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## Measurement of Regional Cerebral Blood Flow, Blood Volume and Oxygen Metabolism in Patients with Sickle Cell Disease Using Positron Emission Tomography

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**SUMMARY** Regional cerebral blood flow, blood volume, fractional oxygen extraction and oxygen consumption were measured by positron emission tomography in six patients with sickle cell disease to see how oxygen delivery to the brain is maintained in the presence of both anemia and a low oxygen affinity hemoglobin. Both regional cerebral blood flow and blood volume were found to be markedly increased compared to values obtained from 14 normal subjects in the same age range. The mean fractional oxygen extraction was not significantly different in the two groups. Mean oxygen consumption in the two groups was also not significantly different but low values in individual patients with sickle cell disease and the presence of atrophy on the CT-scans of three of them were suggestive of some neuronal loss in patients without any history of nervous system involvement. In view of the known high values of cerebral blood flow and metabolism in childhood, it is suggested that when compounded by anemia and abnormal red cells, a hypercirculatory state may make patients in this age-group particularly prone to ischemic infarction.

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STROKE is a relatively common complication of sickle cell disease and contributes substantially to its morbidity and mortality. A recent natural history study, the first in which the nature of the cerebrovascular lesion was established in most patients by CT-scanning, reported a stroke incidence of 6% for all ages.<sup>1</sup> Two thirds of these patients had suffered ischemic cerebral infarction. Infarcts occurred mainly during childhood and adolescence (mean age 7.7 years) and were often repetitive, as had been observed in previous studies.<sup>2-4</sup> Exchange transfusion regimes have been used with some success to prevent the recurrence of strokes and to improve existing neurological deficits in the survivors<sup>4-6</sup> even reversing angiographic abnormalities in some cases.<sup>5</sup>

Although some early reports described pathological

changes in the walls of the larger intracranial arteries,<sup>7,8</sup> later authors generally attributed the ischemic infarction in sickle cell disease to small vessel involvement leading to multiple microinfarcts.<sup>9</sup> However, when it had been shown that angiography could safely be performed after prior exchange transfusion,<sup>10</sup> more and more reports again described occlusions and stenosis of major intracranial vessels in the majority of patients with ischemic infarcts studied.<sup>5,6,10-13</sup> Intimal hyperplasia, often combined with medial fibrosis and hyalinization, was found to be causing the obstructions.<sup>7,8,11,12</sup> Explanations of the origin of these changes and of the occurrence of infarction predominantly in the first two decades of life have, however, remained speculative.

Positron emission tomography (PET) now offers the means to measure regional cerebral blood flow (CBF), oxygen extraction ratio (OER), oxygen utilization (CMRO<sub>2</sub>) and cerebral blood volume (CBV) non-invasively in absolute values. Recently, important information about the pathophysiology of cerebral ischemia has been obtained with this method. In acute stroke it has been shown that when cerebral blood flow falls in relation to the tissue's oxygen requirements, the fraction of oxygen extracted from the blood can rise from

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its normal level of 35–45% to more than 90%.<sup>14</sup> Raised oxygen extraction ratios of a lesser degree have been observed in some patients with occlusive carotid artery disease, implying a state of chronically reduced arterial oxygen reserve.<sup>15, 16</sup>

Sickle hemoglobin (hemoglobin S) has a lower oxygen affinity than hemoglobin A when studied in its natural plasma environment.<sup>17</sup> This should in theory facilitate the unloading of oxygen in the tissues.

We therefore carried out PET-studies in a group of patients with sickle cell disease to investigate how oxygen delivery to the brain is maintained in an anemic state in the presence of a low oxygen affinity hemoglobin. It was hoped to establish in particular whether the better unloading properties of hemoglobin S would lead to an increase in the fraction of oxygen extracted from the blood, and whether there is ever a chronic state of critically reduced cerebral oxygen supply in patients with sickle cell disease.

