Assessment of the Cerebral Vasomotor Reactivity in Internal Carotid Artery Occlusion Using a Transcranial Doppler Sonography and Functional MRI

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ABSTRACT

BACKGROUND AND PURPOSE

Several methods are being used to assess cerebral vasomotor reactivity (CVR), including transcranial Doppler (TCD) sonography and blood oxygenation level-dependent functional magnetic resonance imaging (fMRI). The aim was to assess the correlation of TCD and fMRI in the CVR assessment.

METHODS

Study group consisted of 28 patients (24 males, 4 females; aged 30–82, mean 63.1 ± 10.0 years), presenting with 29 occluded internal carotid arteries. The TCD examination, including breath-holding/hyperventilation test (BH/HV) and breath-holding index (BHI), and fMRI examination were used for the assessment of CVR. fMRI employed a bimanual motor task within both a block paradigm and an event-related paradigm. Cohen's κ was applied when statistically assessing correlation of the methods.

RESULTS

The following correlations were found—between BH/HV and BHI 58.6%, $\kappa = .205$; BH/HV and fMRI 65.5%, $\kappa = .322$; BHI and fMRI 58.6%, $\kappa = .151$; TCD (consistent result of both BH/HV and BHI test) and fMRI 70.6%, $\kappa = .414$.

CONCLUSIONS

In the evaluation of CVR, there is only a minimal correlation between the particular TCD tests (both BH/HV and BHI), and fMRI examination. However, there is a moderate correlation between TCD and fMRI in the case of congruity of both TCD tests.

Keywords: Carotid occlusion, cerebral vasomotor reactivity, transcranial Doppler sonography, functional magnetic resonance imaging, motor cortex.

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Introduction

Several methods are currently used to assess cerebral vasomotor reactivity (CVR), testing the response (vasodilation, vasoconstriction, change of the oxygen extraction) to various stimuli (pCO_2 change, application of vasodilators, motor stimulus). Positron emission tomography (PET) with the assessment of oxygen extraction fraction (OEF) using the inhalation of ^{15}O-labeled gas is considered the "gold standard" of CVR examination. Other methods such as computed tomography (CT) with administration of ^{133}Xe,[1] perfusion CT,[2] single photon emission computed tomography (SPECT), using the ^{99m}Tc-HMPAO tracer, and near-infrared spectroscopy (NIRS) are also used to assess CVR, giving only indirect and semiquantitative information about cerebral vasoreactivity.[3] However, most of these examinations carry a radiation load and are not suitable for longitudinal studies and PET is not widely available.

Noninvasive hemodynamic imaging can be performed also using transcranial Doppler sonography (TCD) and functional magnetic resonance imaging (fMRI). For example, Kleinschmidt et al. used a combination of TCD and fMRI to study vasodilatory response to acetazolamide (ACT) in a single MRI slice through motor cortex and reported agreement of the TCD and fMRI data; however, the patient group was too small to allow statistical analysis.[4] Furthermore, ACT for intravenous application is not universally available. These constraints demonstrate the need for protocols using different vasodilatory stimuli that correlate with each other.

The aim of this study was to assess the correlation of TCD and fMRI, two noninvasive examination methods using different stimuli, in the assessment of CVR.

Patients and Methods

Patients

Study group consisted of 28 patients (24 males, 4 females; aged 30–82, mean 63.1 ± 10.0 years), presenting with 29 occluded internal carotid arteries (ICAs). Only patients who were able to cooperate during the performed examinations, eg, with normal hearing and vision (corrected) and not suffering from major aphasia, motor or other cognitive deficit, and who agreed with their participation in the study were included. The patients were recruited in the Neurosonological Laboratory, Department of

Neurology, University Hospital, Olomouc, Czech Republic, between June 2003 and February 2006.

Transcranial Doppler Sonography

TCD examination was performed using the ultrasound machine Agilent SONOS 4500 (Agilent Technologies, Andover, MA) with a 2 MHz transcranial probe. Echocontrast agent Optison™ (Amersham Health AS, Oslo, Norway) was applied intravenously for signal enhancement in 14 (50.0%) patients with insufficient penetrability of the temporal bone window.

