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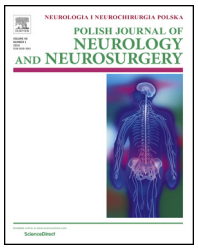

Original research article

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

Table 1 – Clinical characteristics of the patients with stroke.

	Gender	Age [years]	Stroke localisation	Infarct maximum diameter [cm]	NIHSS score (admission; discharge)	Concomitant diseases	Current drug use
1	M	54	Left fronto-temporo-parietal area, putamen and head of the caudate	2.41	11; 8	–	ASA
2	F	61	Left parietal lobe	1.3	5; 1	HT, HTH	ACEI, ASA, L-thyroxine, statin
3	F	72	Left fronto-temporal area	3.8	4; 2	HCh, HT, RA	ASA, BB, diuretic, low dose steroids, methotrexate, PPI, statin
4	M	65	Right parietal lobe	1.09	4; 2	DM, IHD	Insulin, nitrate, statin, ticlopidine
5	M	80	Right fronto-parietal area and posterior putamen	1.15	4; 2	HCh, HT	ACEI, ASA, CCB, diuretic, H1ant, hydroxizine,
6	M	61	Right parietal lobe	1.29	4; 2	HCh, HT, IHD	ACEI, ASA, BB, enoxaparin, statin

F, female; M, male; NIHSS, National Institutes of Health Stroke Scale; DM, diabetes mellitus; HCh, hypercholesterolemia; HT, hypertension; HTH, hypothyroidism; IHD, ischaemic heart disease; RA, rheumatoid arthritis; ACEI, angiotensin-converting enzyme inhibitor; ASA, acetylsalicylic acid; BB, beta blocker; CCB, calcium channel blocker; H1ant, histamine receptor 1 antagonist; PPI, proton pump inhibitor.

Table 2 – Clinical characteristics of the control group.

	Sex	Age [years]	Concomitant diseases	Current drug use
1	F	52	–	–
2	M	56	–	–
3	F	77	HCh, HT, HTH	ACEI, L-thyroxine, statin
4	M	58	–	–
5	M	55	–	–
6	M	50	HT	ACEI, diuretics
7	F	57	–	–
8	F	65	HCh, HT	ARA, diuretics, statin
9	M	78	HT, IHD	ACEI, ASA, BB, nitrates, statin, trimetazidine
10	F	61	–	–
11	M	70	HCh, HT	Diuretics, statin
12	M	48	HT	–
13	F	67	DJD, HCh	NSAID, PPI, statin
14	F	72	–	–

F, female; M, male; DJD, degenerative joint disease; HCh, hypercholesterolemia; HT, hypertension; HTH, hypothyroidism; IHD, ischaemic heart disease; ACEI, angiotensin-converting enzyme inhibitor; ARA, angiotensin II receptor antagonist; ASA, acetylsalicylic acid; BB, beta blocker; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pomp inhibitor.

testing, study participants remained in the supine position for approximately 40 min to ensure stabilization of their cardiovascular systems.

The middle cerebral arteries (MCAs) were insonated bilaterally and mean cerebral blood flow velocity (CBFV) was measured using transcranial Doppler ultrasound (Viasys Healthcare Inc., Madison, WI, USA). Once the MCAs had been identified through the temporal windows and the Doppler signal optimised by standard methods, the probes were attached to the skull in a fixed position using an adjustable head frame. Non-invasive beat-to-beat blood pressure (BP) was monitored by means of finger photoplethysmography (Nexfin Monitor, BMEYE, B.V., Amsterdam, The Netherlands) and heart rate (HR) was recorded continuously from precordial ECG (3 leads) (Biopac Systems, USA). Respiratory frequency was monitored using a respiratory belt placed around the abdomen (Biopac Systems, USA) as well as end-tidal CO_2 ($ETCO_2$) and haemoglobin saturation with oxygen ($SatO_2$) were monitored by means of a capnograph and a pulse oximeter integrated with the Biopac system.

