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Prevalence of Intracardiac Shunting in Children with Sickle Cell Disease and Stroke

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Abstract

Objective—To determine the prevalence of potential intracardiac shunts, including patent foramen ovale (PFO), in children with sickle cell disease (SCD) and stroke.

Study design—We performed a transthoracic echocardiogram (TTE) on 40 children with SCD (39 with hemoglobin SS and 1 with sickle-beta^0 thalassemia) and earlier stroke (overt stroke in 30, silent infarction in 10). We compared 3 TTE techniques: conventional 2-dimensional imaging, color Doppler ultrasound, and intravenous agitated saline contrast injection for the detection of intracardiac shunts. We also evaluated the clinical, laboratory, and radio-graphic findings of the children with and without shunts.

Results—We identified PFO or other potential intracardiac shunts in 10 of 40 children with SCD and earlier stroke (25%; 95% CI, 11.6-38.4). With contrasted TTE, we failed to detect potential shunts in 2 children. In a comparison group of 60 children with stroke but without SCD, retrospective review of clinical echocardiograms identified PFO in 7 of 60 (11.7%; 95% CI, 3.6-19.8). Clinical features significantly associated with the presence of intracardiac shunts were stroke in the setting of vaso-occlusive crisis (P = .026) and headache at stroke onset (P = .014).

Conclusion—One-quarter of children with SCD and stroke have potential intracardiac shunts. A combination of echocardiographic techniques is required for optimal shunt detection. Intracardiac shunting could be a risk factor for stroke in children with SCD because they are predisposed to thrombosis and elevations of right heart pressure, which could promote paradoxical embolization across an intracardiac shunt.

Children with sickle cell disease (SCD) sustain strokes at a rate 220 times higher than other children.[1] Clinically overt stroke occurs in 8% to 11% of patients, and as many as 35% of patients have clinically silent stroke detectable only with magnetic resonance imaging

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(MRI).[2] The identified risk factors for stroke in SCD include previous stroke, sickle vasculopathy, severe anemia, and acute chest syndrome.[3] Transcranial Doppler ultrasound (TCD) can identify children with SCD at highest risk of stroke, but the only treatment shown to prevent stroke is chronic transfusion, with risks of infection and iron overload.[4] Stroke may occur before preventive transfusion therapy can be initiated, and some children with normal TCD study results still sustain stroke. Identification of additional risk factors could lead to improved risk stratification and new strategies for stroke prevention.

Inchildren and young adultswithoutSCD, intracardiacshunting, primarily via a patent foramen ovale (PFO),has been identified as a risk factor for stroke. The mechanism is presumed to be “paradoxical embolization,” in which venous emboli avoid filtration in the pulmonary vasculature by right-to-left shunting through a holein the heart.[5,6]Observations of focalneurologic deficits and MRI lesions consistent with embolicphenomenon in patients withSCD and fat embolization syndrome after vaso-occlusive crisis (VOC) support a role of paradoxical embolization in the neurologic complications of SCD.[7,8] The only route for venous fat emboli from necrotic bone marrow to reach the brain is via right-to-left shunting either at the cardiac or pulmonary level.

Few earlier reports have described the prevalence of PFO or other intracardiac shunts in children with SCD and stroke. We hypothesized that intracardiac shunts, potentially treatable with percutaneous transcatheter closure,[9] may play a causal role in stroke in children with SCD. We conducted a pilot study to determine the prev alence of PFO or other intracardiac shunts in children with SCD and earlier stroke and to evaluate different echocardiographic shunt detection methods in this population. We compared the prevalence of detectible PFO and other intra-cardiac shunts with the prevalence in published reports of children and young adults and with that in a comparison group of children without SCD who sustained stroke and were evaluated with echocardiography according to our institutional pediatric stroke protocol.

