

Acute Myocardial Infarction in a Child: Possible Pathogenic Role of Patent Foramen Ovale Associated With Heritable Thrombophilia

Nicola Carano, MD*; Aldo Agnetti, MD; Donald J. Hagler, MD†; Bertrand Tchana, MD*; Umberto Squarcia, MD*; and Sergio Bernasconi, MD*

ABSTRACT. We report an 8-year-old girl who presented with clinical features of an acute myocardial infarction. The angiographic appearance of the coronary arteries was normal. A thrombophilic state caused by a homozygote genotype for the prothrombin G20210A mutation was detected, and a patent foramen ovale (PFO) with right-to-left shunting after Valsalva maneuver was demonstrated by transesophageal contrast echocardiography. No other embolic source was identified. We suggest that paradoxical embolization through a PFO resulted in a myocardial infarction in this young patient with hereditary thrombophilia. We closed the patient's PFO with a 25-mm PFO occluder. She was anticoagulated with warfarin for 6 months. After 6 months, a contrast echocardiogram showed no evidence of residual atrial shunt. There has been no evident recurrent paradoxical embolization. *Pediatrics* 2004;114:e255–e258. URL: <http://www.pediatrics.org/cgi/content/full/114/2/e255>; *myocardial infarction, patent foramen ovale, hypercoagulable state, prothrombin G20210A, paradoxical embolism.*

ABBREVIATIONS. PFO, patent foramen ovale; MI, myocardial infarction; ECG, electrocardiogram.

Studies of cryptogenic stroke in young patients have shown that the incidence of patent foramen ovale (PFO) is higher than in patients with established causes of stroke.^{1–5} The suggested mechanism for a cerebrovascular event in patients with a PFO is based on a transient increase in right heart pressure, which would cause a transient right-to-left shunt through the PFO, with the possibility that a venous embolus could cross the PFO and embolize the cerebral circulation (paradoxical embolism). Paradoxical emboli could also reach other vascular beds, such as the coronary arteries, and cause acute myocardial infarction (MI).⁶ Recent studies have shown that genetic or acquired prothrombotic disorders may represent risk factors for thromboembolic disease also in children.^{7–9} We report a case of acute MI in an 8-year-old girl in whom, because of the presence of a PFO and inherited prothrombotic abnormality, after excluding all other possible causes, we

presume that the MI had been caused by a paradoxical embolism.

CASE REPORTS

This 8-year-old girl, who previously had been well except for asthma and allergic rhinitis and conjunctivitis caused by pollen allergy, experienced acute chest pain, localized at the sternal area, while she was playing basketball at school. She stopped playing and the pain disappeared within 20 minutes. Her mother arrived when the pain had already ceased and noted that she was pale. In the evening, she developed a mild fever. On the following day, she awoke early in the morning because of a severe precordial pain. She stated that the pain felt like a weight pushing on her chest. The girl appeared extremely ill, pale, and sweaty; therefore, she was taken to the local hospital. On admission, the pain had persisted for ~45 minutes, but the intensity had decreased. The pain disappeared completely in 1 hour. Physical examination did not reveal any abnormality, heart rate was 96 beats/min, blood pressure was 105/60 mm Hg, respiratory rate was 20 breaths/min, and transcutaneous oxygen saturation was 97%. The electrocardiogram (ECG) showed a sinus rhythm with 2.5-mm ST elevation in lead I, aVL, V₄, V₅, and V₆ and ST depression in V₁, V₂, and aVR (Fig 1). The markers of myocardial damage were significantly increased: myoglobin was 224 ng/mL (normal values: 0–70 ng/mL), troponin I was 9.5 ng/mL (normal values: 0–0.1 ng/mL); and CK-MB was 57.6 ng/mL (normal values: 0–4 ng/mL). On the basis of this data, the patient was transferred to our hospital. On admission, she was asymptomatic and physical examination was negative. Laboratory investigations were as follows: red blood cells: 4.130.000/mm³; white blood cells: 10.600/mm³; hemoglobin: 11.7 g/dL; platelets: 420.000 mm³; erythrocyte sedimentation rate: 15 mm; renal function, standard coagulation studies, serum cholesterol, and triglycerides were within the normal limits. Aspartate transaminase was 77 U/L, and creatine phosphokinase was 694 U/L. Figure 1 shows the evolution of serologic markers of myocardial damage. The troponin I levels steadily decreased after the initial high level of 9.5 ng/mL.

Figure 2 shows ECG findings that a pathologic Q-wave never appeared. At 36 hours, the ST segment had returned to isoelectric, and the T-wave was flat. At 60 hours, the T-wave had recovered its polarity and amplitude.

Serial echocardiographic examinations revealed no abnormality of the cardiac structures, proximal coronary arteries, cardiac function, and contractility. No cardioembolic source was detected. No pericardial effusion appeared.

During the entire hospital admission, the patient did not experience additional thoracic pain or any other complaint. No specific therapy for MI was necessary. The cultures for virus Coxsackie, echo, influenza, adenovirus, cytomegalovirus, and Epstein-Barr were negative. No increase of antibody titers against these viruses was found. Our clinical diagnosis was anterolateral intramural or subepicardial MI.

