Microvascular versus Macrovascular Cerebral Vasomotor Reactivity in Patients with Severe Internal Carotid Artery Stenosis or Occlusion

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Rationale and Objectives: In patients with severe internal carotid artery steno-occlusive lesions (ISOL), impaired cerebrovascular reactivity (CVR) is predictive of future ischemic stroke (IS) or transient ischemic attack (TIA). Therefore, the evaluation of CVR in ISOL patients may be a means to evaluate the risk for IS/TIA and decide on an intervention. Our aim was (1) to explore the feasibility of concurrent near-infrared spectroscopy (NIRS-DOS), diffuse correlation spectroscopy, and transcranial Doppler for CVR assessment in ISOL patients, and (2) to compare macrovascular and microvascular CVR in ISOL patients and explore its potential for IS/TIA risk stratification.

Materials and Methods: Twenty-seven ISOL patients were recruited. The changes in continuous microvascular and macrovascular hemodynamics upon acetazolamide injection were used to determine CVR.

Results: Oxyhemoglobin (HbO_2, by near-infrared spectroscopy), microvascular cerebral blood flow (CBF, by diffuse correlation spectroscopy) and CBF velocity (by transcranial Doppler) showed significant increases upon acetazolamide injection in all subjects ($P < .03$). Only macrovascular CVR ($P = .024$) and none of the microvascular measures were significantly dependent on the presence of ISOL. In addition, while CBF was significantly correlated with HbO_2, neither of these microvascular measures correlated with macrovascular CBF velocity.

Conclusions: We demonstrated the simultaneous, continuous, and noninvasive evaluation of CVR at both the microvasculature and macrovasculature. We found that macrovascular CVR response depends on the presence of ISOL, whereas the microvascular CVR did not significantly depend on the ISOL presence, possibly due to the role of collaterals other than those of the circle of Willis. The concurrent microvascular and macrovascular CVR measurement in the ISOL patients might improve future IS/TIA risk assessment.

Key Words: Diffuse correlation spectroscopy; near-infrared spectroscopy; cerebrovascular reactivity; internal carotid artery stenosis.

Severe stenosis or occlusion of the internal carotid artery (ICA) increases the risk of subsequent ischemic stroke (IS) and transient ischemic attack (TIA) (1). Moreover, patients with severe internal carotid artery steno-occlusive lesions (ISOL) are found to be at a particularly higher risk of imminent stroke events when autoregulatory vasodilation capacity of the cerebral terminal arterioles in response to a reduced perfusion pressure, or cerebrovascular reactivity (CVR), is impaired (2–5). Thus, to aid in the decision of the suitable treatment, such as carotid revascularization versus drug therapy, the assessment of CVR has been proposed by several authors as a screening method to stratify ISOL patients based on their assumed risk of future IS or TIA (6).

CVR is normally evaluated by measuring the maximum vasodilation capacity of cerebral vasculature. The maximum vasodilation is induced by introducing a potent vasodilatory stimulus, most commonly CO_2, inhalation or acetazolamide (ACZ) infusion. Consequent cerebrovascular changes are then followed by a method capable of measuring microvascular

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cerebral blood flow (CBF), blood oxygen saturation, blood volume, or macrovascular cerebral blood flow velocity (CBFV).

Many modalities such as positron emission tomography, xenon-enhanced computed tomography (Xe-CT), continuous arterial spin labeling magnetic resonance imaging, single-photon emission CT, transcranial Doppler (TCD), and near-infrared spectroscopy (NIRS-DOS) have been used to evaluate the CVR of ISOL patients (7). In clinics, however, a large number of studies on the role of CVR on subsequent IS/TIA are limited to TCD (macrovascular) since currently available clinical technologies for microvascular CVR assessment are complex and costly and involve patient transport, and ionizing radiation (e.g., positron emission tomography and Xe-CT). Some studies have found correlations between macrovascular CVR measured by TCD and internal carotid artery (ICA) patency, symptom history and IS/TIA risks (8,9). Nevertheless, since the microvascular CVR measures also reflect the efficiency of the collateral vasculature in compensating for blood flow deficiency due to stenosis or occlusion of the ipsilateral ICA, they are believed to be more individualized indicators of CVR condition (10). As a consequence, a bedside noninvasive and relatively simple technology for microvascular CVR assessment would be desirable (1) for more precise IS/TIA risk assessment according to the status of collateral circulation and hemodynamic response of the cerebral vasculature, and (2) based on the proposed risk, to facilitate a decision on the appropriate therapies. Such a bedside and noninvasive modality could also be used after large trials to end the current debate on the significance of CVR function on the precise selection of subgroup of ISOL patients who would benefit from therapies like extracranial/intracranial bypass surgery (11).

