Pediatr Radiol (2014) 44:587–596
DOI 10.1007/s00247-014-2880-9

ORIGINAL ARTICLE

Extracranial carotid arteriopathy in stroke-free children with sickle cell anemia: detection by submandibular Doppler sonography

Suzanne Verlhac · Stéphane Balandra · Isabelle Cussenot · Florence Kasbi · Manuela Vasile · Ahmed Kheniche · Monique Elmaleh-Bergès · Ghislaine Ithier · Malika Benkerrou · Françoise Bernaudin · Guy Sebag

Received: 16 July 2013 / Revised: 18 October 2013 / Accepted: 18 November 2013 / Published online: 6 March 2014

Abstract
Background Cerebral vasculopathy is a serious complication of sickle cell anemia. Overt strokes are largely due to intracranial arteriopathy, detected by routine transcranial Doppler and largely prevented through chronic transfusions. As extracranial internal carotid artery arteriopathy was considered rare, it has not been routinely assessed in sickle cell anemia. Recent cases of overt strokes associated with stenosis/occlusion of the extracranial portion of the internal carotid artery prompted us to include extracranial internal carotid artery assessment to our transcranial Doppler sonography protocol.
Objective The aim of the study was to perform a cross-sectional study in children with sickle cell anemia to evaluate Doppler flow patterns of the extracranial internal carotid arteries and to assess potential associated factors.
Materials and methods Between June 2011 and April 2012, 435 consecutive stroke-free children with sickle cell anemia (200/235 M/F, median age: 7.9 years) were assessed for extracranial internal carotid artery using a 2-MHz transcranial Doppler sonography probe via a submandibular window during routine transcranial Doppler sonography visits. The course of both extracranial internal carotid artery was assessed by color Doppler mapping, and the highest flow velocity was recorded after insonation of the entire length of the artery and analyzed. Intra- and extracranial MR angiographies were available in 104/435 subjects for comparison.
Results Mean (SD) extracranial internal carotid artery time-averaged mean of maximum velocity was 96 (40) cm/s. Extracranial internal carotid artery tortuosities were echo-detected in 25% cases and were more frequent in boys (33% vs.18%; $P<0.001$). Velocity ≥160 cm/s in at least one extracranial internal carotid artery was found in 45 out of 435 patients with sickle cell anemia (10.3%) and was highly predictive of MR angiography stenosis. Simultaneous abnormal intracranial velocity (≥200 cm/s) was recorded in 5/45 patients, while 40 patients had isolated extracranial internal carotid artery velocity ≥160 cm/s. Low hemoglobin (odds ratio: 1.9/g/dL, 95% confidence interval (CI): 1.3–2.9; $P=0.001$) and tortuosities (odds ratio: 19.2, 95% CI: 7.1–52.6; $P<0.001$) were significant and independent associated factors for isolated extracranial internal carotid artery velocities ≥160 cm/s.
Conclusion Adding extracranial internal carotid artery evaluation via the submandibular window to transcranial Doppler sonograpy allowed us to detect 10.3% patients at risk for extracranial internal carotid arteriopathy. Further studies are needed to evaluate the prognosis of these anomalies.

Keywords Sickle cell anemia · Transcranial Doppler sonography · Internal carotid artery · Magnetic resonance angiography · Children

Presented in part at the 50th annual meeting of the European Society of Paediatric Radiology, Budapest, Hungary, June 3–7, 2013, and at the 56th annual meeting of the American Society of Hematology, Atlanta, GA, USA, December 2012.

S. Verlhac · S. Balandra · I. Cussenot · A. Kheniche · M. Elmaleh-Bergès · G. Sebag
Department of Pediatric Imaging, University Paris VII, Assistance-Publique-Hôpitaux de Paris, Hospital Robert Debré, Paris, France

S. Verlhac (✉) · F. Kasbi · M. Vasile
Medical Imaging Department, Centre Hospitalier Intercommunal, 40 avenue de Verdun, 94010 Créteil Cedex, France
e-mail: suzanne.verlhac@chicreteil.fr

G. Ithier · M. Benkerrou
Department of Pediatrics, Division of Hematology/Oncology, University Paris VII, Referral Center for Sickle Cell Disease, Assistance-Publique Hôpitaux de Paris, Hospital Robert Debré, Paris, France

F. Bernaudin
Department of Pediatrics, Referral Center for Sickle Cell Disease, University Paris XII; Centre Hospitalier Intercommunal, Créteil, France

Introduction

Cerebral vasculopathy is a serious complication of sickle cell anemia. Strokes are estimated to occur in 11% of children with sickle cell anemia and may result in permanent neurological and cognitive impairment [1]. The highest incidence (1.02 per 100 person-years) is found in children between 2 and 5 years of age. The risk of ischemic and hemorrhagic strokes is also high in adult patients. Strokes are most often associated with stenoses of the large arteries of the intracranial anterior circulation, resulting from intima-media thickening caused by fibroblasts and smooth-muscle cells proliferation, fragmentation of the internal elastic membrane and superimposed thrombus. The causal mechanism has not been completely elucidated, but may involve several factors such as direct mechanical interactions between the physically altered stiffened and sticky sickle erythrocytes and the endothelial cells, impaired blood rheology in arterial bifurcations and bended segments, increased production of endothelial adhesion and inflammatory molecules, and decreased nitrous oxide production. These stenoses can be detected by transcranial Doppler sonography [2], allowing primary stroke prevention through initiation of chronic transfusions [3]. Transcranial Doppler sonography is recommended from the second year of age in children with sickle cell anemia to evaluate the intracranial arteries via temporal and suboccipital approaches [4, 5]. As significant arterial disease of the extracranial internal carotid artery was considered to be rare in sickle cell anemia, extracranial internal carotid artery evaluation was not recommended. However, recent cases of overt strokes associated with stenosis or occlusion of the extracranial portion of the internal carotid artery prompted us to systematically add the evaluation of extracranial internal carotid artery in all patients during their routine transcranial Doppler sonography visits.

The aim of this study was to assess extracranial internal carotid artery flow patterns by Doppler sonography using the submandibular approach, a newly described acoustic window [6] and to assess potential associated factors.

