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Middle cerebral artery resistivity and pulsatility indices in systemic lupus erythematosus: evidence for hyperperfusion

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Abstract

Background and purpose—Systemic lupus erythematosus (SLE) is associated with significant cerebrovascular and neuropsychiatric disease for which multiple pathogeneses have been proposed. Although global cerebral hypoperfusion has been proposed, there are limited data about intracerebral arterial hemodynamics. Transcranial Doppler (TCD) allows portable, high temporal and spatial resolution, noninvasive blood velocity measurements in the middle cerebral arteries, and calculations of standard resistivity (RI) and pulsatility (PI) indices. RI and PI correlate with cerebral hemispheric arteriolar tone, blood flow resistances, and impedances. Accordingly, we hypothesized that there would be significant differences ($p < 0.05$) in RI and PI between SLE patients and healthy, age and gender matched controls.

Methods—TCD was used to measure RI and PI bilaterally on 34 stable SLE patients (35 ± 11 years) and 15 control subjects (34 ± 10 years). Patients and controls had similar, normal blood pressures and were examined in the supine position during normal, resting respiration. RI and PI were determined by a blinded, experienced observer.

Results—There were no significant differences in RI and PI bilaterally within each cohort. However, SLE patients had significantly lower average RI and PI values compared with controls: 0.45 ± 0.10 versus 0.52 ± 0.05 ($p < 0.05$); and 0.65 ± 0.19 versus 0.77 ± 0.12 , ($p < 0.05$); respectively.

Conclusions—These preliminary data suggest that RI and PI values in the human middle cerebral artery are significantly lower in SLE compared with controls. These indices indicate that middle cerebral arterial resistances and impedances are decreased in SLE. Under normotensive conditions, the results are consistent with hyperperfusion in SLE with increased arteriolar dilation and increased cerebral blood flow.

Keywords

lupus; middle cerebral artery; pulsatility index; resistivity index; transcranial Doppler

Introduction

Systemic lupus erythematosus (SLE) is associated with significant cerebrovascular and Neuropsychiatric disease (NPSLE) for which multiple pathogeneses have been proposed (1–4). Although cerebral hypoperfusion has been proposed as a fundamental aspect of NPSLE, using various techniques in different SLE populations, both increases and decreases in global and regional cerebral blood flows have been reported (1–8). One would expect that the SLE-associated systemic inflammatory processes leading to peripheral endothelial dysfunction, arterial vasoconstriction, and increased arterial stiffness would also occur in the intracerebral circulation (1–8). However, despite descriptions of cerebral blood flow and its patterns in NPSLE, the characteristics of cerebral arterial mechanics and vasomotor tone in SLE have not been well defined (6–8). Thus, the intracerebral arterial hemodynamics of SLE have yet to be fully described, specifically those of cerebral arteriolar resistance and overall cerebral arterial input impedance, physiologic factors that ultimately impact and determine cerebral perfusion (9). TCD allows portable, noninvasive measurement of blood velocity in the accessible cerebral vessels, in particular the middle cerebral arteries (MCA), and permits derivative calculations of standard RI and PI indices (10–16) which correlate linearly with cerebral hemispheric arteriolar tone, blood flow resistances, and impedances, all of which participate in the regulation of cerebral blood flow (17–19). Accordingly, based on reported changes in cerebral perfusion in SLE, we hypothesized that there would be significant differences in RI and PI between SLE patients and healthy, age and gender matched controls (6–8).

Methods

Populations

The study was approved by the Institutional Review Board (IRB), was consistent with the Declaration of Helsinki, and was performed with signed informed consent of each participant. Inclusion criteria included subjects >18 years and <60 years old classified with the diagnosis of SLE by the American College of Rheumatology 1997 criteria (20). Exclusion criteria included subjects who were <18 or >60 years old, or with pregnancy, drug abuse, renal insufficiency, confounding disease, or diabetes mellitus. A total of 34 patients with SLE were consecutively recruited from the Rheumatology services. Subsequently, the 34 SLE patients (age 35 ± 11 years, 33 women) were compared with 15 age (34 ± 10 years), gender (14 women), ethnicity, and body mass index-matched healthy volunteers. Clinical and laboratory data are given in Table 1.

