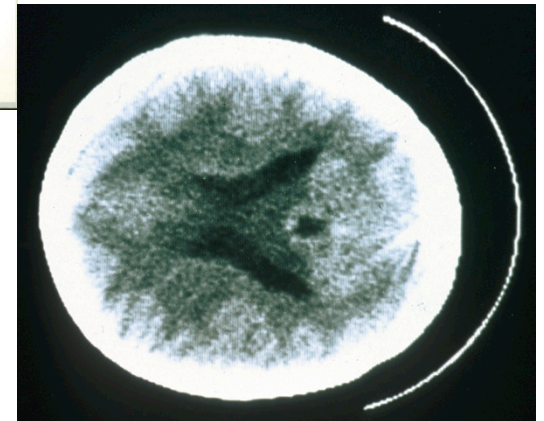


Severe AMS

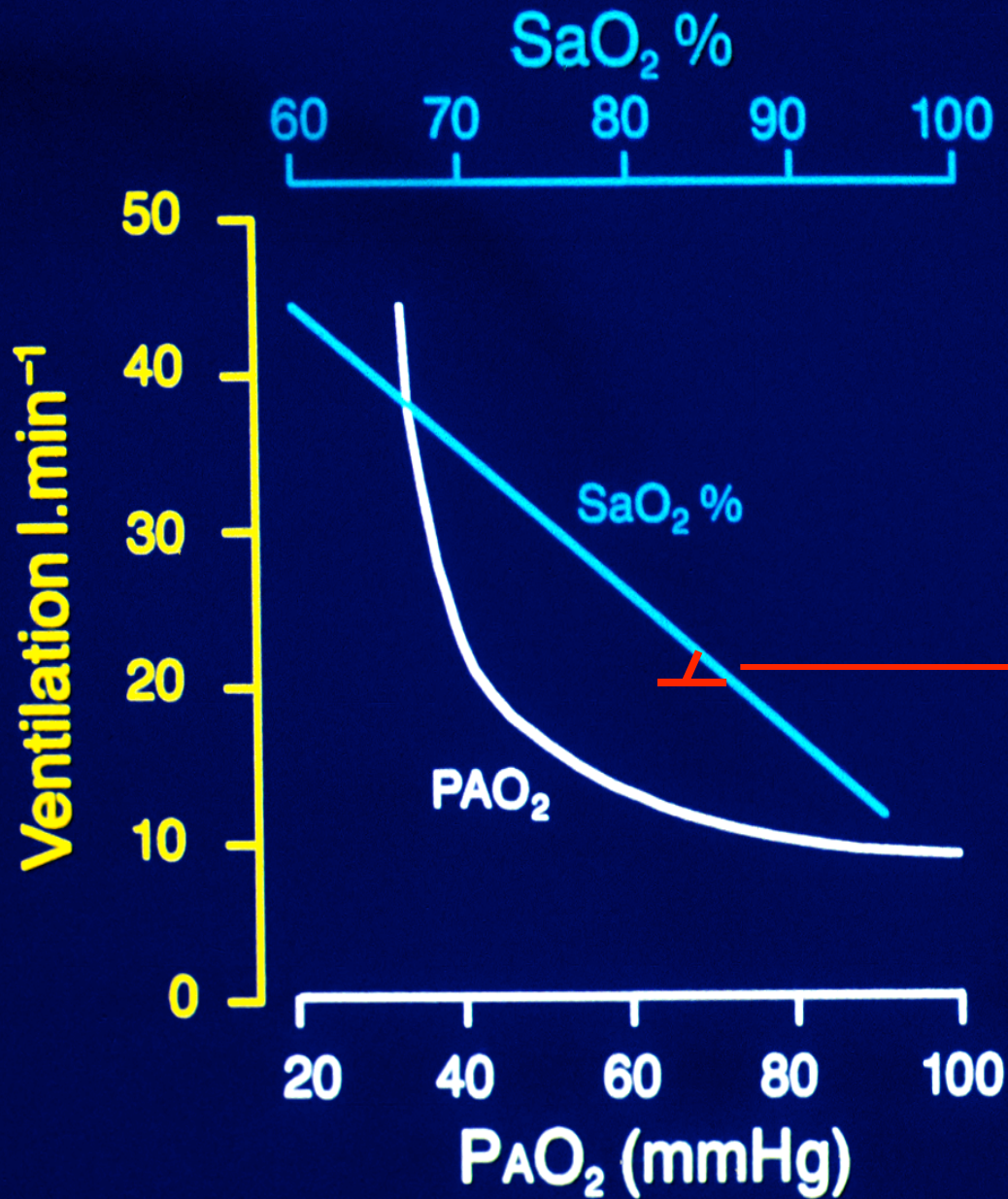


HAPE

**Objective:** detect subjects susceptible to develop severe, incapacitating forms of high altitude illnesses and give them adapted advice.



