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Are morphologic features of recent small subcortical infarcts related to specific etiologic aspects?

Sebastian Eppinger, Thomas Gatteringer, Lena Nachbaur, Simon Fandler, Lukas Pirpamer, Stefan Ropele, Joanna Wardlaw, Christian Enzinger and Franz Fazekas

Abstract

Background: Recent small subcortical infarcts (RSSIs) mostly result from the occlusion of a single, small, brain artery due to intrinsic cerebral small-vessel disease (CSVD). Some RSSIs may be attributable to other causes such as cardiac embolism or large-artery disease, and their association with coexisting CSVD and vascular risk factors may vary with morphological magnetic resonance imaging (MRI) features.

Methods: We retrospectively identified all inpatients with a single symptomatic MRI-confirmed RSSI between 2008 and 2013. RSSIs were rated for size, shape, location (i.e. anterior: basal ganglia and centrum semiovale posterior cerebral circulation: thalamus and pons) and MRI signs of concomitant CSVD. In a further step, clinical data, including detailed diagnostic workup and vascular risk factors, were analyzed with regard to RSSI features.

Results: Among 335 RSSI patients (mean age 71.1 ± 12.1 years), 131 (39%) RSSIs were >15 mm in axial diameter and 66 (20%) were tubular shaped. Atrial fibrillation (AF) was present in 44 (13.1%) and an ipsilateral vessel stenosis $> 50\%$ in 30 (9%) patients. Arterial hypertension and CSVD MRI markers were more frequent in patients with anterior-circulation RSSIs, whereas diabetes was more prevalent in posterior-circulation RSSIs. Larger RSSIs occurred more frequently in the basal ganglia and pons, and the latter were associated with signs of large-artery atherosclerosis. Patients with concomitant AF had no specific MRI profile.

Conclusion: Our findings suggest the contribution of different pathophysiological mechanisms to the occurrence of RSSIs in the anterior and posterior cerebral circulation. While there appears to be some general association of larger infarcts in the pons with large-artery disease, we found no pattern suggestive of AF in RSSIs.

Keywords: cerebral small-vessel disease, etiology, lacunar stroke, magnetic resonance imaging, recent small subcortical infarcts, risk factor

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Introduction

Recent small subcortical infarcts (RSSIs), formerly termed ‘lacunar strokes’ account for approximately 25% of all ischemic strokes.^{1,2} They occur in the supplying area of a single, deep perforating brain artery and are mostly felt to be a consequence of cerebral small-vessel disease (CSVD).¹ However, previous reports have suggested that up to 15% of RSSIs may be caused

rather by embolism or macroangiopathy [e.g. atrial fibrillation (AF) or ipsilateral carotid stenosis], especially in the absence of additional magnetic resonance imaging (MRI) signs of CSVD such as white matter hyperintensities (WMHs), lacunes or cerebral microbleeds.^{1,3–6}

It has also been suggested that certain infarct characteristics, such as a larger size or a tubular/

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cuneiform shape, might be associated with large-artery disease, embolic occlusion or a more proximal occlusion of an arteriole.^{5,7-10} These considerations are in line with an ongoing discussion about two different types of lacunar infarction; on the one hand, those RSSIs caused by an atheroma in the proximal portion of the perforating arteriole or parent artery, a pathology more suggestive of an atherosclerotic cause, and on the other hand, those attributable to lipohyalinosis.^{2,4,11} Furthermore, the association of RSSIs with vascular risk factors and concomitant cerebrovascular changes may vary between different vascular perfusion territories. Lesion features that identified risk factors would be clinically useful to target the diagnostic workup and consequently, secondary stroke prevention.

To further explore these aspects, we investigated a consecutively collected series of patients who had presented with acute stroke related to a single RSSI on MRI.¹² We specifically looked at associations between different RSSI characteristics (such as size and configuration) and specific risk-factor profiles or evidence for possible infarct etiology other than CSVD. We explored different areas of the brain separately, in case there were differences between the anterior and posterior cerebral circulation.

