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Hemorrhagic transformation and cerebral edema in acute ischemic stroke: Link to cerebral autoregulation

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ABSTRACT

Background: Hemorrhagic transformation and cerebral edema are feared complications of acute ischemic stroke but mechanisms are poorly understood and reliable early markers are lacking. Early assessment of cerebrovascular hemodynamics may advance our knowledge in both areas. We examined the relationship between dynamic cerebral autoregulation (CA) in the early hours post ischemia, and the risk of developing hemorrhagic transformation and cerebral edema at 24 h post stroke

Methods: We prospectively enrolled 46 patients from our center with acute ischemic stroke in the middle cerebral artery territory. Cerebrovascular resistance index was calculated. Dynamic CA was assessed by transfer function analysis (coherence, phase and gain) of the spontaneous blood flow velocity and blood pressure oscillations. Infarct volume, hemorrhagic transformation, cerebral edema, and white matter changes were collected from computed tomography performed at presentation and 24 h.

Results: At admission, phase was lower (worse CA) in patients with hemorrhagic transformation [6.6 ± 30 versus 45 ± 38°; adjusted odds ratio 0.95 (95% confidence internal 0.94–0.98), $p = 0.023$] and with cerebral edema [6.6 ± 30 versus 45 ± 38°, adjusted odds ratio 0.96 (0.92–0.999), $p = 0.044$]. Progression to edema was associated with lower cerebrovascular resistance (1.4 ± 0.2 versus 2.3 ± 1.5 mm Hg/cm/s, $p = 0.033$) and increased cerebral blood flow velocity (51 ± 25 versus 42 ± 17 cm/s, $p = 0.033$) at presentation. All hemodynamic differences resolved at 3 months

Conclusions: Less effective CA in the early hour post ischemic stroke is associated with increased risk of hemorrhagic transformation and cerebral edema, possibly reflecting breakthrough hyperperfusion and microvascular injury. Early assessment of dynamic CA could be useful in identifying individuals at risk for these complications.

1. Introduction

Hemorrhagic transformation (HT) and cerebral edema (CE) are feared complications of acute ischemic stroke (IS), which are often associated with poor neurological outcome [1]. HT is especially serious when caused by thrombolysis with recombinant tissue plasminogen activator (rtPA) [2] and in severe strokes. Larger infarcts can also develop malignant CE [3]. Predicting CE and HT could prevent further cerebral damage [4]. Yet, we know very little about their underlying mechanisms and early predictors are still inexistent [5].

Microvascular disruption following brain ischemia are key players in causing vasogenic CE and HT in animal models [4,6] as well as in humans [7]. Imaging studies also suggest that cerebral microvascular injury, manifested as white matter changes, increase the risk of HT [8]. Therefore, impaired microvascular function and less effective CA may be one mechanism linking white matter changes to HT.

Dynamic cerebral autoregulation (CA) can be rapidly and noninvasively assessed at the bedside by transfer function analysis (TFA) between spontaneous oscillations in blood pressure and cerebral blood flow velocity [9–14]. There is an overall agreement that dynamic CA is impaired in acute IS [15,16] but its relationship with HT or CE is not known.

We examined the relationship between dynamic CA, measured within 6 h of symptom-onset through the chronic phase of IS, and the risk to development of HT or CE.

2. Methods

2.1. Population studied

All patients, or proxy, gave written and signed consent. Local ethical committee approved the study. We consecutively included patients

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with acute IS in the middle cerebral artery (MCA) territory admitted to the stroke unit at Hospital São João Centre, Porto. Exclusion criteria included hemodynamic instability requiring vasoactive agents, other central neurological co-morbidities or insufficient temporal acoustic window. We recruited 46 patients. In sixteen patients the symptomatic MCA was occluded. Separate analyses were performed for patients with and without occlusion of symptomatic MCA. In 3 cases we did not have imaging confirmation of the infarcted territory and patients were included based on clinical signs of MCA territory infarction (aphasia). All patients underwent neurological examination at presentation and National Institutes of Health Stroke Scale (NIHSS) scores were recorded from admission to discharge. All participants underwent cervical and transcranial ultrasound studies (Vivid *e*; GE) before evaluation to exclude hemodynamically significant extra- or intracranial stenoses.

2.2. Monitoring protocol

Evaluations were carried out in the stroke unit with head of the bed at 0° during the 10 min of recording. Arterial blood pressure (ABP) was continuously monitored with a finger cuff in the unaffected side using Finometer MIDI (FMS, Amsterdam, Netherlands). Additionally, blood pressure was assessed with oscillometric cuff (Dash 2500, GE, UK). HR was assessed from lead II of a standard 3-lead electrocardiogram (ECG). Cerebral blood flow velocity (CBFV) was recorded bilaterally from M1 segment of MCA (depth of 50–55 mm) with 2-MHz monitoring probes secured with a headband (Doppler BoxX, DWL, Singen, Germany). End-tidal carbon dioxide (CO_2) was evaluated by nasal cannula attached to Respsense capnograph (Nonin, Amsterdam, The Netherlands). All data was synchronized at 400 Hz with Powerlab (AD Instruments, Oxford, UK) and stored for offline analysis. Data collection occurred for 10 min within 6 h and at 24 h from symptoms-onset and also at 3 months in survivors (n = 31).

