# Serum Aldosterone Is Associated with Cerebral Artery Atherosclerosis and Calcification

Shoulong Zhang, MD,*,†,[1] Nuo Wang, MD,*,[1] Lei Chen, MD, PhD,* Ping Zhang, MD, PhD,* Lei Shen, MD,* Shiren Huang, MD,* Chunyang Zhang, MD,* and Benqiang Deng, MD, PhD*,

*Background and Purpose*: Elevated serum aldosterone concentration is known to be linked with elevated risk of cerebrovascular events as a result of vascular senescence. We studied the association between serum aldosterone concentration and cerebral arteriosclerosis status involving cerebral atherosclerosis burden and cerebral vascular calcification. *Methods*: A total of 207 patients (mean age = 62.40 ± 10.54, 70 female patients) admitted with acute ischemic stroke from a single center-based stroke registry were included in the study. The participants were categorized into 4 groups in accordance to the serum aldosterone concentration. Cerebral atherosclerosis burden was derived as the stenosis degree of main intracranial arteries, and cerebral artery calcification was investigated from the cavernous portions of both internal carotid arteries from brain computed tomography angiography. *Results*: The median aldosterone was 146.00 pg/mL; interquartile range was 133.18-172.10 pg/mL. Advanced intracranial atherosclerosis was present in 134 patients (64.7%) and advanced intracranial arterial calcification was present in 77 patients (37.2%). The prevalence of cerebral atherosclerosis burden and cerebral artery calcification showed increasing tendency through the aldosterone quartiles. Multivariable logistic regression analysis including age, sex, vascular risk factors, estimated glomerular filtration rate and aldosterone quartiles disclosed that the highest serum aldosterone quartile was an independent predictor of advanced intracranial atherosclerosis (odds ratio, 5.07; 95% confidence interval, 1.82-14.17; $P_{trend}$ = .001) and advanced intracranial arterial calcification (odds ratio, 6.24; 95% confidence interval, 2.03-19.22; $P_{trend}$ = .001). *Conclusions*: An increased serum aldosterone concentration was independently associated with intracranial atherosclerosis burden and arterial calcification. Future studies should investigate whether aldosterone antagonists prevent stroke in at risk population.

**Key Words:** Aldosterone—atherosclerosis—calcification—stroke—CT angiography



## Introduction

The burden of stroke in China has been the highest all over the world, and stroke is the most common cause of death, affecting approximate 2.5 million people every year.[1,2] Aldosterone is a kind of steroid hormone that regulates blood pressure through acting on renal mineralocorticoid receptors to induce genes in the kidney which then promote sodium retention.[3] Aldosterone is believed

From the *Stroke Center, Changhai Hospital, Second Military Medical University, Shanghai, China; and †Heping Hospital, Shijiazhuang, China.

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Address correspondence to Benqiang Deng, MD, PhD, Stroke Center, Changhai Hospital, Second Military Medical University, 168 Changhai Road, Shanghai 200433, China. E-mailes: longer_human007@126.com, 724128156@qq.com, gloria_leilei@163.com, pingzhang1121@163.com, doc_shenl@163.com, shir@163.com, zhangli_3954@qq.com, xiaocalf@163.com.

[1]Shoulong Zhang and Nuo Wang contributed equally to this work.

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to have deleterious influence on the vascular system through many mechanisms, involving vascular inflammation, vascular remodeling, endothelial dysfunction, and atherosclerosis.[4,5] Actually, compared with those with essential hypertension, patients with primary aldosteronism have an elevated prevalence of stroke.[6,7] Tomashitz et al.[8] suggested that even without primary aldosteronism, an increased serum aldosterone concentration (SAC) is strongly linked with an elevated risk for stroke mortality.

Aldosterone has been shown to be expressed in the arterial wall and to be regulated during atherosclerotic lesion progression.[9] Vascular calcification is an active process that resembles orthotopic bone formation and occurs in the atherosclerotic artery.[10] Although arteriosclerosis is known as a significant risk factor for vascular events, few studies have focused on the relationship between cerebral arteriosclerosis and serum aldosterone concentration. Therefore, we studied the association between serum aldosterone concentration and cerebral arteriosclerosis status, including cerebral atherosclerosis burden and cerebral artery calcification, in patients admitted with acute ischemic stroke from a single center-based stroke registry.

