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Serum levels of endocan and endoglin are associated with large-artery atherosclerotic stroke

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ABSTRACT

Background: Accumulating evidence has suggested that endocan and endoglin may play important roles in cardiovascular disease. However, no previous study has focused on these circulating levels in patients with large-artery atherosclerotic (LAA) stroke.

Methods: Serum levels of endocan and endoglin in 114 patients with LAA stroke and 114 age- and sex-matched controls were measured by ELISA. Serum samples from patients were available on day 1, day 6 and in the 4th week after ischaemic stroke(IS). Stroke severity was determined based on the NIHSS score and the stroke volume. An unfavourable outcome was defined as a mRS score $>$ 2 on day 90 after IS.

Results: The endocan levels were significantly higher in patients with LAA stroke compared with the controls ($p = 0.001$), and after adjustment for other factors ($p = 0.001$). In addition, higher endocan levels were independently associated with unfavourable outcomes on both day 1 and day 6 after IS ($p = 0.018$ and $p = 0.011$). Endoglin levels were decreased on day 6 ($p = 0.002$) and then recovered in the 4th week after IS. No correlation was found between endocan or endoglin and stroke severity.

Conclusions: Endocan levels are higher in patients with LAA stroke and can help in predicting the short-term unfavourable outcome. Endoglin levels are changed after stroke.

1. Introduction

Endoglin (also known as TGF-β receptor III or CD105) and endocan (also known as endothelial cell-specific molecule-1) are mainly expressed and secreted by endothelial cells [1,2]. Increasing evidence has demonstrated that endoglin and endocan are associated with atherosclerosis-related pathologic processes, such as endothelial dysfunction, inflammation and angiogenesis [1,3–6].

A soluble form of endoglin, which is cleaved from the extracellular domain of the full-length membrane endoglin, can be detected in systemic circulation [6,7]. Several studies have investigated the relationships between circulating endoglin and atherosclerosis, although the reported results are controversial. Some studies found that higher levels of endoglin are related to hypertension- and diabetes-associated cardiovascular pathological alterations [8], and plaque instability and rupture [9], whereas other studies have indicated that endoglin levels are lower in patients with severe coronary atherosclerosis compared to those with mild atherosclerosis or normal [10,11].

Similarly, studies on the association between the circulating levels of endocan and atherosclerosis have also generated conflicting results. For example, some studies determined that endocan is positively correlated with the severity of carotid and coronary atherosclerosis [12–14], whereas another study found no correlation [15].

These discrepancies might result from the heterogeneity or clinical differences between the different study populations. Nevertheless, they support the overall conclusion that endocan and endoglin may have pivotal functions in atherosclerosis and may represent biomarkers of the risk and prognosis of cardiovascular disease. Moreover, no previous study has focused on the circulating levels of endoglin or endocan in patients with acute ischaemic stroke (IS).

In the present study, we aimed to compare the serum levels of endocan and endoglin between patients with large-artery atherosclerotic (LAA) stroke and age- and sex-matched controls. In addition, we determined the long-term changes in endocan and endoglin levels in

Abbreviations: IS, ischaemic stroke; LAA, large-artery atherosclerotic; TGF-β, transforming growth factor beta; CD150, cluster of differentiation 150; TOAST, Trial of Org 10172 in Acute Stroke Treatment; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; ELISA, enzyme-linked immunosorbent assay; STEMI, ST-segment elevation myocardial infarction

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patients on day 6 and in the 4th week after IS. We also investigated whether these levels are independently associated with stroke severity and 90-day outcome.

2. Methods and materials

2.1. Study subjects

We conducted a prospective cohort study at the Taizhou Hospital of Wenzhou Medical University. From July 2015 to February 2016, patients who had experienced first-ever LAA stroke admitted within 24 h after symptom onset and without received thrombolysis or interventional therapy, were consecutively recruited. Acute IS was diagnosed according to the World Health Organization criteria [16] combined with brain computed tomography or magnetic resonance imaging. LAA stroke was defined according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria [17]. At least two neurologists confirmed the subtype classifications after reviewing the patients' clinical features and examination results.

In addition, we excluded patients according to the following exclusion criteria: any history of previous stroke, severe coronary heart disease or arrhythmia, a history of malignancy, severe hepatic or renal insufficiency, haematological disease, autoimmune disease, acute or chronic inflammatory disease, recent surgery or trauma, or taking lipid-lowering or glucocorticoids medications.

Age-matched (blocks of 5 years) and sex-matched healthy individuals were assigned to the control group, who were recruited during health check-ups and were free of the conditions stated in the exclusion criteria.

The present study was performed in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Medical Ethics Committee of Taizhou Hospital. Written informed consents were obtained from all individuals or their legal representatives.

2.2. Clinical protocol

A flow chart of the study is shown in Fig. 1. Blood samples after fasting were collected from the 114 patients on the first morning after IS. Additionally, second blood samples were collected from 92 patients on day 6 after IS, and the third blood samples from 41 patients in the 4th week after IS. Blood samples after fasting were collected from the control subjects during their physical check-ups.

