CASE REPORT

How often is patent foramen ovale an innocent bystander?

Francesco Versaci\(^1\), Giampiero Vizzari\(^2\), Domenico Sergi\(^1\), Giuseppe Ando\(^2\), Antonio Trivisonno\(^3\) & Francesco Romeo\(^1\)

\(^1\)Department of Cardiovascular Disease, Tor Vergata University of Rome, Rome, Italy
\(^2\)Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy
\(^3\)Department of Cardiovascular Disease, “Antonio Cardarelli” Hospital, Campobasso, Italy

Correspondence
Giampiero Vizzari, Department of Clinical and Experimental Medicine, University of Messina, Via C. Valeria, 1 – 98100 Messina (ME) – Italy. Tel: 00393494219688; Fax: 00390902212325; E-mail: giampierovizzari@hotmail.it

Funding Information
No sources of funding were declared for this study.

Received: 8 April 2017; Revised: 28 July 2017; Accepted: 19 September 2017

Clinical Case Reports 2017; 5(12): 1992–1994
doi: 10.1002/ccr3.1237

Key Clinical Message
Patent foramen ovale (PFO) is a risk factor for cryptogenetic stroke; its closure should be considered in selected patients. It is not always clear whether symptoms (presyncope, paresthesia) apparently due to paradoxical embolism are related with other cardiovascular disorders such as arrhythmias. Flecainide administration for post-PFO-closure supraventricular arrhythmias can unmask a latent undiagnosed Brugada syndrome.

Keywords
Brugada syndrome, palpitations, patent foramen ovale, PFO closure, presyncope.

Introduction
Patent foramen ovale (PFO) is present in about one-quarter of the adult population, and it has been implicated as a risk factor for cryptogenetic stroke (CS), with a mechanism likely consisting in paradoxical embolism [1, 2]. Recent guidance from the American Heart Association and the American Stroke Association Council on Stroke suggests that PFO closure using dedicated devices could be a therapeutic approach in specific cases [3].

Unfortunately, in patients with PFO, it is not always clear whether symptoms, mostly nonspecific, are clearly consistent with a cryptogenic stroke/transient ischemic attack (TIA) due to the presence of a PFO, rather than with another cardiovascular condition, such as arrhythmias [4]. Moreover, flecainide administration, sometimes used to treat atrial arrhythmias subsequent to PFO closure, has been demonstrated to be an unmasking factor for Brugada pattern on electrocardiogram (ECG)[5].

Case Report
We report the case of a 58-year-old Caucasian female, admitted to our hospital for presyncope. Five years before, due to frequent episodes of migraine, presyncope, and paresthesia, she had undergone cerebral MRI with diffuse subcortical gliosis, ECG which appeared to be normal (Fig. 1A), and transthoracic echocardiography (TTE) showing an atrial septal aneurysm associated with a moderate right-to-left interatrial shunt, increased by Valsalva maneuver. As both contrast-enhanced transcranial Doppler and transesophageal echocardiography had confirmed the presence of a PFO, the patient received device-based percutaneous closure. After closure, she referred frequent palpitations and at that time ECG showed incomplete right bundle branch block and Holter monitoring revealed frequent supraventricular extrasystoles; so administration of oral flecainide therapy (100 mg twice daily) was started. Despite this therapeutic approach, she continued to refer symptoms due to palpitations, especially at night.

A further syncope with falling to the ground and consequent head injury led the patient to our observation. The ECG showed down sloping ST-segment elevation in V1 and V2 leads, which was not evident in any previous ECGs (Fig. 1B).

Based on these findings and especially on the clinical history reported and the ECG morphology, diagnosis of type 1 Brugada syndrome (BrS) was made and the patient
underwent implantable cardioverter defibrillator (ICD) implantation. After discontinuation of flecainide, an improvement of symptoms was referred and serial ECGs showed a progressive normalization of ST segment in V1-V2 (Fig. 1C). The clinical follow-up at 1 year showed absence of symptoms and ICD intervention.

Discussion

The patient received PFO closure, in a first center, for symptoms attributable to transient cerebral ischemia and instrumental evidence of PFO and subcortical gliosis.

On the background of the clinical history of the patient, the morphological and functional characteristics of the PFO and the neuroimaging features of cerebral ischemia may provide useful information to understand the relationship between PFO and symptoms and the probability for PFO to be culprit or bystander [6–8]. However, signs of subcortical gliosis are present in most people but often nonspecific, as well as the detection of a PFO is sometimes occasional and unrelated to the symptoms.