Materials and methods

In this cross-sectional study, consecutive (SS/Sb0) children from two patient cohorts (Creteil and Robert Debre, Paris, France) were assessed between June 2011 and April 2012. Parental informed consent was obtained and data were prospectively and systematically collected in a clinical database. Use of the database was approved for this project by the Creteil Institutional Review Board. Patients with a history of overt stroke were excluded from the study, as was a patient with a known intracranial arteriovenous malformation.

Four radiologists (6–20 years' experience) performed the evaluation of the extracranial carotid arteries and the intracranial arteries by US using color Doppler equipment (Logic 9, GE Healthcare Milwaukee, WI, USA and Aplio, Toshiba Medical Systems Corporation, Tochigi-Ken, Japan). We used the same small-sized, low-frequency (2-MHz) transducer for extracranial and intracranial arteries. For the extracranial internal carotid artery, the transducer was placed below the angle of the jaw and aimed cephalad. As opposed to the linear high-frequency transducer that is commonly used to perform conventional neck Doppler sonography, its small footprint is more convenient with children who have short necks. Moreover, as the probe has a high penetration power, insonation through the submandibular window allows for excellent Doppler evaluation of the entire course of the extracranial internal carotid artery in the carotid space, from its origin at the carotid bifurcation (at a depth of around 1.5 cm) up to the base of skull (at a depth of around 5 cm) (Fig. 1). In addition, the transcranial Doppler sonography probe allows excellent alignment of the Doppler beam axis with the arterial axis, resulting in optimum recording of blood velocity, with no need for angle correction and no risk of overestimation of velocities. In order not to compress the artery and induce a false acceleration of blood flow, particular attention was taken to avoid pressing hard with the probe. The entire course of the artery was interrogated and the highest time-averaged mean of maximum velocity was recorded without angle correction by

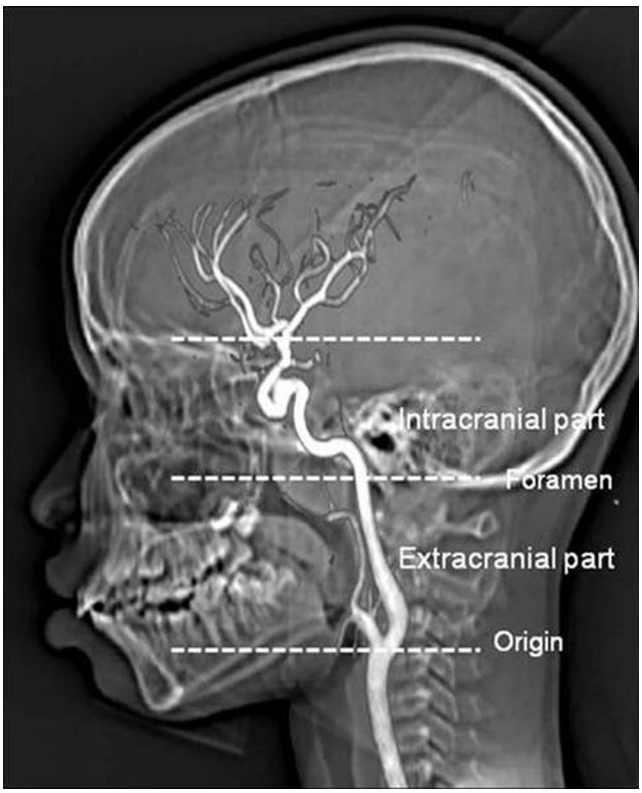

Fig. 1 Photomontage depicts a lateral view of the anatomy of the internal carotid artery. The intracranial part, except the petrous part, is assessed via the temporal window. The extracranial part, including the foramen, is assessed via the submandibular window

outlining the envelope of a single cycle. The course of the extracranial internal carotid artery, assessed by color Doppler mapping, was considered normal if straight, or tortuous if the artery had a change in direction with an angle ≥120° between