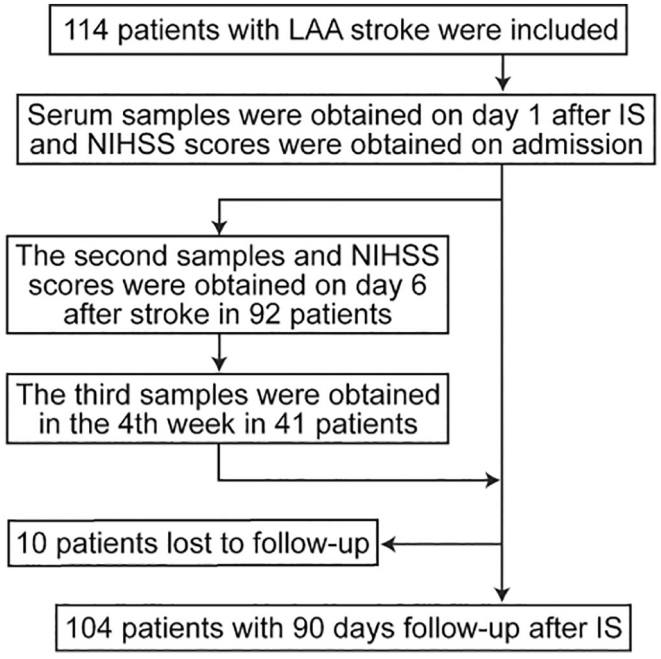

Fig. 1. Study flow chart.
Abbreviations: LAA stroke, large-artery atherosclerotic stroke; IS, ischaemic stroke; NIHSS, National Institutes of Health Stroke Scale.

Stroke severity was assessed based on infarct volume and the National Institutes of Health Stroke Scale (NIHSS; scores range from 0 to 42 with higher scores indicating greater deficits) [18]. Stroke volume was evaluated based on the initial diffusion-weighted imaging lesion volume (in 99 patients) by an experienced neuroradiologist who was blinded to the clinical and laboratory results of the patients. The infarct volume was calculated as the sum of the infarction areas of each slice multiplied by the slice thickness. Functional outcome evaluations were performed on day 90 after stroke (in 104 patients) using the modified Rankin Scale (mRS) by a trained medical investigator who was unaware of the patients' baseline parameters. The mRS scores ≤ 2 and > 2 corresponded to favourable and unfavourable outcomes, respectively.

2.3. Sample quantification and laboratory testing

After centrifugation, serum samples were stored at -80 °C before performing assays. All samples were thawed only once prior to use. Serum levels of endoglin were analysed by a commercially available enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems; Catalogue number DNDG00) with inter-assay and intra-assay coefficients of variation (CVs) of 2.8%–3.2% and 6.3%–6.7%, respectively. The mean minimum detectable dose (MDD) of human endoglin was 7 pg/mL. Endocan levels were measured using an ELISA kit (Boster, Wuhan, China; Catalogue number EK0752) with inter-assay and intra-assay CVs $< 10.0\%$, respectively, and the MDD for human endocan was 2 pg/mL.

Measurements of biochemical parameters such as fasting blood glucose (FBG), triglycerides (TG), total cholesterol (TC) and high-sensitivity C-reactive protein (Hs-CRP) were performed at the clinical laboratory in the hospital.

2.4. Data collection and definition

Demographical data were recorded, including age, sex, weight and height, past medical and medication history, smoking history, and alcohol use.

The risk factors were defined as follows: hypertension (systolic blood pressure (SBP)/average diastolic blood pressure (DBP) $\geq$ 140/90 mm Hg based on the average of two measurements, a history of hypertension, or on antihypertensive treatment), diabetes mellitus (FBG level $\geq$ 7 mmol/L, a history of diabetes, or use of anti-diabetic treatments), dyslipidaemia (serum TG $\geq$ 1.69 mmol/L, low-density lipoprotein cholesterol (LDL-C) $\geq$ 3.37 mmol/L, high-density lipoprotein cholesterol (HDL-C) $\leq$ 0.91 mmol/L, or the use of lipid-lowering drugs), smokers (smoking at the time of admission or had quit smoking within the previous 1 year), and moderate or heavy alcohol consumption ($\geq$ 2 standard alcoholic beverages consumed per day). Body mass index (BMI) was calculated as measured weight (kg) divided by the square of measured height (m^2).

2.5. Statistical analysis

Data normality was assessed using the Kolmogorov–Smirnov test. Data with a normal distribution are expressed as the means $\pm$ standard deviations (SDs), and data with a skewed distribution are expressed as medians [interquartile range (IQR)]. Categorical data are presented as counts (percentages). For univariate analyses, differences between two groups were compared by Student's *t*-test, the Mann-Whitney *U* test, or Pearson's chi-square test, as appropriate; differences between three groups were compared by one-way analysis of variance or the Kruskal-Wallis *H* test, as appropriate. Correlation analysis was performed using the nonparametric Spearman's rank correlation test.

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