## Methods

### *Participants*

This study analyzed 243 consecutive patients admitted to a University Medical Center from February 2017 to April 2018. The inclusion criteria were having ischemic stroke, conducting brain computed tomography angiography (CTA), clinically stable at the time of aldosterone measurement.[11] Subjects who treated with aldosterone antagonists and/or β-blockers before serum aldosterone measurement, which have the strongest impact on the renin-angiotensin-aldosterone system, were excluded.[12] Other exclusion criteria were serum creatinine more than 2.2 mg/dL (194.5 μmol/L), endocrinological or renal artery stenosis, uncontrolled hypertension (systolic blood pressure ≥180 mm Hg and/or diastolic blood pressure ≥110 mm Hg despite treatment), or other major diseases, such as heart failure or severe liver disease.[13] Routine laboratory determinations (blood lipids, blood glucose, etc.) were detected for all enrolled participants at admission. Serum aldosterone concentration was measured 2-4 weeks after the acute ischemic stroke when patients were deemed clinically stable.[14] Patients who had plasma aldosterone concentration to plasma renin activity ratio (ARR) ≥20 ng/dl per ng/mL/h were further excluded to eliminate subjects with primary aldosteronism completely.[15] The remaining 207 participants were studied.

The vascular risk factors in this study involved hypertension, defined as blood pressure more than 140/90 mm Hg or the use of antihypertensive medication; diabetes mellitus, defined as a fasting blood glucose concentration more than 7 mmol/L or 2-hour serum glucose concentration of 11.1 mmol/L (when stress hyperglycemia was suspected, serum glucose level was rechecked after patient had been stabilized) or the use of diabetic medication; and current smoking status.[16] Stroke subtype was categorized according to the Trial of Org 10172 classification criteria.[17] This study was reviewed and approved by the Institutional Review Boards. Written consent was obtained from all study subjects or their immediate family members.

### *Aldosterone Measurement*

Aldosterone was measured between 6 and 10 AM in an upright position after overnight fasting. Analysis was performed by chemiluminescence immunoassay (ALD CLIA Microparticles; Autobio, Zhengzhou, China) with a linear range of 10-1000 pg/mL, coefficient of variation less than or equal to 12%. The patients were categorized into 4 groups in accordance to the serum aldosterone concentration, to investigate the prevalence of cerebral atherosclerosis burden and cerebral artery calcification.

### *Brain Computed Tomography (CTA) Protocol and Cerebral Arterial Evaluation*

All of the patients underwent multidetector brain CTA using a 320-multidetector row (640 slices) CT system (Aquilion ONE; Toshiba Medical Systems, Tokyo, Japan), with a detector width of 16 cm with 320 detector rows. Other scanning parameters includes: 80 kV, 120 mAs, 0.5 mm section thickness. Nineteen whole-head volume data were acquired at 2s intervals for the first 14 volumes and at 3s intervals for the last 5 volumes beginning 5s after 50 mL bolus injection of iodinated contrast agent (Iopamiro, Bracco Sine Pharmaceuticals, Shanghai, China) at 5 mL/s for CT imaging.

Intracranial atherosclerosis degree was examined from the bilateral anterior/middle/posterior cerebral arteries, basilar artery, intracranial portions of the internal carotid arteries, and vertebral arteries. The stenosis was scored as 0, no stenosis; 1, stenosis less than 50%; 2, stenosis 50%-69%; 3, stenosis 70%-99%; or 4, occlusion.[18] Vertebral artery hypoplasia or arterial occlusion due to cardioembolism was not considered a stenoocclusive lesion. The sum of the cerebral atherosclerosis scores was calculated and categorized into quartiles, and advanced intracranial atherosclerosis was defined to include the patients with the 2, 3, and 4 atherosclerosis score. The extracranial atherosclerosis burden was measured from the extracranial portion of the internal carotid arteries and vertebral arteries. The presence of intracranial arterial calcification was examined from both cavernous portions of internal carotid arteries, as arterial calcification degree was scored based on a modification of the method described by Chung PW et al.[19] from the axial and coronal images of CTA. Advanced

calcification was determined when calcification involved a 1 cm or longer segment or 50% or more of the vessel diameter of both cavernous distal internal carotid arteries.