Methods

We retrospectively searched the medical documentation system of our primary and tertiary care university hospital for inpatients diagnosed with 'acute ischemic stroke' (ICD-10 code I63) from 1 January 2008 to 5 February 2013. Of 4118 identified patients, 3363 had undergone brain MRI within 10 days from symptom onset [this time interval served to assure that acute infarcts were reliably captured by diffusion-weighted imaging (DWI)].¹³ MRI scans were reviewed for the presence of RSSIs by two neuroimaging experts without any clinical information and RSSIs were defined according to the STAndards for ReportIng Vascular changes on nEuroimaging (STRIVE) criteria¹⁴ by: (a) presence of a hyperintense DWI lesion with corresponding reduced diffusivity on the apparent diffusion coefficient (ADC) map compatible with acute ischemic infarction; (b) subcortical lesion location in four prespecified regions (basal ganglia including internal capsule, thalamus, centrum semiovale, and pons), suggestive of the

supply area of a penetrating artery; and (c) a maximal axial lesion diameter of ≤ 20 mm.⁶ Patients were excluded if their scans showed multiple acute subcortical infarcts, additional acute infarcts in other locations, or other acute intracranial lesions (e.g. brain hemorrhage, tumor).¹²

MRI protocol and analysis

MRI of the brain was performed on 1.5 T scanners (Siemens Symphony, Siemens, Erlangen, Germany; Philips Intera and Gyroscan ACS, Philips, Eindhoven, the Netherlands) according to a standard protocol for the workup of patients with suspected cerebrovascular events. This included an axial T2-weighted fast-spin-echo sequence, an axial T2-weighted fluid-attenuated inversion-recovery (FLAIR) sequence, a sagittal T1-weighted spin-echo sequence, a gradient-echo T2*-weighted sequence, and an axial diffusion-weighted single-shot echo planar-imaging sequence with ADC maps. All axial scans had a slice thickness of 5 mm.

We recorded the location of the RSSI according to four prespecified regions and the infarct shape was defined as either round/ovoid or tubular (Figures 1 and 2). We also looked for additional signs of CSVD, including WMHs, which were rated according to the Fazekas scale,¹³ microbleeds and lacunes of presumed vascular origin, as defined by the STRIVE criteria.¹⁴ The presence of old cortical or cerebellar infarctions and of old hemorrhages was noted as well.

Clinical data

Demographic and clinical data including the past medical history, cardiovascular risk factors, as well as the National Institutes of Health Stroke Scale (NIHSS) score at admission and discharge were extracted from the electronic medical documentation system of our hospital. Risk factors were defined as arterial hypertension (pre-existing diagnosis or blood pressure $\geq 140/90$ mmHg), hypercholesterolemia (pre-existing diagnosis or fasting total cholesterol ≥ 200 mg/dl), diabetes mellitus [pre-existing diagnosis or glycated hemoglobin (HbA1c) defined by the International Federation of Clinical Chemistry as >42 mmol/mol], smoking, renal insufficiency [glomerular filtration rate (GFR) < 60 ml/min/1.7 m²], coronary heart disease (CHD;