### Patients and Methods

#### Patients

As we are not authorized to administer radioactive substances to children, a group of young adults was studied. Six patients with sickle cell disease (one female and five males), regularly seen by one of the authors (MB) at her sickle cell clinic at Central Middlesex Hospital, volunteered for the study. They ranged in age from 20 to 43 years. Hemoglobin electrophoresis had demonstrated homozygous sickle cell disease in all patients. One subject (study No. 912) was in addition homozygous for  $\alpha_2$  thalassemia. At the time of the study, patients were in a steady clinical condition with no indications of infection or crisis.

Only one of the patients (study No. 912) had a history of neurological symptoms: these took the form of repeated confusional episodes, the last of which had occurred seven months before the study. A full neurological examination was performed prior to each study and was normal in all cases. However, it was noted that all patients had dilatation of the retinal veins. The clinical severity of the disease, as estimated by the number of hospital admissions per year of follow-up ranged from mild (studies Nos. 906 and 946) to severe (study No. 912).

In addition to the PET-study, all patients had a CT-scan without administration of contrast medium. At the beginning of each PET-study, blood samples were taken for a full blood count including the number of irreversibly sickled cells (ISC) and for measurements of whole blood viscosity. Levels of hemoglobin F (HbF) and hemoglobin A<sub>2</sub>, both of which are known to be fairly constant during life in the individual, had been determined earlier.

The results from the six patients with sickle cell disease were compared with those obtained from 14 healthy normal volunteers in the same age range. The mean age, arterial hemoglobin, paO<sub>2</sub>, paCO<sub>2</sub>, arterial oxygen saturation and arterial oxygen content of each group is given in table 1.

TABLE 1 Baseline Physiological Data for Patients with Sickle Cell Disease and Normal Controls

	Normal controls	Patients with sickle cell disease
Number	14 (9M, 5F)	6 (5M, 1F)
Hb (g/100 ml)	13.6 ± 1.4	8.1 ± 1.1*
paCO <sub>2</sub> (kPa)	5.5 ± 0.3	5.2 ± 0.2
paO <sub>2</sub> (kPa)	12.0 ± 1.6	11.1 ± 1.2
Art.O <sub>2</sub> -saturation (%)	96.6 ± 0.9	96.0 ± 1.0
Art.oxygen content (ml/100 ml)	18.5 ± 1.9	11.0 ± 1.7*
Age	34.3 ± 7.0	27.5 ± 8.7

Mean ± SD.

M = male; F = female.

\*Significantly different from normal controls;  $p < 0.01$ .

One patient (study No. 912) had been partially exchange-transfused two months before the study. However, it was calculated that at the time of the study, the level of hemoglobin A in his blood was certainly not more than 15%. The other patients had not had transfusions for more than three months prior to the study.

#### Methods

##### PET-scanning

Regional cerebral blood flow (CBF), oxygen extraction ratio (OER) and oxygen utilization (CMRO<sub>2</sub>) were measured using positron emission tomography and the oxygen-15 steady state inhalation technique.<sup>18</sup> The method involves performing two separate emission scans during the continuous inhalation of oxygen-15 labelled carbon dioxide and molecular oxygen respectively for the measurements of CBF and OER. During the scans, serial blood samples are taken via a fine-gauge radial artery cannula to measure arterial isotope activity and arterial oxygen content (O<sub>2</sub>C). Oxygen utilization can then be calculated from the relationship  $CMRO_2 = CBF \times OER \times O_2C$ . Regional cerebral blood volume (CBV) was measured by an additional emission scan after labelling the red cells with trace amounts of inhaled carbon-11 labelled carbon monoxide.<sup>19, 20</sup> The measurement of CBV gives important physiological information in itself but is also used to correct the OER measurement for the effects of non-extracted hemoglobin-bound oxygen-15.<sup>21</sup> The scans were performed using an 'ECAT-II' (EG & G Ortec) PET scanner with a spatial resolution of  $16.7 \times 16.7 \times 16$  mm at full width half maximum.<sup>22</sup> Emission data were collected from two standard transaxial planes 4.5 and 6.5 cm above and parallel to the orbitomeatal line. All emission scans were corrected for the effects of tissue attenuation by corresponding transmission scans using an external ring source.<sup>18</sup>

##### CT-scanning

Conventional unenhanced CT scanning was performed with a Siemens Somatom 2 whole body scanner (125 kVp, 230 mAs). Scanning time was 10 sec/plane, the slice thickness 8 mm. Scans were performed in 8 mm steps parallel to the orbitomeatal line.