2.3. Data analysis

All signals were inspected and artifacts removed. Systolic, diastolic and mean values of ABP (MBP) and CBFV (MFV) were calculated. Cerebrovascular resistance index (CVRi) was calculated by MBP/MFV reflecting vasomotor function [17]. Transfer function Analysis (TFA) was used to assess dynamic CA by calculating coherence, gain and phase parameters from beat-to-beat spontaneous oscillations in MFV and MBP as previously reported [13,18]. Ten minutes of normalized data were interpolated at 100 Hz into uniform time basis; averaged periodogram was calculated by Welch method [13] with Hanning window of 30 s, with two-third overlap. The cross spectrum between MBP and MFV signals was calculated and used to determine coherence, phase and gain in the low (autoregulatory) frequency range (0.03–0.15 Hz). Lower coherence (correlation coefficient) and gain (damping mechanism) and higher phase (speed of the autoregulatory response) between oscillations of MBP and MFV indicate more effective CA [13].

2.4. Neuroimaging assessment

Head CT (Siemens Somaton Emotion Duo, Erlangen, Germany), with 3 to 6 mm slices, was performed on admission and repeated at 24 h. Any hemorrhagic transformation (from petechial hyperdensities to parenchymal hematoma, defined by ECASS [2] was considered. Cerebral edema was defined as any focal brain swelling causing midline shift [19]. Subtle edema, such as sulci or ventricular effacement was not included. Infarct volume was measured at 24 h following ABC/2 rule [20]. White matter changes were graded by the van Swieten scale [21,22].

2.5. Statistical analysis

Normality was determined by Shapiro-Wilk test. Groups with and without HT or CE were compared with chi-square/Fisher's exact test for nominal variables and Student *t*-test or Mann-Whitney for continuous variables as appropriate. Repeated measures ANOVA was used to find significant differences in hemodynamic variables along time and between groups with multiple comparisons corrected by Bonferonni's post-hoc test. Spearman's rho correlation analysis was performed to evaluate the relationship between TFA parameters and continuous baseline variables. We estimated the effects of CA parameters in HT or CE by calculating the odds ratios and 95% interval confidence using logistic regression with adjustment to baseline variables by forward conditional method. Statistical significance was set at $p < 0.05$.

Table 1
Demographic, clinical and radiographic characteristics of subjects at baseline.

	Total	Hemorrhage		Cerebral edema	
		Yes	No	Yes	No
	n = 46	n = 10	n = 36	n = 8	n = 38
Demographics					
Male	25 (54)	5 (50)	20 (55)	5 (62)	20 (53)
Age, years (mean ± SD)	73 ± 12	76 ± 15	72 ± 11	77 ± 10	73 ± 13
BMI, $kg \cdot m^{-2}$ (mean ± SD)	27 ± 5	26 ± 5	28 ± 4	26 ± 6	28 ± 5
Previous stroke/TIA, n (%)	7 (15)	1 (10)	6 (17)	3 (38)	5 (62)
Atrial fibrillation, n (%)	20 (43)	6 (60)	14 (39)	3 (34)	17 (45)
Hypertension, n (%)	24 (74)	8 (80)	26 (72)	6 (75)	28 (73)
Diabetes mellitus, n (%)	17 (37)	4 (40)	13 (36)	3 (37)	14 (37)
Dyslipidemia, n (%)	37 (73)	7 (70)	27 (75)	8 (100)	26 (68)
Tobacco, n (%)	6 (13)	0 (0)	6 (17)	0 (0)	6 (16)
Ipsilateral carotid stenosis 50–60%, n (%)	6 (13)	0 (0)	6 (17)	0 (0)	6 (16)
Stroke characteristics					
Occlusion of affected MCA, n (%)	16 (35)	4 (40)	12 (33)	4 (50)	12 (31)
Thrombolysis, n (%)	35 (76)	10 (100)	25 (70)	7 (88)	28 (74)
NIHSS score [median(IQR)]	14 (9–22)	20 (8–22)	13 (9–21)	22 (18–22)	*12 (9–20)
Neuroimaging [median(IQR)]					
Infarct volume, mL	19 (2–9)	99 (23 − 212)	*16 (1–104)	§172 (109–333)	15 (1–62)
Severity of white matter changes	2 (1–3)	3 (2–4)	*2 (1–3)	2 (1–3)	2 (1–4)

Body-Mass Index (BMI), Transient Ischemic Attack (TIA), Modified Rankin Scale (MRS), middle cerebral artery (MCA), National Institutes of Health Stroke Scale (NIHSS).

* $p < 0.05$ for Student's *t*-test/Mann-Whitney or Chi-square/Fisher's exact test *p* value for differences in continuous or categorical variables, respectively, between subgroups with and without hemorrhagic transformation or cerebral edema.

§ $p < 0.001$ for Student's *t*-test/Mann-Whitney or Chi-square/Fisher's exact test *p* value for differences in continuous or categorical variables, respectively, between subgroups with and without hemorrhagic transformation or cerebral edema.