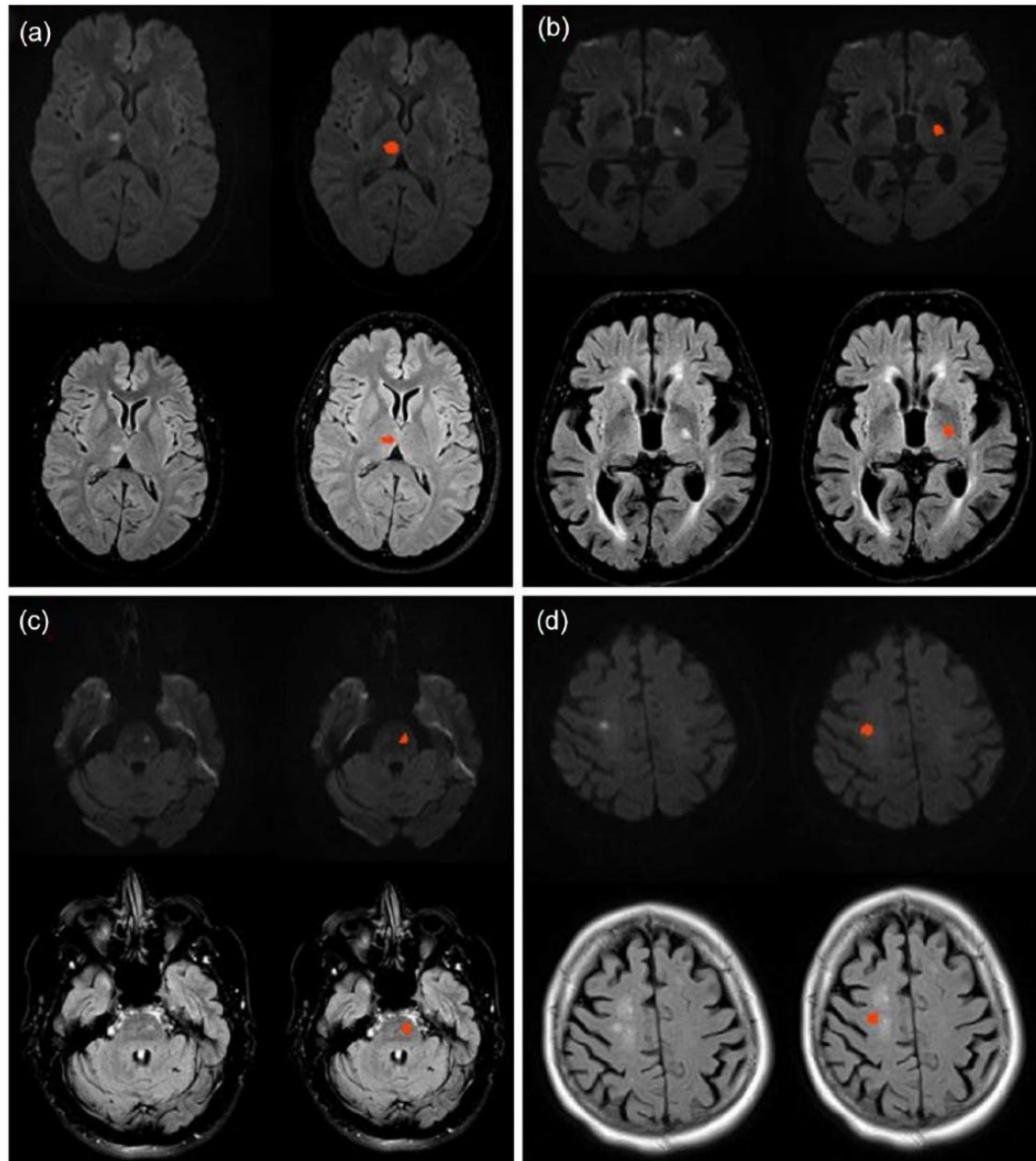


Figure 1. RSSIs in the observed anatomical locations on DWI and FLAIR sequences (upper and lower rows, respectively).

(a) Thalamus; (b) internal capsule; (c) pons; (d) centrum semiovale.

DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; RSSIs, recent small subcortical infarcts.

pre-existing diagnosis or diagnosis during hospitalization), peripheral arterial disease (PAD; pre-existing diagnosis or diagnosis during hospitalization). We also extracted the results of 12-lead electrocardiograms (ECGs) and neurosonographic examinations of the extra- and intracranial brain-supplying vessels which were available on all patients, and recorded the information from 24 h ECG and echocardiography, where available.

Statistical analysis

The Statistical Package for the Social Sciences (version 21.0; SPSS Inc., Chicago, IL, USA) was used for data analysis. Dichotomous variables were analyzed using the Chi-square test. The Mann–Whitney *U* test and Kruskal–Wallis test were used for continuous nonparametric variables. Statistical significance was accepted at $p \leq 0.05$. Analyses included a comparison of RSSI patients with (early confluent or confluent WMH, cerebral microbleeds, lacunes)