During the TCD examination, subjects were placed in a comfortable supine position in a quiet room with standard temperature, without any visual or auditory stimulation. Blood flow velocities were measured in both middle cerebral arteries (MCAs) via the temporal windows at rest (normocapnia). In order to assess CVR, blood flow velocities in the MCA ipsilateral to the occluded ICA were measured also during hyper- and hypocapnia (breath-holding/hyperventilation test, BH/HV), and during hypercapnia alone (apnea test–with the calculation of the breath-holding index, BHI).[5-9] For the first (BH/HV) test, short (10 sec) breath-holding was followed by moderate hyperventilation (40 sec). The decrease in mean blood flow velocity of at least 15% from baseline was considered normal in BH/HV test.[10,11] For BHI, breath-holding for the longest time possible was used. BHI was calculated as the relative increase in mean blood flow velocity during breath holding divided through the time of apnea in seconds. The value of $1.2 \pm .6$ was considered normal.[10] Paradoxical reaction with the mean velocity increase in BH/HV and decrease in BHI test was considered pathological. Apnea test was performed 10 minutes following the BH/HV test.

TCD examination in symptomatic patients was performed at least 3 months after the last ischemic stroke/transient ischemic attack (IS/TIA).

Functional MRI

Tasks and Practice

Prior to the functional brain imaging session, subjects were trained in the laboratory in the active task to be performed in the scanner, namely, bimanual sequential finger-to-thumb opposition at the rate of approximately 1 movement per second. They were instructed to move fingers of both hands in synchrony during the active periods and remain rested in between. Those unable to perform these finger movements because of hand paresis, instead practiced bimanual hand clenching.

fMRI Data Acquisition

Magnetic resonance imaging data were acquired on Siemens 1.5 Tesla scanners (Avanto and Symphony, Siemens, Erlangen, Germany) with a standard head coil. The first part of the MR imaging protocol covered the whole brain with 30 axial slices 5 mm thick, including anatomical T_1-weighted images to provide an immediate overlay with functional data, fluid-attenuated inversion recovery (FLAIR) images to visualize brain lesions, functional T_2^*-weighted, blood oxygenation level-dependent (BOLD) images during task performance and rest, and a high-resolution 3D anatomical scan (MPRAGE). Whole-brain BOLD images were acquired with gradient echo EPI, TR/TE = 2500/50 ms, FOV 220 mm, to provide $3.4 \times 3.4 \times 5$ mm resolution. A total of 144 images were acquired per each functional run (duration 6:00 min). The second part of the protocol used 6 axial slices, 6 mm thick + 1.5 mm gaps, to cover the vertex, including the hand area of the primary motor cortex (M1) in both hemispheres, and included structural T_1-weighted images and BOLD images during task and rest. The second set of BOLD images used TR = 500 msec for a more rapid sampling of the hemodynamic response during the single-trial experiments (see below) and included 720 sets of images per each 6-minute run. Subject's head was immobilized with cushions to assure maximum comfort and minimize head motion. During the structural part of the imaging session, subjects lay in the MR scanner and rested. During fMRI data acquisition, subjects followed auditory instructions announcing the beginning of each active and rest periods, provided in MR-compatible headphones. Block design used active (movement) blocks of 15 sec alternating with 15 sec blocks of rest serving as a control state. Single-trial design was utilized to map the evoked hemodynamic response to brief (4 sec) movement periods, which alternated with long (26 sec) baseline (rest) periods. Both block- and single-trial paradigms were repeated twice, for a total of 4 runs or 24 minutes. Block design was used for its known greater sensitivity to detect the presence of significant, albeit impaired, regional hemodynamic response, whereas the event-related design provided estimates of the hemodynamic response shape and size as reported previously.[12]