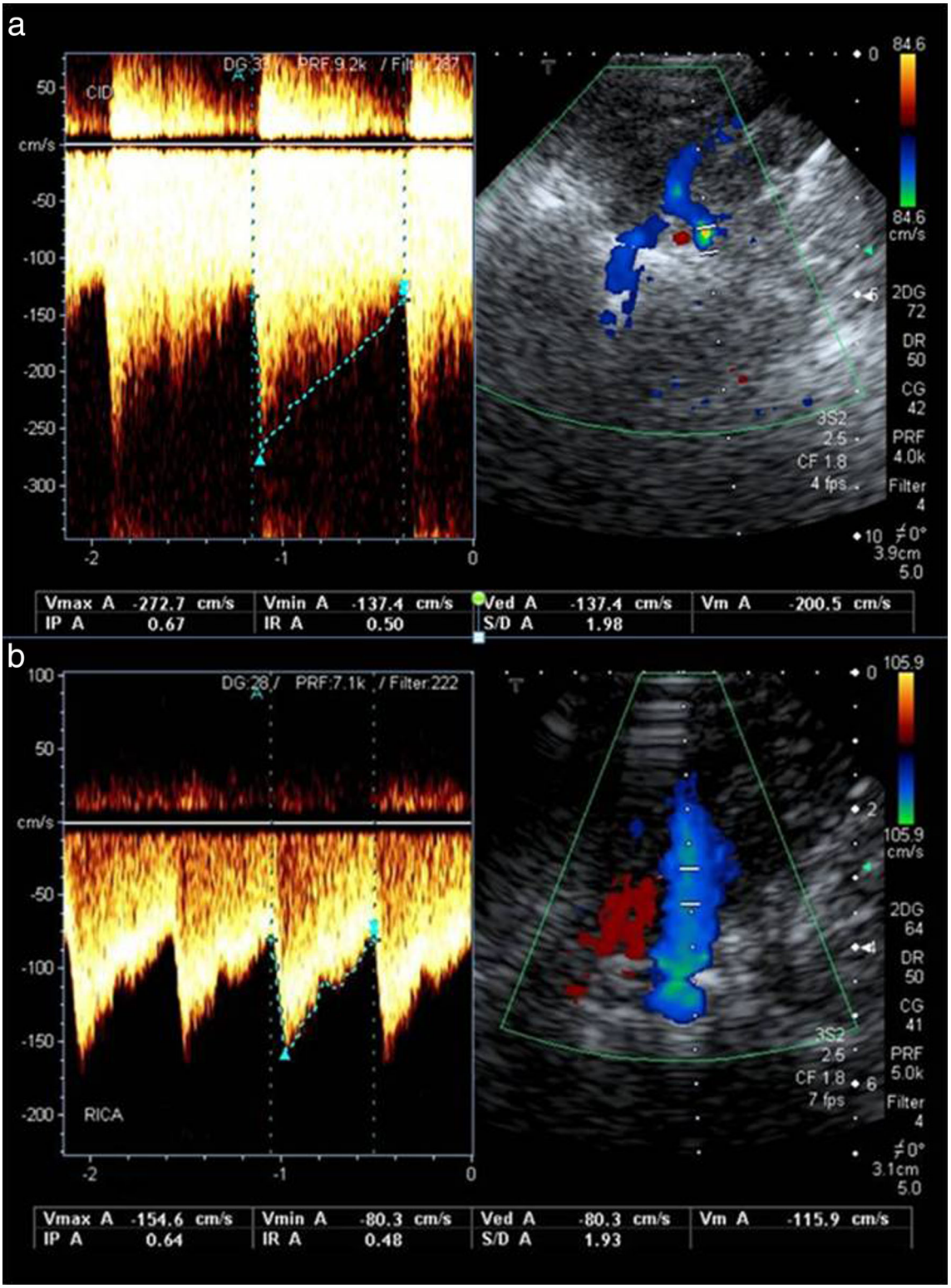

Fig. 2 Color Doppler sonography performed through the submandibular window in two patients. **a** 6-year-old boy. Spectra of extracranial internal carotid artery stenosis at the site of kinking with high velocity extracranial internal carotid artery flow (*top*) (time-averaged mean of maximum velocities: 200 cm/s). **b** 4-year-old girl. Spectra of normal extracranial internal carotid artery flow (*bottom*)(time-averaged mean of maximum velocities: 115 cm/s)

adjacent segments (i.e. looped or kinked) (Fig. 2). The procedure included bilateral transtemporal windows and a suboccipital window for intracranial arteries according to our standardized protocol [5]. Right and left middle cerebral arteries, anterior cerebral arteries and internal carotid arteries were recorded, and their time-averaged mean of maximum velocities without angle correction, middle cerebral artery resistive index (peak systolic-end diastolic velocities/peak

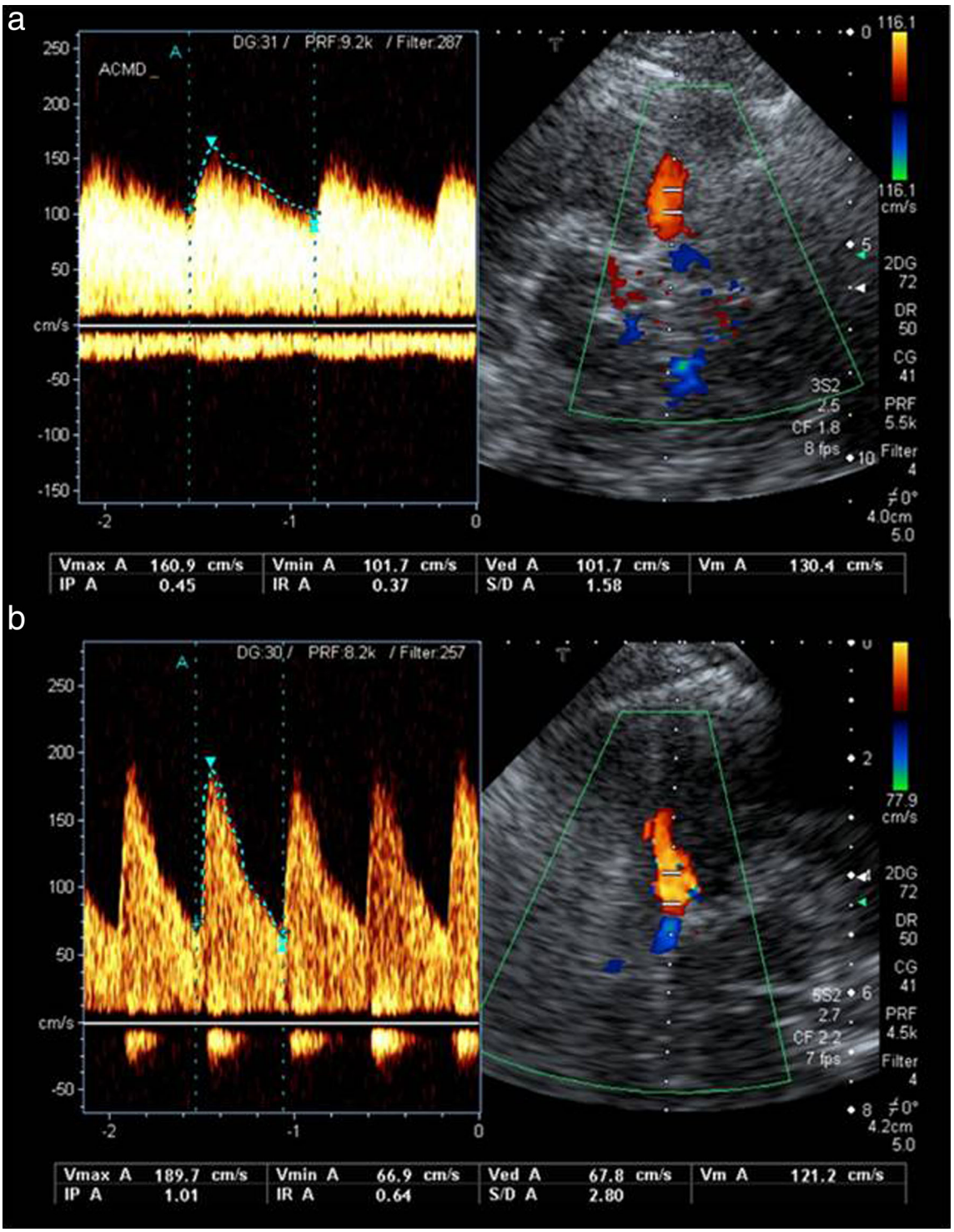

Fig. 3 Transcranial Doppler sonography performed with a 2-Mhz probe through the temporal window in the same two patients as in Fig. 2. **a** Spectra of a low resistive middle cerebral artery flow (*top*) (resistive index 0.37, pulsatility index 0.45) downsteam of an extracranial internal carotid artery stenosis. **b** Spectra of a normal scan with normal middle cerebral artery flow (*bottom*)(resistive index 0.64; pulsatility index 1.01)