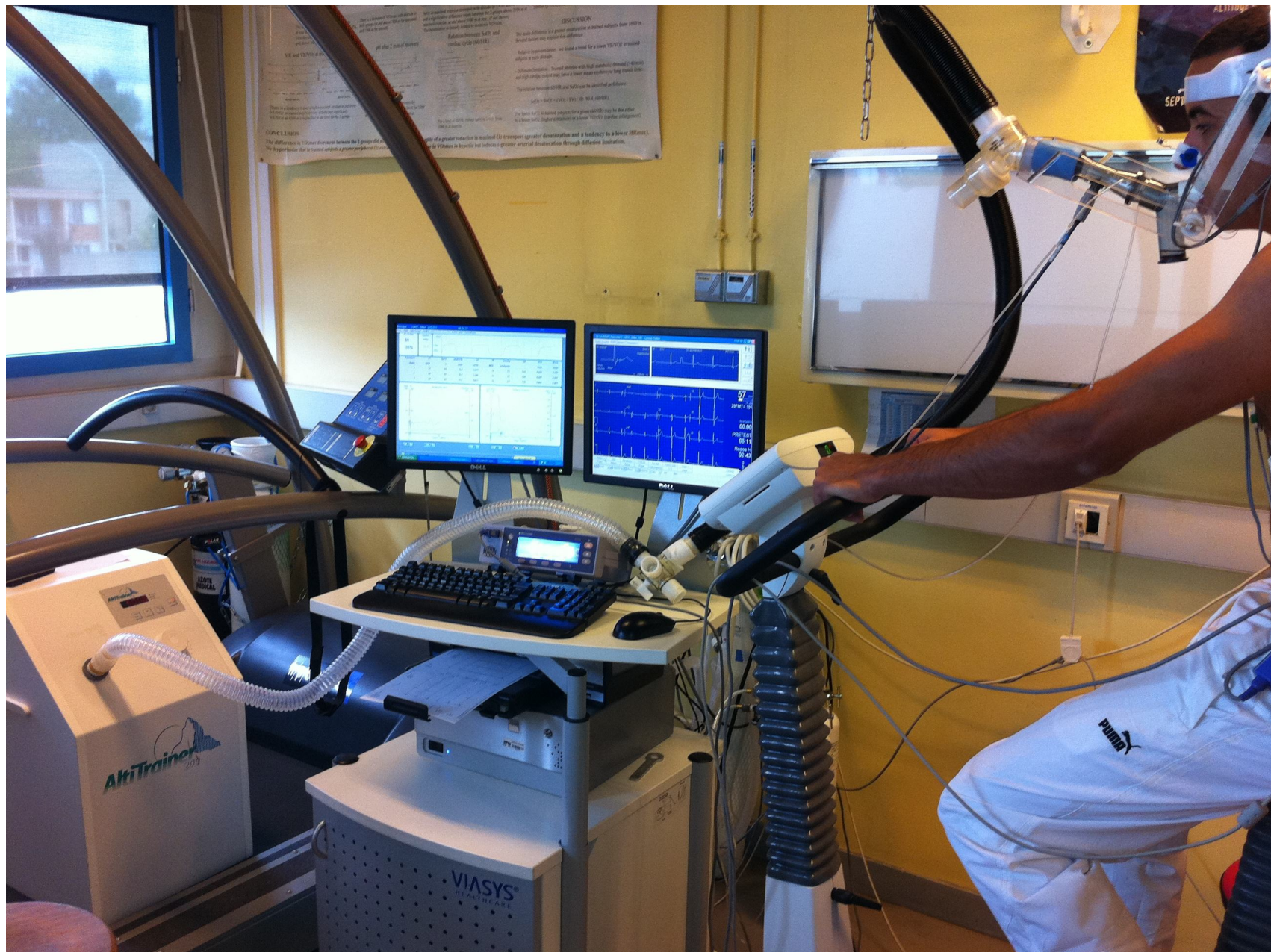
HACE



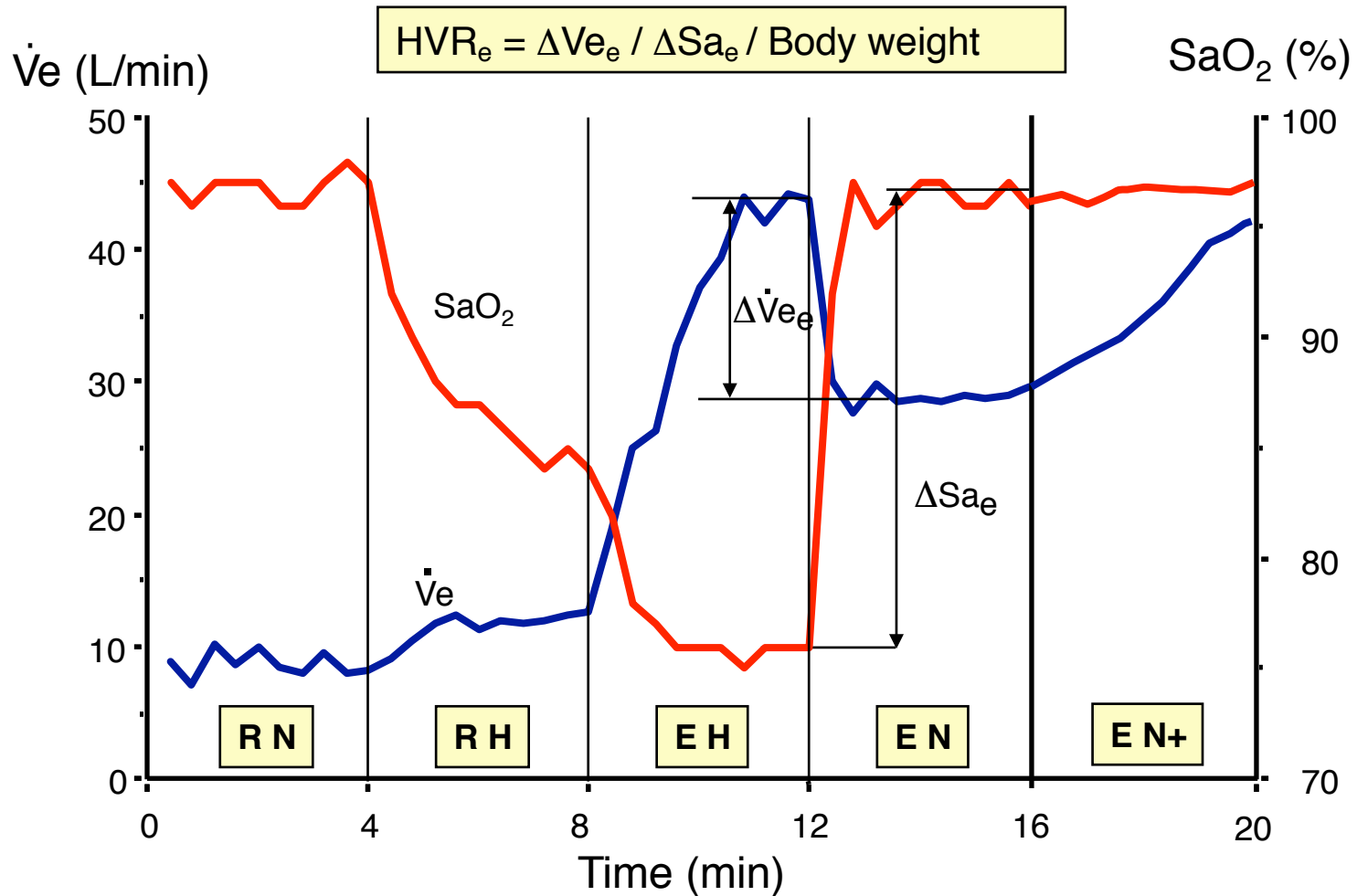
The principle:  
 measure ventilatory  
 response to hypoxia  
 = sensitivity of  
 carotid bodies to  
 hypoxia

