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Intracardiac Shunting and Stroke in Children: A Systematic Review

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Abstract

In adults, patent foramen ovale or other potential intracardiac shunts are established risk factors for stroke via paradoxical embolization. Stroke is less common in children and risk factors differ. The authors examined the literature on intracardiac shunting and stroke in children, identifying the methods employed, the prevalence of detectable intracardiac shunts, associated conditions, and treatments. PubMed searches with keywords related to intracardiac shunting and stroke in children identified articles of interest. Additional articles were identified via citations in these articles or in reviews. The authors found that studies of intracardiac shunting in children with stroke are limited. No controlled studies were identified. Detection methods vary and the prevalence of echocardiographically detectable intracardiac shunting appears lower than reported in adults and autopsy studies. Defining the role of intracardiac shunting in pediatric stroke will require controlled studies with unified detection methods in populations stratified by additional risk factors for paradoxical embolization. Optimal treatment is unclear.

Keywords

patent foramen ovale; intracardiac shunting; stroke; paradoxical embolism; echocardiogram

Stroke is one of the top 10 killers of children. Of the survivors, up to 60% have neurologic deficits and 10% to 25% will suffer recurrent stroke. Improvements in awareness and imaging, as well as the increasing survival of children with conditions placing them at risk

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Dr Dowling conducted the systematic review and wrote the manuscript. Dr Ikemba reviewed the literature and contributed to the manuscript.

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for stroke, such as sickle cell disease, congenital heart disease, and cancer, have led to an increased incidence of arterial ischemic stroke to the range of 2.3 to 13 per 100 000 per year in children outside the neonatal period.^{1–3}

The etiologies of stroke in children differ from those of adults.⁴ However, in younger adults with cryptogenic stroke, patent foramen ovale is an established risk factor.⁵ Early studies identified patent foramen ovale in 40% of young adults with stroke but only 10% of controls.⁶ A similar high prevalence in younger patients (< 60 years) was reported in the Lausanne Study where patent foramen ovale occurred in 140/340 (41%) consecutive patients with stroke or transient ischemic attack.⁷

In the fetus, the foramen ovale allows oxygenated blood from the placenta to pass into the left heart and on to the arterial circulation. After birth, the foramen usually closes, but in some, the foramen remains open beyond the second year of life, producing a potential right-to-left shunt. The increased stroke risk is presumably because of the occurrence of “paradoxical embolization” where emboli escape filtering by the pulmonary vasculature and enter the arterial circulation directly via right-to-left intracardiac shunting. This can contribute to stroke by allowing passage of paradoxical emboli or via formation of thrombosis within the canal of the foramen.

The role of patent foramen ovale or other potential intracardiac shunts in stroke or stroke recurrence in childhood is unclear. Therefore, the focus of this study was to systematically examine the available evidence on intracardiac shunting in children and its relationship to stroke. The specific goals were to assess the different detection methods employed, report the prevalence of detectible intracardiac shunts in children with and without stroke, identify the other risk factors for paradoxical embolization in children, and review the published experience with different treatment options.

Methods

A PubMed search was conducted for relevant articles published from 1970 to 2009. Several broad searches of the literature were conducted looking for all studies in all age ranges. Keywords used included the following: patent foramen ovale, paradoxical embolization, intracardiac shunt, intracardiac shunting, transcranial Doppler ultrasound, and high intensity transient signals. This term refers to the abnormality detectible by transcranial Doppler ultrasound, which corresponds to microemboli in the intracranial vessels and can result from paradoxical embolization across an intracardiac or pulmonary shunt.

These searches were further restricted to human studies and studies of children under the age of 18 years. Abstracts were then manually reviewed for further selection, and additional searches were conducted from the references of identified study articles and literature reviews. Articles restricted to neonates and children with congenital heart disease were manually excluded. Only English language articles were included, although all English language abstracts were reviewed.

Results

PubMed searches identified 4165 articles for review. This group was further limited to the pediatric population with resultant identification of 224 articles. These abstracts and the original pool were manually reviewed to identify articles of interest. Subsequent review of the references of these articles and literature reviews yielded additional studies of interest. Articles that were primarily studies of adults but included a few children under the age of 18 years were excluded if only aggregate data on their primarily adult populations were available for review. Review of non-English language abstracts yielded only case reports relating to patent foramen ovale and stroke in children, but no clinical research studies addressing the mechanism, detection, prevalence, or treatment. Identified articles of interest are listed in the tables or are discussed further below.

Shunt Detection Methods

In autopsy studies, *patency* of a foramen ovale is defined as the ability to pass a calibrated probe through the opening. Thus, their results do not address the question of whether it is functionally patent or if it would be detectable by contrast echocardiography. In live patients, the prevalence of detectable patent foramen ovale is generally lower than in autopsy studies.

