Spontaneous cervical artery dissection (sCAD) is a major cause of stroke in young and middle-aged adults, causing up to 25% of all ischemic strokes in patients 15 to 49 years of age. Depending on the affected vessel, sCAD is divided into spontaneous internal carotid artery dissection (sICAD) and spontaneous vertebral artery dissection (sVAD). The causes of sCAD are poorly understood. Both constitutional and environmental factors play a role. In most studies, sICAD and sVAD were analyzed as one entity. Analogous to aortic dissection, in which pathologies differ between vessel segments, there might be differences in the mechanisms leading to sICAD and sVAD. The Cervical Artery Dissection Ischemic Stroke Patients (CADISP) group recently reported significant differences between sICAD and sVAD. In light of these new findings, we aimed to compare the frequency of potential risk factors, presenting clinical characteristics, and outcome after 3 months in patients with sICAD and sVAD. Furthermore, we investigated whether time to diagnosis differed between sVAD and sICAD and changed over time. To answer these questions, we retrospectively compared patients with sICAD and sVAD enrolled in our ongoing database of 1027 patients with cervicocerebral artery dissection from 3 stroke centers. Patients and Methods Patients
In this observational study, we analyzed prospectively collected data of 1027 consecutive patients with a first-ever sCAD who were treated in 1 of the following 3 tertiary referral hospitals: University Hospital Bern, Switzerland; Department of Neurology, University Hospital Zurich, Zurich, Switzerland (H.S., R.W.B.); and Department of Neurology, Hôpital Lariboisière, APHP, Université Paris-Diderot, Paris, France (C.S., F.B., M.-G.B.).

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Baseline Characteristics and Potential Risk Factors

Baseline characteristics and potential risk factors were assessed by a structured patient interview or reconstructed on the basis of the hospital reports. The following potential risk factors were collected: arterial hypertension, diabetes mellitus, hypercholesterolemia, former or present smoking, migraine with or without aura, current use of anticoagulation or hormone substitution, known connective tissue disorder, febrile infection or minor trauma within the past 4 weeks before sCAD, and family history of stroke, sCAD, or connective tissue disorder.

Arterial hypertension was defined as a positive history of treated or untreated hypertension (before 2000: systolic blood pressure ≥160 mm Hg or diastolic blood pressure >95 mm Hg; after 2000: systolic blood pressure >140 mm Hg or a diastolic blood pressure >90 mm Hg).

Hypercholesterolemia was defined by total venous fasting cholesterol values >5.0 mmol/L or treatment with cholesterol-lowering medication. Current smoking was defined as regular smoking within the past 5 years; former smokers abstained for ≥25 years. History of migraine with or without aura was assessed by a neurologist on the basis of International Headache Society criteria.\(^2\) Assessed connective tissue disorders included Ehlers–Danlos syndrome type IV, Marfan syndrome, and osteogenesis imperfecta type I. Family history of connective tissue disorder, sCAD, or ischemic stroke was considered positive if ≥1 first-degree relative was affected. Febrile infection was defined as ≥1 clinical symptom of infection and body temperature >38°C. Fibromuscular dysplasia was only assessed in patients who underwent digital subtraction angiography.

Clinical Presentation

At initial encounter, all patients underwent a neurological and physical examination by a trained neurologist (including a routine blood sampling and an ECG). Patients were screened for ischemic events (transient ischemic attack [TIA], stroke, amaurosis fugax, and retinal infarction) and local symptoms (neck pain, headache, thunderclap headache, Horner syndrome, pulsatile tinnitus, cranial nerve palsy, cervical radiculopathy, and cervical spinal cord ischemia). Severity of headache or neck pain was assessed using the visual analogue scale.\(^3\) Horner syndrome and cranial nerve palsy were only recorded when not occurring in the context of a brain stem infarction. Ischemic symptoms were classified according to the duration of clinical symptoms: TIA and amaurosis fugax if ≤24 hours, stroke and retinal infarction if >24 hours.

In case of a cerebral stroke, the National Institutes of Health Stroke Scale (NIHSS) score was assessed and a cerebral MRI or computed tomography was performed. If the NIHSS score was not assessed, it was reconstructed from hospital reports. All patients received an evaluation of the cerebral and cervical arteries by MRA/CT angiography, ultrasound examination or digital subtraction angiography. Reversible cerebral vasoconstriction was defined according to Ducros et al.,\(^10\) and its previously reported association with sCAD\(^10\) was further investigated in the present study.

