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CEREBRAL BLOOD FLOW, BRAIN METABOLISM AND CSF ACID-BASE BALANCE IN HIGHLANDERS°

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It is now well documented that residence above 3,500 m induces circulatory changes in most organs including the brain. However, studies on the cerebral circulation have mostly dealt with acute changes in newcomers (Severinghaus, Chodi, Eger, Brandstater & Hornbein, 1966). As far as we are aware, the first data on high altitude residents' brain circulation were published by Milledge and Sorensen (1972). These authors showed a larger arteriovenous O_2 difference in highlanders (HL) at high altitude (HA) than in lowlanders (LL) at sea level (SL). More recently Sorensen, Lassen, Severinghaus, Coudert & Paz-Zamora (In Press) found a decrease in HL cerebral blood flow ($\dot{Q}_c$) confirming preliminary data published by the authors of this paper (Durand, Olesen, Coudert, David & Marc-Vergnes, 1972; Marc-Vergnes, Blayo, Coudert, Antezana, Dedieu & Durand, 1973), whereas Roy reported larger figures for HL than for LL (Roy, 1973)

The present study was carried out on high altitude residents in La Paz at 3,800 m above sea level (mean barometric pressure 493 mmHg). It can be divided into four parts, dealing respectively with :

(1) $\dot{Q}_c$ and brain metabolism under normal HA environmental conditions.
(2) Brain perfusion and arteriovenous oxygen differences (O_2 AVD) while the subjects were hyperventilating or breathing gas mixtures to alter oxygen and/or carbondioxide partial pressure in arterial blood (Pa_{O_2}, Pa_{CO_2}).
(3) Mean cerebral circulatory transit time ($\bar{T}_c$) as function of subjects' hematocrit (Ht).
(4) Cisternal and lumbar cerebrospinal fluid acid-base balance.

Material, techniques and protocol will be only briefly mentioned in this paper since most of them have been previously described (Marc-Vergnes *et al.*, 1973; Marc-Vergnes, Antezana, Coudert, Gourdin & Durand, in Press; Blayo, Lachia & Clavier, 1971; Blayo, Marc-Vergnes & Pocidalo, 1973; Gaudebout, Clavier and Blayo, 1969; Gleichmann & Lubbers, 1960).

PART 1

The 55 subjects studied with this first protocol were young, healthy volunteers, all Amerindian males, born and residing between 3,800 and 4,800 m. All studies were

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made in the morning on subjects who had been fasting since the night before and who were not premedicated.

Cerebral $\dot{Q}_C$ was measured according to the technique of N.A. Lassen (Lassen & Munck, 1955) by ^{85}Kr wash-out after equilibration (Fig. 1).