### Viscosity Measurements

Whole blood viscosity was measured at low shear rates (0.13, 0.775, 1.993 sec<sup>-1</sup>) on a Contraves LS100 rotational viscometer at 37°C. Viscosity was not measured in the group of normal controls. The results of the viscosity measurements of the patients with sickle cell disease could therefore be compared only with standard normal data from the laboratory where the measurements were performed.

### Calculation of Arterial Oxygen Content

As we did not have the opportunity to measure arterial oxygen saturation or oxygen content directly, arterial oxygen saturation (O<sub>2</sub>S) was derived from measured arterial pO<sub>2</sub> using a nomogram based on the standard dissociation curve according to J.W. Severinghaus<sup>23</sup> with temperature and pH corrections according to P. Astrup.<sup>24</sup> Arterial oxygen content was then calculated from the relationship:

$$O_2C = 1.39 \times Hb \times \frac{O_2S}{100} + 0.00315 \times pO_2^{25}$$

The indirect calculation of oxygen saturation probably led to a slight overestimation of O<sub>2</sub>C in the subjects with sickle cell disease. The standard nomogram for calculating oxygen saturation from the pO<sub>2</sub> assumes a normal affinity hemoglobin, and our calculated saturations were very similar for both the patients and normal subjects (table 1). However, direct measurements of oxygen saturation in sickle cell disease have demonstrated arterial desaturation; a mean value of 86.6% arterial oxygen saturation was measured in 14 samples from ten patients<sup>26</sup> which is about 10% lower than our calculated values. A 10% overestimation of the arterial oxygen saturation leads to an almost identical overestimation of the arterial oxygen content and consequently CMRO<sub>2</sub>. These estimated corrections cannot be applied directly to our patient group, but it is likely that the true values for O<sub>2</sub>C and CMRO<sub>2</sub> in the sickle cell cases were somewhat lower than those obtained.

### Data Analysis

The objective method of 'cortical plotting,'<sup>14</sup> having proved useful for the analysis of data from patients with acute and chronic cerebrovascular disease,<sup>14, 15</sup> was applied in this study. Values were obtained from a strip of twelve contiguous rectangular blocks 7.5 × 15 mm corresponding to the superficial distribution of the middle cerebral artery in each hemisphere (schematically shown in fig. 1). The reported values for CBF, OER, CMRO<sub>2</sub> and CBV were obtained by calculating the mean from both hemispheres and both planes. Statistical analysis was performed using Bonferroni t tests for multiple comparisons.

The study was approved by the Hammersmith Hospital Ethics Committee and the Brent Ethical Committee (Central Middlesex Hospital). Permission for the administration of radioisotopes was given by the UK Administration of Radioactive Substances Advisory

Committee. The informed consent of each patient and normal volunteer was obtained prior to the study.

## Results

### CT-scans

Three patients had entirely normal CT-scans. Two scans showed mild generalized atrophy with widening of the cortical sulci and the Sylvian fissures and some enlargement of the ventricles. One of these scans was obtained from the patient with a history of repeated confusional states (study No. 912), the other one from the eldest patient in the study (study No. 946). The third abnormal scan showed moderate generalized atrophy (more marked than in the other two cases) as well as a large area of focal atrophy in the left high parietal region (study No. 883). This scan was obtained from a 26 year old patient with no history of any symptomatic nervous system involvement.

### PET-scans

Figure 1 shows the mean values of cerebral blood flow, oxygen extraction ratio, oxygen utilization and cerebral blood volume for the six patients with sickle cell disease and 14 normal controls. Additionally the ratio CBF/CBV was calculated, since there is evidence that this relationship provides an approximate index of cerebral perfusion pressure<sup>15, 16</sup> when the oxygen-15 steady state inhalation technique is used.