Methods

This study was approved by the institutional review board at the University of Texas Southwestern Medical Center at Dallas. We enrolled children ages 2 to 19 years, from the Pediatric Sickle Cell Clinic of Children's Medical Center Dallas, with a diagnosis of sickle cell anemia (hemoglobin SS, n = 39) or sickle-beta^0 thalassemia (n = 1) and earlier stroke confirmed with MRI. Thirty children had clinically overt stroke, and 10 children had silent infarcts. In this pilot study, we could not, ***a priori***, decide which subgroup of stroke (clinically silent or overt) would be more likely to be caused by paradoxical embolization. In adults without SCD, PFO has been implicated in small strokes similar in appearance to the silent infarcts in SCD.[10] Likewise, PFO has been implicated in paradoxical embolization in adult overt strokes that are similar in appearance and distribution to those in pediatric patients with SCD.[5] In this pilot study, we therefore included children with SCD with either silent or overt stroke. We screened all scheduled patients with SCD and a history of stroke in this cross-sectional study. No patients were excluded, and only 2 patients declined to participate. Patients were approached for consent at the time of their routine clinical appointments.

The gold standard for detection of intracardiac shunting in adults is contrasted transesophageal echocardiography (TEE). In our institutional clinical pediatric stroke protocol, we routinely examine children with stroke for evidence of intracardiac shunting with contrasted transthoracic echocardiography (TTE). Because of the smaller body size and the thinner chest wall of most pediatric patients, the superiority of TEE over TTE may not be great. Further, in this pilot research study in pediatric patients, we felt that TEE was too invasive and the requirement for anesthesia for TEE in pediatric research subjects with SCD was too great a risk. Therefore, we examined our patients with TTE and compared 3 techniques for the detection of intracardiac shunts: conventional 2-dimensional imaging, color Doppler ultra-sound, and intravenous contrast injection with agitated saline. For the latter, the left atrium was observed for the appearance of contrast for a minimum of 5 cardiac cycles after injection, both at rest and with Valsalva maneuver. Detection of contrast in the left atrium provided evidence of right-to-left shunting. We defined the presence of PFO or intracardiac shunt as detection of shunt by any echocardiographic method: 2-dimensional, color Doppler ultrasound, or either of the contrast injections. In adult research studies, the sensitivity of shunt detection has been shown to increase with increasing number of contrast injections, with PFOs detected by up to 11 contrast injections.[11] In this pilot study in pediatric patients, we limited our study to 2 contrast injections. Severity of tricuspid regurgitation was graded on the basis of American Society of Echocardiography recommendations.[12]

We did not include a control group of patients without stroke in this pilot study because of ethical concerns for research in pediatric subjects that involved invasive procedures with limited potential benefit to the control patients: in this case, intravenous access and contrast injection. We felt that in children with SCDand stroke, this evaluation was acceptable because it is part of our standard clinical evaluation of stroke in children without SCD. We made every effort to perform the contrasted TTE when the children had intravenous access obtained for a clinical indication, which most commonly was for blood transfusion. Study TTE was performed, in most cases, either immediately before or after blood transfusion. The children were clinically stable and pain free at the time of TTE.

We did include, as a comparison group, the results of echocardiographic studies obtained for clinical purposes in 60 children without SCD who were examined for stroke with TTE or TEE according to our institutional pediatric stroke protocol. We excluded children <3 months of age because of the high prevalence of PFO in this age group, and we excluded children with known congenital heart disease. In our routine clinical evaluation, we most commonly use TTE, and when a PFO or other potential intracardiac shunt is detected with 2-dimensional or color Doppler ultrasound methods, contrast is not routinely given. Therefore we did not limit our comparison group to only those children with contrasted echocardiogram, because this would have led to under-representation of the proportion with PFO or other potential intracardiac shunts. When clinically indicated, agitated saline contrast is given by the same methods used in our study patients. TEE was performed for clinical indication in 7 patients. These 60 TEE and TTE studies were reviewed retrospectively by the study cardiologist (C.R.).

Demographic, clinical, and radiographic features were abstracted from the medical record with a structured data collection sheet for exploratory, hypothesis-generating analyses. We pilot-tested a structured questionnaire to assess headache and migraine according to International Headache Society Criteria[13] and for headache severity with PedMIDAS scores.[14] Analyses of these factors for association with intra-cardiac shunts were conducted by using χ^2 or Fisher exact test for categorical variables and Student *t* test or Mann-Whitney *U* test for continuous variables, as appropriate. Because these were exploratory analyses, we did not correct for multiple comparisons and a *P* value <.05 was considered to be nominally significant. Clinical information was not available for many subjects in this retrospective review, and clinical symptoms and laboratory data at stroke presentation were not available for many patients, particularly patients with silent infarcts, in which the time of onset was unknown for most. Statistical analyses were performed with SPSS software version 15.0 (SPSS, Chicago, Illinois).