The gold standard for detection of patent foramen ovale in clinical practice is transesophageal echocardiogram with agitated saline contrast.^{8–11} The contrast is injected in a peripheral vein and echobright microcavitations can be observed entering the right atrium. They are normally filtered by the pulmonary capillary bed. In the presence of an intracardiac shunt, however, the echobright microcavitations can be observed passing into the left atrium within 3 to 5 cardiac cycles following injection, either at rest or with Valsalva maneuver. The appearance of contrast in the left side of the heart provides evidence of right-to-left shunting. In research studies involving adults, the shunt detection sensitivity increases with increasing numbers of contrast injections.¹² Patent foramen ovale remained undetected until the eleventh contrast injection in some subjects. There were few contrast echocardiograms performed in the identified pediatric reports. Only 3 of the studies provided specific procedural details, where only a small number of contrast injections were used.^{9,10,13}

It is important to distinguish the prevalence of potential intracardiac shunts at autopsy or surgery, with those clinically detectable by different methods. For example, the addition of agitated saline injection to transesophageal echocardiographic studies in adults improve patent foramen ovale detection by 50%.¹⁰ Direct inspection intraoperatively can have a much higher sensitivity. In a small study (27 patients) of predominately infants and young children with congenital heart disease undergoing cardiac surgery but without evidence of interatrial communication by either transthoracic or transesophageal echocardiography, the addition of agitated saline during transesophageal echocardiography led to the diagnosis of patent foramen ovale in only 1 patient.¹⁴ Surgical inspection, however, revealed an interatrial communication in 14 patients (52%). Seven patients also had cardiac catheterizations prior to surgery that did not detect the interatrial communication. Thus, the prevalence of clinically detectable patent foramen ovale in children likely differs from the prevalence detected by surgical or autopsy studies. Whether these clinically undetectable interatrial communications are important in stroke patients is unknown.

In adults, transthoracic echocardiography has a reported sensitivity of 63% and specificity of 100% compared to transesophageal echocardiography.⁹ The sensitivity appears to be higher in children because of better acoustic windows related to their smaller size and thinner bodies. In a study of 50 children ages 1.2 to 18.6 years comparing patent foramen ovale detection via transthoracic versus transesophageal echocardiography using agitated saline contrast, the 2 modalities differed in only 1 in 43 patients with conclusive transthoracic studies. Transthoracic echocardiography had a positive predictive value of 100%, negative predictive value of 97%, sensitivity of 88%, and a specificity of 100% for detecting a patent foramen ovale.¹⁵

Transthoracic echocardiography provides the advantage of being able to perform Valsalva maneuvers and cough during the procedure, greatly increasing detection of right-to-left shunting. These maneuvers cannot be done during a sedated transesophageal procedure,⁸ although Valsalva can be simulated with positive pressure ventilation and/or manual compression of the liver. Additionally, there is increased risk associated with transesophageal versus transthoracic studies, including the requirement for anesthesia and a small but present risk of esophageal or gastric perforation with the transesophageal approach. Both are important considerations in the poststroke pediatric patient where it is important to be able to clinically follow the neurologic examination and where any bleeding complications can be exacerbated by the frequent use of heparin. Furthermore, transthoracic echocardiography is approximately half the cost of the transesophageal study. Thus, it was advocated that transthoracic approach with agitated saline be used first in pediatric patients, followed by transesophageal studies only if the first study was not conclusive. This strategy would avoid over 85% of transesophageal echocardiograms in the evaluation of pediatric stroke patients.¹⁵

In a study of 40 children with sickle cell disease and stroke, contrast transthoracic echocardiography failed to detect potential intracardiac shunts in 2 of 9 children who had shunts noted by either color Doppler or conventional 2-D echocardiography or both.¹³ In an additional 35 children without sickle cell disease who had stroke in whom color Doppler transthoracic study was negative for intracardiac shunt, no additional shunts were detected with the addition of contrast. In 2 children who had patent foramen ovale identified by color Doppler who also received contrast transthoracic echocardiogram, the shunt was identified in only 1 of the 2 patients in the contrast study.¹³ Thus, 2-D, color Doppler, and contrast echocardiography are required to maximize detection of potential right-to-left intracardiac shunts.