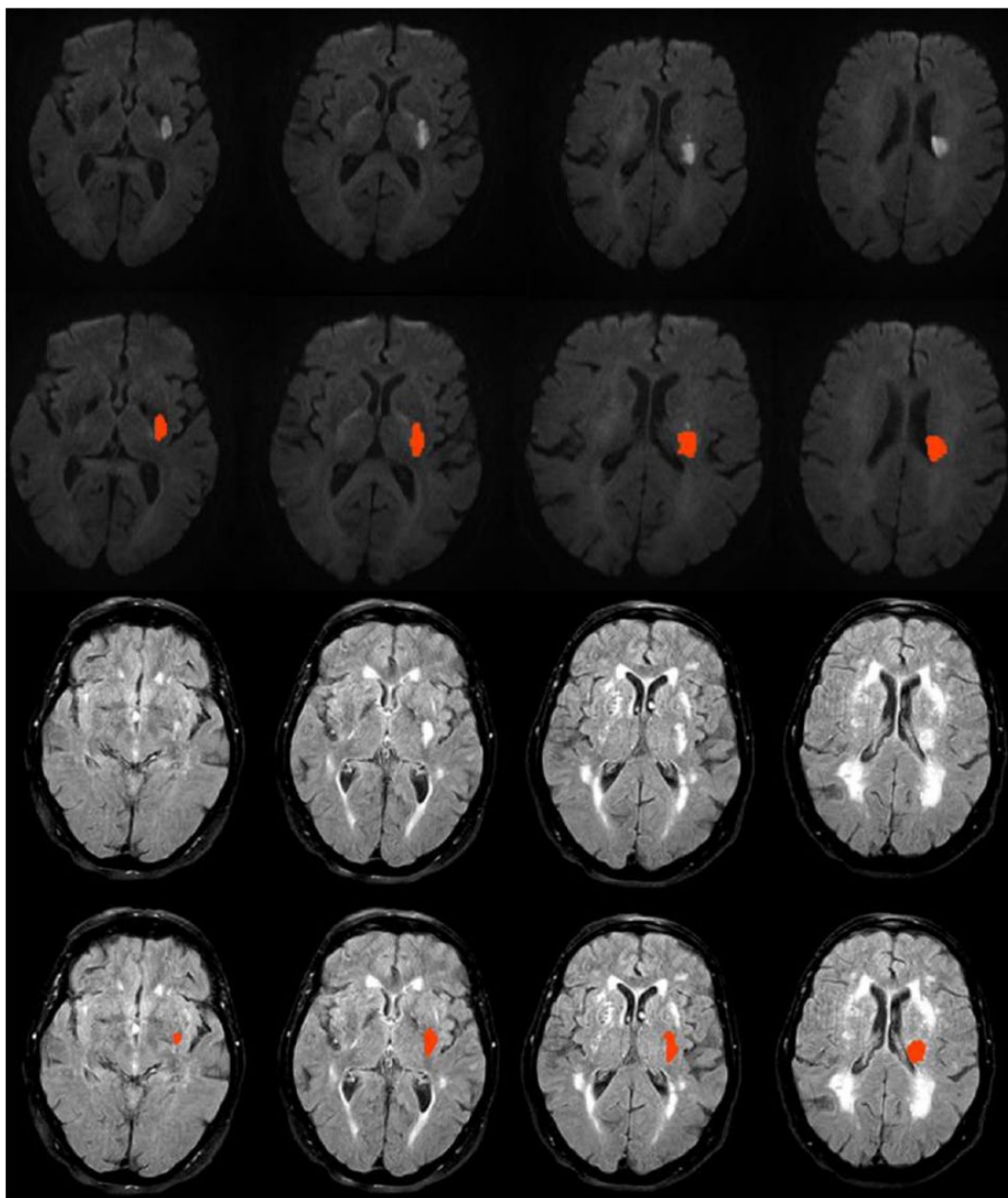


Figure 2. Example of a tubular RSSI in the basal ganglia depicted on DWI (upper half) and FLAIR (lower half). DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; RSSI, recent small subcortical infarct.

versus those without other signs of CSVD. For the latter category, we only accepted the presence of punctate (grade 1) WMH. A comparison was also made between patients with RSSIs in the anterior (i.e. basal ganglia including internal capsule, centrum semiovale) and in the posterior (i.e. thalamus, pons) cerebral circulation.

The study was approved by the ethics committee of the Medical University of Graz (25-409 ex 12/13).

Results

We identified 335 RSSI patients with a mean age of 71.1 (± 12.1) years and 65% were men. The majority of RSSIs were located in the basal ganglia ($n = 108$) followed by pons ($n = 90$), thalamus ($n = 76$) and centrum semiovale ($n = 61$). A total of 131 (39%) RSSIs were >15 mm in axial diameter and 66 (20%) were tubular shaped. Moderate-to-severe WMHs (Fazekas grades 2 or 3) were present in 190 (56.7%) patients, lacunes

in 144 (43%) and microbleeds in 110 (32.8%). AF was found in 44 (13.1%) patients and an upstream > 50% vessel stenosis in 30 (9%) patients. Further characteristics regarding imaging features as well as risk factors are shown in Table 1.

Patient and imaging characteristics according to RSSI location

Patient age and sex were not different according to RSSI location. Arterial hypertension was more prevalent in patients with anterior-circulation RSSIs in the basal ganglia or centrum semiovale, whereas diabetes was more common in patients with pontine or thalamic RSSIs (posterior circulation). Other risk factors were equally frequent across different RSSI locations (Table 1).

Patients with RSSIs in the anterior circulation showed a significantly higher rate of concomitant CSVD signs such as WMH grades 2 or 3, lacunes and microbleeds (Table 1).

An upstream-vessel stenosis > 50% was detected primarily in patients with pontine RSSIs.