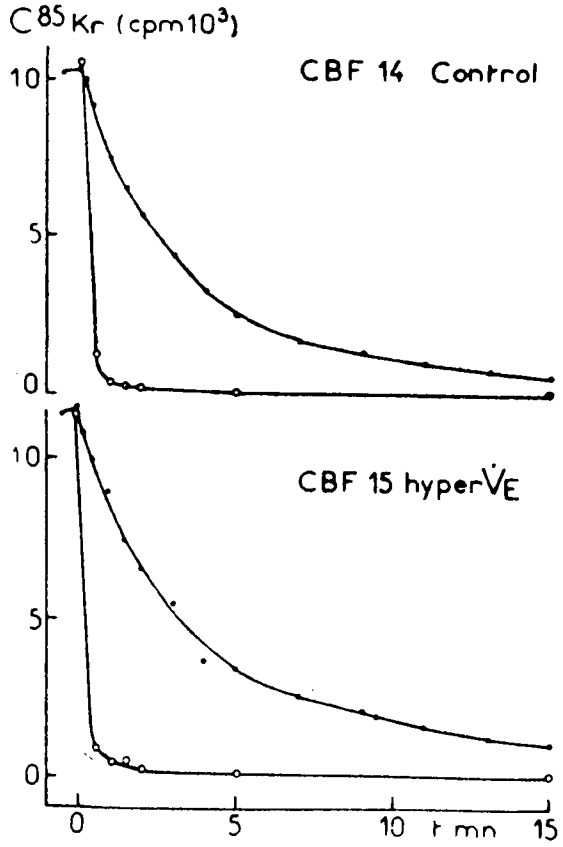

Fig. 1. Concentration of $^{85}K_r$ in arterial (○) and jugular bulb (●) blood during wash-out after a 15 min perfusion. The drop in arterial concentration is abrupt. The upper curve was obtained at rest, the lower one during voluntary hyperventilation.

The main results of this first study are presented in Tables 1 and 2.

— $\dot{Q}_C$ is lower than in comparable studies made in LL at SL by various authors, including the present authors. A difference between sitting and supine posture is also noticed (Table, 2), $\dot{Q}_C$ being significantly lower in the first position.

— O_2 AVD is larger in HL, due to a decrease in oxygen content in the blood sampled from the jugular bulb.

— Cerebral $\dot{V}o_2$, calculated from $\dot{Q}_C$ and O_2 AVD, does not differ from LL.

— Lactic acid production appears to be very small, however values are so scattered, that it is difficult to draw any definite conclusion.

Table 1. *Cerebral blood flow ($\dot{Q}_c$), cerebral arteriovenous difference (Ca_{O_2}-Cvj_{O_2}), brain oxygen uptake ($\dot{V}_{O_2}$), carbondioxide and oxygen partial pressure in arterial blood (Pa_{CO_2}; Pa_{O_2}), cerebral respiratory quotient (R) in high altitude residents and in sea level residents (SL).*

HL	$\dot{Q}_c$ ml/min/100g	Ca_{O_2}-Cvi_{O_2} ml/100g	$\dot{V}_{O_2}$ ml/min/100g	Pa_{CO_2} mmHg	Pa_{O_2} mmHg	R	n
Control Supine	40.21 1.37	8.48 .39	3.36 .13	28.9 .5	59.7 1.2	.94 .05	16
Control Sitting	35.8 1.68	9.32 .51	3.28 .20	31.0 1.0	56.4 1.0	— —	17
Hyper $\dot{V}_E$	33.11 2.84	10.18 1.02	3.37 .11	13.3 .6	68.5 1.6	— —	12
Fi_{CO_2} .10	68.13 9.15	4.77 .71	3.25 .26	43.2 1.7	59.2 1.7	— —	13
Fi_{O_2} .15	47.05*	7.16 .54	— —	22.2 1.6	42.4 1.8	— —	13
Fi_{O_2} .30	30.83*	10.59 .41	— —	24.6 1.9	90.4 2.3	— —	17
Fi_{O_2} .75	27.28*	12.08 .43	— —	23.5 1.2	294.0 8.7	— —	27
Fi_{CO_2} .09 + O_2 .27	45.01*	7.43 .67	— —	42.2 2.7	111.0 3.7	— —	7
SL							
Control Supine	50.08 1.02	6.23 .21	3.12 .17	39.0 1.4	92.3 2.6	.99 .07	6
Fi_{O_2} .95	52.52 1.03	5.90 .24	3.10 .23	41.2 1.8	>250	— —	3

Mean values, standard error and number of observations (n).

Values obtained at rest in ordinary environmental conditions (control), during voluntary hyperventilation (H $\dot{V}_E$), and while breathing various gas mixtures. (*) indicates $\dot{Q}_c$ values calculated assuming an oxygen uptake of 3.36 ml/min/100 g.