systolic velocity) and pulsatility index (peak systolic-end diastolic velocities/time-averaged mean of maximum velocities) indices were obtained (Fig. 3). MRI with a 3-D time-of-flight MR angiography sequence of the intracranial arteries (Sigma 1.5 T, GE Healthcare, Milwaukee, WI, USA and Intera 1.5 T, Philips Medical Systems, Best, The Netherlands) was performed as part of routine assessment of patients with sickle cell anemia every 2 years, starting from the age of 5 years, and in children with abnormal intracranial velocities or with non-straight extracranial internal carotid artery. An additional 3-D time-of-flight multislab MR angiography (non-contrasted) sequence exploring extracranial internal carotid artery and carotid bifurcations was systematically added to the routine procedure from June 2011. The MR angiography images were reconstructed as maximum intensity projections in different planes, and segmentation of each artery was obtained. All MR angiography images were also viewed as axial unreconstructed images. MR angiographies were reviewed independently by three radiologists who were blinded to Doppler sonography findings and clinical history; discrepancies were resolved by consensus. The course of the extracranial internal carotid artery was evaluated and the degree of extracranial internal carotid artery stenosis was determined using the North American symptomatic carotid endarterectomy trial method and graded according to accepted nomenclature as mild (20–50%), moderate (50–69%) or severe (70–99%) [7]. MR angiographies were done within 6 months of Doppler sonography.

Statistical analysis

Mean with standard deviation and median (range) were calculated for time-averaged mean of maximum velocities, resistive index, pulsatility index in the right and left MCA, and for time-averaged mean of maximum velocities in the right and left extracranial internal carotid artery. Analyses included Pearson's correlation coefficients, while Fisher exact tests were used to compare proportions. Association of high extracranial internal carotid artery velocities with other variables such as age, gender, hemoglobin level and tortuosities was assessed using logistic regression with estimated odd ratios and 95% CI. Receiver operating characteristic curves (ROC) were used to determine the cut-off limit of extracranial internal carotid artery velocity that was predictive of extracranial internal carotid artery stenosis on MR angiography. All statistical tests were 2-sided, with *p*-values of 0.05 or less denoting statistical significance. Statistical analysis was performed with SPSS 19 (IBM, Chicago, IL, USA).

Results

The study included 435 stroke-free patients with sickle cell anemia (SS/Sb0; 235 girls, 200 boys), consecutively assessed at the mean (SD) age of 8.5 (4.3) years and median age of 7.9 years (range: 1.3–18.7). Mean (SD) hemoglobin level at time of Doppler was 8.7 (1.4) g/dl.

Extracranial internal carotid artery tortuosities on color Doppler mapping

Tortuosities assessed by Doppler sonography were observed in 109/435 patients (25%). They were unilateral in 49/109 with 25 right-side and 24 left-side and bilateral in 60, and were more frequent in boys (66/200; 33%) than in girls (43/235; 18%; $P<0.001$). Regression logistic analysis showed that tortuosities were not associated with age, but were significantly associated with male gender (odds ratio: 2.2, 95% CI: 1.4–3.4; $P=0.001$).

Velocities on Doppler readings

Right and left middle cerebral artery and extracranial internal carotid artery velocities, along with middle cerebral artery resistive index and pulsatility index for all study participants are shown in Table 1. Mean (SD) extracranial internal carotid artery time-averaged mean of maximum velocities was 96 (40) cm/s on the right and 96 (37) cm/s on the left. Extracranial internal carotid artery velocities were significantly correlated with middle cerebral artery velocities ($r=0.208$, $P<0.001$), inversely correlated with middle cerebral artery resistive index ($r=-0.248$, $P<0.001$), pulsatility index ($r=-0.287$, $P<0.001$) and hemoglobin level ($r=-0.316$, $P<0.001$) and varied with age ($r=-0.278$, $P<0.001$). Figure 4 shows the right and left extracranial internal carotid artery and middle cerebral artery velocities as a function of age. As for middle cerebral arteries, extracranial internal carotid artery velocities were maximal between 3 and 7 years of age and decreased thereafter. Transcranial Doppler sonography showed abnormal velocities, i.e.

Table 1 Blood flow parameters in the extracranial internal carotid arteries obtained with Doppler sonography using a 2-MHz probe via the submandibular window and in the middle cerebral arteries via the temporal window in 435 patients

	Mean values (SD)		Median (range)	
	Right	Left	Right	Left
eICA TAMMV (cm/s)	96 (40)	96 (37)	86 (33–310)	87 (32–292)
MCA TAMMV (cm/s)	127 (32)	129 (31)	127 (60–330)	128 (52–328)
MCA RI	0.54 (0.07)	0.54 (0.07)	0.53 (0.34–0.74)	0.54 (0.36–0.73)
MCA PI	0.78 (0.16)	0.79 (0.16)	0.76 (0.43–1.42)	0.76 (0.48–1.34)

eICA extracranial internal carotid artery, *TAMMV* time-averaged mean of maximum velocity, *MCA* middle cerebral artery, *RI* resistive index, *PI* pulsatility index, *SD* standard deviation

