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Cortical Blood Flow and Reactivity in Systemic Lupus Erythematosus

■ Neurological complications of systemic lupus erythematosus (SLE) may be associated with abnormal cortical blood flow. We tested whether a technique for measuring cortical blood flow might provide useful information about the extent and nature of encephalopathy in SLE. Cortical perfusion was quantified in eighteen SLE patients by the xenon-133 regional cerebral blood flow (rCBF) technique. Vasomotor reactivity, thought to reflect vascular-reserve capacity, was quantified by hypercapnic challenge in sixteen of the eighteen patients. Perfusion and reactivity were compared with groups of healthy controls and patients with major depression. Compared with sex- and age-matched controls, cortical blood flow was lower in female SLE patients (73 mL/100 g/min vs 90 mL/100 g/min, $p < .02$). Cerebrovascular reserve, as measured by hypercapnic reactivity, was abnormally low in the SLE group (.57%/mmHg vs 3.35%/mmHg in depressed controls, $p < .02$) and negative in neurologically affected patients and those on steroids (rCBF decreased after hypercapnic challenge). We conclude that cerebrovascular dysfunction is common in SLE, and abnormal vascular reactivity is associated with neurologic symptoms and steroid treatment. Further longitudinal studies and larger samples are necessary to define the sensitivity and specificity of this finding. ■

Key words: cerebral circulation, systemic lupus erythematosus, xenon-133, hypercapnia

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Introduction

Previous studies have suggested that abnormal global or regional cerebral blood flow (rCBF) is associated with neurologic exacerbation in systemic lupus erythematosus (SLE) (Weinberger et al, 1979; Devous et al, 1985; Kushner et al, 1987; Volkow et al, 1988; Kushner et al, 1990). Currently, there are no sensitive and specific laboratory parameters for neurologic involvement. Electroencephalographic abnormalities are seen in 70% of patients, elevation of cerebrospinal-fluid (CSF) protein concentration is found in 50%, and CSF pleocytosis is present in 30% (Hahn, 1994). Magnetic-resonance imaging (MRI) of the brain is more likely to show abnormalities that are nonspecific (Hahn, 1994). There are no laboratory parameters other than CBF, including measures of general disease severity, that correlate to central-nervous-system (CNS) manifestations (Hahn, 1994).

Measurement of cerebrovascular reserve via hypercapnic reactivity provides more detailed pathophysiologic information than baseline rCBF alone (Tatemichi et al, 1988; Honer et al, 1989). In this study, we investigated hypercapnic reactivity and baseline perfusion in SLE to determine whether reactivity may be a useful index of neurologic involvement.

Materials and Methods

Eighteen consecutive patients meeting the American Rheumatism Association criteria for the diagnosis of SLE were evaluated. Patients were recruited from the outpatient clinics of the Columbia-Presbyterian Medical Center. All had a baseline normocapnic study and sixteen also had a hypercapnic study with inhalation of 4% carbon dioxide. Results of the normocapnic studies were compared with those of eighteen healthy, age-matched controls. Results of the hypercapnic study were compared to a psychiatric control sample of fourteen patients with major depressive disorder (MDD) and no neurologic history or findings. MDD patients were recruited from the New York State Psychiatric Institute. Both subject samples (healthy controls and depressed patients) have been previously described, including their medications and screening (Sackeim et al, 1990).

Studies of rCBF were performed by inhalation of xenon-133 gas (Maximilian et al, 1980) using the Novo Cerebrograph 32c (Novo Diagnostic System, Hallsund, Denmark) and analyzed by the M2 model (Prohovnik et al, 1983). Cerebral blood flow was quantified for cortical grey matter as fg (mL/100 g/min) (Obrist et al, 1980). We report the global mean values calculated from all thirty-two detectors, since there were no significant regional effects. Hypercapnic reactivity was calcu-

