CARDIOLOGY ASSOCIATES, LLC

Thursday, April 26

View Our Locations

Visit our website

A Message from Cardiology Associates, LLC

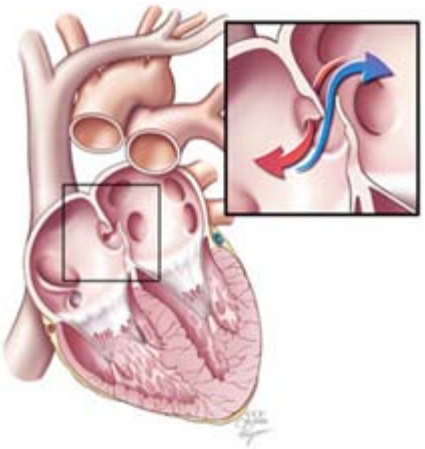
Dear Colleagues,

The April newsletter will draw your attention to a relatively common condition in cardiac patients, called foramen ovale. This small, flap-like opening in the heart usually closes during the first or second year of an infant's life. When the foramen ovale does not close, it is termed patent foramen ovale (PFO). Over 25% of Americans currently live with this condition. While the majority of these individuals never experience any complications from the occasional blood passing through the chamber, should a clot pass through this opening, a high risk of stroke is present. Such was the fairly-recent case with TV star and rocker Bret Michaels, whose last stroke was caused by PFO.

About the author

Dr. Lawrence Jacobs, Jr., sees patients in our Annapolis and Kent Island office locations. He graduated from the Georgetown University School of Medicine and completed his residency in Internal Medicine at the University of Pennsylvania. He is Board-certified in Internal Medicine and Cardiovascular Disease. Dr. Jacobs holds additional certifications from the Board of Nuclear Cardiology and the Board of Echocardiography. He is a fellow of the American College of Cardiology and a member of the American Society of Echocardiography.

Patent Foramen Ovale: Innocent Bystander or Prime Suspect



CASE PRESENTATION

A 44-year-old male with no significant prior medical history reported the sudden onset of tingling in the right side of the face and arm as well as difficulty with speech while on vacation. His evaluation at a local hospital was unremarkable including a normal head CT, MRI, MRA, EKG and blood chemistries. Echocardiography was initially interpreted as normal with no significant valvular disease, ejection fraction of 60% and normal left atrial size. No obvious inter-atrial shunt was evident using color doppler analysis. However, further evaluation with a bubble study was markedly positive, with the rapid passage of a large number of bubbles from right to left atrium. Transesophageal echocardiography was performed, showing normal valvular structure and function. No thrombus was identified in the left atrium or its appendage. Two-dimensional and color doppler evaluation revealed the presence of a moderate-sized patent foramen ovale (PFO) with predominant left to right shunting and an atrial septal aneurysm (ASA). Our patient was very eager to know what he can do to most effectively protect against further neurologic events.

DISCUSSION

During fetal development, a patent foramen ovale (PFO) is required for oxygenated blood to flow from the right to the left atrium. This normal structure can often persist into adulthood. Both TEE and autopsy studies have demonstrated that approximately 25 to 30% of patients have a residual PFO in adulthood.[1,2] This structure is asymptomatic in the vast majority of cases. However, in rare cases, it can be associated with TIA or stroke. Studies show that PFO has increased prevalence among patients with cryptogenic stroke, supporting a causative role. This is especially true among those under 55, in whom a larger percentage of strokes are cryptogenic. Among patients with an unexplained stroke, the prevalence of PFO increases to 35 to 37% and their PFOs tend to be of larger size than those patients in whom the cause of stroke is known.[3,4] In patients with a PFO, retrospective analyses have identified certain risk factors that may increase the likelihood of initial and recurrent stroke.[3,4] These include a history of Valsalva maneuver (cough, straining) preceding the cerebral embolic event, a history of multiple strokes, and possibly a hypercoagulable state.[5,6] The risk of recurrent stroke appears to be increased in those with a large PFO, large right-to-left shunt, spontaneous right-to-left shunt, greater PFO flap mobility, prominent Eustachian valve or Chiari network, and the presence of an atrial septal aneurysm.[7-13]