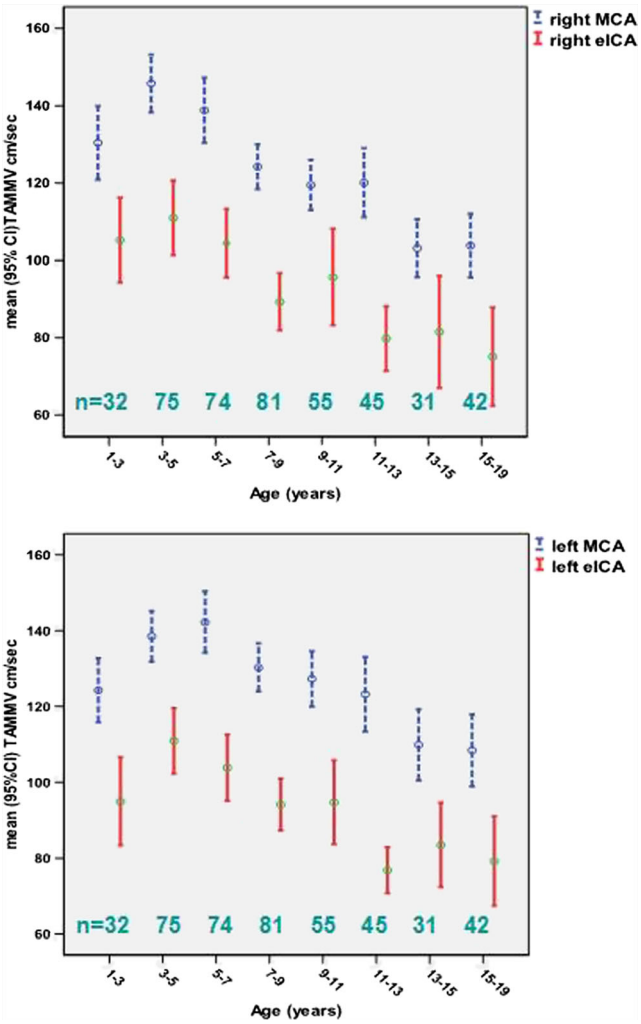

Fig. 4 Mean ± 95%CI time-averaged maximum velocities in the right middle cerebral artery and extracranial internal carotid artery at different age groups in the 435 patients. As for middle cerebral artery, extracranial internal carotid artery velocities peak between 3 and 7 years of age and decrease thereafter

≥200 cm/s in middle cerebral arteries, anterior cerebral arteries or intracranial internal carotid arteries in 22/435 patients.

Stenoses on MRA

MRI/intra- and extracranial MRA was performed in 104 patients. Intracranial stenoses were detected by MR angiography in 28/104 patients whereas extracranial internal carotid artery stenoses were found in 40 patients. Of note, eight patients had both intracranial and extracranial stenoses. Seventeen of the 40 patients had unilateral extracranial internal carotid artery stenosis (10 right-side and 7 left-side) and 23 had bilateral extracranial internal carotid artery stenoses. These 63 stenoses were graded as mild in 38 arteries, moderate in 18 and severe in 7. Analysis of the ROC curve showed that a velocity ≥160 cm/s was predictive of stenosis with 100% specificity and 80% sensitivity. Extracranial internal carotid artery velocities as a function of stenosis severity are shown in Table 2. Velocities (mean, SD) were highly significantly greater in stenotic arteries (174 [58] cm/s vs. 84 [25] cm/s; $P<0.001$). The highest extracranial internal carotid artery velocities were recorded in the more severely narrowed arteries. Extracranial internal carotid artery stenoses were associated with a kinking or looping aspect of the postbulbar internal carotid artery in 48 arteries (Fig. 5). In 15 arteries, the arterial course was straight, and stenosis was present either at the origin (Fig. 6) or at the entry into the skull (Fig. 5).

Table 2 Extracranial internal carotid artery velocities as a function of stenosis severity, as defined by extracranial MR angiography data in 104 patients (208 arteries)

	n	eICA TAMMV (cm/s)	
		Mean (SD)	Median (range)
No stenosis	145	84 (25)[a]	84 (37–150)
Stenosis	63	174 (58)[b]	180 (54–310)
Mild (<50%)	38	158 (49)[c]	168 (59–257)
Moderate (50–69%)	18	191 (53)[d]	200 (54–292)
Severe (70–99%)	7	215 (63)[e]	214 (132–310)

Mean comparison (Student's *t*-test) b/a: $P<0.001$; c/a: $P<0.001$; d/c: $P=0.028$; e/d: $P=0.35$

Prevalence of high extracranial internal carotid artery velocities (≥160 cm/s)

Velocity ≥160 cm/s in at least one extracranial internal carotid artery was found in 45 out of 435 patients with sickle cell anemia (10.3%) at the mean (SD) age of 7.5 (3.8) years (Table 3) and at the median age of 6.6 years (range: 1.4–18.6). In the 45 patients with extracranial internal carotid artery velocities ≥160 cm/s, the right extracranial internal carotid artery was affected in 32/45 with mean (± SD) velocity: 202 cm/s±35, median 196 (range: 162–310) and the left extracranial internal carotid artery in 26/45: 202±30, median 200 (range: 161–292). High extracranial internal carotid artery velocities were found significantly more frequently in boys (30/200; 15%) than in girls (15/235; 6.4%; $P=0.003$), and in patients with tortuous extracranial internal carotid artery (36/109; 33%) than in those with straight extracranial internal carotid artery (9/326; 2.8%; $P<0.001$) (Table 3).

The comparison of middle cerebral artery time-averaged mean of maximum velocities, resistive index and pulsatility index in patients with or without extracranial internal carotid artery ≥160 cm/s showed that, whereas middle cerebral artery velocities were not different between the two groups, resistive index and pulsatility index were significantly lower in patients with extracranial internal carotid artery velocity ≥160 cm/s. The risk of having extracranial internal carotid artery velocity ≥160 cm/s was multiplied by a factor of 9 in patients with