Patients with sickle cell disease showed a markedly increased cerebral blood flow. This was matched by an increase in cerebral blood volume of similar magnitude, such that the ratio CBF/CBV did not differ significantly between patient and control group. Mean OER and mean CMRO<sub>2</sub> were also not significantly different in the two groups.

On analysis of the physiological images in each case, no obvious focal defects were seen. A difference in CBF between the two hemispheres exceeding the maximum difference in the normal group (up to

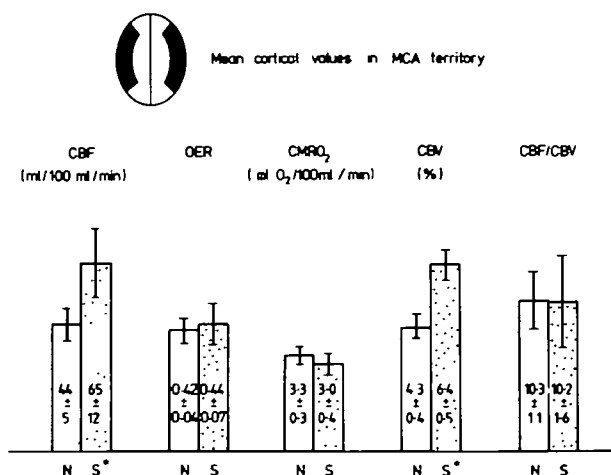


FIGURE 1. Mean cortical values (± SD) in middle-cerebral artery territory for cerebral blood flow (CBF), oxygen extraction ratio (OER), oxygen utilization (CMRO<sub>2</sub>), cerebral blood volume (CBV) and the CBF/CBV ratio in six patients with sickle cell disease and 14 normal controls. \*Significantly different from normal controls; p < 0.01.

12.7%) was found in only one patient (study No. 883) in whom flow in the left hemisphere was 15.2% lower than on the right side. These data were obtained from the patient with an area of focal atrophy in the left parietal region on the CT-scan. However, asymmetry of CMRO<sub>2</sub> in this patient (also lower on the left) was not outside the range encountered in normal subjects (maximum 17.2%).

Data of the individual patients and some of the relevant hematological variables are given in table 2. CBF-values showed a slight overlap with the normal group, the CBV-values no overlap at all. The CBF/CBV ratio was slightly reduced in two patients. In three patients, values for CMRO<sub>2</sub> lay at or below the lower limit encountered in the normal subjects.

Figure 2 shows the relationship between the rate of oxygen supply to the brain ( $\text{CBF} \times \text{O}_2\text{C}$ ) and its consumption by the tissues (CMRO<sub>2</sub>). In four of the six patients, CBF had increased to such an extent that oxygen delivery was maintained at a level well within the normal range, matched to oxygen requirements, such that the OER was normal. In two patients, the rate of oxygen supply in the arterial blood was slightly below the normal range, delivery to the tissues being maintained by a marginal rise in OER.

Figure 3 gives a plot of CBF against the amount of hemoglobin in the arterial blood. A rise in CBF with falling hemoglobin levels is clearly demonstrated. It did not seem feasible to pool data from hemoglobins with different physical properties into one statistical analysis. For patient and control group considered alone, however, the relationship between CBF and hemoglobin level and also the relationship between CBF and arterial oxygen content was not statistically significant, probably because of the small numbers involved.

Because of the anemia, whole blood viscosity uncorrected for hematocrit was predictably below normal in all patients with sickle cell disease. The values at a shear rate of 0.775 sec<sup>-1</sup> are given in table 2. Patients' whole blood viscosity at a shear rate of 0.13 sec<sup>-1</sup> ranged from 5.5–14.1 cP (normal 19.6–53.6), at a shear rate of 1.99 sec<sup>-1</sup> from 3.4–4.7 cP (normal 5.7–10.9). There was no significant correlation between CBF and blood viscosities at low shear rates. There was also no correlation between CBF or OER and the percentage of irreversibly sickled cells, the percentage of hemoglobin F, the percentage of hemoglobin A<sub>2</sub> (ranging from 1.3–5.2%), the mean corpuscular volume (ranging from 77–87 fl), the mean corpuscular hemoglobin (26.4–32.3 pg) or the mean corpuscular hemoglobin concentration (33.1–35.9%).