Stroke severity according to the NIHSS was more severe in patients with RSSIs in the basal ganglia and pons (Table 1).

Patient and imaging characteristics according to RSSI shape and size

There was no association between RSSI shape or size and patients' age, but tubular-shaped RSSIs were more common in men (Table 2).

Round/ovoid RSSIs tended to be smaller than tubular RSSIs, and smaller RSSIs \leq 15 mm occurred more often in the centrum semiovale and thalamus, whereas larger lesions were more concentrated in the pons and basal ganglia (Table 2).

Diabetes mellitus was more prevalent in patients with round-/ovoid-shaped RSSIs and patients with upstream-vessel stenosis > 50% had larger RSSI diameters; otherwise, we found no differences in the distribution of risk factors according to RSSI shape or size (Table 2).

RSSI shape was not associated with stroke severity or outcome, while patients with an RSSI > 15 mm had higher NIHSS scores both at admission and

at discharge and remained more often disabled than patients with an RSSI \leq 15 mm (Table 2).

Differences between RSSI patients with and without additional signs of CSVD

To also look at the impact of coexisting CSVD in a compound manner, we divided patients into those with no other morphologic abnormalities than at maximum punctate WMH according to Fazekas scale scores 0–1 (RSSI–) and those with additional signs of CSVD, that is, coexisting WMH Fazekas scale scores 2 or 3, microbleeds or lacunes (RSSI+). RSSI+ patients were significantly older and had a higher prevalence of old infarcts involving the cortex or the cerebellum.

Smoking, diabetes mellitus, CHD and AF were equally distributed, whereas arterial hypertension and PAD occurred more often in RSSI+ patients (Table 3).

Anterior circulation RSSIs were associated with more (RSSI+), while posterior circulation RSSIs had less severe (RSSI–) accompanying chronic CSVD signs (Table 3).

Discussion

We extended previous work by analyzing a large series of consecutive patients in whom MRI had shown a single RSSI, irrespective of the results of the patients' diagnostic workup.¹² While arterial hypertension prevailed in patients with RSSI in the anterior cerebral circulation, diabetes mellitus was associated with infarcts in the posterior circulation. Signs of concomitant CSVD were also associated to a greater extent with RSSI in the anterior circulation. We found no specific morphologic RSSI features in patients who had AF, but proximal vessel stenosis was related to RSSI in the pons and a larger infarct size.

There is an ongoing discussion whether different RSSI imaging characteristics are associated with a distinct risk-factor profile. It has been argued that larger infarcts might be more likely in patients with an embolic source or branch atheromatous disease (BAD).^{5,9} For AF, we did not find any support for this assumption. Importantly the prevalence of AF was also similar in patients with and without coexisting chronic CSVD signs, which argues against a causative role. Proximal stenosis did show an association with larger infarcts but

Table 1. Clinical data and MRI findings of RSSI according to location and perfusion territory.

