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The augmentation index as a useful indicator for predicting early symptom progression in patients with acute lacunar and atherothrombotic strokes

Yuki Sakamoto *, Kazumi Kimura, Junya Aoki, Kensaku Shibazaki

Department of Stroke Medicine, Kawasaki Medical School, Kurashiki, Japan

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ABSTRACT

Background and purpose: The symptoms of about 30% of acute ischemic stroke patients progress, but the mechanism and predictors of the deterioration are not well known. The augmentation index (AIx), estimated with the arterial pulse waveform, is known to be pathophysiologically relevant to the pathogenesis of cardiovascular diseases. The aim of the present study was to investigate the prognostic value of the AIx for early symptom progression (ESP) in patients with acute ischemic stroke.

Methods: Acute ischemic stroke patients admitted to our stroke center within 24 h from onset were prospectively enrolled. The AIx was measured within 48 h from admission. ESP was defined as ≥2 increase in the NIHSS score during 7 days from admission. All patients were divided into 2 groups according to the ESP (the ESP group and the non-ESP group).

Results: A total of 147 patients (79 males, median age 74 [IQR 64–82] years, and NIHSS score 3 [1–7]) were enrolled. ESP was observed in 23 (16%) patients. There were no differences in clinical characteristics including the AIx between the two groups. However, when only cases with lacunar and atherothrombotic strokes were evaluated, the AIx was higher in the ESP group (37.0 [32.0–38.0]%) than in the non-ESP group (29.5 [21.8–33.3]%, $p = 0.003$). With the optimal cut-off value of >36%, the AIx was independently associated with ESP (OR 37.3, 95% CI 1.71–811, $p = 0.021$).

Conclusion: The AIx level was independently related to ESP in patients with acute lacunar and atherothrombotic strokes. The AIx may have a potential to predict ESP in these patients.

1. Introduction

The symptoms of about 30% of acute stroke patients progress [1–3]. Although it has been suggested that some factors, such as intracranial atherosclerosis [4], lacunar stroke [5], location of the infarct lesion [6], infarct size [7], diabetes mellitus [8], and initial high blood glucose level [9], correlate with symptom worsening, the mechanisms and predictors of the deterioration are not well known.

Central hemodynamics are known to be pathophysiologically more relevant than peripheral pressures to the pathogenesis of cardiovascular diseases [10]. Central hemodynamics can now be reliably assessed non-invasively from the radial artery waveform using applanation tonometry and a validated general transfer function [11]. The arterial pulse wave traveling toward the extremities is partly reflected back to the aorta, and the reflected wave augments the aortic pressure. This can be quantified by the augmentation index (AIx), defined as the percentage of the central pulse pressure attributed to the reflected pulse wave. The reflected wave travels faster in arteries with reduced compliance and reaches the aorta in the systolic rather than the diastolic phase, which increases the AIx. Therefore, the AIx represents arterial stiffness.

Recently, the AIx was found to have a greater association than peripheral blood pressure (BP) with cardiovascular diseases [12–15], and, in addition, short-term outcome in a selected cohort of acute ischemic stroke patients [16]. Patients with intracranial atherosclerosis are at high risk of early neurologic deterioration [17,18]. Therefore, we hypothesized that if advanced arteriosclerosis were present in acute stroke patients, neurological symptoms might progress. The aim of this study was to investigate the prognostic value of the AIx for symptom worsening in acute stroke patients.

2. Methods

2.1. Subjects

From October 2009 to March 2011, consecutive acute ischemic stroke patients admitted to our stroke center within 24 h from symptom onset were prospectively enrolled. Patients presenting with atrial fibrillation (AF) were excluded because the AIx cannot be estimated in patients with an irregular heart rhythm. This study was approved

* Corresponding author at: Department of Stroke Medicine, Kawasaki Medical School, 577 Matsushima, Kurashiki City, Okayama 701-0192, Japan. Tel.: +81 86 462 1111; fax: +81 86 464 1027.
E-mail address: ysakamoto02@gmail.com (Y. Sakamoto).

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by the institutional ethics committee. Written informed consent was obtained from all patients or their next-of-kin.

2.2. Clinical background characteristics

The patients' clinical background characteristics, including age, sex, height, smoking status, past history, and cardiovascular risk factors, were recorded on admission. Cardiovascular risk factors were defined as: 1) hypertension, history of using antihypertensive agents, systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg before or 2 weeks after stroke onset; 2) diabetes mellitus, use of hypoglycemic agents, random glucose level ≥200 mg/dl, or glycosylated hemoglobin >6.4% on admission; and 3) hyperlipidemia, use of antihyperlipidemic agents or a serum total cholesterol level ≥220 mg/dl.

Neurological manifestations were assessed using the National Institutes of Health Stroke Scale (NIHSS) score. Early symptom progression (ESP) was defined as ≥2 increase in the NIHSS score during 7 days from admission. Stroke etiology was determined at hospital discharge using the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria [19]. Routine blood biochemistry examinations were performed on admission, and transthoracic echocardiography was performed during admission.