After 40 min of rest in supine position, we recorded 10 min of baseline measurements and then we instructed our subjects to breathe deeply at a rate of 6 breaths per minute (5 s inspiration, 5 s expiration), following visual and auditory stimuli, for 2 min. The 2-min duration of the challenge manoeuvre was selected, as spectral analysis requires that the length of the analyzed signal be at least as long as the longest wavelength of interest. Duration of the manoeuvre comprised, therefore, as many as twelve such 10-s (0.1 Hz) breathing cycles, i.e. sufficient for further spectral analysis.

Oscillations in BP at frequencies up to 0.20 Hz are dampened by the cerebral vessels, whereas higher frequency changes pass directly to changes in cerebral blood flow [14,17]. Deep breathing paced at 6 cycles per minute (0.1 Hz)

mechanically induces sinusoidal 0.1 Hz oscillations of mean arterial pressure (MAP) that are subsequently transmitted onto the cerebral vessels and result in a similar 0.1 Hz variation in CBFV. Dynamic cerebral autoregulation can be assessed by observing the effects of changes in MAP on CBFV oscillations by means of cross-spectral analysis. Cross-spectral analysis enables comparison of pairs of oscillating signals when there is sufficient coherence (Coh), indicating linear coupling between these oscillations [18].

2.3. Data analysis

Data were recorded and transferred to the computer using Biopac MP150 module and the AcqKnowledge 4.0 software (Biopac Systems, USA). For further analysis, 90–110-s data segments with most stable $ETCO_2$ and CBFV values, i.e. following the first 1–3 inspiration-expiration cycles, were selected. Oscillations in RRI, MAP and CBFV were subjected to fast Fourier transform (FFT) power spectral analysis on overlapping windowed data segments and, subsequently, cross-spectral analysis was conducted to assess the transfer of oscillations in MAP onto the CBFV using a custom-made system.

To assess the transfer of MAP oscillations onto the CBFV, transfer function gain (MAP–CBFV gain) and phase shift angle between MAP and CBFV signals were calculated [14,19]. Wherever needed, phase wrapping was corrected by the factor of 2π.

Higher MAP–CBFV gain values indicate that MAP oscillations are transferred to cerebral blood flow velocity oscillations to a greater extent, which may suggest an impairment of cerebral autoregulation [4,19]. Normally, phase shift angle between MAP and CBFV signals is <0 indicating that CBFV oscillations actually precede MAP oscillations thus ''preparing'' cerebral vascular bed for changes in BP and minimizing potential unfavourable effects of BP fluctuations onto cerebral blood flow. The greater the absolute value of this phase shift, the better the autoregulation [14].

In order to avoid possible differences in cerebrovascular resistance (CVR) and vasomotor reactivity to changes in pCO_2 between the patients and controls, we normalised MAP–CBFV gain by the participant's mean CBFV and MAP and expressed the normalised value in arbitrary units [a.u.] [19,20]. The normalisation factor is the ratio of MAP to CBFV, which reflects CVR. Therefore, the normalised MAP–CBFV gain can be used to estimate the dynamic CBFV responses to MAP oscillations at a given CVR value [20].

2.4. Statistical analysis

The data are presented as means ± standard error of the mean (SEM) or median and range. Due to the skewed distribution of 0.1 Hz spectral powers of MAP and CBFV, these data were subjected to statistical analysis after logarithmic transformation. Student's *t*-test for independent samples was used to compare the observed variables between the stroke patients and the control group. NIHSS scores on admission and discharge from the hospital were compared using the Wilcoxon signed rank test. Mean values of CBFV, CVR during deep breathing, 0.1 Hz CBFV spectral power, MAP–CBFV gain and phase shift angle were compared among patients' hemispheres with ischaemic lesion, patients' hemispheres without the lesion and randomly selected hemispheres of the controls using one-way analysis of variance (ANOVA) with Fisher least significant difference (LSD) post-test where a significant *p*-value was found. The rationale for random selection of one of the control hemispheres was based on the fact that there were no premises to conclude that there may be differences in CA between the left and right hemisphere in persons from our control group.