fMRI Data Analysis

MRI data were processed using the free software packages AFNI[13] and FSL.[14] Analysis steps included: 3D motion correction (within AFNI and/or with Siemens built-in postprocessing of the BOLD image data) and statistical modeling of the data using general linear models. The models included one square-wave regressor for the active task and rest, derived from the paradigm and convolved with a model of the hemodynamic response, a polynomial baseline fit, and 6 estimates of head motion (3 rotations + 3 translations). Significantly active voxels were selected using a statistical threshold (F-value or z-score) as well as a contiguity threshold[15] to achieve a whole-brain $\alpha < .05$. Brain activation was evaluated in anatomically defined regions of interest for the left and right primary motor cortex.[12,16-18] Regional measures included total volume of activation per region and, for the event-related paradigm, the parameters of the regional hemodynamic response. The regional-evoked hemodynamic response was calculated as the average response of all significantly active voxels within the region, expressed as percent signal change and evaluated using the following parameters: magnitude, time-to-peak[12] and full width at half-maximum (FWHM). Full width at half-maximum was employed to protect against asymmetries in the shape of hemodynamic response, possibly shifting the time-to-peak. The estimated parameters were compared between the left and right motor cortices; this

minimizes the effect of statistical thresholding on absolute size of the hemodynamic response.

Unilateral impairment (ie, decrease in magnitude, prolongation of time-to-peak and broadening of the FWHM) in at least two of these parameters within the motor cortex ipsilateral to the side of carotid artery occlusion, causing a significant left-right difference (magnitude: >15%, time-to-peak: >2.5 sec, FWHM: >10%) was interpreted as evidence of impaired cortical hemodynamics. Decrease of the hemodynamic response magnitude more than 25% against the patent side was considered pathological, even when the remaining parameters did not significantly differ between the sides.

The margins of magnitude and time-to-peak (ab)normality were based on the characteristics of the control and patient groups reported by Carusone et al.[12] Specifically, the normal group left-right difference in amplitude was 11%, and all their patients exceeded this difference (decrease on the affected side ranged between 18 and 35%, mean 26%). For time-to-peak hemispheric difference, which was zero in normals, we used the average of the patient group (2.67 sec) as our guiding value and set the normal threshold below that. The 10% cut-off for FWHM was set to suppress the uncertainty resulting from the temporal sampling interval (.5 sec) over the width of the response.

For visualization, hemodynamic responses were plotted together with an empirical model[13] of the hemodynamic response. In cases of bilateral carotid artery occlusion, hemodynamic response magnitude was compared to the empirical model as well as between the left and right motor cortices. If there was no area of significant activation within the primary motor cortex on the occluded side, the hemodynamic response was also considered pathological.

Statistical Analysis

Cohen's κ was applied when statistically assessing correlation of the particular methods used for the CVR assessment. All 28 patients (with both pathological and physiological findings) were included into statistical analysis. The SPSS software version 10.1. (SPSS Inc., Chicago, IL) was used for this purpose.

Ethics Committee Approval

The whole study was conducted in accordance with the Helsinki Declaration of 1975 (as revised in 1983) and it was approved by local ethics committee of our hospital. Informed consent was obtained from each patient.

Results

Twenty-nine occluded ICAs were found in the set of 28 study subjects as one patient presented with a bilateral ICA occlusion. Twenty (69.0%) patients had a history of IS/TIA in the ipsilateral arterial territory. At the time of the CVR assessment, 5 out of these 20 patients had no neurological deficit and 15 presented with mild neurological deficit (NIHSS value 1–6, mean 3.0 ± 1.4). On morphological MR images, asymptomatic ipsilateral cerebral infarction was detected in two (7.1%) more patients. All cerebral infarctions were found in arterial territorial distribution.

In the fMRI data, 13 (46.4%) out of the 28 patients showed normal pattern of bilateral M1 activation without pronounced asymmetry and the bilateral-evoked hemodynamic responses resembled the empirical model, for example, see Figure 1 (patient 4). The BOLD response was missing in 6 (21.4%) out of the 28 patients, each time only in the hemisphere ipsilateral to ICA occlusion.