$$\text{HVR} = \Delta \dot{V}_e / \Delta \text{sa} / \text{BW}$$

# Hypoxia Exercise Test: $\text{FIO}_2=11.5\%$ . Power $\approx 30\% \text{VO}_2\text{max}$ normoxia



# Avicenne cohort = 5000 subjects



Richalet JP, Larmignat P et al., **AJRCCM**, 2012 Lhuissier F,... Richalet JP. **J Appl Physiol**, 2012  
Canouï-Poitrine F,... Richalet JP. **PlosOne**, 2014  
Coustet B,...Richalet JP. **Circulation**, 2015 Winkler, Lhuissier, Richalet. **J Hypertension**, 2017

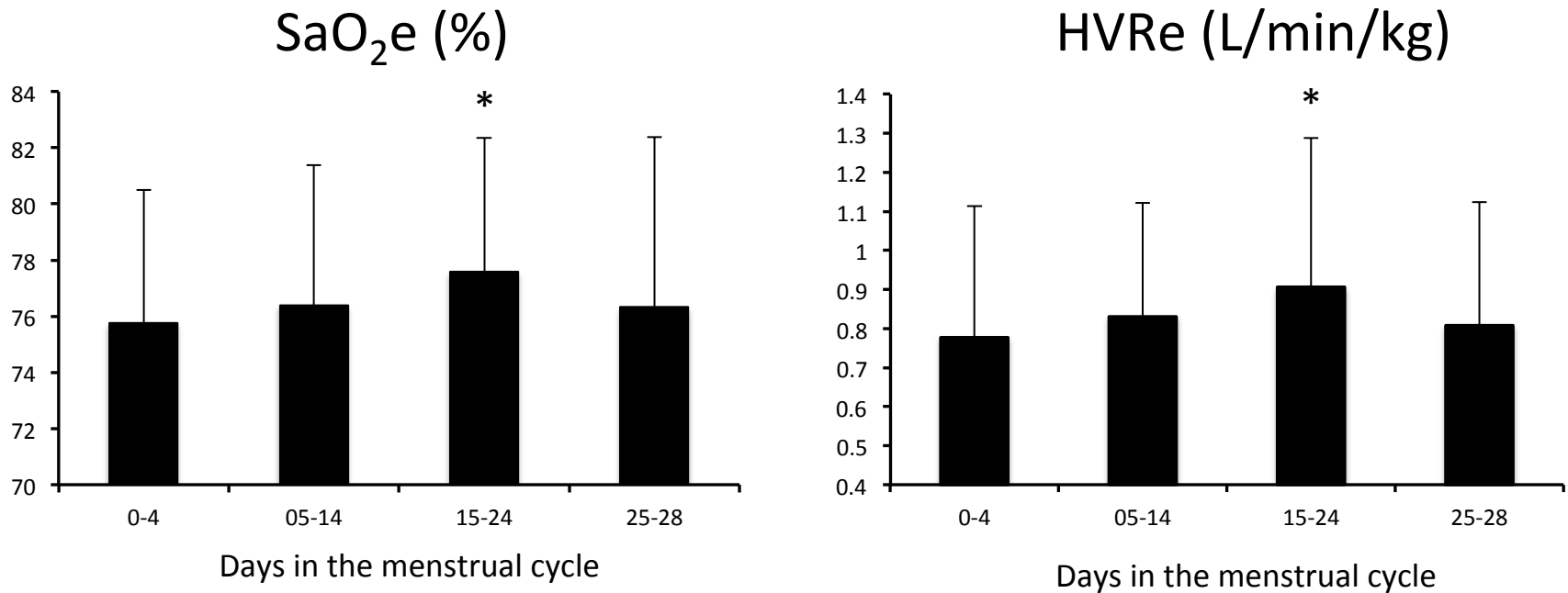


# Risk factors of SHAI: multivariate analysis

Variable	SHAI +	SHAI -	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. SHAI	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)
$\Delta$ 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)