Table 1 Patient Characteristics

Age and Gender	*Steroids* (+/- dose on day of study)	*Prednisone Equivalent* (mg/day)	*CNS Lupus Manifestations*
28F	Solumedrol 192 mg qod (–)	120.00	none
22F	Prednisone 200 mg qod (–)	100.00	none
14F	none	0.00	none
54F	Prednisone 10 mg qod (+)	5.00	none
21F	Prednisone 7.5 mg qod (+)	3.75	none
24F	Prednisone 2.5 mg qod (–)	1.25	none
35F	Prednisone 200 mg qod (–)	100.00	none
25F	Prednisone 100 mg qd (+)	100.00	none
25F	none	0.00	none
34F	none	0.00	cognitive impairment, seizures
25F	Prednisone 250 mg qod (+)	125.00	cognitive impairment
52M	Prednisone 150 mg qod (+)	75.00	cognitive impairment, depression
35F	Prednisone 20 mg qod (–)	10.00	hemicranial headaches, depression
38F	Prednisone 200 mg qod (–)	100.00	psychotic depression
48F	Prednisone 120 mg qd (+)	120.00	psychotic depression
29F	Prednisone 500 mg qod (+)	250.00	partial complex seizures
44F	Solumedrol 1 mg qd (+)	1,250.00	left hemiparesis
9M	Prednisone 125–150 mg qod (+)	68.75	left hemiparesis

M = male; F = female.

lated as % change of flow divided by the difference of end-tidal $peCO_2$, to yield units of %/mmHg.

SLE patients who required treatment were given either oral prednisone or intravenous methylprednisolone (Solumedrol;) by the treating physician. Doses of methylprednisolone were recorded as prednisone dose-equivalent using a ratio of 5 mg of prednisone to 4 mg of methylprednisolone (Williams et al, 1994). Steroids were given either daily (qd) or every other day (qod); average daily doses were used for comparison purposes. The steroid doses and clinical presentations of the eighteen SLE patients are provided (Table 1). All neurologic abnormalities were chronic (greater than 6-months duration).

Table 2 Comparison of Patient and Control Samples

	SLE Patients (mean, SD)	*Normal Controls* (mean, SD)	*Reactivity Controls* (mean, SD)
Number (N)	18	18	14
Gender (M/F)	2/16	8/10	4/10
Age (yrs)	31.2, SD 12.5	32.8, SD 11.9	67.1, SD 5.5
SBP (mmHg)	129.1, SD 22.5	114.9, SD 11.0	133.2, SD 19.5
DBP (mmHg)	76.9, SD 15.0	73. SD 10.8	74.1, SD 10.0
Hemoglobin (mg/dL)	11.8, SD 1.6	13.3, SD 1.3	14.5, SD 1.1
$peCO_2$ (mmHg)	36.6, SD 3.0	39.4, SD 3.7	33.6, SD 3.1
CBF (M2 fg) (M+F)	74, SD 17	82, SD 17	59, SD 11.1
CBF (M2 fg) (F)	73, SD 16	90, SD 18	63, SD 10
Reactivity (M+F)	.57, SD 2.58		3.35, SD 3.41
Reactivity (F)	.46, SD 2.71		2.82, SD 3.75

SBP: systolic blood pressure; DBP: diastolic blood pressure; M2 fg:mL/100-mg brain tissue/min; reactivity: % change in rCBF after hypercapnic challenge.

The rCBF in the SLE patients is compared to the age-matched controls. Since flow is inversely proportional to age, age matching is important. For reactivity, age-matched controls are not available but are compared instead to an older group and to controls in the literature (Levine et al, 1994).

Due to the difference in gender distribution between patients and controls and the known effects of gender on cerebral perfusion (Sackeim et al, 1990), primary analysis consisted of an ANOVA with diagnosis and gender as between-subject factors. Secondary analyses included regressions and t-tests.

Results

There were no significant differences in either diastolic blood pressure (DBP) or mean blood pressure (MPB); the range of mean blood pressures in the SLE patients receiving hypercapnia was 73–119 mmHg. There was a significant difference in systolic blood pressure (SBP) ($F_{2,47} = 4.65$, $p = .01$) with the healthy controls having lower systolic pressure (mean SBP, 115 ± 11mmHg) than either the SLE (129 ± 23mmHg) or the MDD (133 ± 20mmHg) patient groups. Across all three groups (total, n = 50), there was a significant positive age regression for SBP (r = .47, $p < .001$) and MBP (r = .37, $p < .01$).

Mean baseline rCBF in SLE was not significantly different from age-matched controls (Table 2), but the interaction with gender was significant ($F_{2,44} = 3.39$, $p < .05$). Male SLE patients had higher flow (88 mL/100 g/min) than female SLE patients (73 mL/100 g/min), whereas women in the control group showed higher flows compared with the SLE group. There

were only two male SLE patients, and the relatively high mean flow was determined by one of them, a 9-year-old who had a flow of 110 mL/100 g/min.