The exact mechanism by which a PFO contributes to stroke risk is not conclusively known. The traditional explanation suggests that a PFO can serve as a pathway for venous to arterial transit of emboli (paradoxical emboli) via right-to-left shunting when the pressure in the right atrium exceeds that in the left atrium, such as with cough, valsalva or normal respiration. However, in patients with a PFO and/or atrial septal aneurysm (ASA) and an embolic event, low rates of deep venous thrombosis (10 to 22%) are seen, even with aggressive imaging, such as MRI venography.[14] One possible explanation for the absence of detectable thrombus is that the emboli may actually consist of platelet-fibrin particles that normally circulate in the venous system and are too small to be visualized. These particles are normally removed by the efficient lytic system of the lungs, but when shunted across a PFO, they may lodge unlysed in the cerebral circulation. Alternative theories suggest that the source of embolism may originate in the left atrium rather than in the venous circulation. The PFO itself may predispose to the formation of thrombus or platelet-fibrin complexes in the left atrium, which lead to cerebral embolism. This seems to be particularly applicable when the PFO is associated with an inter-atrial septal aneurysm. An ASA is defined as redundant and mobile inter-atrial septal tissue in the region of the fossa ovalis with phasic excursion of at least 10 to 15 mm during the cardiorespiratory cycle. ASA is seen in about 2.2% of unselected individuals. However, there is an increased prevalence of ASAs among patients with cerebral ischemic events. For example, ASA was observed in 7.9% to 15% of patients with a possible embolic stroke, and in 28% of those with a cerebral ischemic event and normal carotid arteries.[15-17] Two mechanisms have been proposed to explain the association between ASA and cryptogenic stroke. Since ASA is commonly associated with PFO and atrial septal defects (ASD), paradoxical embolism may occur via the septal defect. In patients with ASA without an intracardiac shunt, it has been hypothesized that fibrin-platelet particles adhere to the left atrial side of the aneurysm and are dislodged by oscillations of the aneurysm, causing systemic embolism. Another theory proposes that the structural alteration of the left atrium by the presence of a significant ASA induces left atrial systolic dysfunction akin to that seen in atrial fibrillation. One study compared the atrial function in stroke patients with a PFO to patients experiencing atrial fibrillation. They showed that these stroke patients had atrial dysfunction similar to those with atrial fibrillation and that the presence of a significant ASA along with the PFO was the strongest predictor of left atrial dysfunction. Furthermore, percutaneous closure of the PFO reversed these findings of left atrial dysfunction.[18]

It is clear that the discovery of a PFO in an asymptomatic patient is an incidental finding that should require no treatment or intervention. This is supported by the prospective NOMAS study in which asymptomatic patients found to have PFO, ASA, or both had no statistically significant increase in the risk of stroke during 80 months of follow up.[19] However, it is less clear exactly what significance a PFO carries when discovered as part of a stroke evaluation. A 2009 meta-analysis of case-control studies evaluating the prevalence of PFO in patients with cryptogenic stroke suggested that approximately one third of PFOs detected in patients with cryptogenic stroke are likely to be incidental findings.[20] The PFO was less likely to be incidental in younger patients or when a coexisting ASA was present. It's interesting that most studies appear to show that in stroke patients the presence of a PFO alone is not associated with a significantly increased risk of recurrent stroke. One meta-analysis addressing this question compared stroke patients with and without a PFO and found no increase in recurrent stroke in those with a PFO.[21] The French PFO-ASA Study and the cryptogenic stroke portion of the PICCS study similarly showed that PFO alone did not confer a higher risk of recurrent stroke.[3,4] On the other hand, the presence of both ASA and PFO was a significant predictor of an increased risk of recurrent stroke (15.2% versus 4.2% at four years in the absence of either abnormality) in the French PFO-ASA Study. Interestingly, the other study that addressed this issue, the PICCS study, did not demonstrate this same increased risk of PFO and ASA. Conflicting data such as this is what makes treatment decisions in stroke patients with a PFO difficult.