Our literature search strategy did not identify any reports of adverse events or side effects of contrast echocardiogram in the pediatric population. No adverse events or side effects were noted in over 150 children receiving contrast studies.^{13,15}

Transcranial Doppler ultrasound can also be used for the detection of intracardiac shunts and has the advantage of being able to detect right-to-left shunting, whether it is at the cardiac or pulmonary level (via pulmonary arteriovenous malformation).¹⁶ There are few reported studies of transcranial Doppler ultrasound for shunt detection in children. However, 1 study of 39 patients (ages 15–39 years) with stroke or myocardial infarction, evaluated

simultaneously by both contrast transcranial Doppler and transesophageal echocardiography, found no difference in detection rates between the 2 methods, and suggested that the transcranial Doppler ultrasound may provide a better measure of the functional importance of the shunt than transesophageal echocardiography.¹⁷

In a report of 12 children with stroke and 6 with transient ischemic attacks, contrast transcranial Doppler ultrasound identified potential shunts in 4 out of 7 of the children with stroke and in 5 out of 6 of the children with transient ischemic attacks.¹⁸ In this study, children with other identified etiologies for stroke did not undergo transcranial Doppler ultrasound evaluation. Color Doppler transesophageal echocardiography failed to identify intracardiac shunt in 4 out of 9 patients with shunt detected by transcranial Doppler. In 1 of these children, the shunt was presumably at the pulmonary level. It should be noted, however, that contrast echocardiographic studies were not routinely performed and the results of the transthoracic and transesophageal echocardiograms were not specifically reported in this study. Thus, the superiority of transcranial Doppler ultrasound over echocardiography with contrast (transthoracic or transesophageal) is unclear for the detection of intracardiac shunts.

As this study illustrated, not all high intensity transient signals or microemboli detected by transcranial Doppler are the result of intracardiac shunting. Transcranial Doppler can detect right-to-left shunting at the pulmonary level as well. However, other microemboli can be detected by this method that are not the result of shunting at all, but are because of left heart pathology or emboli arising from more distal aortic or carotid artery disease. Intraoperative monitoring during cardiac surgery in adults can detect cerebral microemboli that are presumed to be gaseous, inorganic, or organic particles generated during the surgical procedure, which may be a predictor of cognitive decline after cardiac surgery in adults.^{19,20}

In a noncontrast transcranial Doppler ultrasound study of 32 children undergoing cardiac catheterization procedures, high intensity transient signals were observed in all of them, including a small number in children undergoing right-sided hemodynamic studies (especially pulmonary balloon dilatations) for whom there was no known septal communication.²¹ A higher count was observed in patients with known septal defects. Similarly, high intensity transient signals were noted in 12 out of 13 children monitored continuously by transcranial Doppler during scoliosis surgery.²² Two of these children were noted to have particularly high counts and both were found to have atrial right-to-left shunts by echocardiography. The other children were not evaluated by echocardiography and it was presumed that the low level microemboli detection rates were the result of intrapulmonary shunting. None of the children had clinical stroke although magnetic resonance imaging (MRI) was not performed to evaluate for small silent infarction. High intensity transient signals have also been noted in noncontrast studies in young adult patients with moyamoya, a frequent cause of stroke in children.²³ These microemboli presumably arose from diseased carotid arteries. Thus, contrast transcranial Doppler studies can detect intracardiac shunting, and can also detect procedure-related and spontaneous microembolic events that may be because of intrapulmonary shunting or aortic or carotid artery disease. The relation of these high intensity transient signals to stroke in children is unclear, as it is in adults.

Body Positioning for Detection of Shunt

Echocardiography is performed in the left lateral decubitus position for transthoracic and transesophageal echocardiography under general anesthesia is performed supine. In transcranial Doppler ultrasound, body position, either sitting or supine, may affect the sensitivity of shunt detection. In adults with patent foramen ovale detected by transesophageal echocardiography, contrast transcranial Doppler detection of intracardiac shunting was overall the same in the sitting or supine position in a study of 34 patients.²⁴ However, it was noted that for each individual, 1 of the 2 positions was more sensitive for shunt detection. The authors recommended changing the patient's position in the case of a first negative test. Other studies in adults found the seated position to be more sensitive.²⁵ There were no identified reports of position effects in children, other than a study showing no effect of Trendelenburg (–15 degrees) versus horizontal head position on detection of cerebral microemboli by transcranial Doppler in children during cardiac de-airing after systemic (left-sided) ventricle surgery.²⁶

There has been extensive investigation of the issue in adults undergoing neurosurgical procedures in the sitting position.²⁷ Venous air embolism was noted in 34% of children undergoing neurosurgery in the sitting position versus none operated on in the supine position.²⁸ Thus, positional distinctions may be important in transcranial Doppler-detection of shunting or may be of more functional importance for avoidance of air emboli in neurosurgical procedures performed in the sitting position. Detection of microemboli in the cerebral vasculature by transcranial Doppler ultrasonography may be more directly relevant to the issue of pediatric stroke.

Shunt Prevalence

A large autopsy study of almost 1000 patients found probe patent foramen ovale in 27.2% of all patients ages 1 to 99 years. The incidence decreased with age, with patent foramen ovale present in 34% of children ages 1 to 9 years, in 36% of children ages 10 to 19 years, and 33% in adults ages 20 to 29 years.²⁹ There was a further decline noted with age, to only 25% of those ages 30 to 79 years, dropping to 20% for those ages 80 to 99 years. Patent foramen ovale size, however, tended to increase with increasing age, from a mean of 3.4 mm in the first decade to 5.8 mm in the tenth decade.