In the rest of the patients, impairment of cortical hemodynamics, again ipsilaterally, manifested as diminished extent of active cortex, smaller magnitude and broader shape of the hemodynamic response (increased FWHM) and longer hemodynamic delay (time-to-peak) when compared to the normal side. In some patients, all of these parameters were affected to a similar degree and were all considered abnormal by our ad-hoc criteria described above–see Figure 2, displaying results from one such patient (P21). Note also the pronounced and delayed "initial dip," ie, the early negative BOLD response preceding the main positive peak in the left M1.

Two (7.1%) patients (P22, P20) exhibited a marked unilateral decrease of evoked response magnitude but no side-to-side difference in other parameters, which was also considered pathological as described in Methods. Their hemodynamic data are presented in Figure 3.

Interpretation of the left-right differences was complicated in the patient (P13) with bilateral ICA occlusion. In this patient, the motor cortical hemodynamic response was markedly decreased and broadened bilaterally compared to the empirical hemodynamic model (Fig 4).

Results of the CVR assessment using the particular TCD tests (BH/HV and BHI) and fMRI parameters are presented in the supplementary web-only Table 1A.

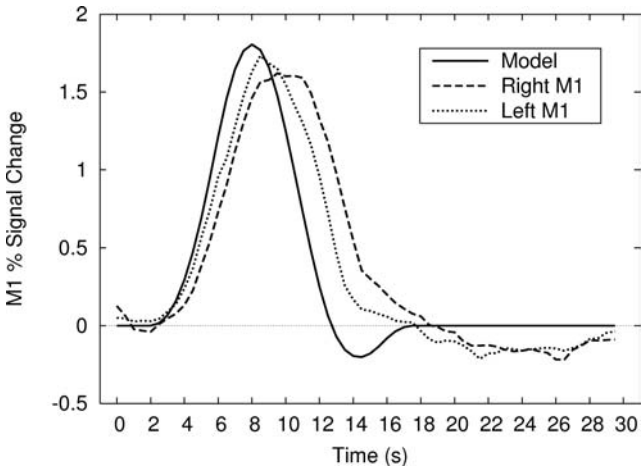

Fig 1. Regional event-related hemodynamic responses in a patient with occluded right internal carotid artery and minimal hemodynamic impairment. Relative (percent) changes of the BOLD MRI signal over time are shown for the right and left primary motor cortices (M1). Solid line: empirical model of the hemodynamic response, dashed line: right primary motor cortex, dotted line: left primary motor cortex. Right motor cortex, ipsilateral to carotid occlusion, manifests only minimal disturbance in amplitude, time to peak, and shape of the hemodynamic response.

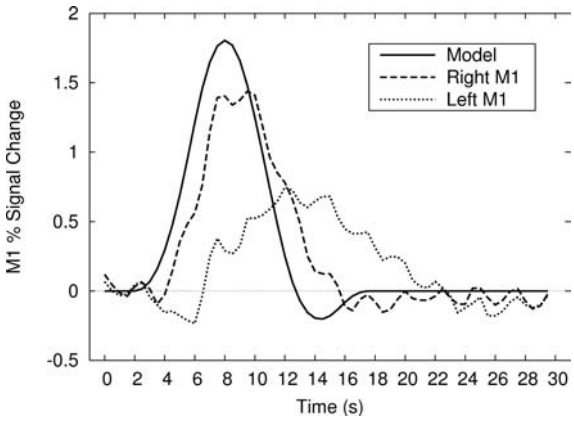

Fig 2. Regional event-related hemodynamic responses in a patient with occluded left internal carotid artery and broad hemodynamic impairment. Relative (percent) changes of the BOLD MR signal over time are shown for the right and left primary motor cortices (M1). Solid line: empirical model of the hemodynamic response, dashed line: right primary motor cortex, dotted line: left primary motor cortex. Left motor cortex, ipsilateral to carotid occlusion, shows markedly decreased amplitude, delayed onset, prolonged time to peak, and broader shape of the hemodynamic response, as well as a more pronounced and delayed "initial dip."

Table 1 demonstrates the summarized comparison of the results of the CVR assessment using the particular TCD tests and fMRI parameters. A good concordance (70.6%) was found between the results of TCD (in the case of consistent result of both BH/HV and BHI tests) and fMRI examination.