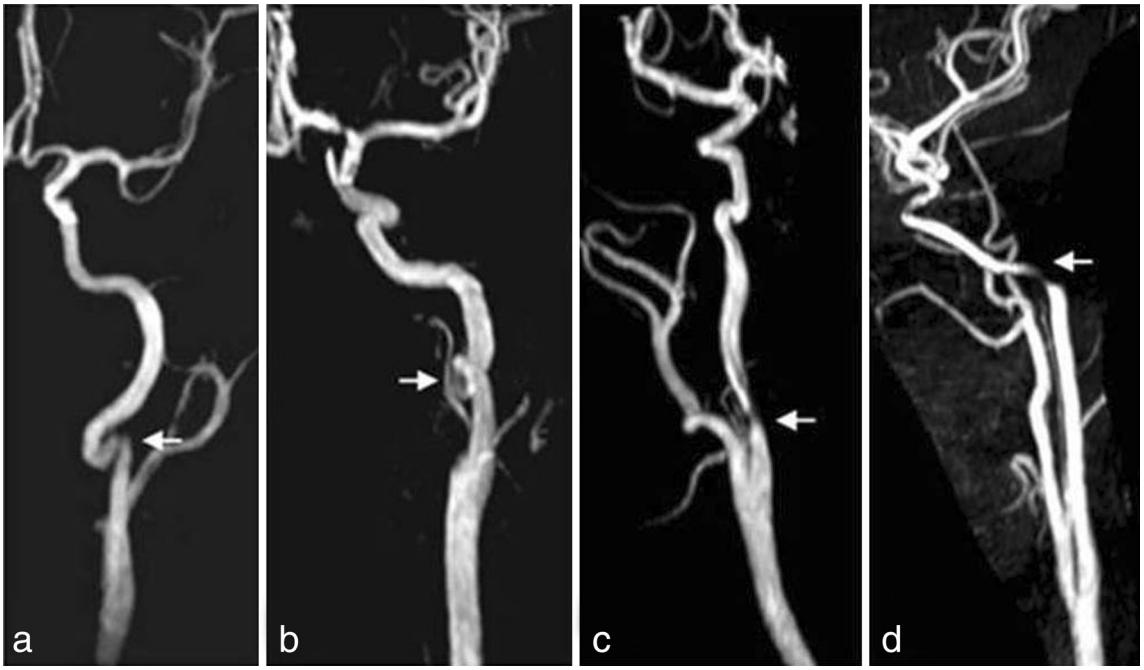

Fig. 5 Extracranial internal carotid artery stenoses depicted by 3-D time-of-flight MR angiography in four patients. **a** 5-year-old boy: the stenosis is located at the site of kinking (*arrow*), (**b**) 7-year-old boy: of a loop (*arrow*), (**c**) 8-year-old boy: on a straight artery at a postbulbar location (*arrow*) and (**d**)12-year-old girl: at the foramen (*arrow*). Note the associated anterior cerebral artery and middle cerebral artery stenoses in (**b**)

resistive index <0.45 (10th percentile; odds ratio=9, 95% CI: 4–21; $P<0.001$) or with pulsatility index <0.60 (10th percentile; odds ratio=10, 95% CI: 4–22; $P<0.001$).

Abnormal transcranial Doppler sonography of the intracranial arteries was observed simultaneously with abnormal Doppler sonography of the extracranial carotid arteries in 5/45 patients. Logistic regression analysis showed a trend ($P=0.055$) but not a significant association between abnormal simultaneous intracranial transcranial Doppler sonography and extracranial internal carotid artery ≥160 cm/s. Consequently, the prevalence of isolated (without abnormal intracranial velocities) high extracranial internal carotid artery velocities was 9.2% (40/435).

Associated factors for isolated high extracranial internal carotid artery velocity (≥160 cm/s)

Univariate logistic regression analysis showed that age was not a risk factor for velocity ≥160 cm/s whereas low

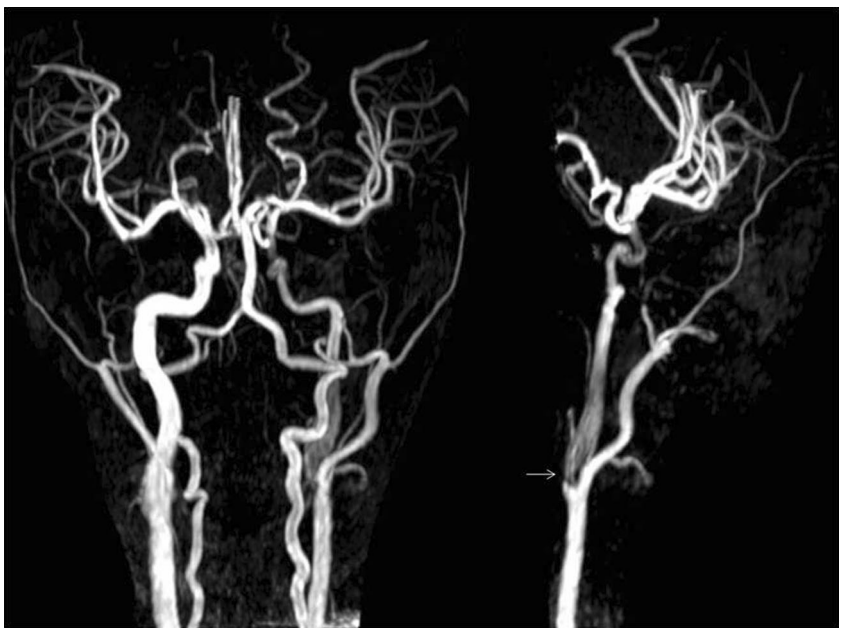

Fig. 6 9-year-old girl. Three-dimensional time-of-flight MR angiography. A frontal view of the cerebral arteries (*left*) shows a severely narrowed left extracranial internal carotid artery. A lateral view of the segmented left carotid system (right) shows a severe proximal left extracranial internal carotid artery stenosis (*arrow*) with decreased flow downstream.

