Effects of Venesection on Cerebral Function in Chronic Lung Disease

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SUMMARY: *Regional cerebral blood flow measurements and neuropsychological testing were conducted before and after venesection on 6 patients with polycythemia secondary to chronic obstructive pulmonary disease. Venesection resulted in lowered viscosity and hematocrit, and an accompanying improvement in cerebral perfusion and mental function. Blood flow was significantly increased in the left cerebral hemisphere following phlebotomy, and there was significant improvement in sensory/mental function. Cerebral function would appear to be related to blood flow alterations influenced by the viscosity of the blood.*

RÉSUMÉ: *Nous effectuames, chez 6 patients avec polycythémie secondaire à une maladie pulmonaire obstructive chronique, des mesures du flot cérébral régional et des tests neuropsychologiques, avant et après venesection. La procédure résulta en une diminution de la viscosité et de l'hématrocrite, ainsi qu'en une amélioration de la perfusion cérébrale et de l'état mental. A la suite d'une phlébotomie, le flot sanguin fut augmenté significativement dans l'hémisphère cérébral gauche et il y eut une amélioration significative des fonctions sensitivo-mentales. Les fonctions cérébrales semblent donc en relation avec les altérations du flot sanguin provoquées par des modifications de la viscosité du sang.*

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INTRODUCTION

Previous investigation has indicated that patients suffering from polycythemia have subnormal cerebral blood flow (CBF) (Thomas et al, 1977; York et al, 1980). These low flows appear to be related to an elevated hematocrit (hct) with an associated increase in blood viscosity. It has also been shown that treatment by venesection which results in a lowered hct and viscosity is correlated with an increase in flow. Previous investigations of the effects of venesection on CBF have reported only global flow values, or supra- and subtentorial flows. There has been no examination of lateralized or regional changes in CBF.

It has also been shown that patients with chronic obstructive pulmonary disease (COPD) have impaired neuropsychological function (Grant et al, 1980). The functions most frequently impaired were perceptual motor integration, abstracting and motor skills. A recent report by Willison et al (1980) concluded that the mental state of patients with even modest degrees of polycythemia improves following phlebotomy. These improvements were demonstrated by a limited battery of four "alertness" tests which did not purport to examine higher cortical function. In the present study, a broad range of neuropsychological tests and CBF measurements were used to examine the effects of phlebotomy on cerebral function in patients with polycythemia secondary to COPD.

METHODS

A total of 6 subjects (5 male, 1 female) with a mean age of 45 ± 19.6 years (Mean ± SD) were studied. Prior to venesection, each patient underwent one regional CBF measurement, and a brief neuropsychological assessment. Following each flow study, an arterial blood sample was drawn for blood gases, hct and viscosity determination. In addition, pulmonary function was assessed by complete pulmonary function testing including the maximum expiratory flow-volume curve. This entire sequence of tests was repeated following venesection.

REGIONAL CBF

Flow was measured using the non-invasive Xenon 133 inhalation technique. Eight regions of the brain were monitored in each hemisphere. The method is ideal for repeated studies, as the absorbed radiation is minimal, being approximately 100 mrads per study. The technique of measurement, system description and normal results are published elsewhere (Menon and Weir, 1979). The flow index used for this study is ISI, the initial slope index of Risberg (Risberg et al, 1975).

NEUROPSYCHOLOGY

An extensive battery of neuropsychological measures has been developed (Reitan and Davison, 1974), but consumes approximately 6-7 hours for administration of the complete battery. In order to minimize fatigue, a selected group of measures was administered. These were the Wechsler Memory Scale (forms I and II), Trail Making Test, Seashore Rhythm Test, Knox Cube Test, Motor Steadiness Test, Raven's Progressive Matrices, Finger Tapping Test, Grooved Pegboard Test, Grip Strength and the Reitan-Klove Sensory Perceptual Examination. Total time for the administration of this battery was approximately 2½ hours. The test-retest interval was approximately 2-3 weeks. Although practice effects may be possible for some measures (Trail Making, Raven's

Matrices), this is not likely for most of them. Alternate forms of the Wechsler Memory Scale were used to minimize practice on this measure.

HEMATORRHEOLOGY AND PULMONARY FUNCTION

An arterial blood sample was drawn from a radial artery to obtain blood gases, hct, hemoglobin and viscosity. Measurements of these were repeated until consecutive measurements yielded results within 5% of each other.

Viscosity was determined by using a Wells-Brookfield Micro-Viscometer; 8 ml. of heparinized blood at a shear rate of 225 sec^{-1} and at 37°C were used (Dormandy, 1970). Blood gases were determined by an IL 133 analyzer. Hct was measured with a microhematocrit tube (Wintrobe, 1974), and was expressed as a percentage of whole blood.