The prevalence of patent foramen ovale or other intracardiac shunts detectable by echocardiography or transcranial Doppler appears to be much lower (Table 1). In normal young adults, the prevalence detectable by echocardiography is between 3% and 22%,³⁰ but the studies vary by technique (transesophageal vs transthoracic) and the use of contrast. A meta-analysis of 9 case-control studies of young adults reported a significant association between patent foramen ovale and stroke, with patent foramen ovale identified in 17.8%, (95% CI, 14.3–21.3) of control patients and in 40.2%, (95% CI, 36.2–44.2) of those with stroke.³⁰

There have been few studies of patent foramen ovale in children who have had stroke, although a causal link to stroke was suggested in a report of 2 cases³¹ and in a series of children with transient ischemic attack or stroke where evidence of left-to-right shunting was

detected in 9 out of 18 (50%) children by contrasted-transcranial Doppler.¹⁸ In this study, a potential intracardiac shunt was detected in 4 out of 7 patients with stroke and in 5 out of 6 patients with transient ischemic attack by contrast transcranial Doppler. The stroke group was enriched for possible paradoxical embolization by the exclusion of an additional 5 patients with other identified stroke risk factors from transcranial Doppler evaluation. No control subjects were included in this study. Intracardiac shunting was detected in 6 out of 30 (20%) of children without history of stroke who were screened by color Doppler transthoracic echocardiography prior to neurosurgery. Contrast was not used in this study.²⁸

In the largest echocardiographic study, a retrospective review of 1000 subjects ages 10 to 99 years in which contrast transesophageal echocardiograms were ordered for clinical indications, potential intracardiac shunt was detected in only 92 out of 1000 (9.2%) patients.³² Stroke or transient ischemic attack was the clinical indication for 391 of the 1000 patients, however, the data were not segregated by stroke or nonstroke clinical indication. The prevalence of patent foramen ovale in patients ages 10 to 29 years was 9.4%, suggesting that detectable prevalence does not change much with age. There were only 5 patients in the 10- to 19-year age range in this study; however, none of these 5 were found to have a patent foramen ovale. These findings conflict with the older autopsy study²⁹ where a much higher prevalence was found along with a decrease with age. These 2 studies emphasize the difference between the presence of probe-patent foramen ovale at autopsy and the presence of echocardiographically detectable patent foramen ovale.

A very low rate of intracardiac shunt detection was reported in a study of risk factors for arterial ischemic stroke in 104 previously healthy children without sickle cell disease or a known history of congenital heart disease using transthoracic echocardiography.³³ Potential intracardiac shunt was detected in only 1 out of 104 of these children; however, only 9 studies utilized contrast. In 45 of the children evaluated by noncontrast transthoracic plus transesophageal (n = 36) or contrast transthoracic echocardiogram (n = 9), no additional findings were noted that were not found on noncontrast transthoracic echocardiogram. This supports the assertion that in the majority of children, transthoracic echocardiography is sufficient.¹⁵

Similar low rates of detection of intracardiac shunting were noted in 2 large pediatric studies. The first was a study screening for bicuspid aortic valves where 817 total 10-year-old children from northern Italy were evaluated by transthoracic echocardiography with color Doppler.³⁴ These were healthy children without history of cardiac disease or stroke. Intracardiac shunts were identified in only 21 of these children (2.6% overall, 20 patent foramen ovale and 1 ventricular septal defect). This study is limited by the fact that an echocardiogram performed to rule out a bicuspid aortic valve may not include the views necessary to rule out a patent foramen ovale and contrast was not used. The second was a study of children with sickle cell disease ages 3 to 18 years, where intracardiac shunting was detected by noncontrast transthoracic echocardiography in only 2 out of 107 (1.9%) children.³⁵ In total, 11 of these 107 children had a history of stroke, but it was not indicated if the intracardiac shunts preferentially occurred in this group.

We excluded studies of neonates in our review; however, the low prevalence of echocardiographically detectable intracardiac shunting in children is supported by a large study of 847 newborns without congenital heart disease.³⁶ The infants were evaluated by serial transthoracic echocardiography without contrast from birth until closure of the interatrial communication to a maximum of 45 months. They found interatrial communications in 100% at birth, with spontaneous closure in 98.6% by the forty-fifth month.