2.3. Measurement of brachial BP and pulse wave analysis

The BP and AIx were determined by one observer (Y.S.) blinded to clinical information within 48 h from admission. BP and AIx were measured at the patients' bedside on a fasting state. The patients' brachial BPs were measured using an automated sphygmomanometer 3 times after resting in the supine position for at least 5 min. The BP and AIx were measured on the arm of the unaffected side (e.g. did not show paralysis, dysesthesia, or ataxia). The mean of the last 2 measurements was recorded as representative of brachial BP. Immediately after recording brachial BP, the AIx was calculated from radial arterial pressure waveforms using applanation tonometry and a generalized transfer function with SphygmoCor version 8.2 (AtCor Medical, Ryde, Australia). The AIx was calibrated using the representative brachial BP, and adjusted to a standard heart rate of 75 bpm. AIx measures had to have an operator index (a quality measure) of 80% or above to be accepted.

2.4. Statistical analyses

All patients were divided into 2 groups: those with ESP (ESP group) and those without ESP (non-ESP group). Clinical background characteristics were compared between the two groups. Univariate analyses were performed using the chi-square test or Fisher's exact test and the Mann–Whitney *U* test. The data are presented as median values (interquartile range [IQR]) or frequencies (%). Next, the relationships between the AIx and stroke etiology or atherosclerotic risk factors including hypertension, hyperlipidemia, diabetes mellitus, and current smoking were evaluated with analysis of covariance adjusting for age, sex, and height. Finally, a multivariate logistic regression analysis was performed to identify independent factors associated with ESP. Age, sex, height, and all variables identified on univariate analyses with p values <0.1 were entered into the model. In addition, large-artery atherosclerosis and initial blood glucose level, which are known predictors from previous studies, were forced into the model. To obtain the optimal cut-off value of the AIx for predicting ESP, a receiver-operating characteristic (ROC) curve analysis was performed. The relative risks of ESP were expressed as odds ratios (OR) with 95% confidence intervals (CI).

All statistical analyses were performed using PASW for Windows version 17.0 software (SPSS Inc., Chicago, IL, USA). Results were considered significant at $p<0.05$.

3. Results

A total of 210 ischemic stroke patients were admitted to our stroke center within 24 h from onset. Of these, 62 were excluded due to: AF in 57 cases; bigeminal rhythm and the AIx could not be measured in 4 cases; and weakness of pulse and the AIx could not be measured in 1 case. There were no patients treated with vasoactive medications. Patients taking antihypertensive drugs before stroke onset that might affect central hemodynamics were included, and all but one patient stopped antihypertensive therapy at least 48 h from admission. Therefore, one patient who continued antihypertensive therapy was excluded. Finally, 147 cases (79 males, median age 74 [IQR 64–82] years, and NIHSS score 3 [1–7]) were enrolled in the present study.

Table 1 shows the clinical background characteristics of all patients. The median time from onset to AIx measurement was 24 h. Of the 147 patients, 23 (16%) developed ESP (ESP group), while ESP was not observed in 124 (84%, non-ESP group). The representative systolic BP tended to be higher in the ESP group (161 [144–174] mm Hg vs. 149 [132–170] mm Hg; $p=0.099$) than in the non-ESP group, but there were no differences in other clinical characteristics including the AIx between the two groups.

When evaluating only cases with lacunar ($n=53$) and atherothrombotic strokes ($n=23$) using the TOAST classification, 7 of 69 (10%) individuals developed ESP (ESP group). Patients were older (89 [77–89] years vs. 72 [62–80] years, $p=0.003$), with fewer males (14% vs. 60%, $p=0.040$), in the ESP group. The AIx was higher in the ESP group (37.0 [32.0–38.0]%) than in the non-ESP group (29.5 [21.8–33.3]%; $p=0.003$, Fig. 1). The deteriorating symptoms were still present 7 days from onset (median NIHSS 6 [0–12] in the ESP group vs. 1 [0–3] in the non-ESP group, $p=0.049$) and at discharge (6 [0–12] vs. 1 [0–2]; $p=0.039$).

Table 2 shows the relationship between the AIx and stroke etiology or atherosclerotic risk factors adjusted for age, sex, and height. There were no differences in the AIx level by stroke etiology or the presence of atherosclerotic risk factors.

Using the ROC curve, the optimal cut-off value of the AIx discriminating the ESP group from the non-ESP group in patients with lacunar and atherothrombotic strokes was >36% (sensitivity 71%; specificity 92%; area under the ROC curve 0.846). The results of multivariate regression analysis are presented in Table 3. AIx >36% (OR 37.3, 95% CI 1.71–811; $p=0.021$) was independently associated with ESP.

4. Discussion

In this preliminary study, the AIx was independently related to ESP only among patients with lacunar and atherothrombotic strokes, but not for all of the included cases.

Central hemodynamics have been reported to be associated with atherosclerotic change [12,14,15], cardiovascular events [20,21], and mortality [22]. However, there are few studies investigating the relationship between central hemodynamics including the AIx and symptom worsening in acute ischemic stroke.

Although the precise mechanisms by which high AIx levels lead to ESP are unclear, some factors may account for this finding. First, it is possible that a high AIx level may represent having some risks for ESP. Indeed, a high AIx level is known to be related to having atherosclerotic risks, including diabetes mellitus [14] and a high level of inflammatory markers [13], which have been proven to correlate with symptom worsening in lacunar stroke [8] and plaque vulnerability in patients with carotid stenosis [23], respectively. In the present study, however, there were no relationships between the AIx and atherosclerotic risk factors when adjusted for age, sex, and height (Table 2). The AIx seems to predict ESP because a high AIx represents having multiple risk factors [14] rather than a single risk factor. Second, a high AIx