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Acute hypertensive response in ischemic stroke is associated with increased aortic stiffness

Mariusz Kwarciany [a], Dariusz Gąsecki [a], Kamil Kowalczyk [a], Agnieszka Rojek [b], Stephane Laurent [c], Pierre Boutouyrie [c], Marcelina Skrzypek-Czerko [a, d], Walenty M. Nyka [a], Krzysztof Narkiewicz [b], Bartosz Karaszewski [a, *]

[a] Department of Adult Neurology, Medical University of Gdansk & University Clinical Centre in Gdansk, ul. Dębinki 7, 80-211 Gdańsk, Poland
[b] Department of Hypertension and Diabetology, Medical University of Gdansk & University Clinical Centre in Gdansk, ul. Dębinki 7, 80-211 Gdańsk, Poland
[c] Department of Pharmacology, Université Paris Descartes 7, INSERM U970, HEGP Assistance Publique-Hôpitaux de Paris, 20 rue Leblanc, 75015 Paris, France
[d] Department of Nursing, Medical University of Gdansk, ul. Dębinki 7, 80-211 Gdańsk, Poland

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ABSTRACT

Background and aims: Acute hypertensive response (AHR) affects more than 60% of patients with ischemic stroke and is associated with poor outcomes. We hypothesized that its development is related to arterial stiffening. "The gold standard" estimate of arterial stiffness is carotid-femoral pulse wave velocity (CF-PWV). We compared CF-PWV and indirect indices of arterial stiffness (central augmentation index (cAIxHR), central systolic (cSBP) and pulse (cPP) pressures) between acute ischemic stroke patients who developed AHR and those who were normotensive in the early phase of stroke.
Methods: AHR was assessed through hourly BP measurements within 24 h from admission using an oscillometric device. The stiffness was assessed using applanation tonometry with a SphygmoCor® device (Atcor, Sydney, Australia) 7 ± 2 days after stroke.
Results: Among 102 patients with acute ischemic stroke, 73(71.5%) met AHR criteria. In an univariate analysis, CF-PWV, cAIxHR, cSBP and cPP were higher in those who developed AHR (10.9 vs. 8.3 m/s, $p < 0.001$; 30.8 vs. 23.9%, $p = 0.004$; 138.2 vs. 117.2 mmHg, $p < 0.001$; 54.6 vs. 44 mmHg, $p = 0.005$, respectively). In a multivariate logistic regression analysis, CF-PWV was independently associated with AHR after adjustment for age and peripheral mean blood pressure (pMBP) ($p = 0.04$), for age, pMBP and diabetes mellitus (DM) ($p = 0.045$), and age, pMBP, DM and hypertension ($p = 0.047$).
Conclusion: This study revealed for the first time that AHR in ischemic stroke is associated with elevated aortic stiffness independently of other clinical factors including age and hypertension preceding stroke. A potential pathophysiological mechanism responsible for this relationship includes impaired baroreceptor function in stiff arteries resulting in impaired BP autoregulation.

1. Introduction

Stroke is estimated to be the second most common cause of death and the third most common cause of disability-adjusted life-years (DALY) worldwide. The numbers of patients with first-ever stroke, stroke survivors, and stroke-related deaths are increasing, especially in low-income and middle-income countries [1].

Acute hypertensive response (AHR) in acute stroke is defined as an increase of systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg found in two recordings taken 5 min apart within the first 24 h after stroke onset [2]. Affecting much over 60% of patients with stroke, AHR is one of the most common consequences of stroke [3]. Occurrence of AHR is associated with poor short- and long-term outcomes after stroke [4,5]. The pathophysiology of AHR is poorly understood; previously considered mechanisms included undiagnosed or improperly treated hypertension, autonomic dysfunction due to acute brain lesion, neuroendocrine dysfunction or other stroke complications such as brain oedema and infections [2]. We hypothesized that AHR

* Corresponding author. Chair of Neurology, Department of Adult Neurology, Medical University of Gdansk, Debinki 7, 80-211 Gdańsk, Poland.
E-mail address: bartosz@karaszewski.org (B. Karaszewski).

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development is related to chronic vascular wall restructure and dysfunction – the arterial stiffening.

Aortic stiffness mirrors advancement of various vascular wall pathologies combined, thus being a hallmark of vascular ageing. It is an independent predictor of vascular morbidity and mortality in healthy and high-risk populations [6,7], and of mortality in stroke [8]. Alternations in the arterial, especially aortic, wall properties lead to an increase in pulse wave velocity (PWV), which in turn eventually leads to the elevation of central systolic pressure and the widening of central pulse pressure. Carotid-femoral pulse wave velocity (CF-PWV) is considered "the gold standard" measurement of arterial stiffness [9]. To verify our hypothesis that arterial stiffening is associated with AHR occurrence, we compared PWV and other aortic stiffness markers in acute ischemic stroke patients who developed AHR and those whose BP in the early phase of stroke was normal.