The correlations between TCD and fMRI examination, including Cohen's κ, are shown in Table 2.

Discussion

It is not known whether fMRI can replace PET in complementing CVR testing with TCD. Transcranial Doppler sonography has become widely used in assessing CVR by providing information regarding cerebral autoregulation and collateral circulation. CVR is defined as a shift between cerebral blood flow (CBF) or cerebral blood velocity before and after the administration of a potent vasodilatory stimulus test, such as the apnea test (dilatatory response of CBF to hypercapnia). This breath-holding maneuver enables assessment of CVR by means of calculating the BHI.[10,19] The apnea test can be replaced by inhalation of 5–8% CO_2.[10] Intravenous ACT administration can be also used as a vasodilatory stimulus for TCD assessment of CVR.[10] The main technical problem is the absence of a standardized examination protocol both for CO_2 inhalation and for ACT administration (in the latter case, the route of administration using either intravenous injection or infusion, the total dose dependent/nondependent on body weight and the monitoring interval are all unsettled).[20,21] The BH/HV test is a combined test for the assessment of CVR during hyper- and hypocapnia.[5-11,22] The assessment of CVR by combining TCD and provocative vasodilatory tests allows the intracranial hemodynamic status to be evaluated in patients with carotid occlusion. It is intended to predict the occurrence of future ischemic brain events, to compare intracranial hemodynamics

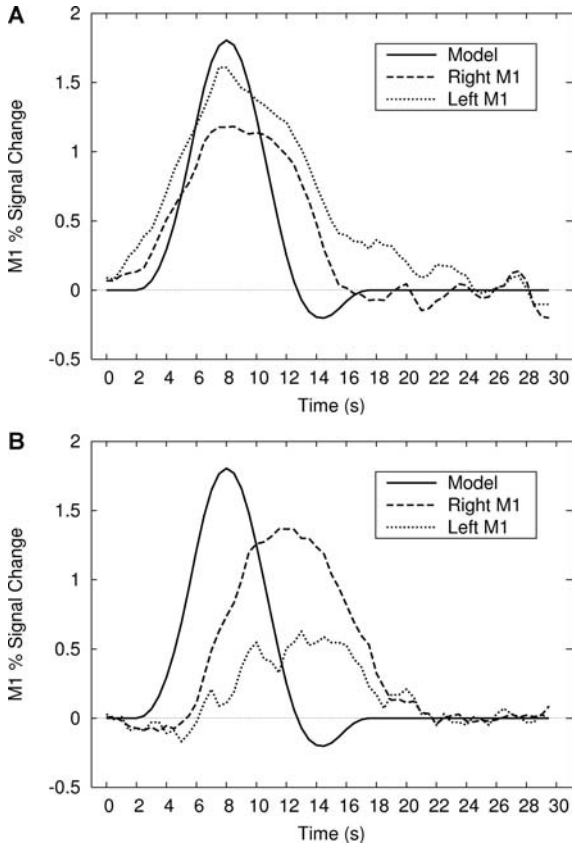

Fig 3. Regional event-related hemodynamic responses in two patients (panels A and B) with unilateral internal carotid artery occlusion and selective impairment of response magnitude. (A) Right-sided occlusion manifests with decreased ipsilateral magnitude and bilateral broadening of the hemodynamic response. (B) Left-sided occlusion accompanied by markedly decreased magnitude of the ipsilateral hemodynamic response; shape is broader and time-to-peak is prolonged bilaterally. Notation as in Figure 1.

and autoregulation before and after extra-intracranial bypass, to measure collateral circulation in the different parts of the circle of Willis, and also to predict dementia after stroke.[8,19,23-25]