Restricting all samples to women only, the SLE patients were found to have rCBF values lower than age-matched female controls (73 mL/100 g/min ± 16 vs 90 ± 18; t24 = 2.57, $p < .02$) without significant differences in age, hemoglobin, or $peCO_2$ between groups. There was a significant age regression in cortical perfusion among the SLE patients (r = –.72). The young patients with SLE had baseline-flow values similar to those of the much older MDD patients.

Three of the patients were unmedicated when first examined. Four others were on doses <20 mg qd of steroids; ten were on doses ranging from 50–250 mg qd, and one patient was on 1,250 mg qd. A comparison of the three unmedicated patients to the fifteen patients receiving ≥ 50 mg qd yielded marginally significant results ($p = .05$); flow was higher and at control levels for unmedicated patients (89 vs 70 mL/100 g/min).

We also assessed the possible influence of neurologic symptoms on cortical perfusion. Nine of the patients had chronic symptoms with lower flow than the asymptomatic patients (72 vs 77 mL/100 g/min), but the difference was not significant. The difference was stronger but still failed to reach significance when only women were considered (67 vs 77 mL/100 g/min). Global flow also seemed related to steroid dose in the six patients with repeated rCBF measurements, but small numbers did not allow for statistical evaluation. No significant interaction was observed between medication status and neurologic symptoms.

Two patients showed flow asymmetries: The first was a forty-four-year-old woman who developed left-sided weakness five days before the rCBF examination. She could not fully cooperate during the procedure, and, therefore, hypercapnia was not attempted. Her baseline perfusion was low and revealed a right parietal deficit. The second was a nine-year-old boy who presented two weeks prior to testing with left hemiparesis. Angiogram and MRI were normal; his symptoms resolved, and he was discharged. He returned to the hospital two days before the rCBF scan with right-sided weakness. Baseline CBF was high and asymmetric (102 mL/100 g/min for the right, 114 for the left). The high flow was consistent with his young age and mild anemia (Hb, 11.4 mg/dL). The asymmetry was due to a large-flow deficit in the right parietal cortex.

Mean hypercapnic reactivity for the sixteen SLE patients with hypercapnia studied was 0.57% ± 2.58%/mmHg (range, –4 to +4%/mmHg); this is lower than expected for age and lower than encountered in occlusive cerebrovascular disease (Tatemichi et al). Excluding the two male patients, the value was even lower for the fourteen women (0.46% ± 2.71%/mmHg). Hypercapnic reactivity was significantly lower ($p < .02$) than the value observed in the MDD group (3.35% ± 3.41%/mmHg). An ANOVA of reactivity by neurologic symptoms (present/absent) and medication (< 20 mg qd vs > 20 mg qd) yielded a significant interaction (F1, 10 = 8.33, $p < .02$). The four female patients with no symptoms who were not receiving medication had normal reactivity (3.27% ± 0.63%/mmHg), whereas the ten with either symptoms, medication, or both had very low values (–.33% ± 2.33%/mmHg) ($p < .001$). The lowest reactivity was observed in two patients, one with severe anemia (Hb, 9.1 mg/dL) and one unmedicated thirty-four-year-old woman with seizures, cognitive impairment, and multiple small infarcts on MRI.

Six of the sixteen SLE patients who underwent reactivity testing showed the most severe form of deficit, usually interpreted as *global steal* (though the current data cannot prove the mechanism). These patients' overall cortical perfusion was reduced rather than increased by hypercapnia. This steal group had a mean reactivity of –2.13% ± 1.8%/mmHg compared with 2.19% ± 1.2%/mmHg in the ten nonsteal SLE patients ($p < .0001$). The six steal patients were characterized by a higher prednisone dose (115 ± 80 mg qd vs 42 ± 52 mg qd, $p < .05$) and a higher diastolic blood pressure (81 ± 11mmHg vs 69 ± 9mmHg, $p < .05$). All six patients were either on steroids or had CNS symptoms. There were no other significant differences between these two subsamples.

Discussion

Our study directs attention to methodologic points not previously addressed. A definitive investigation of cerebral perfusion in SLE requires rigorous control of $peCO_2$, anemia, and gender, since these variables may confound results. The necessity for age-matched controls suggested by others (Melamed et al, 1980; Meyer, 1980) is confirmed by the age regression found. A correlation (in all fifty subjects) of r = –.40 between MBP and CBF ($p < .005$), r = .34 between $peCO_2$ and CBF and r = –.55 between age and CBF ($p < .0001$) was observed. In a multiple stepwise regression, only age remained a significant predictor of baseline cortical perfusion. Therefore, baseline CBF analysis must assess age, gender, and other factors.