Variables	All patients (n = 335)		Location (n or %)		Perfusion territory (n or %)		p
	Pons n = 90	Thalamus n = 76	Basal ganglia n = 108	Centrum semiovale n = 61	Posterior n = 166	Anterior n = 169	
Demographic and clinical data							
Male (%)	217 (64.8)	45 (59.2)	74 (68.5)	38 (62.3)	105 (63.3)	112 (66.3)	n.s.
Age (±SD)	71.1 (±12.1)	69.8 (±13.4)	71.7 (±11.7)	73.1 (±11.5)	69.9 (±12.5)	72.2 (±11.6)	n.s.
Admission NIHSS (median, range)	3.0 (2.0–4.0)	2.0 (1.0–4.0)	3.0 (2.0–4.0)	3.0 (1.0–4.0)	2.5 (1.0–4.0)	3.0 (2.0–4.0)	0.025
Discharge NIHSS (median, range)	1.0 (1.0–2.0)	1.0 (0.0–2.0)	2.0 (1.0–3.0)	1.0 (0.0–2.0)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.003
mRS (median, range)	1.0 (1.0–3.0)	1.0 (1.0–2.0)	1.5 (1.0–4.0)	1.0 (1.0–2.0)	1.0 (1.0–3.0)	1.0 (1.0–3.0)	0.002
Concomitant morphological findings on MRI							
Lacunae (%)	144 (43.0)	27 (35.5)	56 (51.9)	32 (52.5)	56 (33.7)	88 (52.1)	0.001
WMH grade 0–1 (%)	145 (43.3)	41 (53.9)	41 (38.0)	14 (23.0)	90 (54.2)	55 (32.5)	<0.001
WMH grade 2–3 (%)	190 (56.7)	35 (46.1)	67 (62.0)	47 (77.0)	76 (45.8)	114 (67.5)	
Microbleeds (%)	110 (32.8)	15 (20.3)	46 (45.1)	30 (50.0)	34 (21.5)	76 (46.9)	<0.001
Old cortical infarct (%)	59 (17.6)	15 (19.7)	15 (13.9)	9 (14.8)	35 (21.1)	24 (14.2)	n.s.
Old cerebellar infarct (%)	31 (9.3)	7 (9.2)	8 (7.4)	8 (13.1)	15 (9.0)	16 (9.5)	n.s.
Vascular risk factors							
Smoking (%)	97 (28.9)	24 (31.6)	37 (34.6)	14 (23.0)	46 (27.7)	51 (30.4)	n.s.
Arterial hypertension (%)	284 (84.8)	54 (71.1)	97 (89.8)	55 (90.2)	132 (79.5)	152 (89.9)	0.002
Diabetes mellitus (%)	93 (27.8)	27 (35.5)	20 (18.5)	13 (21.3)	60 (36.1)	33 (19.5)	0.008
Hypercholesterolemia (%)	200 (59.7)	48 (63.2)	60 (55.6)	36 (59.0)	104 (62.7)	96 (56.8)	n.s.
Atrial fibrillation (%)	44 (13.1)	10 (13.2)	13 (12.0)	13 (21.3)	18 (10.8)	26 (15.4)	n.s.
Upstream-vessel stenosis > 50% (%)	30 (9)	5 (6.6)	5 (4.6)	6 (9.8)	19 (11.4)	11 (6.5)	0.049
PAD (%)	26 (6.8)	8 (10.5)	7 (6.5)	2 (3.3)	17 (10.2)	9 (5.3)	n.s.
CHD (%)	47 (14.0)	11 (14.5)	13 (12.0)	7 (11.5)	27 (16.3)	20 (11.8)	n.s.
Bold numerals denote statistical significance. CHD, coronary heart disease; n.s., nonsignificant; NIHSS, National Institutes of Health Stroke Scale; MRI, magnetic resonance imaging; mRS, modified Ranking Scale; PAD, peripheral arterial disease; RSSI, recent small subcortical infarcts; WMH, white matter hyperintensity.							

Table 2. Clinical data and risk factors of RSSI according to shape and size.

Variables	All subjects (n = 335)			Shape (n or %)		Size (n or %)	
	Round/ovoid n = 269	Tubular n = 66	p	≤15 mm n = 204	>15 mm n = 131	p	
Demographic and clinical data							
Male (%)	217 (64.8)	52 (78.8)	0.009	126 (61.8)	91 (69.5)	n.s.	
Age (±SD)	71.1 (±12.1)	70.74 (±11.5)	n.s.	71.70 (±11.8)	70.18 (±12.5)	n.s.	
Admission NIHSS (median, range)	3.0 (2.0–4.0)	3.0 (2.0–4.0)	n.s.	2.0 (1.0–4.0)	3.0 (2.0–4.75)	0.001	
Discharge NIHSS (median, range)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	n.s.	1.0 (1.0–2.0)	2.0 (1.0–3.0)	0.0001	
mRS (median, range)	1.0 (1.0–3.0)	1.00 (1.0–3.0)	n.s.	1.0 (1.0–2.0)	1.0 (1.0–3.0)	0.009	
Vascular risk factors							
Smoking (%)	97 (28.9)	18 (27.3)	n.s.	51 (25.0)	46 (35.4)	n.s.	
Arterial hypertension (%)	284 (84.8)	56 (84.8)	n.s.	172 (84.3)	112 (85.5)	n.s.	
Diabetes mellitus (%)	93 (27.8)	9 (13.6)	0.004	62 (30.4)	31 (23.7)	n.s.	
Hypercholesterolemia (%)	200 (59.7)	45 (68.2)	n.s.	116 (56.9)	84 (64.1)	n.s.	
PAD (%)	26 (6.8)	4 (6.1)	n.s.	15 (7.4)	11 (8.4)	n.s.	
CHD (%)	47 (14.0)	14 (21.2)	n.s.	31 (15.2)	16 (12.2)	n.s.	
Atrial fibrillation (%)	44 (13.1)	9 (13.6)	n.s.	29 (14.2)	15 (11.5)	n.s.	
Upstream-vessel stenosis > 50% (%)	30 (9)	5 (7.6)	n.s.	12 (5.9)	18 (13.7)	0.018	
Any-vessel stenosis > 50% (%)	63 (18.8)	9 (13.6)	n.s.	36 (17.6)	27 (20.6)	n.s.	
Location							
Pons (%)	90 (26.9)	22 (24.4)	n.s.	47 (52.2)	43 (47.8)	< 0.001	
Thalamus (%)	76 (22.7)	12 (15.8)		47 (52.2)	43 (47.8)		
Basal ganglia (%)	108 (32.2)	24 (22.2)		51 (47.2)	57 (52.8)		
Centrum semiovale (%)	61 (18.2)	8 (13.1)		48 (78.7)	13 (21.3)		
Bold numerals denote statistical significance. CHD, coronary heart disease; mRS, modified Ranking Scale; NIHSS, National Institutes of Health Stroke Scale; n.s., not significant; PAD, peripheral arterial disease; RSSI, recent small subcortical infarcts; SD, standard deviation; WMH, white matter hyperintensities.							