Time to Diagnosis

We defined the onset of clinical symptoms on the basis of the first symptom, which the treating neurologist could associate with an sCAD. Time to diagnosis was defined as the time interval between the date of symptom onset and the date on which the neurovascular imaging leading to the diagnosis was performed.

Three-Month Follow-Up

A clinical follow-up (n=725) or structured telephone interview (n=82), which included the assessment of the modified Rankin Scale (mRS), was performed at 3 months. A total of 163 follow-ups (17%) were missing (proportionally equally in 112 patients with sICAD [17%] and 50 patients with sV AD [17%]). Recurrent events (dissection, stroke, TIA, and death) and current medication were registered.

Statistical Analysis

Demographic variables, potential risk factors, and clinical parameters were compared between sICAD (or multiple sICAD) and sV AD (or multiple sV AD). Mean and SD of continuous variables were calculated. Differences of continuous variables were assessed with Mann–Whitney U-test, differences of categorical variables with χ2 test, or Fisher exact test, if appropriate. Hormonal anticoagulation was only assessed in women <50 years of age. Multivariate logistic regression analysis was performed to evaluate an independent association among baseline characteristics, potential risk factors, clinical symptoms, and diagnosis of sV AD versus sICAD. The following variables were included: age, sex, center of inclusion, NIHSS score, neck pain, thunderclap headache, pulsatile tinnitus, and subarachnoid hemorrhage (SAH). The cutoff for inclusion in the multivariate analysis was P<0.1 in the univariate analysis. Confidence intervals (95%) were calculated.

To determine the diagnostic delay, we performed a subgroup analysis dividing all sCAD into 2 groups: (1) diagnosis of sCAD between 1991 and 2000, and (2) diagnosis of sCAD between 2001 and 2012.

To compare the 3-month follow-up, we dichotomized the clinical outcome measured by the mRS into 2 groups: good outcome (mRS, 0–2) and poor outcome (mRS, 3–6). We ran a logistic regression analysis correcting for center of inclusion, age, sex, NIHSS score, and site of dissection to determine an independent association between the affected vessel and the outcome.

Results

Baseline Characteristics and Potential Risk Factors

Of 970 patients (59.7% men), 668 (68.9%) presented with unilateral or bilateral sICAD and 302 (31.1%) with unilateral or bilateral sV AD (Table 1).

Patients with sICAD were more often men (62.7% versus 53.0%; P=0.004) and older (46.3±9.6 years versus 42.0±10.2 years; P<0.001; Table 1). Bilateral dissection occurred half as often in patients with sICAD compared with sV AD (7.6% versus 15.2%; P<0.001). Current smoking was significantly less frequent in sICAD than in sV AD (28.7% versus 36.0%; P=0.02). No other investigated potential risk factor showed a different association between sICAD and sV AD in univariate analysis. A total of 35 sCAD were isolated intracranial dissections. Of all 668 sICAD, 6 were isolated intracranial (0.9%); of all 302 sV AD, 29 were isolated intracranial (9.6%). After performing multivariate analysis, the higher frequency...
of sICAD in men compared with women lost its significance (P=0.21); all other variables showed an independent, significant association (Table 1).

Clinical Presentation

Patients with sVAD presented twice as often with neck pain (65.8% versus 33.5%; P<0.001), but neck pain intensity was not significantly higher compared with sICAD (visual analogue scale, 6.5±1.9 versus 6.0±1.7; P=0.12; Table 2). However, headache was equally common in both (sVAD 70.4% versus sICAD 71.4%; P=0.77) but significantly stronger in its intensity in sVAD (visual analogue scale, 7.5±2.1 versus 6.7±1.8; P<0.001). Thunderclap headache occurred more than twice as often in sVAD than in sICAD (9.2% versus 3.6%; P=0.001). Of the 24, 10 patients with thunderclap headache had an SAH. Patients with sVAD were 10 times more often affected by SAH than patients with sICAD (6.0% versus 0.6%; P<0.001). Of the 18, 4 patients with sVAD-related SAH were associated with reversible cerebral vasoconstriction syndrome. Apart from cranial nerve palsy and Horner syndrome, which only appear in carotid artery dissections, pulsatile tinnitus was the only symptom that presented significantly more often in patients with sICAD than in sVAD (10.9% versus 3.4%; P<0.001).