Results

Echocardiographic evidence of PFO or other potential intra-cardiac shunting was identified in 10 of the 40 children (25%; 95% CI, 11.6-38.4) with SCD and stroke. PFO was identified with 2-dimensional echocardiogram in 2 patients, with color Doppler ultrasound in 6 patients, and with agitated saline contrast in 5 patients. Two potential intracardiac shunts that were not identified with contrasted TTE were detected with conventional 2-dimensional echocardiogram or with color Doppler ultrasound methods (Table I). One patient with silent infarct had a ventricular septal defect and was categorized with the intracardiac shunt patients and not included in Table I because contrast injection or further evaluation for PFO was not performed. No other cardiac structural abnormalities were identified. No atrial septal aneurysms were observed. Tricuspid regurgitation categorized as trivial or mild was detected in 32 patients, with no significant difference between patients with shunts and patients without shunts. There were no cases of moderate or severe tricuspid regurgitation. Right ventricular pressure estimates were similar in patients with and without intracardiac shunt. There were no adverse events reported during or after TTE with contrast.

Our comparison group of children without SCD who sustained stroke included 60 children with a mean age of 8.9 years and a male predominance (23 female, 37 male). TTE was performed in 53 children, and TEE was performed in 7 children. PFO was identified in 7 of 53 children (13.2%) with TTE with color Doppler ultrasound. Contrasted TTE was performed in 35 of these 53 children, and no additional cases of PFO were identified. Only 2 children with PFO identified with color Doppler TTE received contrast, demonstrating a PFO in 1 child but not the other. Contrasted TTE was not performed for the other 18 children, including for 5 of the 7 found to have PFO with color Doppler TTE. Of the 7 additional children examined with contrasted TEE, none was found to have a PFO. Overall, we found evidence of PFO in 7 of 60 children (11.7%; 95% CI, 3.6-19.8) in our comparison group without SCD who had stroke and were >3 months old and had no history of congenital heart disease.

In this pilot study, we performed exploratory analyses of demographic and clinical factors obtained with retrospective chart review. There were no statistically significant differences

in the sex, mean age at time of stroke or at examination, blood pressure at time of TTE, or laboratory findings between the patients with shunts and the patients without shunts (Table II). Further, there were no significant differences in the 2 groups for the presence of multiple, bilateral, or anterior circulation infarcts on MRI. The distribution of left and right hemisphere infarcts and silent infarcts were similar as well. Magnetic resonance angiograms were available for 39 of the patients, and the results were abnormal in 29 patients, with abnormalities graded as stenosis, occlusion, or moyamoya pattern. There were no statistically significant differences in abnormalities found with magnetic resonance angiogram in the 2 groups.

The only 2 clinical factors significantly associated with intracardiac shunts were stroke in the setting of VOC ($P = .026$) and headache at the onset of stroke ($P = .014$). There were no significant associations with other concurrent or earlier illnesses, including obstructive sleep apnea, asthma, acute chest syndrome, gallstones, or priapism, and there were no significant differences in patient-reported recurrent migraine or other headache, headache frequency, or PedMIDAS scores. Because 10 patients had silent infarcts and thus their time of onset of stroke and its clinical setting were unknown, we analyzed the clinical features of acute illness, headache, or pain crisis at stroke onset both with and without the missing data. The significance levels did not change for these comparisons (Table II).

Discussion

With a combination of echocardiographic methods, we demonstrated the prevalence of PFO and other potential right-to-left shunts in children with SCD with a history of overt or silent stroke to be 25% (95% CI, 11.6-38.4). In our comparison group of children without SCD who had stroke, a group in which intracardiac shunting is an established risk factor for stroke and in which echocardiographic evaluation is part of routine clinical care, we identified PFO in only 11.7% (95% CI, 3.6-19.8). Autopsy studies have found probe patent PFO in 35% of children 1 to 19 years of age,[15] but the prevalence of those detectable with echocardiography appears to be much lower (Table III). In healthy young adults, the prevalence of PFO that is detectable with echocardiography is between 3% and 22%.[5,16] A meta-analysis of 9 case-control studies of young adults without SCD reported a significant association between PFO and stroke, with PFO identified in 17.8% of control patients (95% CI, 14.3-21.3) and in 40.2% of patients with stroke (95% CI, 36.2-44.2).[5]