*Statistics*

The distribution of aldosterone was displayed as a histogram and a $\log_2$ transformation of aldosterone was used to reduce the influence of skew. Baseline characteristics were investigated in each quartile of the serum aldosterone distribution. Continuous data were expressed as mean ± standard deviation and compared by t test or analysis of variance. Categorical variables were expressed as the number of patients with a percentage and compared by the likelihood ratio test or chi-square test. We compared the demographic and laboratory variables between patients with advanced intracranial atherosclerosis burden and those without. We also compared the high serum aldosterone proportion between patients with advanced intracranial arterial calcification and those without. Multivariable logistic regression analysis was used for both unadjusted and adjusted inference about the effect of serum aldosterone on advanced intracranial atherosclerosis and intracranial cerebral calcification. As serum aldosterone concentration was $\log_2$ transformed to reduce the influence of skew, odds ratios for each outcome measure are interpretable as the relative hazard for a doubling of serum aldosterone concentration. Adjusted covariates involved demographics, medical history, and laboratory results, chosen on the basis of a statistically significant relationship with serum aldosterone concentration or on the basis of clinical importance of the variable in addition to its association with intracranial atherosclerosis and intracranial cerebral calcification. According to these criteria, models were adjusted for the following 8 variables: age, sex, history of hypertension, history of diabetes mellitus, current smoking, triglyceride, low density lipoprotein (LDL), and estimated glomerular filtration rate (eGFR). More than 10 events per variable were included to maintain statistical power for multivariable analysis.[20] Results are presented as 95% confidence intervals and 2-sided $P$ value as $P < .05$ considered statistically significant. All of the statistical analyses were performed using SPSS version 23.0 (IBM SPSS).

## Results

There were a total of 207 ultimately included in the study. Basic demographic and clinical variables of included subjects are illustrated in Table 1 according to the aldosterone quartiles. The distribution of serum aldosterone concentration at baseline is shown in Figure 1. Median serum aldosterone was 146.00 pg/mL; interquartile range was 133.18 -172.10 pg/mL.

Table 1 shows baseline characteristics of the participants in aggregate and according to quartiles of serum aldosterone concentration and the association between each characteristic. Comparative analyses among the 4 groups showed that the increment of atherosclerosis burden by excess aldosterone was maintained for both the intracranial and extracranial vasculature (Table 1). Consequently, patients with elevated serum aldosterone concentration were more likely to have the stroke subtype of large artery atherosclerosis (Table 1). The prevalence of intracranial arterial calcification and advanced cerebral artery calcification increased with increasing aldosterone quartile (Table 1). Higher serum aldosterone concentration was also associated with lower estimated glomerular filtration rate.

When our study population was compared in terms of intracranial atherosclerosis burden and intracranial arterial calcification, advanced intracranial atherosclerosis were more frequently associated with hypertension and diabetes mellitus than those without, while advanced cerebral arterial calcification were more associated with older age, diabetes mellitus, higher triglyceride or LDL cholesterol than those without (Table 2). When serum aldosterone concentration was dichotomized at median (146.00 pg/mL), the patient group with elevated aldosterone was associated with both advanced cerebral atherosclerosis and cerebral artery calcification.