TCD

All 49 subjects underwent bilateral TCD examinations (98 MCAs) in the resting supine position. To control for the effect of blood gases, all TCD measurements were made during normal resting respiration (~10–12 cycles/min). Also, SLE patients and controls had similar normal mean cuff blood pressures (92 ± 10 mmHg and 89 ± 5 mmHg, respectively; $p > 0.05$). Blood pressures were obtained at the time of TCD. A commercially available, bilateral 2MHz TCD (DWL, Doppler Box, Singen, Germany) was used to insonate the left and right MCA by standard methodology as previously described (10–17). After optimization (minimal Doppler angle with maximal signal to noise ratio) of the bilateral Doppler spectral waveforms to determine blood flow velocities, the dual transducers were held securely in position by an adjustable headband. The maximal systolic, minimal diastolic, and the temporal mean blood flow velocity measurements were calculated offline from 6 consecutive blood velocity spectral waveforms. All studies were codified and interpreted by a single experienced observer blinded to subjects' clinical data. The total TCD data

acquisition time to determine the blood flow velocity measurements ranged from 5–10 minutes.

To validate our measurements of systolic, diastolic, and mean blood flow velocities, the Bland–Altman 95% confidence levels for absolute values of the three blood velocity measurements versus a custom in vitro, 4mm lumen diameter, physiological, time collection, phasic flow phantom (accuracy) were $\pm 6\%$ of the mean values. Likewise, the 95% confidence levels of repeated in vivo measures of the blood flow velocity measurements by a single operator (precision) were $\pm 7\%$ of the mean value. Thus, significant differences in RI and PI greater than 7% between the two cohorts could be reliably detected with 95% confidence.

Resistivity and pulsatility indices

As an indirect, noninvasive index of invasively determined arterial input impedances from catheter dynamic blood flow and pressure measurements, the standard RI index was calculated as: $RI = (\text{peak systolic} - \text{peak diastolic velocity}) / \text{systolic velocity}$. As a model, RI is generally applied to less oscillatory and low resistance (vessel geometry driven) and impedance (vessel elasticity driven) vascular beds such as the renal and cerebral circulations. (10–12). RI values range from 0.00 (systolic velocity = diastolic velocity) to 1.00 (diastolic velocity = 0) and represent minimal and maximal arterial input resistances and impedances, respectively. Depending on vascular bed and physiological conditions, normal RI values range between 0.40–0.60.

The standard PI index was calculated as: $PI = (\text{systolic} - \text{diastolic velocity}) / \text{mean velocity}$. PI is generally applied to more oscillatory and high resistance and impedance vascular beds such as in the skin and muscle circulations (10–12). PI values range from 0.00 (systolic = diastolic velocity) to infinity (mean velocity = 0) and represent minimal and maximal arterial input resistances and impedances, respectively. Note that diastolic velocities can be a negative number in flow reversal. Depending on vascular bed and physiological conditions, normal PI values range between 0.50 and 0.90.

Both RI and PI indices increase with increased vascular tone and vasoconstriction and decrease with vascular relaxation and vasodilatation. Importantly, as velocity ratios, both dimensionless indices are independent of the Doppler angle of insonation and thus are simple, inexpensive, robust, and portable noninvasive surrogates of relative arterial impedances (17–19, 23–29).

Statistics

Statistical analyses included comparisons between patient subsets and/or controls by t-tests verified by Wilcoxon test for continuous measures and by Fisher's exact test for binary measures. Means and standard deviations of the measurements of bilateral MCA blood flow velocities and calculations of RI and PI were determined ($n=498$). We used standard paired t-tests to determine left and right side MCA blood flow velocities differences within each cohort. SLE patients and control subjects were compared bilaterally by unpaired t-tests. A two-tailed $p < 0.05$ and a power of 90% were used for significance.

Results

There were no significant differences in RI and PI bilaterally within each cohort. Thus data was combined. As shown in **Figure 1**, SLE patients had lower mean/SD RI values compared with controls: 0.45 ± 0.10 versus 0.52 ± 0.05 ; respectively ($p < 0.05$). Similarly, SLE patients had lower mean/SD PI values than controls: 0.65 ± 0.19 versus 0.77 ± 0.12 ; respectively

($p < 0.05$). Importantly, when comparing SLE patients to controls, the percentage decrease in both RI and PI bilaterally was greater than 95% confidence limits of our methodology (7% for precision).

