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Increased arterial stiffness is an independent risk factor for hemorrhagic transformation in ischemic stroke undergoing thrombolysis☆

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ABSTRACT

Background: Hemorrhagic transformation (HT) is a multifactorial phenomenon and represents a possible complication of ischemic stroke, especially after thrombolytic treatment. Increased arterial stiffness has been associated with intracranial hemorrhage, but there is no evidence of association with HT after thrombolytic therapy. The aim of our study is to investigate a possible link between arterial stiffness and HT occurrence after thrombolytic therapy in patients with ischemic stroke.

Methods: We enrolled 258 patients (135 males, 123 females; mean age: 73 ± 12 years) with acute ischemic stroke undergoing intravenous thrombolysis or/and mechanical thrombectomy. All stroke patients underwent neuroimaging examination, 24-h heart rate and blood pressure monitoring and brain CT-scan after 24–72 h to evaluate HT occurrence. The linear regression slope of diastolic on systolic blood pressure was obtained and assumed as a global measure of arterial compliance, and its complement (1 minus the slope), named arterial stiffness index (ASI), has been taken as a measure of arterial stiffness.

Results: Out of 258, HT occurred in 55 patients. ASI was significantly higher in patients with HT than in patients without HT (0.70 ± 0.12 vs 0.62 ± 0.14, $p < 0.001$). Logistic regression model showed ASI as independent predictors of HT (OR: 1.9, 95% CI: 1.09–3.02, for every 0.2 increase of ASI): in particular, OR was 5.2 (CI: 2.22–12.24) when ASI was >0.71, in comparison with ASI lower than 0.57.

Conclusions: Our results point to arterial stiffness as a novel independent risk factor for HT after ischemic stroke treated with thrombolysis, suggesting a particularly high bleeding risk when ASI is >0.71.

1. Introduction

Hemorrhagic transformation (HT) is a bleeding in the ischemic brain tissue and represents a possible complication of ischemic stroke, especially after thrombolytic treatment, occurring in 13%–43% of patients [1]. HT is a complex and multifactorial phenomenon [2], not fully understood and only partly predictable. Known risk factors include age, blood glucose level, low platelet count, high National Institute of Health Stroke Scale score (NIHSSs), size and location of ischemic area, poor collateral vessels, thrombolytic agent used and time window allowed for the initiation of the therapy [1]. Blood pressure (BP) may also play a role in HT pathogenesis: there is a consensus to maintain BP below 180/105 mm Hg for the first 24 h after thrombolytic therapy [3], but the early BP management after thrombolysis remains inconclusive. Acute hypertensive response in ischemic stroke is associated with poor outcomes and may also be associated with increased aortic stiffness [4].

Arterial stiffness has independent predictive value for cardiovascular events [5]; in particular, in acute ischemic stroke, high arterial stiffness index values have been observed [6]. In our previous study, we suggested a link between deep intracerebral hemorrhage and arterial stiffening that represents a possible pathogenic factor modifying arterial wall properties and contributing to vascular rupture in response to intravascular pressure acute elevation [7]. However, no studies have evaluated the relationship between stiffness and HT occurrence after thrombolytic therapy. The aim of our study is to investigate a possible link between arterial stiffness (evaluated by means of arterial stiffness index [ASI]) and HT occurrence after thrombolytic therapy in patients with ischemic stroke.

☆ The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

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2. Materials and methods

We enrolled 258 patients (135 males, 123 females; mean age 73 ± 12 years), admitted consecutively to the Stroke Unit Department of Siena University Hospital for acute ischemic stroke and submitted to intravenous thrombolysis or/and mechanical thrombectomy.

Neurological status at admission was assessed by using NIHSSs; 3 severity levels were defined: mild (NIHSSs < 8), moderate (NIHSSs: 8–16), and severe (NIHSSs > 16). All patients underwent neuroimaging examination (brain computerized tomography with angio-CT scan and/or brain magnetic resonance imaging), extracranial and transcranial arterial ultrasound examination, transthoracic echocardiography, and 12-lead resting ECG. A 24-h heart rate (HR) and BP monitoring was conducted for all the subjects recording the following parameters: systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), pulse pressure (PP), and heart rate (HR). In all patients, high-sensitivity C-reactive protein (hsCRP) level, creatinine, potassium, sodium plasma levels, HbA1c percentage, serum total-cholesterol level, and LDL- and HDL-cholesterol levels were measured. In patients with age < 60 years ($n = 44$) transesophageal echocardiography and screening for hypercoagulable state were performed. Stroke subtypes were determined according to the ASCOD classification [8]. In all patients a brain CT scan was performed after 24–72 h after thrombolysis to evaluate the occurrence of hemorrhagic transformation. The modified Rankin scale (mRS) was assessed at the time of presentation (preadmission mRS) and at 90 days by a stroke-trained physician, to evaluate 3-month clinical outcome. The study was approved by the Ethics Committee of the University Hospital of Siena, Italy.