TREATMENT

Since it is well established that the incidental finding of a PFO, ASA, or both does not significantly increase a person's chance of embolism, no specific intervention is necessary. This is the case even if the patient has a PFO discovered incidentally while undergoing cardiac surgery for another reason. Retrospective data indicate that the routine closure of incidentally discovered PFOs during cardiac surgery is associated with no benefit or even an increased stroke risk.[22]

For inter-atrial communications found in patients with unexplained stroke, optimal treatment is unclear. Options include antiplatelet or anticoagulant medications or closure of the PFO. Although it seems intuitive that closure of the defect would provide optimal protection, there is no clear evidence that closure is better than medical therapy, at least in part because not all recurrent cerebral events are due to paradoxical embolization. Since isolated PFO does not appear to confer a significantly elevated risk of recurrent stroke, aspirin or other antiplatelet therapy is the recommended first line treatment unless they are documented to have DVT, PE or hypercoaguable disorder, in which case warfarin is recommended. As with all stroke patients, other traditional risk factors should always be addressed, even if the inter-atrial communication is the suspected culprit. This includes control of lipids with statins, antihypertensive medications, smoking cessation and control of diabetes, if applicable.

The data surrounding treatment for stroke in the setting of the combination of PFO/ASA has given conflicting results. Some practitioners point to the French PFO/ASA study which showed that aspirin resulted in a much higher stroke recurrence rate than with warfarin (15.2% vs. 4.2%) and recommend warfarin over aspirin in this patient group. However, there was no difference in outcome between aspirin and warfarin therapy among patients with both an ASA and a PFO in two other studies of similar patients, so this recommendation is by no means definitive. In fact, the 2004 American Academy of Neurology practice parameter concluded that the available data were insufficient to determine the relative efficacy of aspirin and warfarin in this situation.[23] The current recommendation, therefore, is for aspirin; although if the patient is felt to be at high risk for recurrence, warfarin is an acceptable alternative. Subsets of cryptogenic stroke patients that may be at higher risk of recurrence and may derive greater benefit from first-line warfarin are not well defined. However, younger patients with PFO and ASA and who are free of other risk factors such as hypertension, diabetes, and vascular disease may be among those who derive particular benefit from a more aggressive strategy.

In the available studies, the numbers of patients with an isolated ASA (without PFO) were small and, therefore, meaningful inferences are hard to come by. At this point, there is insufficient evidence to determine if cryptogenic stroke with an isolated atrial septal aneurysm (ASA) carries a meaningfully increased risk of recurrent stroke or death compared with cryptogenic stroke without atrial septal abnormalities or if warfarin or aspirin is superior for the prevention of recurrent stroke.

PFO CLOSURE vs. MEDICAL THERAPY

Percutaneous PFO closure was approved by the FDA in December 2001 under a humanitarian device exemption in patients with recurrent cryptogenic stroke due to presumed paradoxical embolism that occurred despite anticoagulation with warfarin. However, this approval was withdrawn in October 2006. Several nonrandomized and retrospective studies have suggested a possible benefit from percutaneous closure of PFOs in those with cryptogenic stroke. The recent CLOSURE I Trial was the first prospective, randomized, independently-adjudicated PFO device closure trial to be completed.[24] Percutaneous closure of a PFO with the STARFlex closure device (NMT Medical) with 24 months of aspirin and six months of clopidogrel vs. medical therapy with aspirin, warfarin or a combination of the two was compared in 909 patients with cryptogenic stroke or TIA. There was an insignificant reduction in both stroke (3.1% to 2.9%) and TIA (4.1% to 3.1%) with the use of this closure device compared to medical therapy. Not surprisingly, the closure group suffered a significant number (3.2%) of major vascular procedural complications. Interestingly, the closure group had a significantly higher incidence of atrial fibrillation during the study (5.7% vs. 0.7%). This was mostly periprocedural atrial fibrillation, probably due to device related atrial irritation.

Stroke recurrence in this population appears to be fairly uncommon. Thus, even a low rate of procedural complications makes it difficult to improve on the natural history of uncorrected PFO.

Closure might benefit a subset of high-risk patients with paradoxical embolization, but until this group can be reliably identified and shown to benefit, routine PFO closure cannot be recommended for cryptogenic stroke. Upcoming results from the recently completed RESPECT trial and the ongoing REDUCE trial may shed more light on this issue. Therefore, at this time, there is no clear evidence that closure is better than medical therapy. Up to this point, multiple organizations, including the American Academy of Neurology (AAN), the American Heart Association/American Stroke Association (AHA/ASA), and the American College of Chest Physicians (ACCP) have concluded that there is insufficient evidence to evaluate the efficacy of surgical or percutaneous closure compared with medical therapy. This most recent evidence from the CLOSURE I Trial is likely to induce a much stronger recommendation for medical therapy for PFO and ASA patients with stroke, although closure may still be appropriate for certain as yet undefined higher risk patients.

