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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 $45 \pm 38^\circ$; adjusted odds ratio 0.95 (95% confidence interval 0.94–0.98), $p = 0.023$] and with cerebral edema [6.6 ± 30 versus $45 \pm 38^\circ$, 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

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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.

Keywords

Cerebral autoregulation; Cerebral vasoreactivity; Cerebral edema; Cerebral hemorrhage; Ischemic stroke; Transcranial Doppler

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 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 ϵ ; 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 (CO₂) 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 Somatom 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 $p < 0.05$.

3. Results

Demographic and clinical characteristics were similar between subgroups with and without HT or CE (Table 1). Four patients had both CE and HT. Ten patients developed HT scored H2 in 3, PH1 in 5, and PH2 in 2. Eight patients developed CE with mean midline shift of 5.6 ± 2.2 mm. Patients with HT, had higher stroke volumes ($p = 0.028$) and greater severity of white matter changes ($p = 0.030$). CE was also associated with larger stroke volumes ($p < 0.001$) and higher NIHSS admission scores ($p = 0.023$). MCA occlusion was detected at admission (after thrombolysis if applied) in 16 (35%) of our cohort by transcranial ultrasound allowing only contralateral MCA to be monitored.

Hemodynamic data is presented in Table 2. MBP was elevated during the first 24 h as compared to 3 months ($p = 0.003$) without differences between subgroups. Most patients, showed increased CVRi in the ischemic hemisphere at acute stage (<6 h compared to 24 h $p = 0.033$ and to 3 months $p = 0.039$), but those who developed CE, had opposite profile, with lower CVRi in the infarcted hemisphere (<6 h $p = 0.033$ and 24 h $p = 0.044$). This subgroup also showed increased MFV in ipsilateral hemisphere during the acute period (<6 h $p = 0.033$ and 24 h $p = 0.020$). All hemodynamic differences resolved at 3 months.

We first examined the relationship between dynamic CA measures and baseline clinical and radiographic characteristics in all cohort. Ipsilateral phase was negatively correlated with stroke volume (Spearman's rho -0.444 , $p = 0.020$), and bilateral gain was positively correlated with severity of white matter changes (ipsilateral $r = 0.368$, $p = 0.040$; contralateral $r = 0.402$, $p = 0.006$).

Next, we examined the relationship between dynamic CA measures at admission and development of HT and CE at 24 h. Figs. 1 and 2 compares dynamic CA measures (phase and gain) between those with and without HT or CE, respectively. At admission, phase was significantly lower in ipsilateral hemisphere in those patients who subsequently developed HT (<6 h $p = 0.033$; 24 h $p = 0.047$) or CE (<6 h $p = 0.002$) on their 24 h head CT. These differences resolved at 3 months ($p = 0.094$ and $p = 0.567$, respectively). Gain was not associated with HT or CE (ipsilateral, $p = 0.597$ and 0.247 ; contralateral side $p = 0.169$ and 0.643). Coherence was not different between groups and times (data not shown).

We estimated the effects of ipsilateral phase <6 h and the risk of HT or CE by calculating the odds ratios and 95% interval confidence using logistic regression adjusted to (stroke volume and white matter changes or NIHSS, respectively) by forward conditional method. Phase (< 6 h) was lower (worse CA) in patients with hemorrhagic transformation [6.6 ± 30 versus 45

$\pm 38^\circ$; adjusted odds ratio 0.95 (95% confidence interval 0.94–0.98), $p = 0.023$] and with cerebral edema [9.9 ± 30 versus $41 \pm 38^\circ$; adjusted odds ratio 0.96 (0.92–0.999), $p = 0.044$].

4. Discussion

Our data show that early impairments in dynamic CA during acute ischemic stroke are associated with development of HT and CE. In these patients, lower phase in the acute (<6 h) period was associated with development of HT and CE on the 24 h CT scan.