Cerebral ischemic events (ie, stroke, TIA, retinal infarction, or amaurosis fugax, combined) affected patients with sVAD significantly more often than patients with sICAD (84.4% versus 70.4%; P<0.001). Ischemic stroke was significantly more frequent in sVAD (69.5% versus 52.2%; P<0.001), but less severe than in sICAD (mean NIHSSsVAD 5±5.9 versus NIHSSsICAD 10±7.1; P<0.001). Rare findings were spinal infarction (C2-4) in 1 patient and cervical radiculopathy (C5-7) in another, both associated with sVAD. One patient with sICAD was asymptomatic.

The most common first symptom was in both sICAD and sVAD, a local symptom (66.2% versus 65.6%; P=0.85). Both had equally often a TIA (10.6% versus 13.0%; P=0.28) or an ischemic stroke (17.2% versus 21.0%, P=0.18) as initial symptom. All independent associations remained significant after multivariate regression analysis (Table 2).

Time to Diagnosis

During the whole observation period, time to diagnosis did not differ between sICAD and sVAD (9.0±11.6 days versus 9.8±13.5 days; P=0.59). However, subgroup analysis showed that patients with sICAD treated between 2001 and 2012 were diagnosed 2 days earlier compared with those treated between 1991 and 2000 (8.0±10.5 days versus 10.7±13.2 days; P=0.004). In sVAD, time to diagnosis did not show a significant difference between the 2 time periods (9.3±13.2 days in 2001–2012 versus 11.8±14.7 days in 1990–2000; P=0.10).

Clinical Outcome and Recurrence

Clinical outcome measured by mRS was significantly better in patients after sVAD than after sICAD (mRS, 0–2: sVAD 88.8%, sICAD 58.4%; P<0.001; Table 3). There was a trend toward higher mortality after sICAD within
the first 3 months after dissection ($P=0.059$) in univariate analysis.

Seven patients (0.9%) had a recurrent isolated dissection, none of them after a multiple dissection. The amount of recurrent dissections did not differ between sICAD and sVAD, but 4 of the 5 recurrent dissections after sICAD affected the vertebral artery, whereas 1 of the 2 recurrent dissections after sVAD affected the contralateral vertebral artery, and the other one affected both the internal carotid and the contralateral vertebral artery. Recurrent TIA and stroke were more common after sVAD (TIA: sVAD 4.8%, sICAD 1.1%, $P=0.001$; stroke: sVAD 2.8%, sICAD 0.7%, $P=0.02$).

Multivariate analysis was performed adjusting for age, sex, center of inclusion, NIHSS score, and site of dissection to determine an independent association between the affected vessel and outcome. Only the higher baseline NIHSS score was highly associated with a poor outcome ($P<0.001$) and higher mortality ($P<0.001$).

## Discussion

This is the second large study analyzing differences in baseline characteristics, clinical symptoms, potential risk factors, and outcome between sICAD and sVAD.

### Baseline Characteristics and Risk Factors

The frequency of sICAD was about twice as high compared with sVAD, which is in line with previous findings. In agreement with previous studies, bilateral dissection affected the vertebral artery twice as often as the internal carotid artery. Patients with sICAD were older and more often men, compared with patients with sVAD, which is consistent with previous findings. These age and sex differences are difficult to explain. However, because patients with sVAD were younger compared with patients with sICAD, it is possible that risk factors or triggering events, such as traumas that are less related to advanced age, are involved more in the pathogenesis of sVAD than sICAD. Of interest, younger age at CAD onset and multiple CADs have been reported to be more common in women. These age and sex differences may suggest that genetic differences, sexual hormones, or even sex-related differences in arterial wall properties may play a role. Moreover, the vertebral artery and the carotid artery do have a different embryological origin. Of interest, current smoking was more frequent in patients with sVAD. This result is in line with the observation that smoking was associated with dilatation of only the thoracic aorta, which has the same embryological origin as the vertebral artery, and not of the ascending aorta, which has the same roots as the internal
Clinical Presentation

A new finding is that thunderclap headache was more than twice as common in sVAD compared with sICAD, which is only partly explained by a higher amount of SAH in sVAD. The reasons for this association remain unknown.