Alternative noninvasive hemodynamic imaging can be performed with fMRI, a more recently developed method utilizing mostly BOLD contrast. BOLD fMRI can be accomplished on a typical 1.5 Tesla scanner, available in all regional and university hospitals. Functional MRI allows higher spatial resolution than PET and also permits longitudinal studies without a cumulative radiation load. Functional MRI studies in cerebrovascular diseases have typically mapped movement-activated areas in stroke patients recovering motor function by comparing them to motor activation patterns in healthy controls. These studies replicated and extended PET findings by demonstrating differences between patients and controls in multiple brain areas including cortical,[16-18,26-31] subcortical, and cerebellar regions.[17] Functional MRI has further been used to detect the cortical hemodynamic impact of large-vessel disease, such as asymptomatic carotid stenosis.[12] This study reported slowing and diminution of the cortical hemodynamic response in the

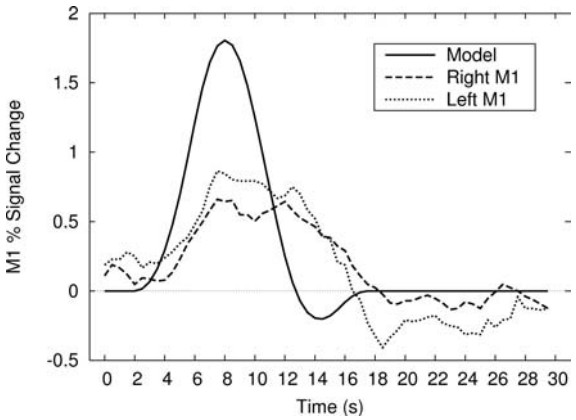

Fig 4. Regional event-related hemodynamic responses in a patient with bilateral ICA occlusion. All hemodynamic parameters are impaired bilaterally, with no left-right difference. Notation as in Figure 1.

hemisphere ipsilateral to carotid stenosis. The same technique was also recently used to assess the CVR in patients suffering from unilateral common carotid artery occlusion and with a patent external carotid artery and ICA.[32]

So far, only a few studies were performed to evaluate the correlation between TCD and fMRI, two noninvasive methods assessing the CVR. Our study used a methodology similar to Carusone et al[12] with several differences. We did not evaluate rise and fall slope of the evoked hemodynamic response, which did not distinguish patients from controls in the previous study.[12] Instead, we added the FWHM parameter to describe the width of the hemodynamic response peak. Rather than evaluating five pixels in each M1,[12] we averaged the significant hemodynamic response across the whole activated region (typically 30-50 voxels). We believe this provides a better estimate of vascular dynamics in the M1 region, which is itself a subset of the whole MCA territory. Our criteria for considering a regional hemodynamic response curve pathological were also somewhat different from Carusone et al.[12]

Table 1. Summarized Comparison of the Results of the CVR Assessment Using TCD and fMRI

Examination (# of cases)	TCD		
	BH/HV	BHI	fMRI
6 (20.7%)	−	−	−
2 (6.9%)	−	−	+
4 (13.8%)	−	+	−
5 (17.2%)	−	+	+
3 (10.3%)	+	−	+
3 (10.3%)	+	+	−
6 (20.7%)	+	+	+

+ = impaired cerebral vasomotor reactivity; − = preserved cerebral vasomotor reactivity; BH/HV = breath-holding/hyperventilation test; BHI = breath-holding index; fMRI = functional magnetic resonance imaging; TCD = transcranial Doppler.

Table 2. Correlations between TCD and fMRI Examination

Methods	Cohen's κ (95% CI)	Methods Agreement (95% CI)
BH/HV vs. BHI	.205 (−.128; 0.445)	58.6% (47.7%; 69.4%)
BH/HV vs. fMRI	.322 (−.028; 0.565)	65.5% (55.3%; 75.0%)
BHI vs. fMRI	.151 (−.196; 0.467)	58.6% (48.0%; 66.2%)
TCD vs. fMRI	.414 (−.058; 0.718)	70.6% (57.2%; 78.6%)

BH/HV = breath-holding/hyperventilation test; BHI = breath-holding index; fMRI = functional magnetic resonance imaging; TCD = transcranial Doppler (consistent result of both BH/HV and BHI test).