Dynamic cerebral autoregulation using transfer function analysis has been widely studied in cerebrovascular disease [9–11,15,16,23–30]. Lower phase shift, reflecting less effective autoregulation, has been demonstrated in poorly compensated carotid or MCA stenosis [27,29, 30] or vasospasm after subarachnoid hemorrhage [27,28] as well as in ischemic stroke [15,16]. However, most prior studies did not assess phase in the early hyperacute period post ischemia, nor did they relate it to HT or CE. We show that in this hyperacute period (<6 h), impaired cerebral autoregulation, as reflected by lower phase, is associated with development of CE and HT. One mechanistic pathway explaining these observations is that the failure of the autoregulatory capability of cerebral resistance vessels results in disruption of Starling's principle and pathological elevation of the hydrostatic pressure across the capillary bed, which could then aggravate the existing blood-brain barrier leakage and cause CE and HT [12,13]. In favor of this hypothesis, we found abnormally lower CVRi and increased MFV in ischemic hemisphere preceding the development of CE. A less effective CA will also endanger the ischemic penumbra [31], which is acutely perfusion dependent. This may be the mechanisms linking low phase values at presentation to larger infarct area at 24 h in our data. Unlike phase, gain has not been linked to ischemic stroke in prior studies [16,26] which is in line with our findings.

Dohmen et al. [32] reported previously that impaired cerebral auto-regulation measured by tissue oxygen pressure correlation seems to play a key role for development of a malignant course and might serve as a predictive marker. We extend their results by showing that this deregulation is already present from in the very early hours of ischemia and also in less severe patients able to be monitored non-invasively with TCD.

Another finding of this study relates to temporal changes in CVRi. Higher CVRi in the early hours post stroke suggests an acute cerebral vasoconstriction response. This may be explained by high endothelin-1 levels [33], a potent cerebral vasoconstrictor, but also by the presence of microthrombosis [6] and/or cytotoxic edema [4]. Curiously, patients who developed CE show a paradoxical response, with lower CVRi at presentation. This maladaptive vasodilatory response could contribute to CE. The molecular mechanisms underlying this observation warrant further investigation and offer a potential target for preventing secondary malignant cerebral edema in large strokes.

Finally, all the acute changes in CA resolved within 3 months. The transient nature of autoregulatory failure is pathophysiologically intuitive and provides biological plausibility for early CA measures as meaningful quantitative markers of disease severity and risk for

CE and HT. Early modulation of cerebral autoregulation [4] may therefore, be a potential therapeutic target towards improve outcome in ischemic stroke.

This study has some limitations. We recognize the limitation on the number of subjects enrolled. For instance patients with HT were 4 years older, 60% vs. 39% had AF, 100% vs. 70% performed thrombolysis. However there was no statistical significance, likely related to the small sample size. This might explain the reason why HT and CE were not found to be significantly related to thrombolysis [2].

Regarding the limitations inherent CA assessment to TCD [34], some non-stationary conditions (e.g., agitation, mental changes) might turn linear methods like TFA less reliable. Further development of nonlinear techniques to assess CA could clarify this point.

Finally, we did not assess MCA patency before thrombolysis. Therefore, we cannot be ascertained about recanalization or non-recanalization. However, the subgroup of patients with non-occluded MCA at presentation represents mostly recanalized (by thrombolysis or spontaneously) cases whereas MCA occlusion subgroup represents mainly non-recanalized (all except one had thrombolysis).

5. Conclusions

In conclusion, our findings provide support for early autoregulatory impairment as a possible mechanism leading to development of HT and CE in patients who present with acute ischemic stroke. Assessment of dynamic CA may help to identify high risk individuals and possibly provide a therapeutic target in the future.