There have been few studies of PFO in children without SCD who have sustained stroke, although a causal link to stroke was suggested in a report of 2 cases[17] and in a small series of children with transient ischemic attack or stroke in which evidence of left-to-right shunting was detected in 9 of 18 children (50%) without SCD with contrasted-TCD.[6] The 25% prevalence of potential intracardiac shunt identified in our study is higher than that reported in a study of the risk factors for arterial ischemic stroke in 104 previously healthy children without SCD or known history of congenital heart disease by using non-contrasted echocardiogram.[18] Atrial septal defect was detected in only 1 of 104 of these children. Of 35 children with SCD and stroke, only 6 were examined with non-contrast echocardiogram, and no atrial septal defects or intracardiac shunts were noted. Contrasted echocardiogram was

performed in 9 children with stroke (presence of SCD not noted), but no shunting was detected.[18]

We were unable to identify any earlier reports of the prevalence of intracardiac shunts or PFO detectable with contrasted echocardiogram in children with SCD with or without stroke. However, recent studies (Table III) with color Doppler TEE identified PFO or other potential intra-cardiac shunts in only 5 of 53 healthy children and young adults (9.4%) without stroke aged 10 to 29 years[19] and in only 21 of 817 of 10-year-old children (2.6%) in a large screening study by using TTE with color Doppler ultrasound.[20] Another study examined 107 children with SCD (including 11 with stroke) by using TTE with color Doppler.[18] PFO was identified in only 2 of these children (1.7%) with SCD. There was no indication whether these children were in the subgroup with stroke. Another small study of children without SCD or stroke on screening TTE with color Doppler ultrasound before neurosurgery found PFO in 6 of 30 patients (20%).[21]

By comparison, we identified PFO or other intracardiac shunts with color Doppler TTE alone (excluding the additional cases identified with contrast) in 7 of 40 of our patients with SCD and stroke (17.5%) and in 7 of 53 of our patients without SCD who had stroke (13.2%). In this pilot study, statistical comparisons with other studies would be inappropriate, but the prevalence of TTE-detectable PFO in children with SCD and stroke that we observed is apparently greater than that in our comparison group of children without SCD who have had stroke, and it is well above that reported in the 3 largest screening studies (Table III). This suggests that further controlled studies are warranted to determine whether the prevalence of PFO is higher in children with SCD and stroke than children with SCD without stroke.

Our observations highlight the difficulty of identifying PFO and other intracardiac shunts in children. Results for contrasted TTE were negative for shunt in 2 patients in whom shunt was detected with color Doppler ultrasound scanning, conventional 2-dimensional echocardiogram, or both. In our comparison group, contrasted TTE results were negative in 1 of 2 children in whom a shunt was detected with color Doppler ultrasound. It is likely that children are less compliant than adults with the Valsalva maneuver, which improves detection of right-to-left shunting.[22] However, paradoxical embolization could still occur in children with color Doppler ultrasound evidence of left-to-right shunting in certain clinical settings, such as VOC, acute chest syndrome, or pulmonary hypertension, in which increased right heart pressures could result in right-to-left shunting. Thus, we included children with PFO detected with any of the 3 methods in our intracardiac shunt/PFO group, and we believe future clinical evaluation and research study designs should incorporate all 3 methods.

Our study has several limitations. Ethical concerns about research in pediatric subjects led us to use the less-invasive technique of TTE rather than TEE and precluded inclusion of a control group in this pilot study. We also included 10 children with silent infarcts. The risk factors for silent infarcts[23] may differ from those of overt stroke, but small MRI lesions similar in appearance to the silent infarcts of SCD have also been described in deep sea divers, in whom an association with PFO has also been suggested.[10] Because of their

clinically silent nature, the time of occurrence is unknown, and thus we were unable to include their clinical and laboratory data at the time of stroke, limiting our analysis. In addition, echocardiograms were performed well after the onset of stroke in most cases. The prevalence of PFO in the autopsy study declined with each decade, so late anatomic closure of PFO appears to occur in some patients.[15] By obtaining delayed studies, we may have underestimated the PFO prevalence at the time of stroke. Further, we did not correct for multiple comparisons in our exploratory hypothesis-generating analyses of the demographic and clinical factors in this pilot investigation. The 2 clinical factors we found to have statistically significant associations with the presence of intracardiac shunts, presentation with VOC and headache at stroke onset, must therefore be viewed as highly speculative, but both have biologic plausibility. First, during VOC, immobility and dehydration favor formation of venous thrombi, a potential source of paradoxical emboli, and pulmonary artery pressures increase, favoring right-to-left shunting.[24] Second, for headache at stroke onset, increasing evidence suggests an association between PFO in migraine.[25-27] These potential associations will need to be explored more fully in larger studies.