Additional Risk Factors for Stroke in the Presence of Shunt

Prothrombotic states have been shown to predispose to paradoxical embolization in adult patients with patent foramen ovale.^{37,38} Karttunen and colleagues assessed the occurrence of several prothrombotic conditions and classical risk factors for venous thrombosis in 57 adult patients with cryptogenic stroke and patent foramen ovale and 104 matched controls. They found that prothrombotic states, migraine with aura, and classical risk factors for venous thrombosis were independent risk factors for cryptogenic stroke. In particular, Factor V Leiden and the prothrombin G20210A mutations showed highly significant associations with cryptogenic stroke. They note that the Valsalva maneuver, which can result in right-to-left shunting, was common at the onset of stroke. In the Lausanne Study, Valsalva maneuver at onset of stroke was noted in one-sixth of the patients with patent foramen ovale and stroke.⁷

There are often multiple risk factors for stroke in children. In a case series of 4 adolescents with stroke, it was noted that all had evidence of intracardiac shunting (atrial septal defect in 2 and patent foramen ovale in 2), coagulation abnormalities, and migrainous headaches or headache at presentation.⁴⁰ Prothrombotic risk factors were identified in 2 of 4 patients with stroke and patent foramen ovale and in 3 of 5 patients with transient ischemic attack and patent foramen ovale.¹⁸ Other case reports of pediatric stroke with presumed paradoxical embolization (Table 2) highlight this association of shunting with a hypercoagulable state.

Patent Foramen Ovale and Stroke in Sickle Cell Disease

Recently a case report⁴¹ and a prospective echocardiographic study of 40 children¹³ have highlighted a possible association of intracardiac shunting and stroke in children with sickle cell disease. Children with sickle cell disease suffer clinically overt strokes at a rate 220 times higher than other children⁴² with 8% to 11% of children affected by age 16 years. Additionally, up to 35% of children with sickle cell disease have clinically silent stroke detectable only by MRI.⁴³ We reported a patient without sickle cerebral vasculopathy with acute overt stroke in a cardioembolic pattern who had a patent foramen ovale as well as antiphospholipid antibodies and elevations in factor VIII and lipoprotein-a, demonstrating that there may be alternative etiologies for stroke in children with sickle cell disease, and specifically that paradoxical embolization may play a role.

There are several physiologic features of sickle cell disease that may serve to predispose to stroke by paradoxical embolization. First, the disorder is, in itself, a hypercoagulable state. Old and new thrombi are observed in the pulmonary vasculature in postmortem studies of patients with sickle cell disease, illustrating the effective pulmonary filter. Patients have been

shown to have high levels of circulating thrombin, activation of fibrinolysis, decreased levels of anticoagulant proteins, and platelet activation.⁴⁴ Furthermore, right-to-left shunting is favored in sickle cell disease given the pathophysiologic changes secondary to anemia and pulmonary hypertension, especially in the setting of acute chest syndrome. These conditions will raise right heart pressures, increasing the likelihood of right-to-left shunting and therefore potential for paradoxical embolization.

Additionally, positive end-expiratory pressure used to improve oxygenation in intubated patients with adult respiratory distress syndrome and acute chest syndrome can increase shunting, and the sudden release of high levels of positive end-expiratory pressure (as in suctioning) can have an effect similar to the Valsalva maneuver and may increase shunting. Furthermore, in the setting of pulmonary hypertension, pulmonary embolism, or acute chest syndrome, the use of exogenous vasoconstrictors or the release of endogenous vasoconstrictors can lead to right ventricular pressure overload, promoting right-to-left shunting and potentially worsening hypoxemia.⁴⁵

In a study of 40 children with sickle cell disease and stroke, potential intracardiac shunt was detected in 10 out of 40 (25%) by a combination of conventional 2-D, color Doppler, and agitated saline contrast transthoracic echocardiography. This was higher than observed in a comparison group of children with stroke but without sickle cell disease where intracardiac shunt was identified in only 7 out of 60 (11.7%).¹³ This was also higher than the detectible patent foramen ovale prevalence reported in normal children (2.6%)³⁴ or in other children with sickle cell disease without stroke (1.9%).³⁵ These observations suggest that patent foramen ovale could represent an independent and potentially modifiable risk factor for stroke in these children who are at extremely high risk.

Gender and Racial Differences in Intracardiac Shunts

The large autopsy study of 1000 patients found no sex differences in patent foramen ovale prevalence.²⁹ No differences were found overall or when the data were analyzed by decade. Similarly, there was an equal prevalence in male and female subjects in 1000 patients evaluated by contrast transesophageal echocardiography (9.5% vs 8.9%, $P =$ not significant).³² The numbers of children in this autopsy and large transesophageal echocardiographic screening study were small, however. In the study of children with sickle cell disease and stroke, there were no significant gender differences observed.¹³ The 3 other larger studies reporting intracardiac shunting in children did not report patient gender.^{33–35}

In adults, the prevalence of patent foramen ovale in patients with cryptogenic stroke or transient ischemic attack was higher in men than in women (38% vs 28%, $P = .014$) in a study of 500 adults by transesophageal echocardiography.⁴⁶ This study did not evaluate children and is confounded by possible gender differences in other risk factors for adults for cryptogenic stroke, so it does not directly address the question of gender differences in patent foramen ovale, per se. Thus, it is possible that there are gender differences in patent foramen ovale prevalence or closure rate that could be more pronounced in childhood, but no studies addressing this question were identified.