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References

1. Wardlaw JM, Murray V, Berge E, del Zoppo G, Sandercock P, Lindley RL, Cohen G. Recombinant tissue plasminogen activator for acute ischaemic stroke: an updated systematic review and meta-analysis. *Lancet*. 2012; 379(9834):2364–2372. [PubMed: 22632907]
2. Fiorelli M, Bastianello S, von Kummer R, del Zoppo GJ, Larrue V, Lesaffre E, Ringleb AP, Lorenzano S, Manelfe C, Bozzao L. Hemorrhagic transformation within 36 hours of a cerebral infarct: relationships with early clinical deterioration and 3-month outcome in the European Cooperative Acute Stroke Study I (ECASS I) cohort. *Stroke*. 1999; 30(11):2280–2284. [PubMed: 10548658]
3. Steiner T, Ringleb P, Hacke W. Treatment options for large hemispheric stroke. *Neurology*. 2001; 57(5 Suppl 2):S61–S68. [PubMed: 11552058]
4. Balami JS, Chen RL, Grunwald IQ, Buchan AM. Neurological complications of acute ischaemic stroke. *Lancet Neurol*. 2011; 10(4):357–371. [PubMed: 21247806]
5. Whiteley WN, Slot KB, Fernandes P, Sandercock P, Wardlaw J. Risk factors for intracranial hemorrhage in acute ischemic stroke patients treated with recombinant tissue plasminogen activator:

a systematic review and meta-analysis of 55 studies. *Stroke*. 2012; 43(11):2904–2909. [PubMed: 22996959]

6. Wang X, Lo EH. Triggers and mediators of hemorrhagic transformation in cerebral ischemia. *Mol Neurobiol*. 2003; 28(3):229–244. [PubMed: 14709787]
7. Bang OY, Buck BH, Saver JL, Alger JR, Yoon SR, Starkman S, Ovbiagele B, Kim D, Ali LK, Sanossian N, Jahan R, Duckwiler GR, Vinuela F, Salamon N, Villablanca JP, Liebeskind DS. Prediction of hemorrhagic transformation after recanalization therapy using T2*-permeability magnetic resonance imaging. *Ann Neurol*. 2007; 62(2):170–176. [PubMed: 17683090]
8. Curtze S, Haapaniemi E, Melkas S, Mustanoja S, Putaala J, Sairanen T, Sibolt G, Tiainen M, Tatlisumak T, Strbian D. White matter lesions double the risk of post-thrombolytic intracerebral hemorrhage. *Stroke*. 2015
9. Castro PM, Santos R, Freitas J, Panerai RB, Azevedo E. Autonomic dysfunction affects dynamic cerebral autoregulation during Valsalva maneuver: comparison between healthy and autonomic dysfunction subjects. *J Appl Physiol*. 2014; 117(3):205–213. [PubMed: 24925980]
10. Purkayastha S, Fadar O, Mehregan A, Salat DH, Moscufo N, Meier DS, Guttmann CR, Fisher ND, Lipsitz LA, Sorond FA. Impaired cerebrovascular hemodynamics are associated with cerebral white matter damage. *J Cereb Blood Flow Metab*. 2014; 34(2):228–234. [PubMed: 24129749]
11. Nakagawa K, Serrador JM, LaRose SL, Sorond FA. Dynamic cerebral autoregulation after intracerebral hemorrhage: a case-control study. *BMC Neurol*. 2011; 11:108. [PubMed: 21884574]