Table 3 shows the relationships between serum aldosterone concentration and advanced cerebral atherosclerosis and cerebral artery calcification both in unadjusted and adjusted models. Multivariable logistic regression analysis showed that serum aldosterone concentration was associated with risk of advanced cerebral atherosclerosis and cerebral artery calcification, both in univariate analysis (odds ratio 3.89, 95% confidence interval [CI], 1.62-9.36, $P_{trend} = .001$ and odds ratio 3.24, 95% CI, 1.41-7.44, $P_{trend} = .006$) and after adjustment for the 8 demographic, medical history and laboratory variables (odds ratio 5.07, 95% CI, 1.82-14.17, $P_{trend} = .001$ and odds ratio 6.24, 95% CI, 2.03-19.22, $P_{trend} = .001$). Each SD increase of serum aldosterone concentration (log transformed) was also associated with risk of advanced cerebral atherosclerosis and cerebral artery calcification, both in univariate analysis (odds ratio 1.65, 95% CI, 1.20-2.30, $P = .002$ and odds ratio 1.70, 95% CI, 1.26-2.29, $P = .001$) and after adjustment (odds ratio 1.73, 95% CI, 1.18-2.53, $P = .005$ and odds ratio 2.24, 95% CI, 1.47-3.40, $P < .001$).

## Discussion

The key novel finding of this study was that aldosterone was frequently associated with excess intracranial atherosclerosis burden and intracranial arterial calcification from brain CTA, independent of sex, age, vascular risk factors, and laboratory variables. It is noteworthy that this finding was investigated in a stroke population in whom primary aldosteronism had been ruled out by standardized criteria of (ARR) ≥20 ng/dL per ng/mL/h. This is the first report evaluating the relationship between serum aldosterone concentration and cerebral arteriosclerosis status by

**Table 1.** *Baseline characteristics according to quartiles of SAC*

| | All n = 207 | Quartile 1 n = 52 | Quartile 2 n = 52 | Quartile 3 n = 51 | Quartile 4 n = 52 | *P* value |
|---|---|---|---|---|---|---|
| Age, y | 62.40 ± 10.54 | 63.65 ± 8.39 | 62.14 ± 9.26 | 59.90 ± 13.36 | 63.79 ± 10.37 | .209 |
| Female | 70 (33.8) | 16 (30.8) | 21 (40.4) | 19 (37.3) | 14 (26.9) | .476 |
| Hypertension | 165 (79.7) | 38 (73.1) | 40 (76.9) | 42 (82.4) | 45 (86.5) | .336 |
| Diabetes mellitus | 70 (33.8) | 16 (30.8) | 16 (30.8) | 18 (35.3) | 23 (44.2) | .431 |
| Smoking | 91 (44.0) | 30 (57.7) | 22 (42.3) | 27 (52.9) | 12 (23.1) | .002 |
| Large artery atherosclerosis | 106 (51.2) | 19 (36.5) | 26 (50.0) | 28 (54.9) | 33 (63.5) | .048 |
| Cardioembolism | 12 (5.8) | 5 (9.6) | 3 (5.8) | 2 (3.9) | 3 (5.8) | .749 |
| Small vessel occlusion | 68 (32.9) | 20 (38.5) | 19 (36.5) | 17 (33.3) | 13 (25.0) | .479 |
| eGFR, mL/min/1.73m$^2$ | 87.94 ± 21.28 | 91.61 ± 14.54 | 90.47 ± 30.71 | 89.40 ± 16.88 | 80.30 ± 17.70 | .025 |
| Extracranial atherosclerosis score | 1.37 ± 0.70 | 1.14 ± 0.84 | 1.19 ± 0.66 | 1.49 ± 0.54 | 1.67 ± .058 | <.001 |
| Intracranial atherosclerosis score | 2.24 ± 1.29 | 1.89 ± 1.37 | 2.00 ± 1.37 | 2.37 ± 1.15 | 2.69 ± 1.11 | .005 |
| Intracranial arterial calcification score | 1.90 ± 1.39 | 1.42 ± 1.33 | 1.73 ± 1.34 | 1.96 ± 1.41 | 2.48 ± 1.29 | .001 |
| Advanced intracranial atherosclerosis | 134 (64.7) | 27 (51.9) | 30 (57.7) | 33 (64.7) | 42 (80.8) | .015 |
| Intracranial arterial calcification | 158 (76.3) | 35 (67.3) | 37 (71.2) | 41 (80.4) | 46 (88.5) | .048 |
| Advanced intracranial arterial calcification | 77 (37.2) | 13 (25.0) | 18 (34.6) | 19 (37.2) | 27 (51.9) | .040 |

Abbreviations: eGFR, estimated glomerular filtration rate; SAC, serum aldosterone concentration.