History of frequent supraventricular arrhythmias and palpitations has been described in the follow-up of patients who underwent PFO closure [9]. One of the

Figure 1. (A) Previous ECG, registered before PFO closure, appeared to be normal. (B) ECG performed in the emergency room of our hospital, showing type 1 Brugada pattern; the chronic oral intake of flecainide, prescribed because of supraventricular ectopic beats, likely unmasked the ECG pattern and contributed in symptoms worsening. (C) ECG normalization after flecainide discontinuation.
most common antiarrhythmic drug, flecainide, is currently used for the diagnosis of Brugada syndrome, administered intravenously, under ECG monitoring [10, 11]. In our case, flecainide administration was crucial to unmask a latent Brugada pattern on the ECG, leading, also based on the clinical history, to ICD implantation for prevention of malignant ventricular arrhythmias [12–14].

Considering this case presentation it is possible, in our opinion, that initial symptoms were not related to the presence of a PFO but already first manifestations of a BrS.

Another possible interpretation could be that the presyncope, before PFO closure, was really due to paradoxical embolization (as flecainide had not been administered at that time) leading to a proper PFO closure and then starting all the subsequent developments related to flecainide administration. In this perspective, the danger of improper flecainide prescription to patients with undiagnosed latent BrS needs to be pointed out.

**Conclusion**

This report shows that careful evaluation of the clinical history and symptoms is extremely helpful for the correct diagnosis. It seems therefore evident that symptoms, presumed to be due to paradoxical embolism, may probably be caused by arrhythmic events related to the BrS; anyway, their following exacerbation can be triggered by an incautious flecainide administration after PFO closure. The presence of PFO is too often considered the first responsible for patient’s symptoms when no other causes are apparently evident, leading to frequent misdiagnosis; however, a PFO is not always the guilty, but in many cases, it is just an innocent bystander.

**Conflict of Interest**

None declared.

**Authorship**

FV: involved in clinical care, decision making, and manuscript revision. GV: involved in writing and revision of the manuscript. DS, FR: revised the manuscript. GA: wrote and revised the manuscript. AT: involved in clinical care, decision making, and image preparation.

**References**

1. Homma, S., and R. L. Sacco. 2005. Patent foramen ovale and stroke. Circulation 112:1063–1072.
2. Leong, M. C., A. Uebing, and M. A. Gatzoulis. 2013. Percutaneous patent foramen ovale occlusion: current evidence and evolving clinical practice. Int. J. Cardiol. 169:238–243.
3. Sacco, R. L., R. Adams, G. Albers, M. J. Alberts, O. Benavente, K. Furie, et al. 2006. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. Circulation 113:e409–e449.
4. Mirzada, N., P. Ladenvall, P. O. Hansson, P. Eriksson, and M. Dellborg. 2015. Recurrent stroke in patients with patent foramen ovale: An observational prospective study of percutaneous closure of PFO versus non-closure. Int. J. Cardiol. 195:293–299.
5. Brugada, P., and J. Brugada. 1992. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. J. Am. Coll. Cardiol. 20:1391–1396.
6. Gaspardone, A., and C. Iani. 2008. Papa M [Percutaneous closure of patent foramen ovale: a wise approach]. G. Ital. Cardiol. 9:593–602.
7. Pristipino, C., G. P. Anzola, L. Ballerini, A. Bartorelli, M. Cecconi, M. Chessa, et al. 2013. Management of patients with patent foramen ovale and cryptogenic stroke: a collaborative, multidisciplinary, position paper: executive summary. Catheter. Cardiovasc. Interv. 82:122–129.
8. Ando, G., F. Tomai, and P. A. Gioffre. 2004. Left ventricular decompression through a patent foramen ovale in a patient with hypertrophic cardiomyopathy: a case report. Cardiovasc Ultrasound. 2:2.
9. Gaspardone, A., A. Giardina, M. Iamele, G. Gioffre, M. Polzon, F. Lamberti, et al. 2013. Effect of percutaneous closure of patent foramen ovale on post-procedural arrhythmias. J. Am. Coll. Cardiol. 62:2449–2450.
10. Antzelevitch, C., P. Brugada, M. Borggreve, J. Brugada, R. Brugada, D. Corrado, et al. 2005. Brugada syndrome: report of the second consensus conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. Circulation 111:659–670.
11. Calvo, D., J. M. Rubin, D. Perez, J. Gomez, J. P. Florez, P. Avanzas, et al. 2015. Time-dependent responses to provocative testing with flecainide in the diagnosis of Brugada syndrome. Heart Rhythm 12:350–357.
12. Bayes de Luna, A., J. Brugada, A. Baranchuk, M. Borggreve, G. Breithardt, D. Goldwasser, et al. 2012. Current electrocardiographic criteria for diagnosis of Brugada pattern: a consensus report. J. Electrocardiol. 45:433–442.
13. Benito, B., R. Brugada, J. Brugada, and P. Brugada. 2008. Brugada syndrome. Prog. Cardiovasc. Dis. 51:1–22.
14. Priori, S. G., A. A. Wilde, M. Horie, Y. Cho, E. R. Behr, C. Berul, et al. 2013. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. Heart Rhythm 10:1932–1963.