Intracardiac shunts such as PFO could be an independent modifiable risk factor for stroke or recurrent stroke in children with SCD. A large, controlled study of the prevalence of intra-cardiac shunts or PFO in children with SCD could demonstrate that intracardiac shunts are a risk factor for stroke in SCD. This could lead to improved risk stratification in screening and therapeutic trials and offers the possibility of a novel preventative treatment for stroke in children with SCD.

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Glossary

MRI	Magnetic resonance imaging
PFO	Patent foramen ovale
SCD	Sickle cell disease
TCD	Transcranial Doppler ultrasound
TEE	Transesophageal echocardiogram
TTE	Transthoracic echocardiogram
VOC	Vaso-occlusive crisis

References

1. Earley CJ, Kittner SJ, Feeser BR, Gardner J, Epstein A, Wozniak MA, et al. Stroke in children and sickle-cell disease: Baltimore-Washington Cooperative Young Stroke Study. Neurology. 1998; 51:169–76. [PubMed: 9674798]

2. Steen RG, Emudianughe T, Hankins GM, Wynn LW, Wang WC, Xiong X, et al. Brain imaging findings in pediatric patients with sickle cell disease. Radiology. 2003; 228:216–25. [PubMed: 12775848]

3. Quinn CT, Miller ST. Risk factors and prediction of outcomes in children and adolescents who have sickle cell anemia. Hematol Oncol Clin N Am. 2004; 18:1339–54.

4. Adams RJ, McKie VC, Hsu L, Files B, Vichinsky E, Pegelow C, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. N Engl J Med. 1998; 339:5–11. [PubMed: 9647873]

5. Overell JR, Bone I, Lees KR. Interatrial septal abnormalities and stroke: a metaanalysis of case-control studies. Neurology. 2000; 55:1172–9. [PubMed: 11071496]

6. Benedik MP, Zaletel M, Megli NP, Podnar T. Patent foramen ovale and unexplained ischemic cerebrovascular events in children. Catheter Cardiovasc Interv. 2007; 70:999–1007. [PubMed: 18044736]

7. Vichinsky E, Williams R, Das M, Earles AN, Lewis N, Adler A, et al. Pulmonary fat embolism: a distinct cause of severe acute chest syndrome in sickle cell anemia. Blood. 1994; 83:3107–12. [PubMed: 8193347]

8. Horton DP, Ferriero DM, Mentzer WC. Nontraumatic fat embolism syndrome in sickle cell anemia. Pediatr Neurol. 1995; 12:77–80. [PubMed: 7748367]

9. Bartz PJ, Cetta F, Cabalka AK, Reeder GS, Squarcia U, Agnetti A, et al. Paradoxical emboli in children and young adults: role of atrial septal defect and patent foramen ovale device closure. Mayo Clin Proc. 2006; 81:615–8. [PubMed: 16706258]

10. Schwerzmann M, Seiler C, Lipp E, Guzman R, Lovblad KO, Kraus M, et al. Relation between directly detected patent foramen ovale and ischemic brain lesions in sport divers. Ann Internal Med. 2001; 134:21–4. [PubMed: 11187416]

11. Johansson MC, Helgason H, Dellborg M, Eriksson P. Sensitivity for detection of patent foramen ovale increased with increasing number of contrast injections: a descriptive study with contrast trans esophageal echocardiography. J Am Soc Echocardiogr. 2008; 21:419–24. [PubMed: 17928199]

12. Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr. 2003; 16:777–802. [PubMed: 12835667]

13. Hershey AD, Winner P, Kabbouche MA, Gladstein J, Yonker M, Lewis D, et al. Use of ICHD-II criteria in the diagnosis of pediatric migraine. Headache. 2005; 45:1288–97. [PubMed: 16324160]