2. Materials and methods

Adult patients with acute ischemic stroke (≤24 h from onset), hospitalized at the Stroke Unit of the Department of Adult Neurology at the Medical University of Gdansk, were enrolled into the study between October 2008 and July 2012 according to the following criteria: (1) well-defined time of onset of stroke signs or symptoms, (2) absence of serious "chronic" cerebral pathology in neuroimaging including previous vascular lesions other than those characteristic for small vessel disease, (3) sinus rhythm on admission, (4) good cooperativeness and no consciousness impairment, (5) no significant pre-stroke disability (0 or 1 in modified Rankin scale [10]), and (6) no carotid artery stenosis >70%.

Each patient was examined by an experienced stroke physician who collected demographic and baseline clinical data including cardiovascular risk factors, subsequently estimating stroke severity according to the National Institutes of Health Stroke Scale (NIHSS), and assessing the stroke subtype by the Oxford Community Stroke Project (OCSP) classification [11]. Computed tomography and/or magnetic resonance imaging was performed on each patient upon admission and 3–7 days after stroke. Finally, each stroke (each patient) was determined etiologically using the TOAST classification [12].

The study was approved by the Independent Bioethical Commission at the Medical University of Gdansk. Informed consent or assent was received from each patient.

2.1. AHR estimation

AHR was assessed as defined above. During the first 24 h after admission blood pressure was measured hourly, by trained nurses, in the supine position, on the non-paretic arm, using a properly sized cuff, with an oscillometric device.

2.2. Arterial stiffness

The time from stroke onset to arterial stiffness assessment was 7 ± 2 days – long enough to minimize the influence of stroke acute phase factor for the measured parameters, and short enough to obtain data on the arterial stiffness possibly similar to that immediately preceding stroke. This assumption is partially supported by our preliminary, pilot data from six randomly selected ischemic stroke patients having post-stroke long–term serial assessments of PWV and pMBP showing that if there are any factors appearing immediately after the acute cerebrovascular incident (eg, dysautonomia) that temporally alter PWV (with or without its relation to pMBP), they are already ineffective after 5 days from stroke.

The stiffness and central BP were measured using applanation tonometry (AT) with a SphygmoCor® device (Atcor, Sydney, Australia) by one of two physicians trained specifically in this technique (MK, KK). Carotid-femoral PWV was calculated by dividing the distance covered by the waves by the transit time (PWV = distance/time). The latter was measured using the foot-to-foot method (the time interval between the onset of the carotid and femoral pulse wave upstrokes), whereas the distance covered by the waves was calculated by subtracting the distance from the carotid location to the sternal notch from the distance between the sternal notch and the femoral site of the measurement. The central aortic waveform was calculated with device software using a generalized transfer function, and BP values were derived from this curve. Following the central augmentation index (cAIx) measurement, the cAIx at a heart rate of 75 beats per minute (cAIx75) was calculated through the software. All measurements were performed with standardized conditions recommended by expert consensus [9] and as described previously for other projects from our group [13,14]. Repeatability and reproducibility of applanation tonometry measurements were calculated using two-way mixed single measures with an intraclass correlation coefficient (ICC) for absolute agreement: interobserver and intra-observer reliabilities, calculated by the ICC, were 0,86 and 0,96 respectively (thus indicating excellent reproducibility and repeatability).

2.3. Statistical analysis

All data were expressed as being a mean ± standard deviation or median (interquartile range) for skewed data. Comparisons between patients with AHR and non-AHR were performed by unpaired Student's *t*-test or Mann Whitney *U* test where appropriate for continuous variables, and chi-square test for categorical variables.

The relation of PWV with AHR was assessed using logistic regression models. Potential confounders from the univariate analyses entered the initial logistic regression model and were removed by a backward stepwise selection. A P value of <0.05 was considered significant. The statistical analysis was performed by means of Statistica 10.0 (StatSoft, USA).

3. Results

3.1. General cohort characteristics and AHR

250 consecutive acute ischemic stroke patients hospitalized at our Stroke Unit were considered as participants of the study (within some institutional limitations eg, no weekend or holiday recruitment). From this cohort, applying inclusion - exclusion criteria and validating the quality of applanation tonometry data, we eventually enrolled 102 subjects. 73 patients (71.5%) met the International Society of Hypertension (ISH) criteria for AHR [mean SBP 151.6 mmHg ± 20.4, mean DBP 89.4 mmHg ± 13.3], whereas the remaining 29 (28.5%) had normal BP values within the designated period [mean SBP 117.7 mmHg ± 10.3, mean DBP 71.6 mmHg ± 10.3]. The mean of BP measurements obtained in both groups was 12,7 (±7,5).

AHR subjects were older than non-AHR patients. Otherwise, considering important cardiovascular risk factors (prominently history of hypertension), pre-stroke antihypertensive treatment, neurological deficit upon admission, stroke subtype or thrombolytic therapy, there was no difference between the groups except a tendency towards higher incidence of diabetes mellitus in AHR patients (Table 1).