Table 2. *Cerebral blood flow* ($\dot{Q}_c$), *oxygen and carbondioxide partial pressure and content in arterial and jugular bulb blood* (Pa_{co_2}, Pa_{o_2}, Pvj_{o_2}, Ca_{o_2}, Cvj_{o_2}), *oxygen arterio-jugular difference* (O_2 AVD), *cerebral oxygen consumption* ($\dot{V}_{o_2}$), *local respiratory quotient* (R), *glucose uptake* ($\dot{m}$ gl) *and lactic acid production* ($\dot{m}$ LA), *in high altitude residents*, 16 *in supine and* 17 *in sitting position. Mean values and standard error.*

	$\dot{Q}_c$ ml/min 100g	Pa_{co_2} mmHg	Pa_{o_2} mmHg	Pvj_{o_2} mmHg	Ca_{o_2} ml/100 ml	Cvj_{o_2} ml/100 ml	O_2AVD ml/100 ml	$\dot{V}_{o_2}$ ml/min 100g	R	$\dot{m}$gl mg/min/100g	$\dot{m}$LA
Supine	40.2	28.8	59.7	29.0	18.38	9.94	8.48	3.36	.94	—	—
16 HL	1.4	.5	1.2	1.2	.42	.49	.39	.13	.05	—	—
Sitting	35.8	31.0	56.4	26.3	19.90	10.58	9.32	3.28	—	4.33	.95
17 HL	1.7	1.0	1.0	1.0	.56	.63	.51	.20	—	.70	.23

— Glucose uptake accords closely with $\dot{V}o_2$. This, together with local respiratory quotient value close to unity, suggests that glucose oxydation provides the major part of the energy, if not all the energy, used by the brain in HL, as it does in LL.

PART 2

The second protocol was planed to study $\dot{Q}_c$ as functions of Pa_{co_2} and Pa_{o_2}. Twenty-seven subjects, comparable to the first group, were studied.

Results are expressed as $\dot{Q}_c$ for easier comparison, although $\dot{Q}_c$ was only measured 13 times. In other cases it was assumed that cerebral oxygen uptake was constant (3.36 ml min^{-1} $.100_g^{-1}$) and unaffected by respiratory gases content or partial pressure in the arterial blood; O_2 and CO_2 partial pressures were altered by breathing appropriate gas mixtures for 20 min before blood samples were taken, or by voluntary hyperventilation.

Results are presented in Table I and in Figs. 2 and 3; variations of $\dot{Q}_c$ as a function of Pa_{co_2} are similar in HL and LL, however the set point of the curve is higher in HL; *i.e.* for a given Pa_{co_2} value and for Pa_{o_2} ranging from 55 to 65 mmHg, $\dot{Q}_c$ would be higher in HL than LL. HL $\dot{Q}_c$ is also influenced by Pa_{o_2} : increasing Pa_{o_2} reduces $\dot{Q}_c$ and *vice versa*. Finally, control values of $\dot{Q}_c$ in HL in their natural environment are lower than in LL at SL; when only hypocapnia is corrected, $\dot{Q}_c$ rises above SL values; when only hypoxia is corrected, $\dot{Q}_c$ decreases below SL values; when both hypocapnia and hypoxia are corrected, $\dot{Q}_c$ is lower in HL than in LL.

PART 3

The third part of the present study deals with $\dot{Q}_c$ and Ht. It was shown that the red blood cell count or the amount of hemoglobin available for O_2 transport could interfere