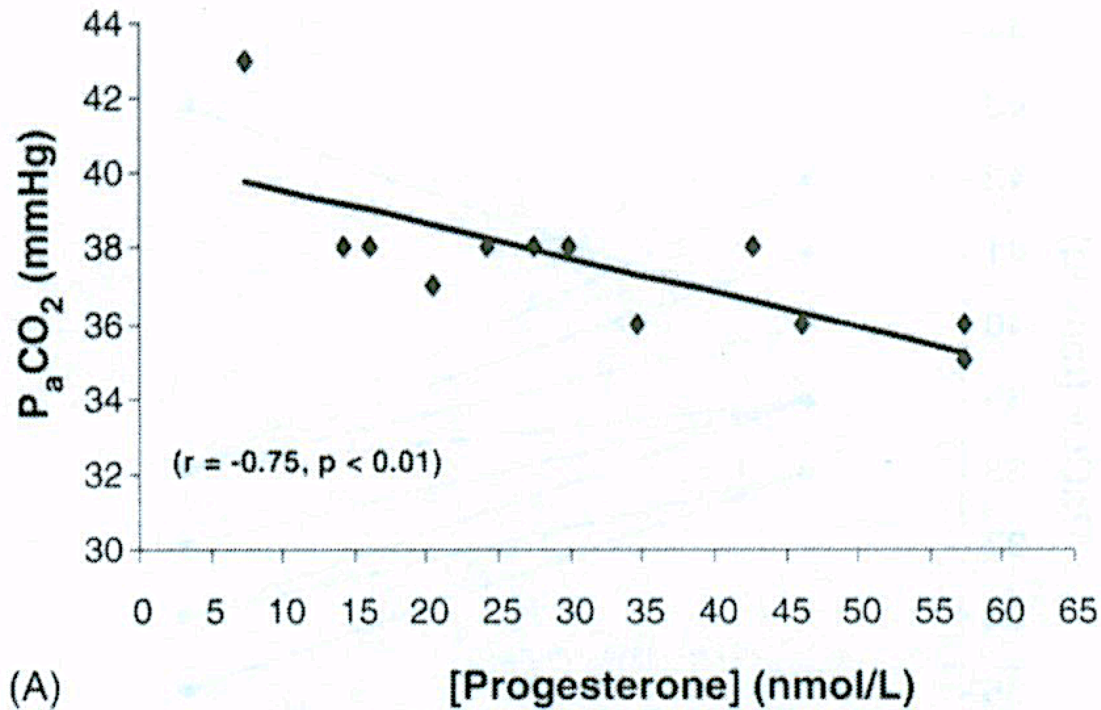
# Results pre-trek

Influence of the day within the menstrual cycle  
on ventilatory response to hypoxia



\*:  $p < 0.05$  vs 0-4 period - non menopausal, no contraception (group A)