Quartiles 1, 2, 3, and 4 were defined by SAC of ≤133.17, 133.18-145.99, 146.00-172.09, ≥172.10, respectively.

Data were presented as mean ± SD or n (%).

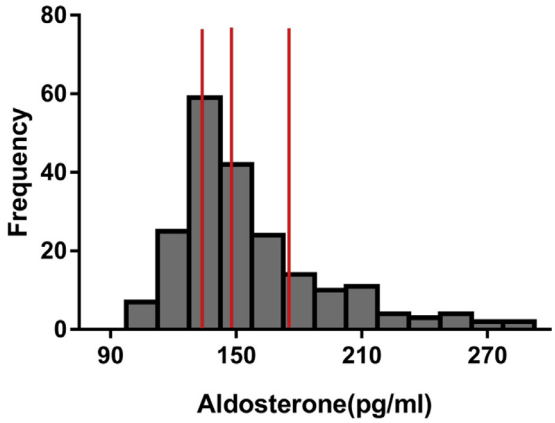


**Figure 1.** *Distribution of SAC at baseline. Measurements were made 2-4 weeks after an acute ischemic stroke event. Median and interquartile range are indicated by red lines. Abbreviation: SAC, serum aldosterone concentration. (Color version of figure is available online.)*

atherosclerosis burden and vascular calcification among a stroke population.

Stroke is a major cause of death and disability, and the prevalence is increasing steadily.[2] Vascular remodeling occurs in response to endothelial damage and leads to vascular pathologies including vascular stiffness due to aging, hypertension, atherosclerosis, etc.[21] Vascular risk factors including hypertension, diabetes, dyslipidemia, or smoking contributes to endothelial damage.[22] In the area of endothelial damage the normally quiescent smooth muscle cells proliferate and produce extracellular matrix which leads to vascular thickening and fibrosis.[23] Although much has been studied about mechanisms of vascular remodeling, our current vascular therapies are still limited by adverse remodeling that leads to stroke, myocardial infarction and the high failure rate of vein grafts, transplants and even stents. Our finding that serum aldosterone concentration was independently associated with intracranial atherosclerosis burden and intracranial vascular calcification strongly suggests that aldosterone plays an important role in atherosclerosis and direct endothelial damage.

For over half a century, aldosterone has been known to regulate blood pressure by renal sodium retention.[24] In accordance to this knowledge, the detrimental vascular effects of aldosterone have been attributed to secondary vascular responses to increased blood pressure.[25] Studies in animal models have shown the detrimental role of aldosterone in a context of sodium repletion on heart and vessels, beyond its effects on electrolyte handling and blood pressure regulation. Aldosterone in excess relative to sodium levels can promote vascular inflammation,[26] induce interstitial fibrosis in different organs and tissues,[27] and determine endothelial dysfunction,[28] which precedes the development of atherosclerosis that is accelerated through different mechanisms.[29-31] To date, most of the evidence on the role of aldosterone in the pathogenesis of