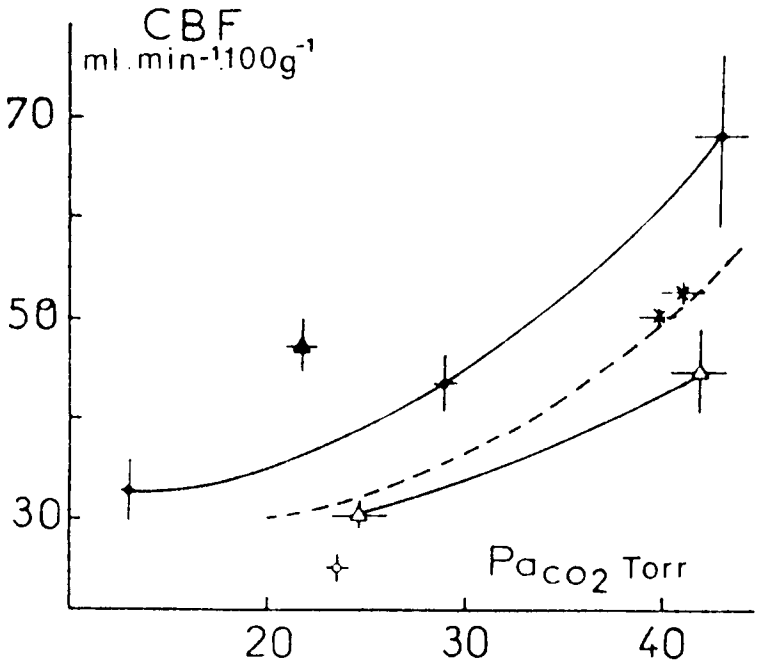

Fig. 2. Cerebral blood flow in high altitude residents in supine posture ($\dot{Q}c$) as a function of carbondioxide partial pressure in arterial blood (Pa_{co_2}) and for different values of inspired oxygen fraction: Fi_{o_2}=.21 (●); .33 (Δ); .75 (○): .16 (▲). Dotted line represents the curve obtained in lowlanders at sea level and (*) the values obtained by the authors of the present study. (Mean value and standard errors).

with $\dot{Q}c$ (Heyman, Patterson & Duke, 1952; Lassen, 1959) and this could explain $\dot{Q}c$ reduction in HL.

Here again $\dot{Q}c$ was not measured but the mean cerebral transit time ($\bar{T}c$) was. For this purpose, intravenous injection of ^{99m}Tc and external counting were used; one of the counting devices being focussed perpendicularly on the right subclavian artery, the other one tangentially on the torcular Herophili. $\bar{T}c$ was computed as the difference between the mean transit time of the "arterial" and "venous" curves (Fig. 4). It was assumed that theoretical conditions for $\bar{T}c$ measurement were fulfilled and that $\dot{Q}c$ and cerebral blood volume were constant, and therefore $\bar{T}c$ is inversely related to flow.

As shown in Fig. 5, there is a curvilinear relationship between $\bar{T}c$ and Ht. LL mean transit time fits with this relationship and the product $\dot{Q}c \times Ht$ is the same in both groups, *i.e.* when $\dot{Q}c$ is expressed, not as total blood flow but only as red blood cell flow, it is identical in both LL and HL.

This seems to be a general feature of regional nutritive blood supply in high altitude residents. All local blood flows measured up to now were lower than at SL and in a ratio which approximates that of normal hematocrit at SL and HA; that is about .8, in the case of residents dwelling around 4,000 m. Reduction in local blood flows and increase in