Table 3. Comparison of patients with RSSI and different degrees of cerebral small-vessel disease.

	All subjects (n = 335)	CSVD		p
		No/mild CSVD (RSSI-) (n = 123)	Severe CSVD (RSSI+) (n = 212)	
Characteristics:				
Age (\pm SD)	71.1 (\pm 12.1)	67.25 (\pm 13.1)	73.33 (\pm 10.9)	< 0.0001
Male (%)	217 (64.8)	80 (65.0)	137 (64.6)	n.s.
Round/ovoid shape (%)	269 (80.3)	95 (77.2)	174 (82.1)	n.s.
Tubular shape (%)	66 (19.7)	28 (22.8)	38 (17.9)	n.s.
\leq 15mm (%)	204 (60.9)	73 (59.3)	131 (61.8)	n.s.
>15mm (%)	131 (39.1)	50 (40.7)	81 (38.2)	n.s.
Pons (%)	90 (26.9)	43 (35.0)	47 (22.2)	0.001
Thalamus (%)	76 (22.7)	36 (29.3)	40 (18.9)	
Basal ganglia (%)	108 (32.2)	31 (25.2)	77 (36.3)	
Centrum semiovale (%)	61 (18.2)	13 (10.6)	48 (22.6)	
Old cortical infarct (%)	59 (17.6)	11 (8.9)	48 (22.6)	0.002
Old cerebellar infarct (%)	31 (9.3)	2 (1.6)	29 (13.7)	0.0001
Smoking (%)	97 (28.9)	38 (30.9)	59 (28.0)	n.s.
Arterial hypertension (%)	284 (84.8)	89 (72.4)	195 (92.0)	< 0.0001
Diabetes mellitus (%)	53 (15.8)	28 (22.8)	65 (30.7)	n.s.
Hypercholesterolemia (%)	200 (59.7)	82 (66.7)	118 (55.7)	0.050
PAD (%)	26 (6.8)	4 (3.3)	22 (10.4)	0.019
CHD (%)	47 (14.0)	18 (14.6)	29 (13.7)	n.s.
Atrial fibrillation (%)	44 (13.1)	13 (10.6)	31 (14.6)	n.s.
Upstream-vessel stenosis > 50% (%)	30 (9)	13 (10.6)	17 (8)	n.s.
Any-vessel stenosis > 50% (%)	63 (18.8)	23 (18.7)	40 (18.9)	n.s.
Bold numerals denote statistical significance. CHD, coronary heart disease; CSVD, cerebral small-vessel disease; n.s., nonsignificant; NIHSS, National Institutes of Health Stroke Scale; PAD, peripheral arterial disease; RSSI, recent small subcortical infarcts; SD, standard deviation.				

not with tubular shaped lesions and this association was largely driven by brainstem infarcts. Although there was an excess concurrence of ipsilateral vessel stenosis among patients with lesions > 15mm, notably, the impact of stenosis of the ipsilateral carotid artery has been disputed and is

considered incidental rather than causative.^{15,16} Our cohort did not differ substantially from others regarding carotid stenosis or embolic sources, such as AF; especially with regard to the latter, it was representative in mean age.¹⁷ Compared with the findings from two previous studies, we also

found no association between shape or size and AF;^{7,10} though larger, primarily pontine infarcts were associated with an upstream stenosis. One should also consider that different shape, as well as size, might reflect a highly individually disparate branching pattern of the perforating arteries, particularly in the basal ganglia.¹⁸