### Discussion

This study confirms that cerebral blood flow is substantially increased in patients with sickle cell disease, a finding which has been demonstrated both in sickle cell anemia and other kinds of anemia using other techniques for measuring CBF.<sup>27–30</sup>

Investigations of the response of CBF to changes in arterial oxygen content and blood viscosity in animals

and in humans have led to the conclusion that arterial oxygen content is the major determinant of CBF such that oxygen delivery to the tissues ( $\text{CBF} \times \text{O}_2\text{C}$ ) is maintained at constant levels.<sup>31–36</sup> A recent study, using the intravenous Xenon-133 clearance technique, has demonstrated a close inverse relationship between the total oxygen content of the arterial blood and CBF in patients with a wide range of hemoglobin values from severe anemia to moderate polycythemia;<sup>30</sup> multiple regression analysis of the data suggested that blood viscosity does not influence the level of cerebral blood flow once the arterial oxygen content is taken into account. Our results are consistent with the concept that the level of cerebral blood flow in anemic subjects is determined by the arterial oxygen content rather than by changes of blood viscosity. At the low viscosity values measured in the blood of the patients with sickle cell disease, viscosity is unlikely to cause much flow restriction. The relationship between CBF and hemoglobin level is clearly shown in Figure 3 although the different physical properties of the hemoglobins do not allow statistical analysis of the pooled data.

Previous PET studies have shown that in cortical regions similar to those studied here, cerebral blood flow and cerebral blood volume tend to be closely coupled in the normal brain.<sup>15</sup> Our findings show that this relationship is generally maintained even at the very high flow rates of these severely anemic patients. Uncoupling of CBF and CBV has been demonstrated in patients with carotid occlusive disease, in whom a presumed reduction of cerebral perfusion pressure is associated with increased CBV, while CBF remains constant or decreases.<sup>15, 37</sup> In this study, two patients with sickle cell disease showed a proportionally greater increase of CBV than of CBF, suggesting some reduction of cerebral perfusion pressure. In the context of carotid occlusive disease, it has been suggested that the observed increase of cerebral blood volume reflects mainly vasodilatation of existing vessels rather than neovascularization.<sup>15</sup> However, animal studies have shown that in frank hypoxia both the number of perfused capillaries and the capillary diameter can increase.<sup>38, 39</sup> Pathological examination of the brains of five patients with sickle cell disease and neurological involvement revealed dilatation of especially the pre-capillary arterioles to one and a half to four times their normal diameter.<sup>9</sup> Tortuosity and dilatation of the capillary network of the retina with microaneurysm formation and neovascularization has been observed in a great number of patients with sickle cell disease,<sup>40</sup> and all our patients showed dilatation of retinal veins. More recently, angiographic studies have demonstrated the presence of multiple collateral vessels in patients with sickle cell disease and cerebrovascular involvement, resulting in an appearance similar to Moya-Moya disease.<sup>12, 41</sup> Postmortem examinations of one of these cases showed numerous and dilated vessels in the basal ganglia.<sup>12</sup> Thus both vasodilatation and new vessel formation may contribute to the increase in CBV in sickle cell disease.