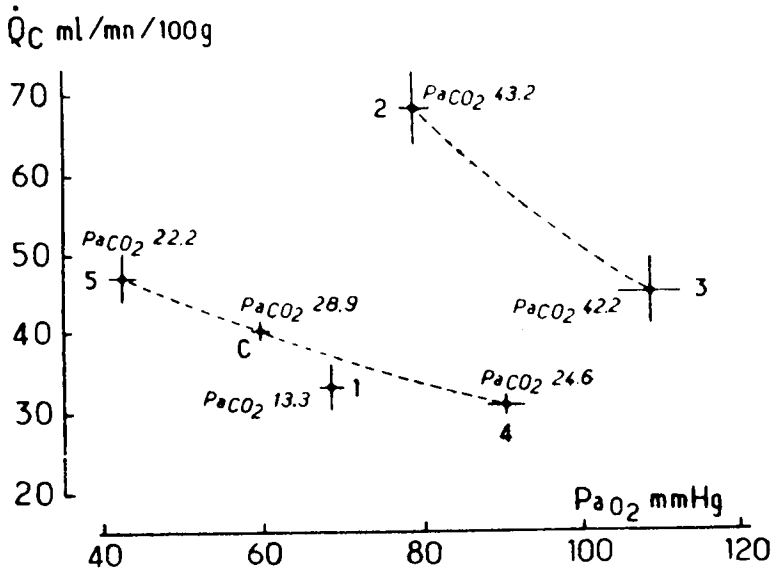

Fig. 3. Cerebral blood flow in high altitude residents in supine posture ($\dot{Q}_C$) as a function of oxygen partial pressure in arterial blood (Pa_{O_2}) for different values of carbondioxide partial pressure in arterial blood (Pa_{CO_2} in mm Hg). (C) : values obtained in ordinary ambient conditions; (1) : during voluntary hyperventilation, while breathing ; (2) : hypercapnia ; (3) : hypercapnia and hyperoxia; (4): hyperoxic gas mixture ; (5) : hypoxic gas mixture - (see Table 1). Mean values and standard errors. Dotted lines join isocapnic values.

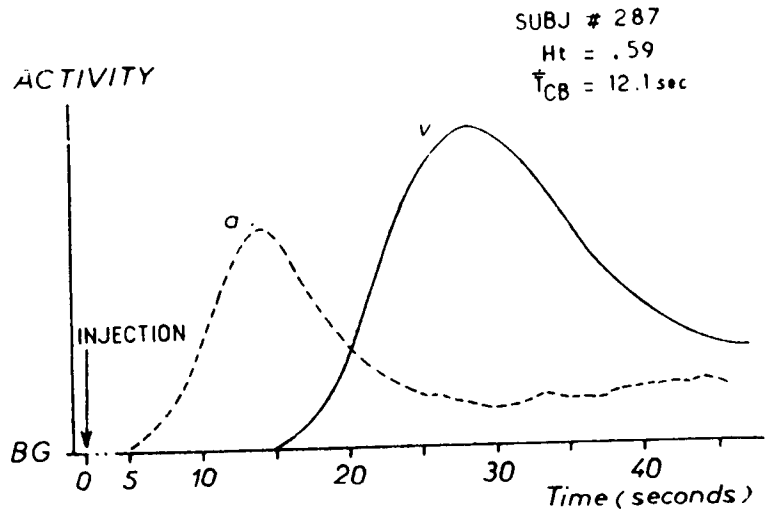

Fig. 4. Dilution curves obtained after intravenous injection of 1 mC $^{99m}T_c$. (a) counting rate on the right subclavian artery; (v) counting rate on the torcular Herophili—Ht: venous hematocrit; $\bar{T}_{CB}$: calculated mean cerebral circulatory transit time.

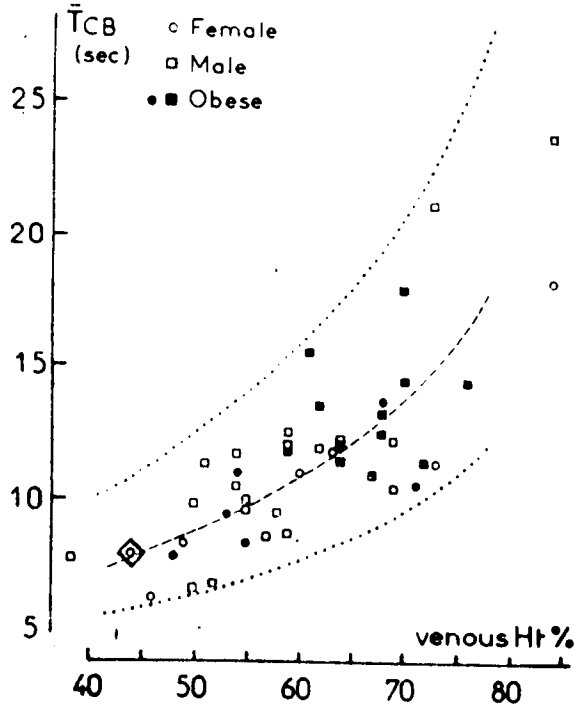

Fig. 5. Mean cerebral circulatory transit time ($\bar{T}_{CB}$) of high altitude residents in sitting posture as a function of the venous hematoerit (Ht); Individual values■. Mean value and standard errorat sea level are given for comparison◇.

local mean transit time are not in contradiction with the increase in blood vessel density reported by morphologists; it suggests a decrease in blood velocity.