In this study, we have applied a novel hybrid diffuse optical technology for real-time bedside assessment of microvascular CVR based on simultaneous microvascular CBF and oxygenation measurements (12). The hybrid diffuse optical monitor consisted of two diffuse optical modalities: diffuse correlation spectroscopy (DCS) and NIRS-DOS. DCS (13–15) measures the microvascular CBF continuously, at the patient bedside without any need for exogenous markers and has been extensively validated in vivo (15,16). The blood oxygenation and blood volume changes in the brain were followed by NIRS-DOS. Concurrently, we have also assessed the bilateral CBFV (macrovascular) by TCD. The normal CVR response range available for DCS/NIRS-DOS hybrid diffuse optics technique was established in our previous study (17), where we have applied a similar methodology to healthy volunteers and found a significant agreement between microvascular and macrovascular CVR. We also demonstrated the potential of the combined DCS/NIRS-DOS technique for cerebral metabolic rate of oxygen assessment. Here, our main goals were to demonstrate the potential of hybrid diffuse optics for noninvasive bedside assessment of microvascular CVR and to compare the bilateral CVR responses in anterior middle cerebral artery (MCA) territory (microvascular) and at the MCA trunk (macrovascular) in the presence of severe ISOL by a relatively simple technique. Finally, we classified our CVR findings according to the presence of normal CVR or its total absence, and, since our measures were continuous, we assessed the temporal properties of the response in both the microvasculature and macrovasculature.

MATERIALS AND METHODS

Subjects

The population was selected from patients with symptomatic and asymptomatic steno-occlusive ICA disease who were referred to the neurovascular laboratory at the hospital de la Santa Creu i Sant Pau, Barcelona, Spain for carotid artery ultrasound examination. The patients were approached for recruitment in the study if they had a unilateral or bilateral severe $\geq$70% stenosis or occlusion of the ICA as determined by published criteria using a carotid artery ultrasound (multifrequency linear array transducer; Aplio-XG, Toshiba, Tochigi, Japan) (18).

In these patients, the ICA stenosis or occlusion was further confirmed by magnetic resonance angiography (MRA), CT angiography (CTA), and/or digital subtraction angiography (DSA) according to North American Symptomatic Carotid Endarterectomy Trial criteria (19). Patients were excluded if they had an inadequate temporal bone window for sufficient TCD examination or the evidence of an additional intracranial stenosis of the carotid siphon, the MCA, or the anterior cerebral artery. Patients were asked to avoid coffee, antihypertensive drugs, and smoking on the day of measurement.

Information about demographic and vascular risk factors such as age, gender, history of smoking, hypertension, diabetes, hypercholesterolemia, and previously diagnosed coronary heart disease and vascular peripheral disease were recorded.

The study was approved by the institutional ethics committee at the hospital de la Santa Creu i Sant Pau.

Diffuse Optics and TCD Protocol

The measurement protocol, instrumentation, optode design, and analysis methods are explained in detail in our previous work (17). Briefly, relative changes in oxyhemoglobin (HbO_2) and deoxyhemoglobin (Hb) concentration were followed by a custom-made frequency domain NIRS-DOS device (95230 Imagent, ISS, Champaign, IL, USA) with 16 lasers at $\sim$ 690 nm, $\sim$ 785 nm, and $\sim$ 830 nm and two photomultipliers for detection. The relative microvascular CBF was measured by DCS at the patient's bedside (15). The optical fibers were placed on the right and left side of the forehead of subjects approximately 1 cm above the eyebrows and as far away as possible from the midline (17). The CBFV in the right and left MCA were obtained by TCD (MultiDop-T, DWL Elektronische Systeme, Singe, Germany). Two probes in a range-gated and pulsed-wave mode at 2 MHz and at a depth