12. Panerai RB. Assessment of cerebral pressure autoregulation in humans—a review of measurement methods. *Physiol Meas*. 1998; 19(3):305–338. [PubMed: 9735883]
13. Zhang R, Zuckerman JH, Giller CA, Levine BD. Transfer function analysis of dynamic cerebral autoregulation in humans. *Am J Phys*. 1998; 274(1 Pt 2):H233–H241.
14. Meel-van den Abeelen AS, van Beek AH, Slump CH, Panerai RB, Claassen JA. Transfer function analysis for the assessment of cerebral autoregulation using spontaneous oscillations in blood pressure and cerebral blood flow. *Med Eng Phys*. 2014; 36(5):563–575. [PubMed: 24721458]
15. Aries MJ, Elting JW, De Keyser J, Kremer BP, Vroomen PC. Cerebral autoregulation in stroke: a review of transcranial Doppler studies. *Stroke*. 2010; 41(11):2697–2704. [PubMed: 20930158]
16. Reinhard M, Wihler C, Roth M, Harloff A, Niesen WD, Timmer J, Weiller C, Hetzel A. Cerebral autoregulation dynamics in acute ischemic stroke after rtPA thrombolysis. *Cerebrovasc Dis*. 2008; 26(2):147–155. [PubMed: 18560218]
17. Panerai RB. The critical closing pressure of the cerebral circulation. *Med Eng Phys*. 2003; 25(8): 621–632. [PubMed: 12900178]
18. Aaslid R, Lindegaard KF, Sorteberg W, Nornes H. Cerebral autoregulation dynamics in humans. *Stroke*. 1989; 20(1):45–52. [PubMed: 2492126]
19. Strbian D, Meretoja A, Putaala J, Kaste M, Tatlisumak T, Helsinki G. Stroke Thrombolysis Registry. Cerebral edema in acute ischemic stroke patients treated with intravenous thrombolysis. *Int J Stroke*. 2013; 8(7):529–534. [PubMed: 22405327]
20. Sims JR, Gharai LR, Schaefer PW, Vangel M, Rosenthal ES, Lev MH, Schwamm LH. ABC/2 for rapid clinical estimate of infarct, perfusion, and mismatch volumes. *Neurology*. 2009; 72(24): 2104–2110. [PubMed: 19528517]
21. van Swieten JC, Hijdra A, Koudstaal PJ, van Gijn J. Grading white matter lesions on CT and MRI: a simple scale. *J Neurol Neurosurg Psychiatry*. 1990; 53(12):1080–1083. [PubMed: 2292703]
22. Pantoni L, Simoni M, Pracucci G, Schmidt R, Barkhof F, Inzitari D. Visual rating scales for age-related white matter changes (leukoaraiosis): can the heterogeneity be reduced? *Stroke*. 2002; 33(12):2827–2833. [PubMed: 12468777]
23. Reinhard M, Neunhoeffer F, Gerds TA, Niesen WD, Buttler KJ, Timmer J, Schmidt B, Czosnyka M, Weiller C, Hetzel A. Secondary decline of cerebral autoregulation is associated with worse outcome after intracerebral hemorrhage. *Intensive Care Med*. 2010; 36(2):264–271. [PubMed: 19838669]
24. Lang EW, Diehl RR, Mehdorn HM. Cerebral autoregulation testing after aneurysmal subarachnoid hemorrhage: the phase relationship between arterial blood pressure and cerebral blood flow velocity. *Crit Care Med*. 2001; 29(1):158–163. [PubMed: 11176177]