2.1. ASCOD classification

Every patient was graded into one of the 5 predefined phenotypes: A (atherosclerosis), S (small-vessel disease), C (cardiac pathology), O (other cause), and D (dissection), assigning a degree of likelihood of causal relationship to every potential disease (1 "potentially causal", 2 "causality is uncertain", 3 "unlikely causal but the disease is present", 0 "absence of disease", and 9 "insufficient workup to rule out the disease"). The ASCOD system allowed us to weigh the potentially causal relationship between every disease detected and the ischemic stroke. According to this system, when the patient was classified as "degree 1" in one of the 5 phenotypes of ASCOD, the stroke etiology was respectively "atherosclerosis", "small vessel disease", "cardioembolic", "other causes" (polycythemia, thrombocytemia, systemic lupus, disseminated intravascular coagulation, antiphospholipid syndrome, Fabry's disease, sickle cell disease, ruptured intracranial aneurysm, severe hyperhomocysteinemia, Horton's disease, cerebral inflammatory angiitis, and Moyamoya disease) and "arterial dissection". Instead, the etiology of stroke was classified as "cryptogenic" when the patients were grade 0 (absence of disease), 9 (insufficient workup), or 2 and 3 (being unable to establish a direct causal relationship between these diseases and the ischemic stroke).

2.2. Hemorrhagic transformation

According to European Cooperative Acute Stroke Study (ECASS) radiological classification [9], hemorrhagic transformation has been classified in the following different types: hemorrhagic infarct type 1 (HI1; small petechiae along the periphery of the infarct), hemorrhagic infarct type 2 (HI2; confluent petechiae within the infarcted area without a space-occupying effect), parenchymal haematoma type 1 (PH1; bleeding <30% of the infarcted area with a mild space-occupying effect), parenchymal haematoma type 2 (PH2; bleeding >30% of the infarcted area with a significant space-occupying effect), and remote parenchymal hemorrhage (PHr; bleeding in brain areas remote from infarcted tissue).

Table 1
Demographic characteristics of the patients of the study.

	Pt. without HT ($n = 203$)	Pt. with HT ($n = 55$)	*P* value
Age (years)	72.8 ± 13	75.2 ± 11.6	0.24
Women/men	94:109	29:26	0.44
Neurological deficit (at admission)			
Patients number with NIHSSs < 8	83 (40.9%)	6 (10.9%)	<**0.001**
Patients number with NIHSSs 8–16	61 (30%)	17 (30.9%)	0.76
Patients number with NIHSSs > 16	59 (29.1%)	32 (58.2%)	<**0.001**
ASCOD phenotype			0.37
Atherosclerosis, *n* (%)	49 (24%)	18 (33%)	
Small vessel disease, *n* (%)	6 (3%)	1 (2%)	
Cardioembolic, *n* (%)	60 (29.5%)	18 (33%)	
Other, *n* (%)	3 (1.5%)	1 (2%)	
Dissection, *n* (%)	6 (3%)	3 (5%)	
Cryptogenic, *n* (%)	79 (39%)	14 (25%)	
Cardiovascular risk factors			
Hypertension, *n* (%)	143 (70%)	44 (80%)	0.18
Diabetes mellitus, *n* (%)	40 (19.7%)	13 (23.6%)	0.6
Hypercholesterolemia, *n* (%)	97 (47%)	29 (52%)	0.5
Atrial fibrillation, *n* (%)	67 (33%)	23 (41%)	0.3
Previous CAD, *n* (%)	19 (9%)	9 (16%)	0.15
Previous stroke, *n* (%)	41 (20%)	10 (18%)	0.85
Smoking, *n* (%)	41 (20%)	7 (12.7%)	0.24
Antihypertensive drugs, (%)	127 (62%)	40 (72%)	0.27
ACE/angiotensin II receptor inhibitors	89 (43%)	25 (45%)	0.88
Diuretics	63 (31%)	19 (34%)	0.63
Beta-blockers	52 (25%)	18 (32%)	0.31
Calcium channel blockers	29 (14%)	6 (10%)	0.66
Laboratory parameters			
Glucose (mg/dl)	131 ± 45	123 ± 29	0.5
Platelets (n/mm^3)	219,774 ± 82,590	194,509 ± 55,198	**0.01**
INR	1.09 ± 0.2	1.08 ± 0.2	0.4
Creatinine (mg/dl)	0.9 ± 0.3	1.02 ± 0.6	0.25
sodium	140 ± 3.8	140 ± 5.9	0.5
potassium	4 ± 0.4	3.9 ± 0.4	0.3
Total cholesterol (mg/dl)	185 ± 42	186 ± 43	0.8
LDL-cholesterol (mg/dl)	114 ± 37	116 ± 35	0.6
HbA1c (%)	6 ± 0.8	5.9 ± 0.8	0.3
C reactive protein (mg/dl)	2.01 ± 4.49	2.77 ± 6.4	0.11
Hemodynamic parameters			
SBP (mm Hg)	133 ± 15	142 ± 18	**0.0007**
DBP (mm Hg)	69 ± 9	72 ± 11	0.12
MBP (mm Hg)	90.8 ± 10.2	95.9 ± 12.6	**0.008**
PP(mm Hg)	64 ± 15	70 ± 16	**0.005**
HR (beats/m)	74 ± 13	72 ± 15	0.5

Data are expressed as mean ± SD. NIHSSs: National Institutes of Health Stroke Scale score. CAD: coronary artery disease. ACE: angiotensin converting enzyme. SBP: systolic blood pressure. DBP: diastolic blood pressure. MBP: mean blood pressure. PP: pulse pressure. HR: heart rate.