Similarly, there could be racial or ethnic difference in patent foramen ovale prevalence or closure rates with development. Again, there were no reports of ethnic or racial differences in children, and race was not defined except for those implied by studies in children from northern Italy,³⁴ or in those with sickle cell disease from Brazil,³⁵ or the United States.¹³ These studies cannot be directly compared because of differences in technique. Race and ethnicity were not reported in the large autopsy or transesophageal echocardiography studies. One older study found no difference in patent foramen ovale prevalence between white and black patients.⁴⁷ In a study of 630 adults with ischemic stroke evaluated by transesophageal echocardiography, no racial or ethnic differences were found in the frequency; however, larger patent foramen ovale and right atrial anatomy favoring paradoxical embolization were significantly more prevalent among white and Hispanics compared with blacks.⁴⁸

Treatment Options

Optimal treatment to prevent recurrence in children with stroke and evidence of intracardiac shunting is unclear. Given the relatively high prevalence of patent foramen ovale or other intracardiac shunting in the general population and the low incidence of stroke overall, it is difficult to assign a causal role to paradoxical embolization in individual patients. Rather, this diagnosis is one of exclusion, further complicating treatment decisions. There currently are no evidence-based or consensus-based guidelines for the management of children with stroke and patent foramen ovale.⁴⁹ Treatment options include antiplatelet therapy with aspirin or anticoagulation with low molecular weight heparin or warfarin. Alternatively, the intracardiac shunt can be closed surgically or by a percutaneous closure device.

Most of the isolated case reports of stroke because of intracardiac shunting describe treatment with a closure device (Table 2). Exceptions include a case of a girl with sickle cell disease and multifocal bilateral infarcts (cardioembolic pattern) in the setting of antiphospholipid antibodies, and elevated factor VIII and lipoprotein a levels who was treated with anticoagulation with warfarin⁴¹ and a case of a young boy with cerebellar infarction presumed secondary to paradoxical embolization who was treated with aspirin, but for whom future surgical intervention was planned.⁵⁰

Percutaneous patent foramen ovale closure was performed in 15 out of 24 children with sequelae of cerebral ischemia.⁵¹ The children were treated with oral aspirin at 2 to 3 mg/kg/day for 6 months after the procedure. All remained free of complications and no recurrent thromboembolic events were observed, but they do not report the observation period. In another study, percutaneous closure was attempted in all 9 children who had patent foramen ovale identified by contrasted transcranial Doppler ultrasound in 4 out of 6 children with stroke and 5 out of 6 children with transient ischemic attack.¹⁸ Closure with an Amplatzer occluder was successful in 8 out of 9 patients. The patient with an unsuccessful closure attempt had no identifiable shunt by color Doppler or contrasted transesophageal echocardiogram, or with contrast injected directly into the tunnel of the foramen ovale via catheter. This patient had only a small number of microemboli detected by transcranial Doppler and which were presumed to be secondary to an undiagnosed pulmonary arteriovenous malformation. In this group of treated children, aspirin therapy was continued

for 6 months. There were no complications from the procedure and no further stroke or transient ischemic attack noted in 6 to 21 months (median, 15) of follow-up.

The issue of patent foramen ovale closure in adults with cryptogenic stroke (stroke of undefined cause) is highly controversial and is currently under investigation in several ongoing randomized controlled clinical trials. Noting that enrollment in several of these trials was lagging and that there has been a dramatic increase in percutaneous patent foramen ovale closure in adults without adequate evidence of safety or efficacy, the American Heart Association, American Stroke Association, American College of Cardiology Foundation, and the American Academy of Neurology have recently issued an advisory calling for the completion of these studies. They urge that adult patients with patent foramen ovale and cryptogenic stroke be referred for enrollment in 1 of these randomized clinical trials of patent foramen ovale closure device versus medical therapy with antiplatelets or anticoagulants.⁵²

Given the relative novelty of percutaneous patent foramen ovale/atrial septal defect closure, there may be a reporting bias in the literature toward reporting those cases of stroke with patent foramen ovale or other intracardiac shunting treated with these new devices. An assessment of closure device safety and efficacy is beyond the scope of this review. There were no studies identified that had data comparing medical versus device closure therapies in children. Successful long-term recurrence free treatment has been reported for both types of therapy in children.

Conclusions: Recommendations for Implementation of Future Studies

No controlled studies of the prevalence of patent foramen ovale or other intracardiac shunting in children with stroke were identified in this systematic review. This highlights the clear need to obtain such data in well designed, controlled studies in children, as adult data on shunt prevalence in stroke, associated stroke risk factors, stroke recurrence, and shunt treatment may not apply to children. The risk factors, recurrence rates, consensus treatment recommendations, and outcomes for ischemic stroke in children differ greatly from those of adults with stroke.⁴⁹ The implications and consequences of intracardiac shunting in children with stroke are likely to differ as well. On the basis of this systematic literature review, the following recommendations are offered for future study designs that address the mechanism of paradoxical embolization through intracardiac shunts in children with stroke.