TABLE 2 Clinical Data, CT and PET Findings and Hematological Data in Six Patients with Sickle Cell Disease

Study No.	Age/Sex	No. of admissions per year of follow-up	Atrophy on CT-scan	CBF (ml/100 ml/min)	OER	CMRO <sub>2</sub> (ml O <sub>2</sub> /100 ml min)	CBV (%)	CBF/CBV	Hb (g/100 ml)
883	26/M	0.6	+	83.3	0.38	3.1	6.9	12.1	7.2
897	32/M	1.0	—	73.6	0.44	3.7	7.0	10.6	8.7
906	21/M	0.1	—	64.8	0.37	2.9	6.1	10.6	8.8
912	23/M	2.5	+	54.2	0.39	2.7	6.2	8.7	9.4
928	20/F	1.2	—	63.1	0.52	2.7	5.6	11.2	6.3
946	43/M	0.4	+	50.9	0.51	2.8	6.6	7.7	8.1
Range in normal group	23–47			35.9	0.34	2.8	3.6	8.9	10.5†
				54.4	0.48	3.8	5.0	13.0	15.2

\*No data available.

†Normal range of laboratory for PCVs from 37.5–54.0.

‡Two females mildly anaemic with Hbs of 10.5 g/100 ml and 11.2 g/100 ml respectively; for the remainder of the normal group the range was 12.8–15.2 g/100 ml.

O<sub>2</sub>C = oxygen content; ISC = irreversibly sickled cells.

Previous studies with the nitrous oxide method have shown cerebral oxygen utilization to be moderately reduced in patients with sickle cell anemia and other types of chronic anemia.<sup>27, 29</sup> In our studies, the difference in CMRO<sub>2</sub> between the patient group and the normal group did not reach statistical significance, probably because of the small numbers involved. However, two of our patients (studies No. 912 and 928), both in their early twenties, had a lower oxygen consumption than any of the normal controls. These low CMRO<sub>2</sub> values strongly suggest the presence of some ischemic neuronal loss even in patients without any history or signs of cerebro-vascular involvement. Further evidence for this is provided by the finding of atrophy on three of the CT-scans. To reinforce this point, it is likely that the true values of CMRO<sub>2</sub> in the sickle cell cases were somewhat lower than those ob-

tained. This is because of the potential overestimation of arterial oxygen saturation in the presence of a low affinity hemoglobin, as discussed earlier.

It has been suggested that in hemolytic anemias associated with low oxygen affinity hemoglobins, the effect of anemia may be compensated at least partly by an increased peripheral release of oxygen to the tissue.<sup>42</sup> Our findings do not show any evidence of such a mechanism: no significant difference in mean fraction-

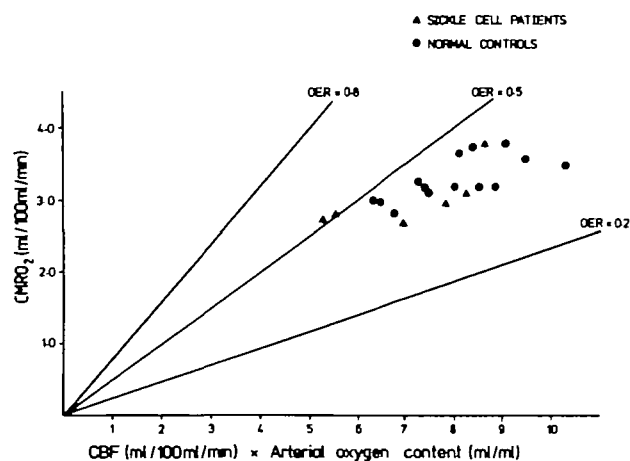


FIGURE 2. Relationship between cerebral oxygen utilization (CMRO<sub>2</sub>) and oxygen availability (CBF × O<sub>2</sub>C) in the middle-cerebral-artery territories from six patients with sickle cell disease and 14 normal controls. The slope of the relationship reflects the oxygen extraction ratio (OER).