**Table 2.** *Factors associated with advanced intracranial arterial atherosclerosis and calcification*

| | Advanced intracranial atherosclerosis (+) n = 134 | Advanced intracranial atherosclerosis (−) n = 73 | *P* value | Advanced intracranial arterial calcification (+) n = 77 | Advanced intracranial arterial calcification (−) n = 130 | *P* value |
|---|---|---|---|---|---|---|
| Age, y | 63.18 ± 10.41 | 60.92 ± 10.68 | 0.121 | 66.81 ± 8.20 | 59.76 ± 10.92 | <.001 |
| Female | 45 (33.6) | 25 (34.2) | 0.923 | 22 (28.6) | 48 (36.9) | 0.220 |
| Hypertension | 114 (85.1) | 51 (69.9) | .009 | 63 (81.8) | 102 (78.5) | 0.562 |
| Diabetes mellitus | 52 (38.8) | 18 (24.9) | .040 | 39 (50.6) | 31 (23.8) | <.001 |
| Smoking, n (%) | 56 (41.8) | 35 (47.9) | .394 | 33 (42.9) | 58 (44.6) | 0.805 |
| eGFR, mL/min/1.73m$^2$ | 87.56 ± 20.25 | 88.64 ± 23.18 | .726 | 87.67 ± 15.57 | 88.10 ± 24.09 | 0.887 |
| Triglyceride, mmol/L | 4.76 ± 1.44 | 4.40 ± 1.02 | .061 | 4.94 ± 1.60 | 4.44 ± 1.09 | .008 |
| LDL cholesterol, mmol/L | 2.93 ± 1.25 | 2.73 ± 0.85 | .222 | 3.15 ± 1.40 | 2.69 ± 0.89 | .005 |
| Serum aldosterone, ≥146 pg/mL | 77 (57.5) | 27 (37.0) | .005 | 47 (61.0) | 57 (43.8) | .017 |

Abbreviation: eGFR, estimated glomerular filtration rate.
Data were presented as mean ± SD or n (%).

**Table 3.** *Odds ratios and 95% confidence intervals of advanced atherosclerosis and advanced calcification according to serum aldosterone quartiles in ischemic stroke patients*

| Advanced atherosclerosis | Quartile 1 n = 52 | Quartile 2 n = 52 | Quartile 3 n = 51 | Quartile 4 n = 52 | $P_{trend}$ | Each SD increase of Log-SAC |
|---|---|---|---|---|---|---|
| Model 1 | 1 | 1.26 (0.58-2.74) | 2.03 (0.91-4.52) | 3.89 (1.62-9.36) | .001 | 1.65 (1.20-2.30) |
| *P* values | | 0.556 | .085 | .002 | | .002 |
| Model 2 | 1 | 1.28 (0.58-2.83) | 2.13 (0.92-4.94) | 3.54 (1.37-9.20) | .004 | 1.58 (1.11-2.26) |
| *P* values | | 0.545 | .078 | .009 | | .012 |
| Model 3 | 1 | 1.20 (0.52-2.76) | 2.69 (1.12-6.43) | 5.07 (1.82-14.17) | .001 | 1.73 (1.18-2.53) |
| *P* values | | 0.669 | .026 | .002 | | .005 |
| **Advanced calcification** | | | | | | |
| | Quartile 1 n = 52 | Quartile 2 n = 52 | Quartile 3 n = 51 | Quartile 4 n = 52 | $P_{trend}$ | Each SD increase of Log-SAC |
| Model 1 | 1 | 1.59 (0.68-3.71) | 1.78 (0.76-4.15) | 3.24 (1.41-7.44) | .006 | 1.70 (1.26-2.29) |
| *P* values | | 0.285 | 0.181 | .006 | | .001 |
| Model 2 | 1 | 1.95 (0.78-4.86) | 2.65 (1.03-6.84) | 3.39 (1.30-8.86) | .009 | 1.78 (1.25-2.55) |
| *P* values | | 0.151 | .044 | .013 | | .002 |
| Model 3 | 1 | 2.00 (0.71-5.41) | 4.02 (1.41-11.43) | 6.24 (2.03-19.22) | .001 | 2.24 (1.47-3.40) |
| *P* values | | 0.171 | .009 | .001 | | <.001 |

Abbreviations: LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate; SAC, serum aldosterone concentration; TG, triglyceride.

Model 1, unadjusted. Model 2, adjusted for age, sex, history of hypertension, history of diabetes mellitus and current smoking. Model 3, further adjusted for LDL, TG and eGFR.

atherosclerosis has been studied on animals; our study is the first to provide direct evidence in human subjects that aldosterone is independently associated with cerebral arteriosclerosis status by atherosclerosis burden and vascular calcification.