PART 4

During the last few years, investigators have shown an increasing interest in CSF pH regulation, since pH value of extracellular cerebral fluid is thought to be the regulating factor of both pulmonary ventilation and cerebral blood flow.

High altitude natives possess a particular acid-base balance which corresponds to a chronic state of both hypocapnia and hypoxia. Studies carried out in such subjects have yielded rather conflicting conclusions as far as CSF pH is concerned. According to some authors CSF pH remains normal (Severinghaus & Carcelen, 1964; Lahiri & Milledge, 1967) whereas according to others it tends to be low although pH_a has returned to its normal value (Sorensen & Milledge, 1971).

The main purpose of the 4th part of the present study was to further investigate the acid-base balance of HL CSF.

Twenty young male adult volunteers were investigated. In 11 lumbar CSF and in 9 cisternal CSF were sampled and analysed for lactate, glucose, P_{O_2}, P_{CO_2} and pH; [HCO^{3-}] being computed according to the Henderson-Hasselbach equation; simul-

taneously blood samples were drawn from the brachial artery and from the jugular bulb and the same determinations were made as in the case of CSF.

Table 3. *Oxygen and carbondioxide pressures* (P_{O_2}, P_{CO_2}), *pH and bicarbonate concentration* [HCO^{3-}] *in arterial blood (a), jugular bulb (vj) blood and in cerebrospinal fluid either cisternal* (CSF_C) *or lumbar* (CSF_L) *in two groups of high altitude residents; "cisternal" : 9 subjects mean age* 24.5; *"lumbar" : 11 subjects mean age* 25.0.

CISTERNAL

P_{O_2} mmHg			P_{CO_2} mmHg			pH			[HCO^{3-}]meq/l		
a	vj	CSF_C	a	vj	CSF_C	a	vj	CSF_C	a	vj	CSF_C
56.6	28.0	32.0	31.0	41.8	37.3	7.413	7.349	7.366	20.04	23.18	20.46
±1.0	0.6	0.8	0.5	0.7	0.8	0.008	0.010	0.008	0.53	0.66	0.68

LUMBAR

P_{O_2} mmHg			P_{CO_2} mmHg			pH			HCO^{3-}]meq/l		
a	vj	CSF_L	a	vj	CSF_L	a	vj	CSF_L	a	vj	CSF_L
59.4	32.1	25.0	32.7	41.4	44.0	7.414	7.370	7.317	22.11	23.91	21.38
±0.8	1.4	0.5	2.1	2.0	2.8	0.005	0.004	0.006	0.36	0.33	0.37

Measurements were made in sitting position. Mean values ± standard error.

Table 4. *Lactate and glucose concentrations in arterial (a) and jugular bulb (vj) blood and in cisternal cerebral fluid* (CSF_C).

LACTATE mMol.l^{-1}			GLUCOSE g.l^{-1}		
a	vj	CSF_C	a	vj	CSF_C
1.14	1.16	1.85	.88	.77	.69
±.10	.07	.17	.11	.12	.07

Measurements made in 9 high altitude residents. Mean values and standard error.

Results, summarized in Tables 3 and 4, mainly show a significant lack of homogeneity n CSF, except for [HCO^{3-}]. Value of pH in cisternal fluid does not significantly differ from SL (Van Heijst, Maas & Visser, 1966), whereas it is lower, although not significantly, when it is measured in spinal fluid. Lactate concentration, measured by enzymatic technique, in cisternal fluid is comparable to SL value.