25. Panerai RB, White RP, Markus HS, Evans DH. Grading of cerebral dynamic autoregulation from spontaneous fluctuations in arterial blood pressure. *Stroke*. 1998; 29(11):2341–2346. [PubMed: 9804645]
26. Reinhard M, Roth M, Guschlbauer B, Harloff A, Timmer J, Czosnyka M, Hetzel A. Dynamic cerebral autoregulation in acute ischemic stroke assessed from spontaneous blood pressure fluctuations. *Stroke*. 2005; 36(8):1684–1689. [PubMed: 16020768]
27. Reinhard M, Hetzel A, Lauk M, Lueking CH. Dynamic cerebral autoregulation testing as a diagnostic tool in patients with carotid artery stenosis. *Neurol Res*. 2001; 23(1):55–63. [PubMed: 11210431]
28. Otite F, Mink S, Tan CO, Puri A, Zamani AA, Mehregan A, Chou S, Orzell S, Purkayastha S, Du R, Sorond FA. Impaired cerebral autoregulation is associated with vasospasm and delayed cerebral ischemia in subarachnoid hemorrhage. *Stroke*. 2014; 45(3):677–682. [PubMed: 24425120]
29. Hu HH, Kuo TB, Wong WJ, Luk YO, Chern CM, Hsu LC, Sheng WY. Transfer function analysis of cerebral hemodynamics in patients with carotid stenosis. *J Cereb Blood Flow Metab*. 1999; 19(4):460–465. [PubMed: 10197516]
30. Haubrich C, Kruska W, Diehl RR, Moller-Hartmann W, Klotzsch C. Dynamic autoregulation testing in patients with middle cerebral artery stenosis. *Stroke*. 2003; 34(8):1881–1885. [PubMed: 12843352]
31. Tikhonoff V, Zhang H, Richart T, Staessen JA. Blood pressure as a prognostic factor after acute stroke. *Lancet Neurol*. 2009; 8(10):938–948. [PubMed: 19747655]
32. Dohmen C, Bosche B, Graf R, Reithmeier T, Ernestus RI, Brinker G, Sobesky J, Heiss WD. Identification and clinical impact of impaired cerebrovascular autoregulation in patients with malignant middle cerebral artery infarction. *Stroke*. 2007; 38(1):56–61. [PubMed: 17122439]
33. Ziv I, Fleminger G, Djaldetti R, Achiron A, Melamed E, Sokolovsky M. Increased plasma endothelin-1 in acute ischemic stroke. *Stroke*. 1992; 23(7):1014–1016. [PubMed: 1615534]
34. Claassen JA, Meel-van den Abeelen AS, Simpson DM, Panerai RB, N. International Cerebral Autoregulation Research. Transfer function analysis of dynamic cerebral autoregulation: A white paper from the International Cerebral Autoregulation Research Network. *J Cereb Blood Flow Metab*. 2016