14. Hershey AD, Powers SW, Vockell A-LB, LeCates SL, Kabbouche MA, Maynard MK. PedMIDAS: development of a questionnaire to assess disability of migraines in children. Neurology. 2001; 75:2034–9. [PubMed: 11739822]

15. Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent foramen ovale during first 10 decades of life: an autopsy study of 965 normal hearts. Mayo Clin Proc. 1984; 59:17–20. [PubMed: 6694427]

16. Cramer SC. Patent foramen ovale and its relationship to stroke. Cardiol Clin. 2005; 23:7–11. [PubMed: 15676264]

17. Agnetti A, Carano N, Sani E, Tchana B, Allergri V, Bernasconi S, et al. Cryptogenic stroke in children: possible role of patent foramen ovale. Neuropediatrics. 2006; 37:53–6. [PubMed: 16541369]

18. Ganesan V, Prengler M, McShane MA, Wade AM, Kirkham FJ. Investigation of risk factors in children with arterial ischemic stroke. Ann Neurol. 2003; 53:167–73. [PubMed: 12557282]

19. Fisher DC, Fisher EA, Budd JH, Rosen SE, Goldman ME. The incidence of patent foramen ovale in 1000 consecutive patients: a contrast transesophageal echocardiography study. Chest. 1995; 107:1504–9. [PubMed: 7781337]

20. Basso C, Boschello M, Perrone C, Mecenero A, Cera A, Bicego D, et al. An echocardiographic survey of primary school children for bicuspid aortic valve. Am J Cardiol. 2004; 93:661–3. [PubMed: 14996606]

21. Fuchs G, Schwarz G, Stein J, Kaltenbock F, Baumgartner A, Oberbauer RW. Doppler color-flow imaging: screeing of a patent foramen ovale in children scheduled for neurosurgery in the sitting position. J Neurosurg Anesthesiol. 1998; 10:5–9. [PubMed: 9438611]
22. Kenny D, Turner M, Martin R. When to close a patent foramen ovale. Arch Dis Child. 2008; 93:255–9. [PubMed: 17827196]
23. Kinney TR, Sleeper LA, Wang WC, Zimmerman RA, Pegelow CH, Ohene-Frempong K. for the Cooperative Study of Sickle Cell Disease. Silent cerebral infarcts in sickle cell anemia: a risk factor analysis. Pediatrics. 1999; 103:640–5. [PubMed: 10049969]
24. Machado RF, Mack AK, Martyr S, Barnett C, MacArthur P, Sachdev V, et al. Severity of pulmonary hypertension during vaso-occlusive pain crisis and exercise in patients with sickle cell disease. Br J Haematol. 2007; 136:319–25. [PubMed: 17156401]
25. Morandi E, Anzola GP, Angeli S, Melzi G, Onorato E. Transcatheter closure of patent foramen ovale: a new migraine treatment? J Intervent Cardiol. 2003; 16:39–42. [PubMed: 12664816]
26. Post MC, Thijs V, Herroelen Budts WIHL. Closure of a patent foramen ovale is associated with a decrease in prevalence of migraine. Neurology. 2004; 62:1439–40. [PubMed: 15111695]
27. Schwerzmann M, Wiher S, Nedeltchev K, Mattle HP, Wahl A, Seiler C, et al. Percutaneous closure of patent foramen ovale reduces the frequency of migraine attacks. Neurology. 2004; 62:1399–401. [PubMed: 15111681]
28. Caldas MC, Meira ZA, Barbosa MM. Evaluation of 107 patients with sickle cell anemia through tissue Doppler and myocardial performance index. J Am Soc Echocardiogr. 2008; 21:1163–7. [PubMed: 18926392]

Table I

Detection of patent foramen ovale/intracardiac shunt with echocardiographic technique

Patient	2-dimensional echocardiography	Color Doppler	Agitated saline contrast
1	–	+	+
2	–	+	+
3	–	+	–
4	–	–	+
5	+	+	–
6	–	–	+
7	+	+	ND
8	–	–	+
9	–	+	ND

+, PFO/shunt detected with this method; –, PFO/shunt not detected with this method; *ND*, not done.