Discussion

It is important to note that we did not directly evaluate cerebral perfusion.

We recorded blood velocities in the MCA and calculated indirect, but robust, indices of regional arterial vascular resistances and impedances. These indices can be easily, inexpensively, and noninvasively determined as an extension of the clinical exam. As shown in **Figure 1**, both RI and PI were reduced significantly in SLE subjects compared with controls beyond the measurement of uncertainty ($p < 0.05$ for both). As both cohorts were normotensive and with similar systolic, diastolic, and mean arterial blood pressures, the differences in RI and PI were not related to blood pressure. Age, gender, and body mass index were similar in patients and controls. Therefore, the differences in RI and PI were probably not related to aging, hormonal influences, or cardiac output.

Consistently reduced RI and PI values in SLE highly suggest a relatively decreased vascular tone or increased vasodilatation, and/or cerebral hyperperfusion when compared with age and gender matched controls. Again, without concurrent MRI images of brain morphology and perfusion data, we can only speculate about possible cerebral hyperperfusion. Nevertheless, the unique observational data of the present study obtained by noninvasive transcranial Doppler support our recent report of increased cerebral blood flow in SLE using other methodologies (30). Despite the widespread reports of heterogeneous hypoperfusion in NPSLE, cerebral hyperperfusion in SLE has been noted in a number of prior reports using single photon emission tomography (SPECT), positron emission tomography (PET), or magnetic resonance perfusion-weighted imaging (MRPWI) (30–32). Hyperperfusion and altered vascular tone also have been reported in other neurological disorders, including stroke (33), occlusive sickle cell disease (34), transient ischemic attack (35) seizures and epilepsy (36), traumatic brain injury (37), metabolic brain disease (38), and migraine (39). Increased cerebral perfusion can also be observed in non-enhancing lesions and normal appearing tissue in multiple sclerosis (40). The increased cerebrovascular blood volume reported in stroke may indicate intact vascular beds with potentially salvageable areas in the penumbra of the lesion (41). Furthermore, increases in cerebrovascular blood volume with associated decreased vascular tone and increased vasodilatation can be a sign of vasomotor instability, a compensatory mechanism indicating resolving injury, or a reduction of compensatory capacity in response to further ischemia or injury (42).

It is also possible to speculate that the decreased cerebral vascular tone, increased vasodilatation, and/or hyperperfusion may be due to other reactive physiologic or pathogenic factors underlying SLE, such as compensatory mechanisms for resolving injury, low-grade excitotoxicity due to autoantibody-mediated stimulation of N-methyl D-aspartate (NMDA) receptors, or other inflammatory factors (43).

Also, an increase in inducible endothelial nitric oxide synthetase (iNOS) activity with increased production of nitric oxide and nitric oxide derivatives and consequent vasodilatation as a possible compensatory reparative process has been demonstrated in patients with SLE in general, and in those with lupus nephritis (44,45). The increased productions of nitric oxide and high serum nitrate levels in SLE patients are associated with disease activity and dosage of steroids (46–48). These data suggest that systemic or local immune-mediated inflammation with increased production of cytokines and chemokines induce endothelial nitric oxide synthetase with increased production of nitric oxide levels and consequent local

or systemic vasodilation. Also, in patients with acute coronary syndromes, including myocardial infarction and cardiogenic shock, myocardial necrosis and release of cytokines and chemokines stimulate nitrate oxide synthetase with consequent increased production of nitric oxide and nitriles and severe peripheral vasodilation (49,50). Similar pathogenesis may occur in SLE patients, especially those with inflammatory or thrombotic ischemic cerebrovascular disease. In any event, the net effect of SLE in the cerebral circulation, as shown in the present study, is reduced RI and PI, suggesting increased conduit blood flow and perfusion.