The maximum expiratory flow volume loop was used to assess lung function. The forced vital capacity (FVC) was $\dot{V}_{50}$ and $\dot{V}_{75}$, the flow rates after 50% and 75% respectively, of the forced vital capacity had been exhaled, were measured.

RESULTS

The effects of phlebotomy on blood viscosity, hct and arterial pO_2 and pCO_2 are demonstrated in Table 1. Although the mean hct after venesection is still in the above-normal range, there has been a significant reduction ($p<0.05$) from the pre-venesection values. Phlebotomy has also significantly reduced blood viscosity. A one-tailed Student's t-test has been employed for the analysis. Only p values less than 0.05 are considered to be statistically significant. On the basis of a flow-volume loop (Table 2) and arterial blood gases (Table 1), there is little change in pulmonary function from before to after venesection.

The alterations in CBF patterns following venesection are summarized in Table 3 and Figure 1. Hemispheric changes are documented in Table 3; the left hemisphere flow is significantly increased ($p<0.05$) while the increase in the right hemisphere is not statistically significant. Regional changes are demonstrated in Figure 1. Areas where significant increases were

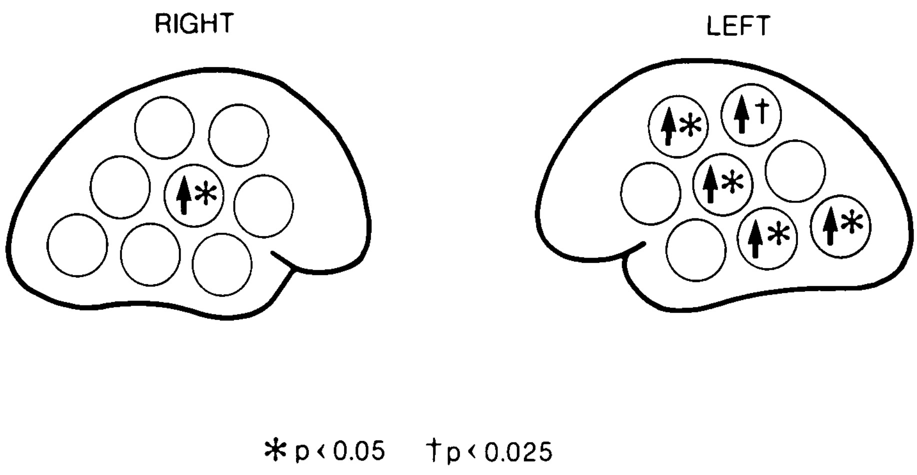

Figure 1 — Changes in regional cerebral blood flow. Five of 8 regions on the left side and 1 of 8 on the right had significantly increased flows after phlebotomy, as the arrows indicate. (* increase significant at the 95% level; † increase significant at the 97.5% level)

TABLE 1

Change in Hematocrit, Viscosity and Blood Gases

	Pre-venesection	Post-venesection	p*
Hematocrit (%)	53.5 ± 3.62	48.1 ± 2.62	<0.05
Viscosity (centipoises)	5.11 ± 0.18	4.35 ± 0.39	<0.025
pCO_2 (mm Hg)	45.2 ± 2.92	43.9 ± 4.77	NS
pO_2 (mm Hg)	56.7 ± 5.50	56.2 ± 4.71	NS
pH	7.43 ± 0.014	7.24 ± 0.019	NS

All values are expressed as mean ± 1 S.D.

* p-value indicating level of significance of change from pre- to post-venesection value; NS: not significant

TABLE 2

Changes in Pulmonary Function

	Pre-venesection	Post-venesection	p††
FVC (liters)*	2.33 ± 0.94	2.20 ± 0.64	NS
$\dot{V}_{50}$†	1.65 ± 2.05	1.19 ± 1.38	NS
$\dot{V}_{75}$†	0.49 ± 0.50	0.53 ± 0.61	NS

All values are expressed as mean ± 1 S.D.

*FVC: forced vital capacity

†$\dot{V}_{50}$: flow at 50% FVC; $\dot{V}_{75}$: flow at 75% FVC

††p — value indicating level of significance of change from pre- to post-venesection values; NS: not significant

registered are marked with arrows. There is clearly a lateralized increase, with 5 of 8 detectors on the left showing significant changes, as compared to only 1 of 8 on the right.