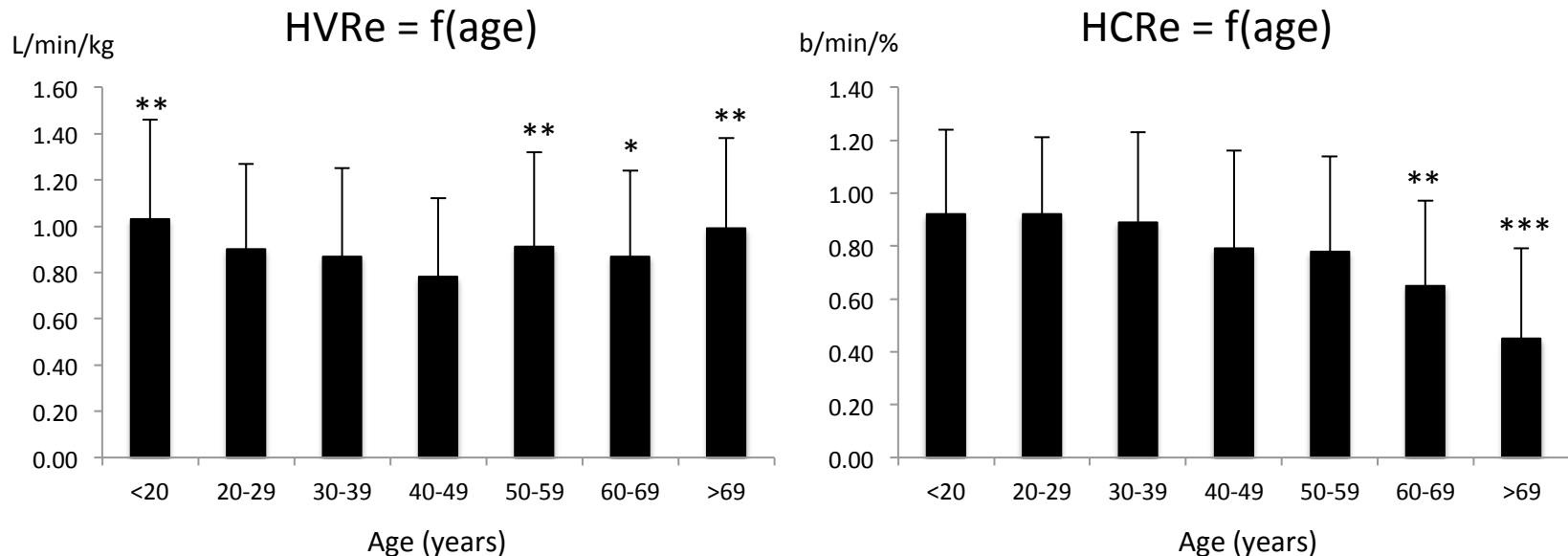
**Both SaO<sub>2</sub>e and HVRe are maximal during the early and mid luteal phase**



Slatkowska L, Jensen D, Davies GA, Wolfe LA. Phasic menstrual cycle effects on the control of breathing in healthy women. *Respir. Physiol. Neurobiol.* 2006;154:379–388

# Results pre-trek

## Variation of ventilatory and cardiac responses to hypoxia as a function of age category



\*:  $p < 0.05$ , \*\*:  $p < 0.01$  vs 40-49 yrs

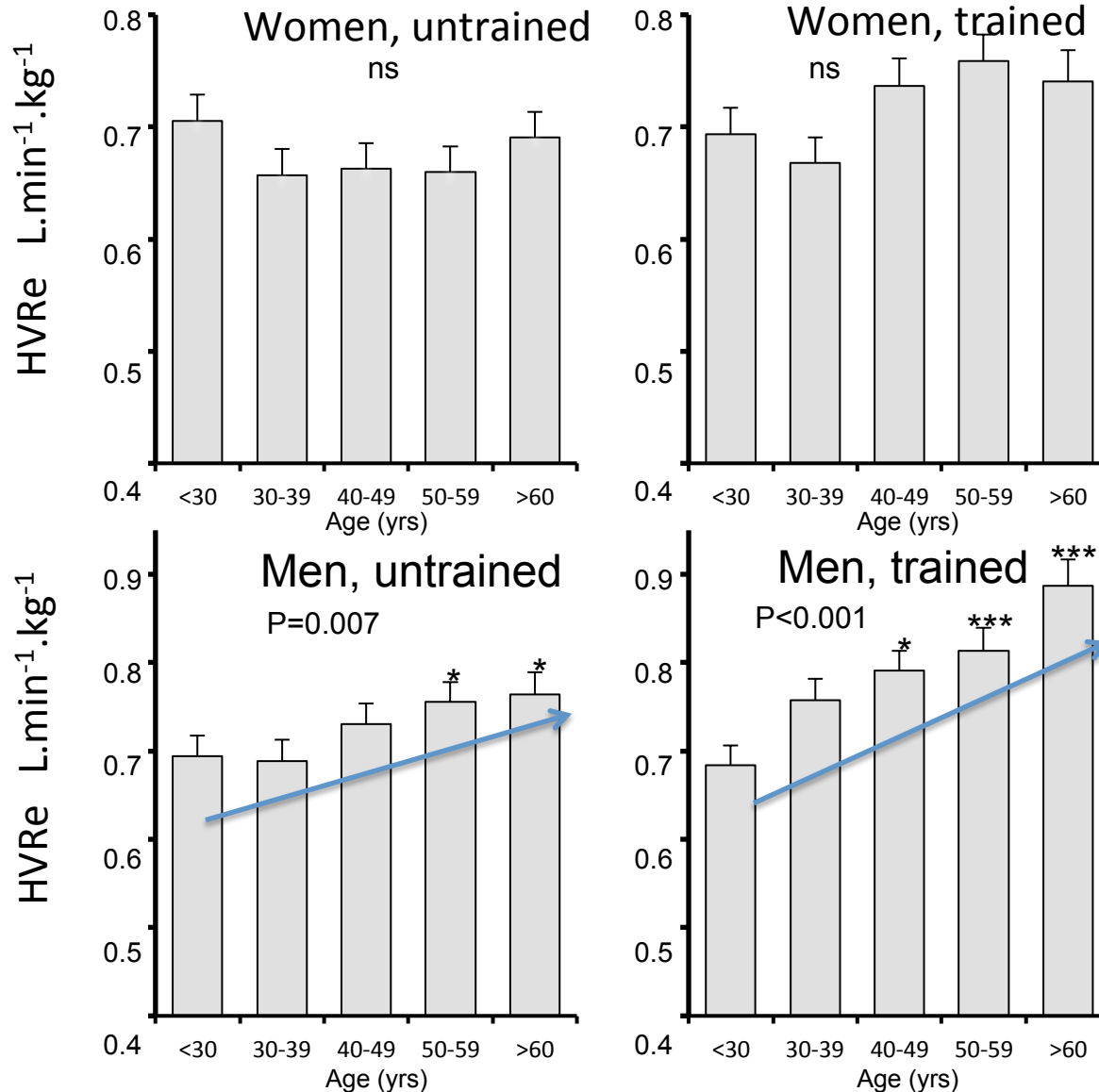
\*\* :  $p < 0.01$ , \*\*\*:  $p < 0.001$  vs <20 yrs