Alternatively, the present findings are also consistent with autonomic dysfunction in the cerebrovasculature as a component of the well-described systemic autonomic dysfunction present in many SLE patients (51–54). Lass et al. described lack of response of the cerebrovasculature to acetazolamide, consistent with baseline vasodilation and lack of cerebrovascular reserve (55). The present findings of RI and PI are consistent with exactly this type of vasomotor defect associated with central autonomic dysfunction.

The present study also suggests that the cerebral imaging abnormalities and infarcts of SLE, clinically manifested or not, may not be a result of a lack of adequate global mass transport, but rather to localized pathology of the cerebrovasculature as recent autopsy studies have indicated (.56,57). Serial measurements of RI and PI by transcranial Doppler have the potential to permit a simple method to monitor the natural history and cerebrovascular effects of SLE and intracranial responses to systemic inflammation and therapeutic interventions. Clearly, these preliminary results need to be confirmed in a larger cohort. If further validated these indices, which are measured with a handheld, convenient, inexpensive device, could be used as an important adjunct clinical tool.

Conclusions

Our initial data suggest that RI and PI values in the middle cerebral arteries were significantly lower ($p < 0.05$) in SLE patients than in gender and age matched controls. These observations suggest that middle cerebral arterial resistances and impedances are decreased in SLE and are consistent with increased arteriolar dilation and increased cerebral blood flow. The mechanisms of the decreased cerebrovascular resistance and impedances in SLE patients is unknown, We speculate that they may be the result of compensatory mechanisms for acute or resolving cerebrovascular injury, low-grade excitotoxicity due to antibody impairment of NMDA receptors, or local or systemic inflammation resulting in increased endothelial production of nitric oxide and, consequently, in cerebral vasodilatation.

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Figure 1. Resistivity (RI) and pulsatility (PI) indices: means/SD in SLE and controls (CON). * $p < 0.05$ versus control.

TABLE 1**Clinical, and Laboratory Characteristics of Patients with SLE**

Characteristic	Patients (N = 34)
	Mean $\pm$ SD, n (%)
Duration of SLE (years)	8 $\pm$ 6
Age of diagnosis of SLE (years)	28 $\pm$ 13
Total SLEDAI (U)	12 $\pm$ 10
Non-Neuro-SLEDAI (U)	7 $\pm$ 6
Neuro-SLEDAI (U)	5 $\pm$ 7
Total SLICC (U)	3 $\pm$ 2
Non-Neuro-SLICC (U)	2 $\pm$ 2
Neuro-SLICC (U)	0.9 $\pm$ 1.3
Prednisone therapy	29 (85%)
Prednisone current dose (mg/d)	7 $\pm$ 8
Cyclophosphamide therapy	11 (32%)
Mycophenolate, Methotrexate, or Rituximab therapy	8 (24%)
Hydroxychloroquine or chloroquine therapy	21 (62%)
Statin therapy	2 (6%)
Aspirin, warfarin, or both	6(18%), 6 (18%), 13 (38%)
DNA titer (dilutions)	41 $\pm$ 59* (n = 33)
ANA titer (dilutions)	373 $\pm$ 445
C3 (mg/dl)	92 $\pm$ 30
C4 (mg/dl)	21 $\pm$ 30
CH50 (mg/dl)	74 $\pm$ 41* (n = 30)
Fibrinogen (mg/dl)	341 $\pm$ 83* (n = 25)
C-reactive protein (mg/dl)	1.0 $\pm$ 1.0
Erythro sedimentation rate (mm/hr)	19 $\pm$ 20
Smith antibody positive	11 (32%)
SSA antibody positive	14 (41%)
SSB antibody positive	4 (12%)
Any antiphospholipid antibody positive	19 (56%)
Beta-2 glycoprotein I antibody positive	7/30 (23%)
Lupus-like inhibitor positive	11/33 (33%)
IgG, IgM, or IgA anticardiolipin positive	13 (38%)
IgM anticardiolipin antibody (IU)	9 $\pm$ 9
IgG anticardiolipin antibody (IU)	16 $\pm$ 24
IgA anticardiolipin antibody (IU)	7 $\pm$ 13

ANA = antinuclear antibody, DNA = deoxyribonuclease antibody, SLEDAI = SLE disease activity index (20,21), SLICC = SLE International Collaborating Clinics Damage Index (22).