Our findings support the association of diabetes mellitus with lesions in the posterior circulation, especially in the brainstem.^{19–22} This might suggest a higher vulnerability of the vertebrobasilar system to diabetic macro- and microangiopathy. The exact underlying mechanisms remain unknown to this day. A recent study addressing histopathological changes in the anterior and posterior cerebral arteries revealed a higher predisposition of the basilar artery to dilate, and vertebral arteries to be prone to concentric intima thickening and stenosis.²³ Different embryological origins of the posterior and anterior circulation might be constitutive for those differences in the aging process of the vessels.²³ Another important factor might be the concept of BAD, meaning an occlusion of the orifice of the branching perforation artery by a proximal atheroma or a luminal plaque in the parent artery. An autopsy study performed in the 1970s showed a high frequency of diabetes mellitus associated with lesions in the posterior perfusion territory, especially in patients with an infarct pattern suggestive of BAD.²⁰ Recently, high-resolution (HR) and high-field MRI has enabled the detection of atheromatous plaques in the basilar artery, as well as the middle cerebral artery, potentially causing occlusions of perforators.^{5,24–26} Therefore, these sophisticated methods could be of particular interest in further investigations, specifically regarding the posterior circulation.

It was also interesting to note that old cortical or cerebellar infarcts were visible on MRI with a comparable frequency between patients with anterior *versus* posterior circulation RSSIs. However, other chronic features of CSVD were found preferentially in patients with RSSIs in the anterior circulation. This is consistent with a higher prevalence of hypertension in patients with RSSIs in the anterior circulation. The reason for a preponderance of CSVD in the anterior circulation has not yet been determined, although other studies have noted it as well.¹⁹ As endothelial failure seems to play an important role in CSVD, differences in the wall composition of arterioles and

capillaries might be of specific interest. On the one hand, there is evidence for an age-related increase in endothelial permeability; on the other hand, vascular risk factors do seem to play an important role as well.⁴ Therefore, it is quite interesting that especially patients with infarcts in the centrum semiovale showed pronounced signs of CSVD in our study, as well as a high incidence of cardiovascular risk factors. In this brain region, there is an increased number of capillaries, the barrier function of the endothelium on the capillary level is hypothesized to be more resistant than the arteriolar level.⁴ Our findings support these observations. Although not statistically significant, those were also the oldest patients.

RSSI patients with severe CSVD signs were older than patients with no or only mild accompanying chronic cerebrovascular lesions. In general, WMHs tend to appear in the cerebral hemispheres before they occur in the brainstem area. There was no significant difference in age according to the location of the acute ischemic lesion. Nonetheless, it has to be considered that these observations might reflect different stages of CSVD. The question of whether occurrence of an isolated RSSI without concomitant signs of CSVD can be considered as a first sign of diffuse cerebral disease cannot be answered yet.^{4,27} Morphological characteristics of RSSIs did not allow prediction of future functional disability, except when it came to size and a location in the basal ganglia or pons, although this study did not follow up patients after discharge and cannot offer long-term functional prognoses. Like other studies, we also found that the larger the lesion, the worse the (at least short term) outcome.^{10,28} As the fibers are more tightly packed in subcortical regions, especially in the internal capsule and the brainstem, relatively small lesions are disconnecting a larger representative section of the cortex.²⁹

We have to consider several limitations of our work. The selection of patients for our study was carried out based solely on imaging criteria according to STRIVE, irrespective of the clinical stroke syndrome. As our study was conducted risk-factor free, inclusion of strokes of different etiologies might not have been entirely avoided. Most of the other studies of RSSI populations are subtyped or included by a risk-factor-based stroke classification system, thus, excluding patients with more severe vessel stenosis or a potential cardioembolic source. For our retrospective study, we used pre-existing

imaging material provided for diagnostics. These clinical standard images did not include coronal slices, making a definitive measurement of the longitudinal extent of a lesion difficult. Due to our study design, we could not provide a specific clinical protocol. Thus, some examinations such as echocardiography and 24 h ECG were not performed on every patient, potentially limiting the detection of cardiac-stroke causes in some patients. Notably, all patients received at least ECG and neurovascular sonography.

Further studies including and comparing RSSIs in the anterior- and posterior-perfusion territory with explicit attention to the presence of diabetes mellitus, as well as impaired glucose tolerance, could provide further crucial information. HR-MRI of relevant vessels could be meaningful for depicting subtle atheromatous changes, which may be causative of RSSIs. In the long term, it will be of interest whether those patients do show a different response to therapy or might even profit from a different treatment regime.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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