1. The prevalence of detectible intracardiac shunt in identified cases of pediatric stroke from reported case series ranges from 0.96% to 25%, while the limited prevalence data on detectible shunts in healthy children without stroke ranges from 0% to 20%. These prevalences are overall lower than those reported in meta-analyses of adult studies and suggest that the detectible prevalence of patent foramen ovale or intracardiac shunts may be lower in children than adults. This could be secondary to underreporting, lack of evaluation by color Doppler echocardiogram, lack of contrast, or decreased compliance with the Valsalva maneuver in children compared to adults. These observations and the paucity of published control data on the prevalence of detectible intracardiac

shunting in children strongly suggest that future studies must include adequate pediatric control subjects.

2. Patent foramen ovale and other potential intracardiac shunts are more prevalent in children than adults based on autopsy studies.²⁹ The progressive decline in prevalence with age suggests that there may be a slow process of late closure of intracardiac shunts outside of early infancy when the normal physiologic changes after birth lead to closure of this necessary conduit essential for the fetal circulation. This late closure process continues over the lifespan, continuing well after early childhood. This slow decrease in patent foramen ovale prevalence with age suggests that future studies will require age matching of control subjects.
3. The optimal detection method for patent foramen ovale or other intracardiac shunts in children is unclear. The evidence suggests that contrast transthoracic echocardiography may have sufficient sensitivity for shunt detection in children so that the more invasive transesophageal approach, the gold standard in adults, may not be necessary in children.¹⁵ Compared to transthoracic, transesophageal echocardiography is more invasive and requires sedation. The additional ethical and practical considerations of medical research in children versus adults may preclude transesophageal echocardiography in future studies in the pediatric population.
4. The detection of potential shunts by conventional 2-D or color Doppler echocardiography that were not detected by contrasted studies¹³ suggests that a combination of 2-D, color Doppler, and multiple contrast injections is optimal for the detection of potential intracardiac shunting in children.
5. Transcranial Doppler ultrasonography has not been extensively evaluated in children for shunt detection. Transcranial Doppler also detects shunting across pulmonary shunts (eg, pulmonary arterio-venous malformations) and microemboli arising from diseased (atheromatous) carotid arteries distal to the heart. Thus, adult transcranial Doppler studies cannot be directly applied to children given the low prevalence of atheromatous disease in children compared to adults. Future studies with simultaneous transcranial Doppler and echocardiographic evaluation during contrast injection could allow for direct comparison of the 2 techniques in children.
6. Different body positions (sitting, supine) may lead to different shunt detection rates utilizing transcranial Doppler. Future transcranial Doppler studies should have standardization of body position during evaluation or, ideally, include evaluation in both the sitting and supine position.
7. Children with sickle cell disease are routinely evaluated by transcranial Doppler ultrasonography for detection of cerebral vasculopathy and assessment of stroke risk.⁵³ In this review, no studies of shunt detection by transcranial Doppler in children with sickle cell disease were identified. Future studies of transcranial Doppler for the detection of intracardiac shunting, or microemboli arising from

diseased carotid arteries, could be performed in children with sickle cell disease as they already undergo routine screening.

8. Coincident prothrombotic state and intracardiac shunting may increase the risk of paradoxical embolization leading to stroke or increase the risk of recurrence. Current data and guidelines⁴⁹ suggest that it is reasonable to evaluate children with stroke for at least the more common prothrombotic states, particularly if a potential intracardiac shunt is identified. Treatment decisions may need to be based more on the associated prothrombotic state than on the presence of the potential intracardiac shunt alone. Future studies of the role of intracardiac shunting in stroke in children will need to better evaluate and access coincident prothrombotic states.
9. The optimal treatment approach for patent foramen ovale or intracardiac shunting in children with stroke is not clear. No controlled studies comparing medical (antiplatelet or anticoagulation) therapy versus percutaneous device closure were identified. There is, as yet, no evidence to suggest that routine patent foramen ovale closure in children, even after stroke, is indicated. Ongoing controlled clinical trials in adults addressing this issue may aid in guiding future therapies for children. Current evidence and consensus based guidelines for the treatment of stroke in children offer no specific recommendations for the treatment of patent foramen ovale.^{49,54} However, future studies to determine the optimal therapies in children are required given the different risk factors for stroke in children compared to adults, the differences in coagulation systems between children and adults, and the longer time span of risk exposure for recurrence in children as compared to adults.