Because of non-homogeneity of variances of CVR values obtained in the studied hemispheres at baseline, the two-sided Jonckheere–Terpstra test was applied for the comparison of baseline CVR among patients' hemispheres with ischaemic lesion, patients' hemispheres without the lesion and the control hemispheres [21]. All *p*-values were two-sided and statistical significance level was set at $p < 0.05$.

3. Results

Median NIHSS score assessed in stroke patients at discharge from the hospital was significantly lower than that on admission (2.0, range: 1–8 vs. 4.0, range 4–11; $p = 0.028$).

Table 3 – Mean values of the variables recorded during baseline period in stroke patients and the control group: R-R intervals (RRI), mean arterial pressure (MAP), mean cerebral blood flow velocity (CBFV), cerebrovascular resistance (CVR) and end-tidal CO_2 ($ET\ CO_2$).

	Patients ($n = 6$)	Controls ($n = 14$)	*p*-Value
RRI [ms]	858 ± 21.4	879 ± 25.5	0.625[a]
MAP [mm Hg]	90.75 ± 5.57	84.66 ± 3.57	0.365[a]
ET CO_2 [mm Hg]	31.45 ± 3.88	32.16 ± 1.77	0.847[a]

	Ischaemic hemispheres	Non-ischaemic hemispheres	Controls ($n = 14$)	*p*-Value
CBVF [cm s^{-1}]	27.72 ± 5.95	26.96 ± 2.94	34.46 ± 4.78	0.540[b]
CVR [mm Hg s cm^{-1}]	4.17 ± 0.93	3.45 ± 0.44	2.86 ± 0.25	0.184[c]

Values are means ± standard error of the mean.
[a] Student's *t*-test for two independent samples.
[b] ANOVA.
[c] Jonckheere–Terpstra test.

Table 4 – Mean values of the variables recorded during 0.1 Hz paced deep breathing in stroke patients and the control group: R-R intervals (RRI), mean arterial pressure (MAP), mean cerebral blood flow velocity (CBFV), cerebrovascular resistance (CVR), end-tidal CO_2 (ET CO_2), MAP and CBFV oscillations, normalized MAP–CBFV gain and phase shift angle at 0.1 Hz.

	Patients ($n = 6$)	Controls ($n = 14$)	p-Value
RRI [ms]	831 ± 33.88	886 ± 32.7	0.335[a]
MAP [mm Hg]	87.84 ± 5.22	80.87 ± 4.58	0.385[a]
ET CO_2 [mm Hg]	30.74 ± 3.81	29.39 ± 2.34	0.759[a]
lg 0.1 Hz power of MAP [lg mm Hg^2]	0.85 ± 0.16	1.16 ± 0.09	0.096[a]

	Ischaemic hemispheres	Non-ischaemic hemispheres	Controls ($n = 14$)	p-Value
CBVF [cm s^{-1}]	24.55 ± 4.40	22.27 ± 3.50	27.68 ± 4.29	0.704[b]
CVR [mm Hg s cm^{-1}]	4.44 ± 1.02	4.57 ± 0.83	3.38 ± 0.30	0.269[b]
lg 0.1 Hz power of CBFV [lg cm^2 s^{-2}]	0.09 ± 0.24	−0.09 ± 0.13	0.17 ± 0.13	0.552[b]
MAP–CBFV gain normalized [a.u.]	2.06 ± 0.57	1.76 ± 0.43	2.02 ± 0.27	0.874[b]
Phase shift angle [rad]	−0.70 ± 0.51	0.39 ± 0.95*	−1.59 ± 0.33	0.045[b]

Values are mean ± standard error of the mean.
[a] Student's t-test for two independent samples.
[b] ANOVA.
* $p < 0.05$ compared with controls, Fisher LSD post-test.

