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Dynamic cerebral autoregulation is compromised in ischaemic stroke of undetermined aetiology only in the non-affected hemisphere

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ABSTRACT

Background and purpose: To assess dynamic cerebral autoregulation (CA) in patients with acute ischaemic stroke of undetermined aetiology, within 72 h of stroke onset.
Materials and methods: In 6 patients with ischaemic stroke of undetermined aetiology (aged 66 ± 9 years, National Institutes of Health Stroke Scale [NIHSS] score on admission: 4.0, range: 4–11), selected based on screening of 118 consecutive ischaemic stroke patients and in 14 volunteers (aged 62 ± 10 years), we continuously monitored RR intervals (RRI), mean arterial pressure (MAP) by means of photoplethysmography, mean cerebral blood flow velocity (CBFV) using transcranial Doppler ultrasonography, end-tidal CO_2 ($ETCO_2$) and respiration during 2-min deep breathing paced at 6 min^{-1} (0.1 Hz). To assess CA, we evaluated the impact of breathing-induced MAP oscillations on fluctuations of CBFV in the hemispheres with stroke, the non-involved hemispheres and randomly selected hemispheres of controls by applying cross-spectral analysis and calculating coherence, transfer function gain (CBFV–MAP gain) and phase shift angle between the two oscillating signals.
Results: Phase shift angle between MAP and CBFV oscillations showed values >0 and was significantly reduced in the hemispheres without stroke as compared to controls (0.39 ± 0.95 vs. −1.59 ± 0.33 rad, $p = 0.015$), whereas in the hemispheres with stroke, phase shift angle did not differ significantly from that observed in the control hemispheres. Clinical status of stroke patients significantly improved at discharge from the hospital (NIHSS: 2.0, range: 1–8, $p = 0.028$).
Conclusions: During the first days of ischaemic stroke of undetermined aetiology, dynamic cerebral autoregulation is compromised in the non-affected hemisphere, but not in the hemisphere with ischaemic lesion.

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1. Introduction

Cerebral ischaemic stroke is a leading cause of disability worldwide [1,2]. There are multiple well established risk factors for stroke such as age, hypertension, diabetes mellitus, heart diseases, atherosclerosis, cigarette smoking, previous occurrence of stroke and many other medical or behavioural conditions [1,2].

However, precise mechanisms leading to occurrence of stroke at a particular time in individual persons at risk still remain largely unknown, although several factors that may trigger a stroke have been identified. Yet, because of large heterogeneity of risk factors for stroke and potential stroke triggers, it is difficult to precisely determine, which mechanisms are mostly involved in the development of index cerebral infarction in different patients.

Maintenance of appropriate cerebral blood flow is largely dependent on preserved cerebral autoregulation (CA) involving metabolic, myogenic and cardiovascular autonomic, mainly sympathetic, mechanisms [3–5]. These mechanisms are responsible for maintenance of relatively stable cerebral blood flow despite changes in systemic blood pressure [3–5].

Therefore, it seems possible that impairment of CA may play a crucial role in the development of stroke, especially in conditions facilitating cerebral ischaemia such as metabolic disturbances or blood pressure fluctuations accompanying, e.g. intense emotions, rapid changes in body posture or occurring upon arousal from sleep [1,6–9]. Compromised CA has already been described in ischaemic stroke, particularly in patients with severe or moderate stroke of various aetiology [10–14]. However, it is still not clear whether an impairment of CA contributes to the occurrence of stroke or if CA becomes compromised as a result of stroke itself [13], especially that in some studies, CA impairment was demonstrated also in the non-affected hemispheres [10–12]. Such bilateral CA dysfunction, described in patients with lacunar stroke [12], was suggested to actually precede and participate in the pathogenesis of strokes due to small vessel disease [12].

Nonetheless, still, in approximately 30% of ischaemic stroke cases, it is not possible to establish its aetiology, even in the presence of specific risk factors [1,7]. Considering the fact that older age and diseases affecting the cardiovascular system are frequently associated with arterial and endothelial pathology, including cerebral resistance vessels [1,7], it seems possible that CA may be compromised in such states and may be not sufficiently effective in preventing cerebral blood flow decreases in conditions known to predispose to cerebral ischaemia [1,6].

Therefore, the aim of our study was to assess cerebral autoregulation in the affected and non-affected brain hemispheres of patients with hemispheric cerebral ischaemic stroke of undetermined aetiology.

2. Materials and methods

2.1. Study participants

One hundred eighteen patients with ischaemic stroke, diagnosed according to WHO criteria [15] admitted to the Stroke Unit at our Department of Neurology were screened for the study.

Risk factors profile, clinical features and results of diagnostic tests were assessed in the stroke patients. The latter included cranial computed tomography (CT), magnetic resonance imagining (MRI), extracranial arterial and transcranial Doppler ultrasound examination, transthoracic/transoesophageal echocardiography, intracranial/extracranial CT angiography, and/or angiography, electrocardiography (ECG), 24 h Holter (ECG) monitoring and blood tests for hypercoagulability, where indicated. We excluded 74 patients, in whom the aetiology of ischaemic stroke was established; according to TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria, they were classified as strokes due to large vessel disease, strokes due to small vessel disease, strokes due to cardioembolism, strokes due to other causes (e.g. vasculitis, coagulation disorder) or concurrent origin [16]. In addition, subjects with incomplete diagnostic procedures required for the TOAST criteria (21 cases) or admitted to the Stroke Unit beyond 48 h after stroke onset, were also excluded from the study (13 cases).

Consequently, we selected a study group of 10 patients with ischaemic stroke of undetermined aetiology. In 3 subjects, there was an inadequate acoustic window and one patient was not able to follow the breathing pattern included in the study protocol. Finally, we analysed the data of 6 patients; 2 women and 4 men, aged 66 ± 9 (mean ± standard deviation [SD]) years with acute stroke of undetermined aetiology localised in the middle cerebral artery territory; 3 patients had lesions in the left and 3 in the right hemisphere (Table 1). After admission to the hospital and on discharge, stroke severity was quantified by means of National Institutes of Health Stroke Scale (NIHSS).

Within the stroke group, hypertension was present in 4 patients (66%), hypercholesterolaemia in 3 (50%), ischaemic heart disease in 2 (33%), hypothyroidism (in euthyreotic state) was present in one patient and diabetes mellitus in another one. Detailed clinical characteristics of the patients are listed in Table 1.

The control group comprised 14 age-matched volunteers; 7 women and 7 men, aged 62 ± 10 (mean ± SD) years, with no history of stroke or other cerebrovascular disease. To determine the effects of the stroke itself on cerebral autoregulation, in our control group, we included persons with diseases and medication affecting the cardiovascular system similarly as concomitant diseases and medication in the stroke patients, such as: hypertension (43%), hypercholesterolaemia (29%), hypothyroidism (in euthyreotic state) or ischaemic heart disease in one patient. Detailed individual data are presented in Table 2.

Each participant was asked not to drink coffee, strong tea, or alcohol and not to smoke cigarettes within 6 h prior to the examination. All procedures were approved by the local ethics committee and written informed consent was obtained from each subject prior to testing, according to the Declaration of Helsinki.

2.2. Protocol and measurements

The patients were studied within 72 h following the first clinical signs of stroke. The study took place during morning hours in a dedicated research room kept at constant temperature of 21 °C and constant humidity. Prior to the