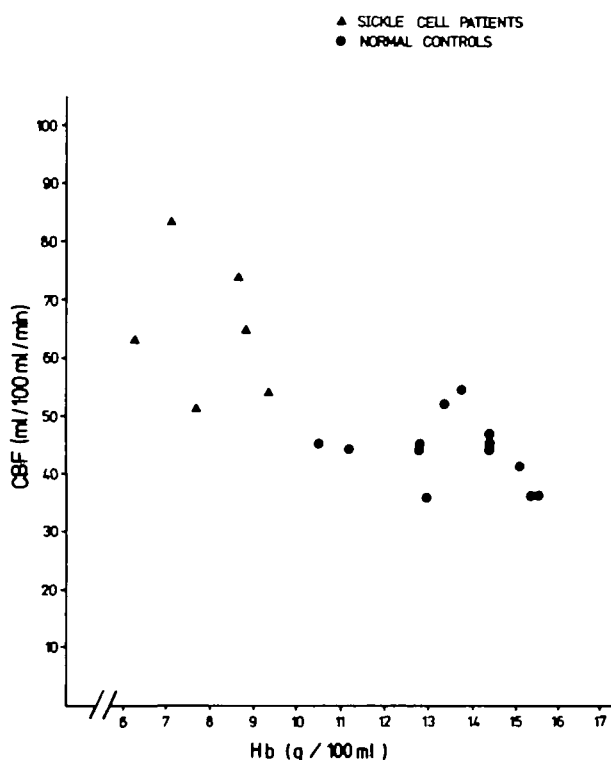


FIGURE 3. Relationship between hemoglobin concentration and cerebral blood flow in the middle-cerebral-artery regions in six patients with sickle cell disease and 14 normal controls.

TABLE 2 (Continued)

Arterial O <sub>2</sub> C (ml/100 ml)	Viscosity at 0.775 sec <sup>-1</sup> (cP)	PCV	ISC (%)	HbF (%)
9.9	—*	20.4	22	7.0
11.8	3.9	26.1	11	14.8
12.2	4.8	27.5	6	5.6
12.9	5.7	29.9	6	0.9
8.4	3.2	19.8	13	3.9
10.9	4.3	24.6	13	1.0
14.5	6.5†			
—	—			
20.7	16.5			

al oxygen extraction was found between our two groups, oxygen delivery being maintained in the anemic subjects by an increase in cerebral blood flow only. Diffusion of oxygen from blood to the tissues is determined by the partial pressure gradient between the two compartments. It therefore seems that the unloading properties of the hemoglobin will influence the OER only if affinity is high, leading to a limitation of transfer due to a small soluble oxygen concentration. If the affinity is low, soluble oxygen in the plasma will be adequate, resulting in a normal pO<sub>2</sub> gradient between blood and tissues and hence a normal OER. Our findings in patients with sickle cell disease (when studied in a stable clinical state) can thus be considered representative of anemic patients in general.

The study of a small number of neurologically normal young adults with sickle cell disease suffers from several shortcomings. Confident conclusions are difficult to make when differences between the anemic and normal subjects are only small, as in the case of oxygen metabolism. More important, the patients in this study were well beyond the age range in which the highest incidence of cerebral infarction is known to occur.<sup>1-4</sup> They were therefore unlikely to show features of any major cerebrovascular disturbance when studied in a stable clinical state during early adult life. The more marked predisposition to cerebral infarction in young children with sickle cell disease remains unexplained. Studies in animals and in normal human subjects have shown both cerebral blood flow and metabolism to be significantly higher in childhood than in adulthood.<sup>43-47</sup> It is speculated that children with sickle cell disease would need to meet the increased oxygen demands of their age with even higher flows than we found in our series of young adults. A hyperdynamic circulation not only leads to greater vulnerability in situations of hypotension and hypovolemia but may also increase the risk of physical damage to the endothelium by sickled cells. This in turn may result in the intimal hyperplasia which has been found to be the major cause of the vascular obstructions in sickle cell disease.

Faster PET-scanners and tracer techniques will reduce duration and radiation dose of PET-studies in the

near future. Such studies might then more readily be justified in young children with severe sickle cell disease who are known to be at risk from stroke. Our demonstration of normal coupling between cerebral blood flow and oxygen metabolism (as expressed in the OER) and between cerebral blood flow and blood volume (as expressed in the CBF/CBV ratio) gives the baseline physiological information for the assessment of pathology. As in adult patients with occlusive carotid artery disease, PET could provide a useful tool in helping to identify children at risk of stroke and in assessing the optimal duration of exchange transfusions and other therapeutic strategies.

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