Our fMRI task was either bimanual sequential finger-to-thumb opposition (in patients with no hand/finger weakness) or bimanual hand clenching (in patients with hand paresis). We believe this did not significantly confound the results, for two reasons. First, in both cases, we are comparing task-related activation between the two brain hemispheres, second, the relatively easier task may require the same effort in patients with paresis.[33]

Volumes of activation from both block- and event-related designs were inspected to confirm the expectation that impairment of cortical hemodynamics would be manifested as diminished extent of active cortex (see Results), they were not used when judging hemodynamic abnormality (see Methods).

Rossini et al[34] used BOLD fMRI with electrical median nerve stimulation as the hemodynamic challenge as well as TCD with CO_2 inhalation, and studied 10 patients with a history of IS or TIA, 3 of whom had ICA occlusion (2 ipsilateral and 1 contralateral to the ischemic lesion). Across the patient group, they noted a strong relationship between impaired vasomotor reactivity and missing BOLD fMRI activation of the primary somatosensory cortex (in 8 out of 20 hemispheres), which was observed in both stroke-affected (3) and unaffected (5) hemispheres. In our study, the BOLD response was missing in 6 out of the 56 hemispheres, each time only on the side of ICA occlusion. All of these hemispheres exhibited impaired CVR by TCD assessment, four out of six had both tests and two out of six had one test pathological. Therefore, we can confirm the implication[34] that missing cortical BOLD response appears to strongly suggest impaired MCA CVR. However, preservation of BOLD fMRI response as defined by our criteria did not exclude TCD CVR abnormality, as discussed below.

The study of Roc et al[35] examined seven patients with major arterial stenoses in the anterior circulation, mostly left-sided, including one patient with left ICA occlusion. Use of BOLD fMRI during a motor task was complemented with resting MR perfusion measurement. Their major observations from an event-related fMRI design include a delayed and more pronounced "initial dip" or early negative BOLD response and a delayed peak of the main positive hemodynamic response. In our data, a pronounced and delayed "initial dip" was occasionally observed as well, eg, see Figure 1, but it was not a common feature of the impaired hemodynamic response. Longer MR repetition time (TR = 2 sec), resulting in coarser sampling of the temporal

dynamics, and reporting of mostly group, rather than individual, fMRI data, precludes more specific comparisons of Roc et al.[35] with our observations.

In the assessment of CVR, a good concordance between the results of TCD (in the case of consistent result of both BH/HV and BHI tests) and fMRI examination was found in the majority (70.6%) of our patients. However, different results were detected in 29.4% of these patients–with CVR assessed as normal by TCD and impaired by fMRI in two, and on the contrary as impaired by TCD and normal by fMRI in three other patients. The latter case can be explained by individually variable engagement of specific collaterals (ie, ophthalmic circulation, anterior and posterior communicating arteries, leptomeningeal collaterals from the territory of the posterior cerebral artery–PCA), since it is known that collateral circulation plays an important role in patients with ICA occlusion.[36] Under the physiological circumstances, motor cortex controlling the movement of the hand is supplied by the terminal MCA branches. In some patients suffering from ICA occlusion, leptomeningeal collaterals from the PCA may contribute to the blood supply for the distal MCA territory.[36] In such situation, we speculate that TCD may reveal impaired CVR in the MCA, whereas fMRI, which is more likely to detect hemodynamic changes in small regions, may show normal cortical hemodynamics. However, one may argue that TCD should reflect a good response to hypercapnea in the case of the adequate blood flow by any collateral route because the TCD response is not generated "in" the MCA, but it detects the changes of the flow through the MCA due to distal vasodilation of cerebral arterioles.

The opposite discrepancy, the finding of the impaired CVR on fMRI and normal CVR in TCD examination, may be expected, for example, in diffuse microangiopathy with leukoencephalopathy; however, this disease typically impairs hemodynamic response on both sides[34] and would not cause side-to-side differences required by our fMRI criteria. Nevertheless, this discrepancy may also be caused by the higher sensitivity of the fMRI examination to reveal impaired hemodynamics. Depending on the vasodilatory stimulus, BOLD reactivity maps may provide information on the whole MCA territory reactivity and may identify small regions of impaired reactivity, which are not detectable using TCD, which also determines CVR for the whole MCA territory but with poor spatial resolution.[3,34]

Both types of discrepancies between the results of TCD and fMRI can be caused also by the facts that different areas or volumes of brain tissue may be evaluated with the two tests and the response of tissues with impaired hemodynamic responses may be different according to test modality, ie, different pathophysiologic processes may be measured by these techniques.