Table 3 Comparison of mean hemoglobin, age, gender and tortuosities as a function of extracranial internal carotid artery velocities

	Extracranial internal carotid artery velocities (cm/s)			Total
	<160a	≥160b	Isolated ≥160c	
Patients	390 (89.7%)	45 (10.3%)	40 (9.2%)	435
Mean Hb (g/dl)	8.8 (1.4)	7.8 (0.9)	7.8 (0.9)	8.7 (1.4)
Mean age (SD) years	8.6 (4.3)	7.5 (3.8)	7.6 (3.8)	8.5 (4.3)
Male	170 (85.0%)	30 (15.0%)	29 (14.5%)	200
Female	220 (93.6%)	15 (6.4%)	11 (4.7%)	235
Tortuosities on ultrasound				
Absent	317 (97.2%)	9 (2.8%)	5 (1.5%)	326
Present	73 (67.0%)	36 (33%)	35 (32%)	109

Hb hemoglobin, *SD* standard deviation

Comparison of mean hemoglobin (b/a: $P<0.001$; c/a: $P<0.001$) and age (b/a: NS; c/a: NS)

Comparison of proportion (Fisher exact test) male/female (b/a: $P<0.001$; c/a: $P<0.001$); tortuosities by US, present/absent (b/a: $P<0.001$; c/a: $P<0.001$)

hemoglobin level (odds ratio: 2.2 per 1 g/dl decrease, 95% CI: 1.5–3.0, $P<0.001$), male gender (odds ratio: 3.5, 95% CI: 1.7–7.1; $P=0.001$), and tortuosities (odds ratio: 30.3, 95% CI: 11.5–83.3; $P<0.001$) were significantly associated with an increased risk for high extracranial internal carotid artery velocity. Multivariate analysis using hemoglobin, gender and tortuosities as risk factors retained low hemoglobin level (odds ratio: 1.9/1 g/dl decrease, 95% CI: 1.3–2.9; $P=0.001$) and the presence of tortuosities (odds ratio: 19.2, 95% CI: 7.1–52.6; $P<0.001$) as independent and significant associated risk factors.

Discussion

Early transcranial Doppler sonography screening and chronic transfusion therapy have been proven extremely efficient for primary overt-stroke prevention [3, 8]. Nevertheless, transcranial Doppler sonography of intracranial vessels does not detect all patients at risk for stroke, indicating the need for identification of additional risk factors. Furthermore, approximately a quarter of patients with clinical findings of cerebral ischemia have a normal angiogram of the circle of Willis [9] and up to 37.1% children with sickle cell anemia develop clinically silent, small brain infarcts detected on MRI before the age of 14 [8], whose pathogenesis has not been clearly elucidated. It has been assumed that silent infarcts were due to small vessel disease; however, the tendency of silent infarcts to occur in the watershed areas of the brain suggests that they could be due to distal hemodynamic impairment, secondary to large artery stenosis. Extracranial internal carotid artery disease, which is an important cause of stroke in the non-sickle adult population, may explain some of these strokes without detectable intracranial arteriopathy and some of the silent infarcts. Since the first case report of a 19-year-old man who suffered a stroke due to extracranial internal carotid artery bulbar occlusion with a contralateral postbulbar extracranial internal carotid artery stenosis [10], recent literature has reported that extracranial internal carotid arteriopathy could be associated with risk of overt stroke in sickle cell anemia patients [6, 11, 12]. In a retrospective study including 236 children with sickle cell anemia, Deane et al. [11] found that extracranial internal carotid artery disease was strongly associated with stroke. It is worth noting that in two children, extracranial internal carotid artery stenosis preceded stroke in the absence of overt intracranial arteriopathy [11]. In our study, we found that extracranial internal carotid artery velocities change with age, with a peak increase between 3 and 7 years old, and more importantly that extracranial internal carotid artery time-averaged mean of maximum velocities ≥160 cm/s is highly predictive of stenosis. The color Doppler sonography technique we used is easily and quickly performed and well tolerated by children. We used the same low frequency transducer for extracranial and intracranial arteries because it allows insonation of the upper part of the extracranial internal carotid artery distal to the bulb, which runs deep behind the mandibular branch. The prevalence of extracranial internal carotid artery time-averaged mean of maximum velocities ≥160 cm/s was 10.3% in the overall cohort, and was significantly higher in males and in those with tortuous extracranial internal carotid artery. This prevalence is higher than those previously reported [6, 11], which is probably due to the differences in the ultrasonic techniques used. Gorman et al. [6] used non-imaging Doppler, and detected extracranial internal carotid artery stenosis in 4/131 children with sickle cell anemia with extracranial internal carotid artery velocities ≥160 cm/s, 1 of them having a history of stroke. Deane et al. [11] described occlusion or stenosis in 13/236 (5.4%) children with sickle cell anemia, 8 of them having a history of stroke. Color Doppler US scans were

performed with a linear 6- to 9-MHz probe that, despite being adequate for common carotid artery and bifurcation, does not allow assessment of the upper part of the extracranial internal carotid artery. The color imaging and the 2 MHz probe used in our study permitted a more extensive and precise exploration of the extracranial internal carotid artery. However, we failed to detect extracranial internal carotid artery high velocity in 13 narrowed extracranial internal carotid artery (10 mild stenoses, 2 moderate and 1 severe). This underlines the necessity of a careful exploration of the entire course of the artery by moving the pulsed wave Doppler sample gate to detect the focal blood flow acceleration.

The high prevalence of tortuosities in our patients (25%), especially in males, was an unexpected finding. Nevertheless, this high rate of extracranial internal carotid artery tortuosities is in accordance with a recently published study [13], which reported that, contrary to the general opinion, tortuosities as kinking and coiling are frequent in non-SCA children (31%) and in adults (25%), supporting the congenital origin of these extracranial internal carotid artery patterns. A failure of the process of transformation of the embryonic aortic arch system may explain these congenital anatomical variations as the internal carotid artery arises from two different embryological structures, the third aortic arch and the cranial portion of the dorsal aorta. In non-SCA adults, tortuosities are known to be associated with a risk of cerebrovascular insufficiency [14, 15]. We suspect that tortuosities may constitute a trigger factor for blood flow disturbances, shear stress gradients and subsequent endothelial dysfunction in children with sickle cell anemia, leading to stenosis in a process quite similar to that occurring in the carotid siphon [16–19]. This mechanism may also explain the distal location of the extracranial internal carotid artery stenoses at the entry of the artery into the carotid canal, as the artery passes through a rigid osseous ring with a curved course.