We used a healthy control group for rCBF results and an older depressed group to compare reactivity results. The healthy group is not ideal for three reasons: gender distribution, age range, and hypercapnia availability. The SLE patient group is mainly female. If a female-only control group is selected, gender effects on cortical perfusion would not be verified. Our analysis, including the subsample analysis of women only, ad-

equately addressed this gender issue. The age range of the normal controls (19–55 years) cannot be entirely matched to that of the SLE patients (9–54 years), because radioisotopes cannot be administered to control-group children for research purposes. Good matching of the mean and upper limit of the age distribution and the well-known, replicated age regression of CBF suggest that the lack of healthy pediatric controls is not a serious limitation. Finally, the healthy adults did not undergo hypercapnic challenge in our laboratory. We added a control group of elderly patients with major depression, screened for neurologic disease, to compare with the SLE patients for reactivity. Elderly depressed patients commonly have low flow and low reactivity (Sackeim et al, 1990) and, therefore, are a more conservative control group than young healthy adults.

In addition to gender differences, SLE patients have lower hemoglobin and $peCO_2$ values than controls. Lower $peCO_2$ in SLE would result in lower baseline perfusion, but SLE vasomotor reactivity to increased $peCO_2$ is negligible. Because the SLE cerebrovascular system is, on the average, insensitive to $peCO_2$, there is no need to correct for this factor. Lower hemoglobin values are not surprising, since anemia is common in SLE (Hahn, 1994). Anemia is almost always associated with higher flow (Prohovnik et al, 1989) and thus does not explain the lower flows observed. In fact, the metabolic demand indicated by the CBF in SLE patients is likely much lower due to the anemia. Corrected by the regression equation for hemoglobin proposed in sickle-cell disease (Prohovnik et al, 1989), the current SLE patients should have flows around 100 mL/100 g/min. Thus, the anemia only serves to underscore the low flow seen in SLE.

We previously suggested that hypercapnic reactivity is an informative predictor of vascular disease in other conditions (Tatemichi et al, 1988) as well as in SLE (Honer et al, 1989). Such reactivity appears to reflect cerebrovascular reserve. Reactivity levels in the SLE sample are abnormally low compared with published control values (Honer et al, 1989; Meyer, 1980; Levine et al, 1994), patients with moyamoya disease (Tatemichi et al, 1988), and our elderly depressed controls. Our depressed controls had a mean reactivity of 3.35%/mmHg compared with [18F]fluoromethane positron-emission tomography (PET) studies, which showed reactivity values of about 5%/mmHg in healthy subjects and 4.2%/mmHg in the nonstenosed hemisphere of patients with transient ischemic attacks (Tatemichi et al, 1990). Thus, SLE is associated with striking reductions of cerebrovascular reactivity, similar in magnitude to values observed in patients with known occlusive hemodynamic disease. (Tatemichi et al, 1990). In addition, six of the fourteen patients studied show a reduction in flow after hypercapnic challenge. This diminished reactivity is related to neurologic symptoms and steroid treatment.

The female SLE patients in our study had lower baseline global CBF. Prior reports suggest that flow is reduced only during acute neurologic exacerbation (Kushner et al, 1987, 1990). There was no correlation between reactivity and baseline perfusion within the SLE group. This is in contrast to previous findings of a negative correlation between flow and reactivity in sickle-cell disease (Prohovnik et al, 1989) and occlusive cerebrovascular disease (Tatemichi et al, 1988). Reduced reactivity seems to be related to neurologic involvement and steroid dose, suggesting a vascular derangement as the etiology for SLE-related cerebral disease (Weinberger et al, 1979; Awada et al, 1987; Mills, 1994). Deficient cerebrovascular reserve is compatible with neuropathologic findings seen in SLE consisting of scarring and intimal changes in small arterioles (Mills, 1994). Such pathologic abnormalities could be associated with reduced cerebrovascular reactivity.

We conclude that SLE seems to be characterized by cerebrovascular abnormalities that may be potential markers for CNS involvement. Further longitudinal studies are necessary to determine the sensitivity and specificity of this technique in elucidating the neurologic involvement found in SLE. Larger samples must be used, however, to separate the effects of steroid therapy from those of CNS involvement.

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