Fig. 1.

Variations in phase (degrees) and gain (%/mmHg), in the ischemic and contralateral hemispheres, over time in subgroups with and without hemorrhagic transformation. Bars/whisker represents mean/side deviation. P value obtained with repeated-measures ANOVA. Significant differences are identified by asterisks.

Fig. 2.

Variations in phase (degrees) and gain (%/mmHg), in the ischemic and contralateral hemispheres, over time in subgroups with and without cerebral edema. Bars/whisker represents mean/side deviation. P value obtained with repeated-measures ANOVA. Significant differences are identified by asterisks.

Table 1

Demographic, clinical and radiographic characteristics of subjects at baseline.

	Total n = 46	Hemorrhage		Cerebral edema	
		Yes n = 10	No n = 36	Yes n = 8	No 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·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.

Table 2

Temporal changes in systemic and cerebral hemodynamics.

	Total	Hemorrhage		Cerebral edema		
		Yes	No	Yes	No	
n = 46						
n = 10						
n = 36						
n = 8						
n = 38						
Systemic hemodynamics (mean ± SD)						
Systolic ABP, mm Hg	<6	$\dot{V}144 \pm 19$	$\dot{V}148 \pm 18$	$\dot{V}146 \pm 19$	$\dot{V}154 \pm 19$	$\dot{V}142 \pm 19$
	24	$\dot{V}142 \pm 19$	$\dot{V}141 \pm 24$	$\dot{V}142 \pm 18$	$\dot{V}135 \pm 19$	$\dot{V}143 \pm 20$
	3 M	124 ± 17	113 ± 21	126 ± 19	120 ± 18	124 ± 17
Mean ABP, mm Hg	<6	$\dot{V}101 \pm 14$	$\dot{V}97 \pm 7$	$\dot{V}101 \pm 11$	$\dot{V}97 \pm 12$	$\dot{V}101 \pm 14$
	24	$\dot{V}97 \pm 11$	$\dot{V}96 \pm 11$	$\dot{V}97 \pm 10$	$\dot{V}91 \pm 10$	$\dot{V}98 \pm 11$
	3 M	87 ± 11	78 ± 11	90 ± 11	87 ± 16	87 ± 11
Diastolic ABP, mm Hg	<6	$\dot{V}75 \pm 11$	$\dot{V}72 \pm 9$	$\dot{V}77 \pm 11$	$\dot{V}71 \pm 12$	$\dot{V}76 \pm 10$
	24	$\dot{V}74 \pm 10$	$\dot{V}73 \pm 9$	75 ± 10	$\dot{V}69 \pm 10$	$\dot{V}75 \pm 10$
	3 M	69 ± 10	60 ± 7	72 ± 9	70 ± 15	69 ± 10
Heart rate, bpm	<6	67 ± 11	61 ± 10	$*71 \pm 11$	58 ± 8	$*70 \pm 11$
	24	67 ± 11	67 ± 14	68 ± 12	67 ± 17	67 ± 11
	3 M	71 ± 15	83 ± 23	69 ± 13	87 ± 22	70 ± 13
EtCO ₂ , mm Hg	<6	36 ± 7	35 ± 7	36 ± 7	37 ± 6	37 ± 7
	24	36 ± 6	37 ± 7	36 ± 7	38 ± 6	36 ± 7
	3 M	37 ± 7	34 ± 7	35 ± 7	38 ± 6	39 ± 7
Cerebral hemodynamics (mean ± SD)						
Subgroup without MCA occlusion	n = 30	n = 6	n = 24	n = 4	n = 26	
Infarct hemisphere						
MFV, cm/s	<6	±25	41 ± 25	25 ± 17	$*51 \pm 25$	42 ± 17
	24	51 ± 18	51 ± 18	46 ± 18	$*57 \pm 16$	46 ± 17
	3 M	43 ± 21	43 ± 21	39 ± 16	44 ± 20	43 ± 17
CVRI, mm Hg/cm/s	<6	$\dot{V}2.1 \pm 0.9$	2.1 ± 1.3	2.2 ± 1.2	$*1.4 \pm 0.2$	2.3 ± 1.5
	24	1.6 ± 0.2	1.6 ± 0.2	1.8 ± 0.8	$*1.2 \pm 0.3$	1.8 ± 0.7

	Total n = 46	Hemorrhage		Cerebral edema	
		Yes n = 10	No n = 36	Yes n = 8	No n = 38
Non-infarct hemisphere	3 M	1.8 ± 0.8	1.8 ± 0.8	1.7 ± 0.8	1.8 ± 0.8
MFV, cm/s	<6	49 ± 15	50 ± 18	56 ± 11	48 ± 15
	24	53 ± 16	60 ± 18	60 ± 10	52 ± 17
CVRI, mm Hg/cm/s	3 M	46 ± 17	45 ± 17	39 ± 12	48 ± 17
	<6	1.8 ± 1.3	1.4 ± 0.6	1.3 ± 0.2	1.8 ± 0.7
	24	1.5 ± 0.2	1.2 ± 0.3	1.0 ± 0.4	1.5 ± 0.6
	3 M	2.0 ± 0.8	1.9 ± 0.5	2.3 ± 0.6	1.7 ± 1.3
Subgroup with MCA occlusion (only non-infarct hemisphere monitored)					
	n = 16	n = 4	n = 12	n = 4	n = 12
Non-infarct hemisphere					
MFV, cm/s	<6	53 ± 17	47 ± 15	53 ± 25	53 ± 23
	24	58 ± 26	47 ± 15	59 ± 11	58 ± 15
CVRI, mm Hg/cm/s	3 M	52 ± 24	39	53 ± 26	55 ± 20
	<6	1.7 ± 1.2	1.6 ± 0.6	1.8 ± 0.8	1.7 ± 0.6
	24	1.4 ± 0.7	1.4 ± 0.4	1.2 ± 0.4	1.5 ± 0.5
	3 M	2.0 ± 0.8	2.2	1.9 ± 1.4	1.9 ± 1.0

Mean flow velocity (MFV), cerebrovascular resistance index (CVRI), arterial blood pressure (ABP), end-tidal carbon dioxide (EtCO₂), within 6 h (< 6) and at 24 h from symptom-onset; 3 months (3 M).

* $p < 0.05$ for Repeated-Measures ANOVA p value for differences between subgroups with and without hemorrhagic transformation or cerebral edema.

† $p < 0.05$ for Repeated-Measures ANOVA p value for variations with time (3 months as a reference).