It is also worth noticing that neither cisternal nor spinal fluids are in equilibrium with jugular blood.

Such discrepancies between lumbar and cisternal CSF pH have been demonstrated at SL (Plum & Price, 1973; Van Heijst *et al.*, 1966). However they appear to be larger at HA in accordance with a broader P_{CO_2} difference. This heterogeneity in CSF probably arises from local differences in metabolic rate and blood perfusion; a decrease in HL $\dot{Q}_C$, mainly in sitting posture, would tend to broaden such differences.

As a conclusion one may say that at HA:

— Hypocapnia in cisternal fluid (and in arterial blood) is associated with a decrease in [HCO^{3-}] so that the pH value does not differ from that observed at SL, and lactate concentration does not account for the decrease in [HCO^{3-}]

— Some of the differences between lumbar CSF pH values previously and presently reported could be explained by the fact that in this study CSF samples were taken in sitting posture, thus further reducing HL brain perfusion.

— The existence of a consistent inhomogeneity of CSF acid-base content emphasizes the difficulty of using any CSF pH to estimate local extracellular pH in the central nervous system.

SUMMARY

Cerebral blood flow ($\dot{Q}_C$), local arterio-venous oxygen difference (O_2 AVD); and pH, O_2 and CO_2 partial pressures in arterial and jugular blood and in lumbar and cisternal cerebrospinal fluids (CSF) were measured in subjects born and residing at high altitude (3,800 — 4,800 m). $\dot{Q}_C$ was determined by ^{85}Kr wash-out. Studies were made while subjects were breathing room air as control, while breathing gas mixtures or while voluntarily hyperventilating to alter Pa_{O_2} and/or Pa_{CO_2}. (1) $\dot{Q}_C$ control values are lower than at sea level, O_2 AVD larger and cerebral oxygen consumptions identical; cerebral respiratory quotient is close to 1.0, lactic acid production is negligible and glucose uptake fits with the local O_2 consumption. (2) $\dot{Q}_C$ as function of Pa_{CO_2} describes a curve similar to that obtained at sea level but with a higher setting : therefore, for a given Pa_{CO_2}, $\dot{Q}_C$ is higher in highlanders than in lowlanders Correction of altitude hypoxia reduces highlanders' $\dot{Q}_C$ to a lower value. Conversely, when deeper hypoxia is induced, $\dot{Q}_C$ rises above control values. This influence of Pa_{O_2} on $\dot{Q}_C$ contrasts with what is observed at sea level. (3) A curvilinear relationship is found between cerebral mean circulatory transit time and hematocrits ranging from .35 to .84: sea level values fall on the same curve. Cerebral red cell flow is comparable at sea level and at altitude. (4) A consistent difference is found between cisternal and lumbar CSF : pH, and P_{O_2} are lower in lumbar CSF and P_{CO_2} higher than in cisternal fluid, whereas [HCO^{3-}] is not significantly different at the two sites: CSF heterogeneity is larger in highlanders than in lowlanders. Cisternal pH was not significantly different from sea level values.

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DISCUSSION

Purves: Would you like to give an estimate of the precision of your method of measuring cerebral blood flow at altitude? You showed a slide in which when you had high oxygen to breathe the slope returned and slightly overshot the control one? You suggested that this was significantly lower than the control one.

Durand: Yes during O_2 breathing CBF decreases if simultaneous changes in Pa_{CO_2} are taken into account. It also should be noted that during O_2 breathing CBF values were figured out using cerebral O_2 AVD and assuming that cerebral O_2 consumption was not altered by such a manoeuvre.

Purves: How close do your values lie with repeated estimations?

Durand: About 12% ($\pm$ 6%) for CBF and 4% for O_2 blood contents.

Semple: I think although you have shown a precise difference between lumbar and cisternal CSF — I am sure there is a precise difference between cisternal and brain extra cellular fluid — I don't think you or anybody else has produced evidence that changes in these fluids are accurately reflected in lumbar CSF.