Results of neuropsychological testing are contained in Table 4. Clearly, there are several measures that demonstrate significant improvements following venesection. On some matters (WMQ, Raven's Matrices and Finger Tapping) higher scores indicate improved performance while in the remaining measures improvement is indicated by reduced scores. Although the improvements observed on Raven's Matrices and the Trail Making Tests may be due in part to practice effects, it is unlikely that such is the case in motor and sensory measures. It is interesting, therefore, that the right hand sensory and motor measures improved significantly while no such improvement was observed on the left hand trials of the identical tasks. At the same time, these motor and sensory function improvements are consistent with the improvement in the left hemisphere perfusion. On a more focal level, the individual detectors which show increased flow appear to overlie the sensory-motor cortex of the left hemisphere, as one would expect from the neuropsychological test results.

TABLE 3

Changes in Hemispherical Blood Flow

	Pre-venesection	Post-venesection	p†
Left hemisphere ISI*	34.8 ± 6.0	37.8 ± 8.3	<0.05
Right hemisphere ISI*	35.2 ± 6.3	37.8 ± 8.6	NS
Global ISI*	35.0 ± 8.0	37.8 ± 8.1	<0.01

All values are expressed as mean ± 1 S.D.

*ISI: initial slope index

†p — value indicating level of significance of change from pre- to post-venesection value; NS: not significant

TABLE 4

Changes in Neuropsychological Performance

Variable	Pre-venesection	Post-venesection	p††
WMQ*	94.5	101.17	NS
Raven's Matrices	38.2	43.6	<0.05
Trails A (Time)†	41.2	30.2	<0.05
Trails B (Time)†	129.6	102.4	NS
Pegboard (Right)	94.5	85.17	<0.01
Pegboard (Left)	102.5	82.84	NS
Fingertap (Right)	39.84	43.67	<0.025
Fingertap (Left)	38.17	39.84	NS
Sensory (Right)	6.34	2.00	<0.01
Sensory (Left)	3.34	1.34	NS

* Wechsler Memory Quotient

† Parts A and B of the Trailmaking test

††p — value indicating level of significance of change from pre- to post-venesection value

NS: not significant

DISCUSSION

This study shows that venesection results in a reduction of blood viscosity and hct, and that concomitant increases in CBF and improvements in mental function take place. That flow increases take place following venesection has been demonstrated before; however, previous work has only demonstrated global, supra- or subtentorial increases (Thomas et al, 1977; York et al, 1980). The effects of the procedure on neuropsychologic performance has been documented but with a more limited battery of tests than those used here (Willison et al, 1980). These authors reported that their patients did not complain of difficulties in higher cortical function, but Grant et al (1980) have reported that patients with COPD do have deficits on a wide range of psychological tasks.

The post-venesection hct in the present group of patients was still above the normal range, although it had been lowered by venesection. This post-venesection mean was the same as that reported by Grant et al (1980) in their series of patients with COPD. They concluded that there appeared to be no relationship between hct and neuropsychological function. Our results, on the contrary, demonstrate that improvements in test performance as well as in CBF occur in association with reductions in hct and viscosity. Flow, though improved relative to pre-venesection levels, did remain subnormal; similarly, post-venesection neuropsychological performance was subnormal. This finding tends to corroborate the finding of Grant et al (1980) that there was some degree of mental impairment in his group of COPDs.

The pulmonary function tests once again corroborate previous impressions that there is no substantial change in lung function after venesection as measured by mechanical lung performance or arterial blood gases. The patients, due to their impaired lung function, will show CBF values that are artifactually slightly reduced because of the method of CBF measurement employed (York et al, 1980).

Grant et al (1980) were unable to suggest a physiological basis for their findings of mental impairment in

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COPD. The present study suggests that elevated hct levels are related to depressed flows, and that this in turn is the physiological mechanism underlying the mental impairment.

The role of hct in mental performance has been previously studied in a series of patients undergoing carotid endarterectomy. Bornstein et al (1980) found that in a group of 55 cases, hct measured prior to endarterectomy was related to post-operative mental improvement. Patients with hct<46.5% improved on a significantly greater number of measures than those with hct>46.5%.

A final point, and a key one at that, is our finding that improvements in both measures of cerebral function — regional CBF and neuropsychological tests — implicate the left cerebral hemisphere. The very close relationship between the improvement in sensory/motor function and the regional increases within the left hemisphere strongly argue against any artifact of measurement. The reason for such a lateralised improvement in cerebral function is not obvious at this time. However, a recent report by Gur et al (1980) has suggested that the cerebral hemispheres differ in neural organization. This may in some way be related to a differential response to venesection. There is obviously a need for a much larger study with more subjects, and hopefully a much wider range of hct. Such an approach could exand on our findings and perhaps explain the lateralized hemispheric involvement.

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