Lythgoe et al[3] compared BOLD 6% CO_2 reactivity in the MCA territory to MCA velocity reactivity determined using TCD in 16 patients with unilateral carotid artery stenosis or occlusion. Although a significant correlation was found between interhemispheric MCA reactivity difference (contralateral − ipsilateral to the stenosis or occlusion) determined by BOLD fMRI and TCD ($r = .75$, $P < .001$), no correlation between the absolute BOLD and TCD MCA CO_2 reactivities was found when treating each hemisphere individually ($r = .08$, $P = .67$). This appeared to be due to a variable BOLD signal change in the nonstenosed hemisphere between subjects, with little change in the normal hemisphere of a few subjects. In one subject, focal regions of reduced reactivity were seen in noninfarcted regions of the hemisphere supplied by the stenosed ICA, in the borderzones between arterial territories (between the MCA and both the anterior and the posterior cerebral arteries). Two possible reasons to explain this situation were offered by the authors. First, a lack of increase in blood flow in response to a rise in inspired CO_2 will not give an increase in blood oxygenation, with its corresponding signal change in BOLD images. Second, previous studies suggested a trend toward increased OEF associated with decreased hemodynamic reserve capacity in the borderzones between the MCA and the anterior cerebral artery perfusion territories.[37] This would lead to an increase in paramagnetic deoxyhemoglobin, and a corresponding reduction in signal intensity. This regional information cannot be provided using TCD and is a major advantage of a technique with a high spatial resolution such as a BOLD fMRI.[3]

One should mention that both (TCD and fMRI) techniques have some technical limitations. For example, in BH/HV test, depending on patient cooperation, the same change in pCO_2 is not guaranteed in all situations. Although inhalation of 5–8% CO_2 or intravenous ACT administration can be used alternatively for TCD, as mentioned above, no "gold standard" exists for this examination and the risk of the error is relatively small in well cooperating patients. CVR assessment can be also influenced by other factors, such as air temperature, patient position and blood pressure, and others. This bias should be minimized by its performance in standard conditions. Poor correlation between the TCD tests (BH/HV and BHI) found in this study can be also caused by nonblinding, nonrandom performance of testing or different baseline pCO_2 levels before each test in the same patient. TCD technique used in this study provided only semi-quantitative data because no capnometer was used to assess the actual pCO_2 that was achieved with breath holding or hyperventilation. However, the use of real-time capnometry allows the TCD to be quantitative. On the other hand, BOLD reactivity maps only appear to provide semi-quantitative rather than quantitative data[3] and, for a localized hemodynamic stimulus, such as hand movement or peripheral nerve stimulation, may not evaluate vascular reactivity in the MCA territory as a whole. The estimated inter-hemispheric differences in the BOLD response could have been influenced by statistical thresholding if the relationship between neuronal activity and BOLD response differs between sides (ie, becomes nonlinear in the impaired hemisphere).

Finally, we have to acknowledge that our experimental design correlates TCD with fMRI, two alternative tests for assessing CVR, rather than each against the "gold standard" PET.

Conclusions

In summary, several problems are evident in the CVR assessment and include the limited availability of the "gold standard" PET examination, and also the radiation load involved in this

examination. Additionally, no standardized protocols exist for the TCD evaluation of CVR. Although there was only a minimal correlation between the particular TCD tests (both BH/HV and BHI), and fMRI examination, a moderate correlation was found between TCD and fMRI in the case of congruity of both TCD tests in our study. However, neither the TCD nor the fMRI examinations were fully sensitive in the detection of the impaired CVR in their mutual comparison. Thus, further studies are needed to assess the correlation of not only TCD and fMRI, but also with the "gold standard" of PET in the evaluation of CVR and there is clear need for standardization of the performance of all employed tests.

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