Pulsatile tinnitus, which corresponds to noise evoked by turbulent, nonlaminar blood flow and transmitted to the inner ear, occurred thrice more often in sICAD. This may be explained by the anatomic proximity of the typical location of ICAD to the inner ear. Two patients with sVAD presented with rare manifestations: 1 patient with a cervical radiculopathy and another with a cervical spine infarction.

In agreement with the CADISP study, ischemic stroke was less frequent but more severe in patients with sICAD compared with sVAD. Ischemic strokes in the anterior circulation of undefined pathogenesis have previously been explained by the anatomic proximity of the typical location of ICAD to the inner ear. Two patients with sVAD presented with rare manifestations: 1 patient with a cervical radiculopathy and another with a cervical spine infarction.

A 10-fold amount of patients with sVAD experienced an SAH compared with patients with sICAD. Most of them affected either only the intracranial segment of the vertebral artery or extended to the intracranial segments. Of the 18, 4 patients with sVAD-related SAH were associated with a reversible cerebral vasoconstriction syndrome, which is known to cause SAH in some patients without evidence for intracranial extension of the cervical artery dissections and which was diagnosed in 12 patients in total.

Time to Diagnosis

Local clinical symptoms of sVAD are not specific compared with those of sICAD, which are typically a painful Horner syndrome or lower cranial nerve palsies. Hence, the diagnosis of sVAD poses a challenge. However, we could not find a significant diagnostic delay of sVAD compared with sICAD. An interesting observation is the earlier diagnosis of sICAD between 2001 and 2012 compared with the diagnosis made between 1990 and 2000. This indicates a diagnostic improvement, probably because of a progress in imaging modalities and an increased awareness of the disease. In sVAD, no diagnostic improvement in the later time period could be shown. This points out that there is still much room for improvement of the clinical and diagnostic work-up in sICAD.

Clinical Outcome and Recurrence

In univariate analysis, a good outcome (mRS, 0–2) in patients who experienced an sICAD-related stroke was significantly less common compared with patients with an sVAD-related stroke. After multivariate analyses, the only parameter independently predicting functional outcome was the NIHSS score, which was higher in patients with stroke because of sICAD as opposed to sVAD.

Recurrent dissections within the first 3 months were as rare in sICAD as in sVAD, and there were no recurrent dissections after multiple dissections. Interestingly, recurrent dissections were mostly located in the vertebral artery, no matter whether the initial dissection affected the vertebral or carotid artery, which to our knowledge, has not been previously reported. Only 1 recurrent dissection affected the same vessel on the same side again.

Both recurrent TIA and recurrent ischemic stroke were more common after sVAD. We observed a nonsignificant trend toward higher mortality in patients with an sICAD-related ischemic stroke.

Strengths and Limitations

Strengths of this study are the large sample size and the significant results after correction for multiple comparisons. Because of the low incidence of sCAD in the general population, we had to include patients over a long time period and from 3 different centers. The centers of inclusions consisted only of university hospitals. Thus, a selection bias with more severe cases, especially more patients with strokes, might have occurred and patients with only local symptoms might have been underrepresented. In addition, one-sixth of the patients had no 3-month follow-up examination. However, the rate of patients with lost follow-up did not differ between sVAD and sICAD patients.

Conclusions

Although patients with sICAD and sVAD have many features in common, they differ in age, clinical presentation, risk factors, outcome, and rates of early recurrent ischemic events. The observed differences do not provide enough evidence to propose different treatment strategies for sVAD and sICAD. However, future studies on sCAD should perform separate analyses of the 2 entities.
References


Differences and Similarities Between Spontaneous Dissections of the Internal Carotid Artery and the Vertebral Artery (Revision 2)

Michelle von Babo, Gian Marco De Marchis, Hakan Sarikaya, Christian Stapf, Fréderique Buffon, Urs Fischer, Mirjam R. Heldner, Jan Gralla, Simon Jung, Barbara Goeggel Simonetti, Heinrich P. Mattle, Ralf W. Baumgartner, Marie-Germaine Bousser and Marcel Arnold

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