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Table 1

Detection of Patent Foramen Ovale or Intracardiac Shunting in Children

Study Type	Study (Year)	Patient Age	# Patients	Shunt # (%) by TTE Doppler	Shunt # (%) by TTE Doppler or contrast	Shunt # (%) by TCD	Shunt # (%) Any Method	Comments
Autopsy	Hagen (1984) ²⁹	1–9 y	100	–	–	–	34%	Autopsy data
		10–19 y	100	–	–	–	36%	Probe patent PFO
		1–99 y	965	–	–	–	27.3%	Non-SCD
Adult studies	Overall (2000) ³⁰	<55 y	Meta-analysis	–	–	–	Stroke 228/566 (40.2%)	Meta-analysis of 9 case control studies of young adults
Pediatric echo studies	Fuchs (1998) ²⁸	1–14 y	1022	6/30 (20%)	–	–	Control 81/456 (17.8%)	Non-SCD
			30				6/30 (20%)	Children without stroke screened for PFO prior to neurosurgery
								Non-SCD
	Fisher (1995) ³²	10–19 y	5	–	–	–	0	TEE for clinical indication
		10–29 y, combined	53	–	–	–	(0%)	stroke/TIA in 391/1000
		10–99 y	1000	–	–	–	5/53 (9.4%)	Proportion with stroke not reported for 10–29 y subgroup
	Ganesan (2003) ³³	21 d–19.7 y	104	1 ASD/104 (0.96%)	–	–	92/1000 (9.2%)	Non-SCD
							1/104 (0.96%)	Previously healthy children with stroke
								Non-SCD
	Basso (2004) ³⁴	10 y	817	20 PFO and 1 VSD = 21/817 (2.6%)	–	–	21/817 (2.6%)	Healthy children w/o stroke
								Non-SCD
								Children with SCD (11/107 with stroke)
	Dowling (2010) ¹³	3–18 y	107	2/107 (1.9%)	–	–	2/107 (1.9%)	Children with SCD over (30)
SCD points with stroke		2–19 y	40	6 PFO and 1 VSD = 7/40 (17.5%)	9 PFO and 1 VSD = 10/40 (25%)	–	10/40 (25%)	

Study Type	Study (Year)	Patient Age	# Patients	Shunt # (%) by TTE Doppler	Shunt # (%) by TTE Doppler or contrast	Shunt # (%) by TEE	Shunt # (%) by TCD	Shunt # (%) Any Method	Comments
	Dowling (2010) ¹³	0.25–19 y	60	7/53 (13.2%)	7/53 (13.2%)	0/7 (0%)	–	7/60 (11.7%)	or silent (10) stroke Children with stroke, excluding known congenital heart disease
	Non-SCD points with stroke								Non-SCD
Pediatric TCD studies	Benedik (2007) ¹⁸	2–17 y	13	–	–	5 + TEE/9 with PFO by TCD	4/7 Stroke (57%) 5/6 TIA (83%)	9/13 (69%)	Stroke or TIA, excluding other stroke etiologies

Abbreviations: PFO, patent foramen ovale; SCD, sickle cell disease; TCD, transcranial Doppler ultrasound; TEE, transesophageal echocardiogram; TTE, transthoracic echocardiogram; ASD, atrial septal defect; VSD, ventricular septal defect.

Table 2

Case Reports of Stroke and Intracardiac Shunting in Children

Author (Year)	Age	Cardiac Findings	Associated Conditions	Treatment Comments
Evers (1998) ⁵⁵	17 y	PFO	TIA while playing Trumpet Hypercoag testing (–)	Surgical closure
Devidayal (2003) ⁵⁰	–	PFO	–	Aspirin with planned surgical closure
Wirrell (2004) ⁵⁶	18 m	PFO	Recent Varicella vaccination	Aspirin
	14 m	PFO	Hypercoag (–)	Transfusion
			Recent Varicella vaccination	Iron therapy
			Hypercoag (–)	
Perkins and Butler (2005) ⁴⁰	16 y	PFO	Elevated lipoprotein a	Low molecular weight
	16 y	PFO	Elevated lipoprotein a	Heparin > warfarin > device closure
	12 y	PFO	Elevated Antithrombin III	
	17 y	ASD	Anticardiolipin antibodies	Aspirin > device closure
			Myotonic dystrophy	Aspirin > device closure
Agnetti (2006) ³¹	6y	PFO with atrial septal aneurysm in both cases	Hypercoag testing (–) for both	Open closure of ASD
	11 y			Device closure for both
de la Cruz-Cosme (2009) ⁵⁷	18 y	PFO with atrial septal aneurysm	Hypercoag testing (–)	Device closure
Dowling (2009) ⁴¹	11 y	PFO	SCD, Antiphospholipid antibodies, elevated factor VIII and lipoprotein a	Warfarin

Abbreviations: PFO, patent foramen ovale; ASD, atrial septal defect; SCD, sickle cell disease.