HVRe decreases from the 20' to the 40' then increases from the 40' to the 80'.

HCRe declines with ageing, the difference being significant from the 60'

All groups A,B,C,D pooled

# Chemosensitivity to hypoxia **ameliorates with ageing**, possibly because of increasing prevalence of intermittent hypoxia during sleep apneas (5000 subjects)



Lhuissier FJ, Canoui-Poitaine F, Richalet JP. *J. Physiol*, 2012.

Richalet JP and Lhuissier FJ, *HAMB*, 2015

# Results post-trek

Group		Age (yrs)		SHAI	Aspirin	Acetazolamide	Max altitude reached (m)	Mean daily altitude gain (m)
Non-menopausal (n=108)	Without oral contraception (n=63)	35±10	36±10	26 (24%)	11 (10%)	53(44%)	4982±683	412±182
	With oral contraception (n=33)		31±9 ***					
Menopausal (n=151)	Without hormonal treatment (n=132)	60±6 +++	60±6	41 (27%)	18 (12%)	68(56%)	4810±662 +	392±167
	With hormonal treatment (n=19)		59±5					

Incidence of Severe High Altitude Illness (SHAI), menopause and hormonal treatment.

\* : p<0.05 ; \*\*\* : p<0.001 with vs without treatment.

+++ : p<0.001 ; + : p<0.05 non-menopausal vs menopausal

# Results post-trek

Without acetazolamide	HVRe (ml/min/kg)	SHAI score (a.u.)
SHAI + (n=35)	0.86±0.39 *	5.5±1.9 **
SHAI – (n=104)	1.02±0.41	4.6±1.8

Correlation between Hypoxia Exercise Test and tolerance to high altitude

\* : p<0.05 ; \*\*\* : p<0.001 SHAI+ vs SHAI-

# Summary and conclusions

Ventilatory response to hypoxia depends on the ovarian cycle phase:  $\text{SaO}_2\text{e}$  and  $\text{HVRe}$  are maximal during the early luteal phase

Prevalence of SHAI was similar in all groups.

Women taking oral contraception took more frequently aspirin than the other groups.

Oral contraception, menopause and hormonal treatment have no influence on response to hypoxia and tolerance to high altitude

$\text{HVRe}$  and  $\text{HCre}$  vary with ageing, independently of hormonal status

SHAI score is confirmed as a good predictor of SHAI