Intracranial carotid artery calcifications are linked to history of stroke and vascular risk factors.[32,33] Cerebral artery calcification is also related to mortality and recurrent vascular events among the stroke population.[34] Calcifications are easily detectable on CTA and are present in the more severe atherosclerotic plaques and can therefore be used as a marker of atherosclerosis.[35] We showed that increased serum aldosterone was independently associated with advanced cerebral artery atherosclerosis and calcification, suggesting elevated aldosterone might aggravate cerebral arterial senescence, which may result in atherosclerosis and arterial calcification.

The prevalence of intracranial atherosclerotic stenosis accounts for 33%-67% of transient ischemic attack (TIA) or stroke cases in China and other countries in Asia,[36-38] consistent with our study which accounted for 51.2%. Our study showed that the prevalence of the stroke subtype of large artery atherosclerosis increased with increasing aldosterone quartile, possibly by accelerated cerebral arteriosclerotic changes. This hypothesis is supported by previous studies showing serum aldosterone concentration was an important independent predictor of progression of carotid plaque measured with duplex ultrasound scanner.[25]

Some studies suggest that individuals with high serum aldosterone concentration are more common in hypertensive subjects,[39,40] but results of our investigation highlight that relative aldosterone excess in at risk stroke adults, involving normotensive subjects, should not be ignored. Because the association of serum aldosterone concentration with atherosclerosis burden was slightly weakened after adjustment for hypertensive status, the hypertensive condition might involve pathogenetic link between an elevated aldosterone and atherosclerosis burden.

Strengths of this study are that cerebral arteriosclerosis status by atherosclerosis burden and vascular calcification was studied in a relatively large amount of consecutive participants and wide distribution of serum aldosterone concentrations. Second, arterial calcifications can be assessed and quantified easily with computed tomography angiography, an imaging modality often used in daily clinical work-up of patients with acute ischemic stroke, which is a robust and suitable marker of detecting atherosclerosis. Third, in this analysis serum aldosterone concentration was measured in the stable period after acute ischemic stroke, rather than measured at the time of presentation with acute ischemic stroke. In the immediate period after acute ischemic stroke, hemodynamics and serum aldosterone concentration themselves are in flux.[14,41] Besides, many subjects with acute ischemic stroke begin treatment with an angiotensin receptor blocker or an angiotensin-converting enzyme

inhibitor during hospitalization for acute ischemic stroke, and these drugs suppress serum aldosterone concentration.[12] Thus, information derived from serum aldosterone concentration when subjects are at a therapeutic and physiologic steady period is complementary to measurements of the hormone immediately after acute ischemic stroke.

Our study has also some limitations. First, this was a cross-sectional study, so the causality of the detected relationships could not be proved. The absence of a CTA in 11 patients was the second limitation. Reasons for not performing a CTA were kidney failure or severe ischemic stroke. These might result in selection bias and limit the generalization of the present findings. Moreover, subjects without a CTA were older than subjects with a CTA as it is known that the prevalence of vascular calcifications elevates with age.[35] This may have led to an underestimation of the true link between serum aldosterone concentration and cerebral arteriosclerosis status among stroke population. Third, this was a single center study of Chinese patients. Multicenter trials with larger cohorts and diverse races and ethnicities are needed. Fourth, we had only a single aldosterone measurement rather than other neurohormones over time, including cortisol, which may have associated with aldosterone to affect the cerebral arteriosclerosis status.

Our findings suggest an association between higher serum aldosterone concentration and greater intracranial atherosclerosis burden and excess intracranial arterial calcification. Our results support a significant role for aldosterone in cerebral arteriosclerosis, even adjusted for several risk variables. This relationship provides novel insights into the pathophysiology of overall cerebral arterial degeneration. In light of results from randomized controlled trials of aldosterone blockade, which have shown blood pressure independent reductions in arterial stiffness in subjects with hypertension,[42,43] future studies should investigate whether aldosterone antagonists prevent stroke in at risk population.

## Supplementary Materials

Supplementary data to this article can be found online at doi:10.1016/j.jstrokecerebrovasdis.2018.09.053.

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