Table II

Exploratory, hypothesis-generating analysis of the characteristics of patients with sickle cell and a history of stroke with presence or absence of intracardiac shunt

	Shunt present, n (%) n = 10	Shunt absent, n (%) n = 30	*P* value
Mean age at TTE (years)	11.2 (± 4.2)	12.4 (± 4.8)	.494
Mean age at stroke (years)	7.0 (± 4.2)	6.0 (± 4.0)	.573
Sex (% male)	50.0%	53.3%	.855
Silent infarct	2 (20.0%)	8 (26.7%)	.673
Systolic blood pressure	110.5	112.1	.669
Diastolic blood pressure	61.8	63.6	.619
Hgb at time of stroke (g/dL)	6.2	7.3	.134
WBC at time of stroke ($\times 10^9$/L)	22.2	18.0	.574
Platelets at time of stroke ($\times 10^9$/L)	277.8	380.8	.223
Multiple infarcts	7 (70.0%)	21 (70.0%)	1.000
Bilateral infarcts	5 (50.0%)	10 (33.3%)	.457
Abnormal MRA	7 (70.0%)	22 (73.3%)	.838
Acute illness at stroke onset*	6 (60.0%)	7 (23.3%)	.122
Headache at stroke onset†	4 (40.0%)	1 (3.3%)	.014
Pain crisis at stroke onset‡	4 (40.0%)	2 (6.7%)	.026
TR (trivial or mild)	7 (70.0%)	25 (83.3%)	.361

Hgb, Hemoglobin level; *WBC*, white blood cell count; *MRA*, magnetic resonace angiography; *TR*, tricuspid regurgitation.

*Comparison remained non-significant (*P* = .109) when excluding patients with missing data (eg, those with silent infarction for whom clinical setting of acute stroke was unknown or others with missing data).

†Comparison remained significant (*P* = .010) when excluding patients for whom headache status at onset of stroke was unknown or not reported.

‡Comparison remained significant (*P* = .029) when excluding patients for whom clinical status at onset of stroke was unknown or was not reported.

Table III

Echocardiographic detection of patent foramen ovale or intracardiac shunting in children

Study, year	Patient age	Number of patients	Shunt with TTE Doppler, n (%)	Shunt with TTE Doppler or contrast, n (%)	Shunt with TEE, n (%)	Shunt with any method, n (%)	Comments
Hagen et al, 1984[15]	1-9 years 10-19 years 1-99 years	100 100 965	–	–	–	34% 36% 27.3%	Autopsy data Probe patent PFO Non-SCD
Overell et al, 2000[5]	<55 years	Meta-analysis 1022	–	–	–	Stroke 225/566 (39.8%) Control 81/456 (17.8%)	Meta-analysis of 9 case control studies of young adults Non-SCD
Fuchs et al, 1998[21]	1-14 years	30	6/30 (20%)	–	–	6/30 (20%)	Children without stroke screened for PFO before neurosurgery Non-SCD
Fischer et al, 1995[19]	10-29 years 10-99 years	53 1000	–	–	5/53 (9.4%) 92/1000 (9.2%)	5/53 (9.4%) 92/1000 (9.2%)	TEE performed for clinical indication: stroke/TIA in 391/1000 Proportion with stroke not reported for 10- to 29-year-old subgroup Non-SCD
Ganesan et al, 2003[18]	21days-19.7 years	104	1 ASD/104 (0.96%)	–	0/36	1/104 (0.96%)	Previously healthy children with stroke Non-SCD
Basso et al, 2004[20]	10 years	817	20 PFO and 1 VSD, 21/817 (2.6%)	–	–	21/817 (2.6%)	Healthy children without stroke Non-SCD
Caldas et al, 2008[28]	3-18 years	107	2/107 (1.9%)	–	–	2/107 (1.9%)	Children with SCD (11/107 with stroke)
Present study, patients with SCD and stroke	2-19 years	40	6 PFO and 1 VSD, 7/40 (17.5%)	9 PFO and 1 VSD, 10/40 (25%)	–	10/40 (25%)	Children with SCD with overt (30) or silent (10) stroke
Present study, patients without SCD with stroke	0.25-19 years	60	7/53 (13.2%)	7/53 (13.2%)	0/7 (0%)	7/60 (11.7%)	Children with stroke Excluding those with known congenital heart disease Non-SCD

ASD, atrial septal defect; *VSD*, ventricular septal defect.