Blood oxygen saturation in all subjects during baseline and deep breathing test was within normal limits and did not differ between the stroke patients and controls ($p > 0.05$). Mean values of RRI, MAP and $ETCO_2$ did not differ significantly between patients and controls during baseline or during 0.1 Hz deep breathing (Tables 3 and 4). At baseline, CBFV or CVR did not differ among patients' hemispheres with ischaemic lesion, patients' hemispheres without the lesion and hemispheres of the controls (Table 3).

Metronomic breathing induced similar oscillations in MAP in the stroke patients and controls ($p = 0.096$), as well as similar CBFV oscillations in the ischaemic, non-ischaemic and control cerebral hemispheres ($p = 0.552$) (Table 4). Coherence between 0.1 Hz oscillations in MAP and CBFV during deep breathing was above 0.4 in all study participants. There were no differences in MAP–CBFV gain among patients' hemispheres with ischaemic lesion, hemispheres without such lesion and control hemispheres ($p = 0.874$) (Table 4).

However, phase shift angle was significantly reduced in the hemispheres without stroke as compared to controls (0.39 ± 0.95 vs. −1.59 ± 0.33 rad, $p = 0.015$) and its value was even >0, indicating that CA is compromised in these hemispheres, with CBFV oscillations passively following changes in MAP (Fig. 1). In contrast, phase shift angles between MAP and CBFV oscillations assessed in the ischaemic hemispheres, similarly to control hemispheres, were <0 (Table 4), indicating preserved CA, with CBFV oscillations leading MAP fluctuations.

4. Discussion

In our study, we showed that cerebral autoregulation in the acute phase of ischaemic stroke of undetermined aetiology is impaired in the hemisphere not affected by stroke, but not in the hemisphere with the ischaemic focus. This was demonstrated by reduced phase shift between MAP and CBFV oscillations observed in the non-affected hemispheres of patients with stroke.

This result may seem not to support previous findings of impaired CA in the hemispheres with infarct due to large vessel occlusion [12–14]. However, in ischaemic stroke of this aetiology, haemodynamic disturbances of blood flow in any larger vessel are sufficiently pronounced to significantly

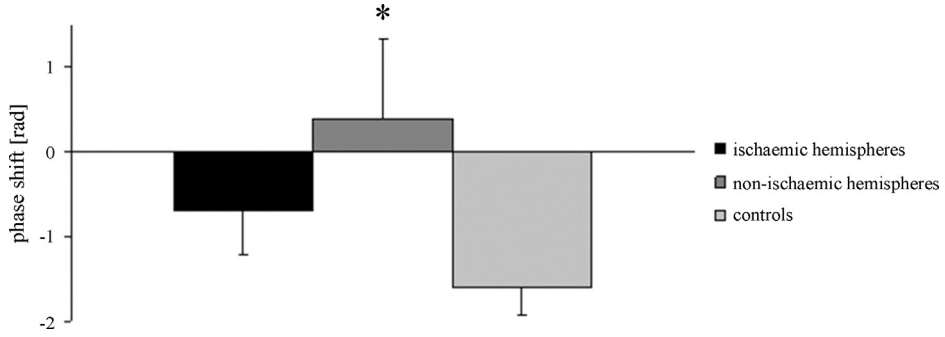

Fig. 1 – Phase shift angle between mean arterial pressure (MAP) and cerebral blood flow velocity (CBFV) oscillations in the ischaemic hemispheres, the non-ischaemic hemispheres and the control group during 0.1 Hz paced breathing. Significant differences from the controls are indicated by * ($p < 0.05$, ANOVA with Fisher LSD post-test).