Our study demonstrated that low hemoglobin level was a risk factor for abnormally high extracranial internal carotid artery velocities indicative of stenosis. Previous studies demonstrated that low hemoglobin level was a risk factor for ischemic stroke [1], for abnormally high cerebral velocities measured by transcranial Doppler sonography [8] and also for silent infarcts [8, 20, 21]. It has been shown that anemia results in hypervolemia, increased cardiac and cerebral blood flow and cerebral vasculature vasodilation in order to maintain enough oxygen delivery to the brain. These mechanisms may be involved in the development of cerebral vasculopathy and cerebrovascular events through compromised cerebrovascular reserve capacity and disturbed hemorheology resulting in endothelial activation and arterial wall damages in bended segments.

The association of significantly lower middle cerebral artery resistive index and pulsatility index in patients with abnormally high extracranial internal carotid artery velocities, indicative of stenosis, in our series, indicates an alteration in intracranial perfusion. It is known that these indices, which always change in parallel, reflect peripheral vascular resistance. A decrease of these indices is usually observed downstream from a hemodynamically significant stenosis, related to the elevation of pCO_2 in the ischemic territory, leading to reflex arteriolar vasodilatation. Further studies are warranted to assess the hemodynamic consequences of extracranial internal carotid artery stenoses, by studying, for example, cerebral perfusion patterns and the cerebral vascular reactivity, which might be affected in these patients.

Among the 45 patients with at least one extracranial internal carotid artery velocity ≥160 cm/s, only 5/45 had simultaneous abnormal intracranial transcranial Doppler sonography (velocity ≥200 cm/s) and there was no significant association between abnormal simultaneous intracranial TCD and eICA ≥160 cm/s. Therefore, 40/435 or 9.2% of patients would not have been identified as being at risk for cerebrovascular complications without the use of the submandibular window.

Conclusion

Evaluation of the extracranial internal carotid artery via a submandibular approach with a 2-MHz probe can be easily included in routine transcranial Doppler sonography evaluation as it is straightforward to perform, even in young children. It allowed us to detect 10.3% of patients at risk for extracranial arteriopathy. Tortuosities, which are normal congenital variants as frequent in sickle cell anemia as in subjects without sickle cell anemia, may be trigger factors for development of stenoses in children with sickle cell anemia. Further prospective studies may test the reproducibility of the technique in non-expert centers, elucidate the potential role of screening for extracranial internal carotid arteriopathy in stroke prevention in sickle cell anemia patients and assess the best treatments.

Acknowledgments We wish to thank Dr. Martine Torres for her critical reading of the manuscript and editorial assistance.

Conflict of interest None.

References

1. Ohene-Frempong K, Weiner SJ, Sleeper LA et al (1998) Cerebrovascular accidents in sickle cell disease: rates and risk factors. Blood 91:288–294
2. Adams RJ, McKie VC, Carl EM et al (1997) Long-term stroke risk in children with sickle cell disease screened with transcranial Doppler. Ann Neurol 42:699–704

3. Adams RJ, McKie VC, Hsu L et al (1998) Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. N Engl J Med 339:5–11
4. Lowe LH, Bulas DI (2005) Transcranial Doppler imaging in children: sickle cell screening and beyond. Pediatr Radiol 35:54–65
5. Verlhac S (2011) Transcranial Doppler in children. Pediatr Radiol 41: S153–S165
6. Gorman MJ, Nystrom K, Carbonella J et al (2009) Submandibular TCD approach detects post-bulb ICA stenosis in children with sickle cell anemia. Neurology 73:362–365
7. Debrey SM, Yu H, Lynch JK et al (2008) Diagnostic accuracy of magnetic resonance angiography for internal carotid artery disease: a systematic review and meta-analysis. Stroke 39:2237–2248
8. Bernaudin F, Verlhac S, Arnaud C et al (2011) Impact of early transcranial Doppler screening and intensive therapy on cerebral vasculopathy outcome in a newborn sickle cell anemia cohort. Blood 117:1130–1140, quiz 1436
9. Gerald B, Sebes JI, Langston JW (1980) Cerebral infarction osecndary to sickle cell disease: arteriographic findings. AJR Am J Roentgenol 134:1209–1212
10. Calviere L, Viguier A, Guidolin B et al (2007) Cervical artery stenoses in sickle cell disease. Eur Neurol 58:120–121
11. Deane CR, Goss D, Bartram J et al (2010) Extracranial internal carotid arterial disease in children with sickle cell anemia. Haematologica 95:1287–1292
12. Telfer PT, Evanson J, Butler P et al (2011) Cervical carotid artery disease in sickle cell disease: clinical and radiological features. Blood 118:6192–6199
13. Beigelman R, Izaguirre AM, Robles M et al (2010) Are kinking and coiling of carotid artery congenital or acquired? Angiology 61:107–112
14. Ballotta E, Abbruzzese E, Thiene G et al (1997) The elongation of the internal carotid artery: early and long-term results of patients having surgery compared with unoperated controls. Ann Vasc Surg 11:120–128
15. Koskas F, Bahnini A, Walden R et al (1993) Stenotic coiling and kinking of the internal carotid artery. Ann Vasc Surg 7:530–540
16. Switzer JA, Hess DC, Nichols FT et al (2006) Pathophysiology and treatment of stroke in sickle-cell disease: present and future. Lancet Neurol 5:501–512
17. Greenhill NS, Stehbens WE (1985) Haemodynamically-induced intimal tears in experimental U-shaped arterial loops as seen by scanning electron microscopy. Br J Exp Pathol 66:577–584
18. Davies PF (2009) Hemodynamic shear stress and the endothelium in cardiovascular pathophysiology. Nat Clin Pract Cardiovasc Med 6: 16–26
19. Stehbens WE, Stehbens GR, Fee CJ (1987) Flow through S-shaped glass models simulating arterial tortuosities. Q J Exp Physiol 72:201–213
20. Kwiatkowski JL, Zimmerman RA, Pollock AN et al (2009) Silent infarcts in young children with sickle cell disease. Br J Haematol 146: 300–305
21. DeBaun MR, Sarnaik SA, Rodeghier MJ (2012) Associated risk factors for silent cerebral infarcts in sickle cell anemia: low baseline hemoglobin, sex, and relative high systolic blood pressure. Blood 119:3684–3690