SUMMARY

- PFO is a very common finding, which does not carry an increased risk of stroke in asymptomatic individuals.
- Among those with cryptogenic stroke, PFOs are present at a higher rate than in a comparable population without stroke.
- Isolated PFO does not appear to increase the risk of a second stroke and is simply an incidental finding in the stroke workup in approximately one third of cases.
- The combination of PFO & ASA may pose a higher risk of recurrent stroke.
- Patients with cryptogenic stroke and PFO can be treated with aspirin or other antiplatelet regimen as well as other usual risk reduction strategies for stroke. Warfarin is reserved for those found to have DVT, pulmonary embolism, or hypercoaguable disorder.
- In those with cryptogenic stroke and PFO/ASA, aspirin or another antiplatelet agent may be sufficient, unless the patient is felt to be at higher risk of recurrence, in which case warfarin is recommended.
- Percutaneous closure of PFO or PFO/ASA has not been shown to significantly reduce recurrent events in a randomized trial and is associated with periprocedural risk including stroke, vascular damage and atrial fibrillation. This treatment modality may still be appropriate for very specific patient subsets and those who fail medical therapy. Further study is needed on this subject.

References:
1. Mayo Clin Proc 1984; 59:17.
2. Mayo Clin Proc 1999; 74:862.
3. Stroke. 2002;33(3):706.
4. Circulation. 2002;105(22):2625.
5. Neurology. 1996;46(5):1301.
6. Thromb Haemost. 2009;101(5):813.
7. Arch Intern Med. 2004;164(9):950.
8. Am J Med. 2000;109(6):456.
9. Stroke. 1994;25(3):582.
10. Stroke. 2000;31(10):2407.
11. Am Heart J. 1996;131(1):158.
12. Stroke. 1994;25(4):782.
13. Catheter Cardiovasc Interv. 2008;72(7):973.
14. Stroke. 2004;35(1):46.
15. Circulation. 1999;99(15):1942.
16. J Am Coll Cardiol. 1991;18(5):1223.
17. Eur Heart J. 2001;22(3):261.
18. J Am Coll Cardiol: Cardiovasc Intervent 2009; 2:655-662.
19. J Am Coll Cardiol. 2007;49(7):797.
20. Stroke. 2009;40(7):2349.
21. Neurology. 2009;73(2):89.
22. JAMA. 2009;302(3):290.
23. Neurology. 2004;62(7):1042.
24. N Engl J Med 2012; 366:991-999.

Please Join Our Mailing List

We are offering you this monthly newsletter as a way to provide cardiovascular news and update you on developments within our field. For your convenience, we are distributing our newsletter via e-mail. Visit our site at (www.heartcapc.com) and click the Referring Physician Newsletter link at the upper left corner of our home page. You will receive an e-Newsletter every month featuring an article or a case report from one of our physicians and links to other sources featuring new trends in the field of cardiology.

Our focus will be on real questions and issues that we encounter in our day-to-day medical practice. In fact, if there is a topic that is of particular interest to you (or a question that is related to any of our articles) please e-mail your inquiries to our Project Manager, Nazar Snihur at nsnihur@heartcapc.com. (Of course, we will not share your e-mail address outside of our offices.)

Our Locations

Annapolis Cardiology Office
2002 Medical Parkway, Suite 500
Annapolis, MD 21401
Phone: 410-573-6480
Fax: 410-573-9413

Annapolis Vascular Office
2002 Medical Parkway, Suite 520
Annapolis, MD 21401
Phone: 410-571-8430
Fax: 410-573-5981

Bowie Office
4175 N. Hanson Court
Suite 100
Bowie, MD 20716
Phone: 301-809-6880
Fax: 301-805-4233

Irving Street 4800N
106 Irving Street, NW
Suite 4800N
Washington, DC 20010
Phone: 202-726-5484
Fax: 202-726-4587

Kent Island Office
1630 Main Street
Suite 208
Chester, MD 21619
Phone: 410-643-3186
Fax: 410-643-4098

K Street Office
2131 K Street, NW
Suite 800
Washington, DC 20037
Phone: 202-822-9356
Fax: 202-331-0451

Olney Office
18109 Prince Philip Drive
Suite 225
Olney, MD 20832
Phone: 301-774-5810
Fax: 301-774-0188