affect cerebral blood flow in the whole hemisphere and thus influence CA effectiveness [12,14]. In contrast, our patients had only mild disability (only 1 patient had NIHSS >8 on admission) and small ischaemic changes found in neuroimaging. Moreover, our findings are consistent with results of some studies showing that CA can be intact or only transiently impaired in patients with mild stroke [22–24]. Furthermore, evaluation of CA in stroke due to small vessel disease, a condition underlying the majority of lacunar strokes, demonstrated that CA can be compromised in both hemispheres of the brain and not only in the hemisphere affected by stroke [12]. The study by Immink et al. also suggests that impairment of CA is likely present before occurrence of stroke and may largely contribute to the pathogenesis of lacunar strokes [12]. Yet, at the time of this study, our patients did not have radiologic manifestations of small vessel disease.

It is also not clear if CA dysfunction observed in our study resulted from the stroke itself or if CA impairment was present before stroke onset. The finding of impaired CA in the hemisphere without ischaemic focus suggests that there may have been CA abnormalities already before the occurrence of stroke. However, it is unclear, why CA was not impaired in the ischaemic hemisphere. One possible explanation is that prior to stroke onset, CA might have been compromised in both hemispheres and the occurrence of stroke in one of them elicited systemic and local mechanisms serving to restore blood flow to the ischaemic region. Such mechanisms usually include increase in systemic BP and local release of metabolites with vasoactive properties [25,26]. Local vasodilation and the rise in BP may have, therefore, improved, at least partially, cerebral haemodynamics in the affected hemisphere. Secondly, considering that neural, mainly sympathetic, control of the cerebral resistance vessels plays a crucial role in the mechanism of dynamic CA [5,17,27–29], it seems possible that the improvement of CA observed in our study was at least in part mediated by sympathetic activation associated with systemic haemodynamic changes and superimposed on local metabolic perturbations.

Although there is no information on whether CA was impaired or not in our study patients before the stroke, our findings of asymmetrical CA dynamics may suggest that relative CA improvement might have occurred in response to cerebral ischaemia. This observation is also supported by results of some studies showing that bilateral impairment of CA can occur not only in small vessel disease but also as a result of a more severe stroke [28,29]. In our study, however, stroke severity was quite low as was the range of local haemodynamic disturbances. This may explain, why CA was not compromised in the hemisphere with stroke in this study. Nonetheless, our results do seem to be consistent with findings of stroke-induced impairment of CA – in fact, phase shift angle between MAP and CBFV oscillations observed in the ischaemic hemispheres, although not significantly different from that of controls, did show a tendency to smaller values.

One of limitations of this study is the small number of patients. However, our goal was to include only such ischaemic stroke patients, in whom the cause of stroke could not be found despite use of all the recommended laboratory studies. Therefore, we did not include those patients with unknown stroke aetiology, where not all the diagnostic procedures required for TOAST classification were performed. Considering also the fact that our patients were selected from quite a large number of over one hundred consecutive patients with ischaemic stroke, it seems that our study participants do constitute quite a uniform group, where the course of stroke was affected mainly by changes in cerebrovascular autoregulation.

Concomitant cardiovascular diseases, such as hypertension, may be associated with CA disturbances. However, it is unlikely that they significantly affected our results, as the number of cardiovascular diseases was similar between the patients and persons from the control group. To avoid any bias in our study, we included such patients, as they represented quite a typical population susceptible to stroke.

5. Conclusions

To our knowledge, this is the first study to demonstrate that in mild ischaemic stroke of undetermined aetiology, CA is compromised only in the not affected hemisphere.

Furthermore, dynamic CA can be relatively improved in the ischaemic hemisphere and this might be associated with better outcome, as stroke severity at discharge from the hospital was markedly improved in our patients. Moreover, our findings may also suggest that impairment of dynamic cerebral autoregulation may play an important role in the pathomechanism of at least some ischaemic strokes of undetermined aetiology.

Conflict of interest

None declared.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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