Specific studies for thrombophilia demonstrated a homozygote genotype for prothrombin G20210A mutation and a heterozygote genotype for C677T methylenetetrahydrofolate reductase gene mutation (serum homocysteine: 7 μmol/L; normal values: <15 μmol/L). Protein C and S activities were normal. Antithrombin III levels were within the normal range. Factor V Leiden mutation, lupus anticoagulant, and anticardiolipin antibodies were absent. Both parents were heterozygous for prothrombin G20210A mutation (the mother had experienced deep venous thrombosis of the

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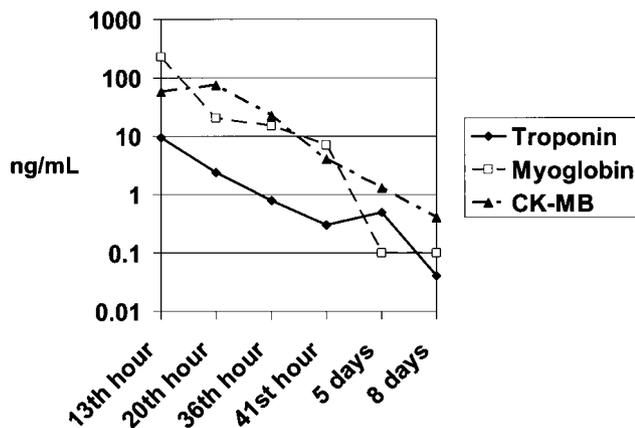


Fig 1. Graphic presentation of troponin, myoglobin, and CK-MB myocardial enzymes.

legs). Echo Doppler evaluation of the abdominal and lower limb veins and arteries were normal. Selective right and left coronary angiography showed normal coronary arteries.

Both congenital and acquired coronary artery diseases therefore were ruled out. Because prothrombin G20210A mutation determines a hypercoagulable state with an increased risk of venous thrombosis and despite the failure to demonstrate a PFO with transthoracic echocardiography, we decided to investigate further other conditions responsible for paradoxical embolism. In the catheterization laboratory, under general anesthesia, transesophageal echocardiography with echo contrast injections were performed to determine whether a PFO was present. A catheter was placed in the right atrium in front of the fossa ovalis, and agitated saline solution was injected while the anesthesiologist induced a Valsalva maneuver. An immediate right-to-left passage of bubbles through a PFO was demonstrated (Fig 3). Pulmonary angiography also excluded pulmonary arteriovenous fistulas. Thus, a transcatheter closure of the PFO using a 25-mm Amplatzer PFO Occluder was performed without complication. Warfarin anticoagulation therapy was given for 6 months.

DISCUSSION

MI in the pediatric age is rare. The most common cause of MI is perinatal asphyxia in neonates and congenital anomalies of coronary arteries (mainly anomalous origin of the left coronary artery from the pulmonary artery) in infants, children, and adolescents. Other possible causes of MI are coronary arteritis (mainly in Kawasaki disease), some metabolic diseases (mucopolysaccharidosis, Fabry disease, gangliosidosis, and homocystinuria), myocardial bridging, coronary artery trauma in open or closed thoracic trauma, mediastinal irradiation, chronic rejection in heart transplantation, metastatic tumors that compress coronary arteries, primary thrombocytosis, sickle cell disease, cocaine abuse, and cardiac surgery for congenital heart diseases in which surgical correction requires coronary artery reimplantation. Also, coronary embolism can cause MI in children. Coronary emboli may be of spontaneous origin (from aortic or mitral valve in infectious endocarditis, from left atrium and ventricle in dilative cardiomyopathy or myocarditis, or from intracardiac tumors), iatrogenic (cardiac surgery, cardiac catheterization, or coronary angiography), and paradoxical.

Paradoxical embolism is the passage of a venous embolus into the systemic circulation via a communication in the cardiac septa or a pulmonary arterio-

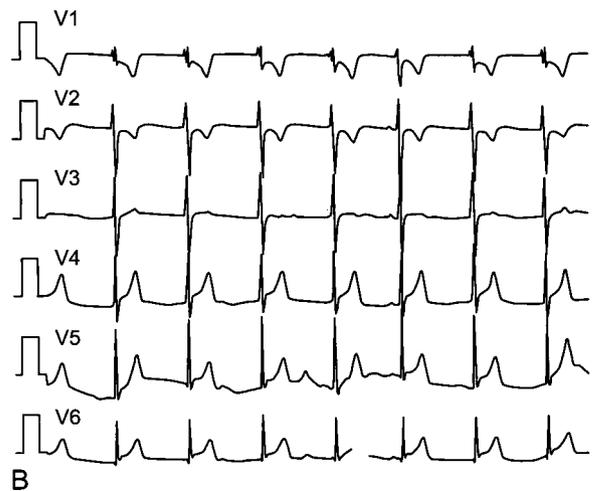
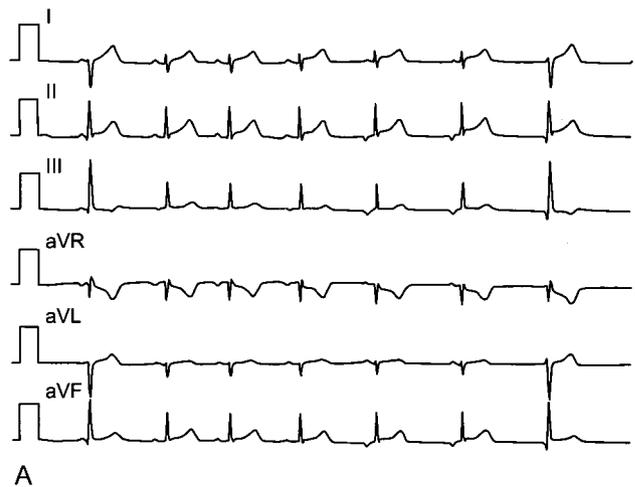
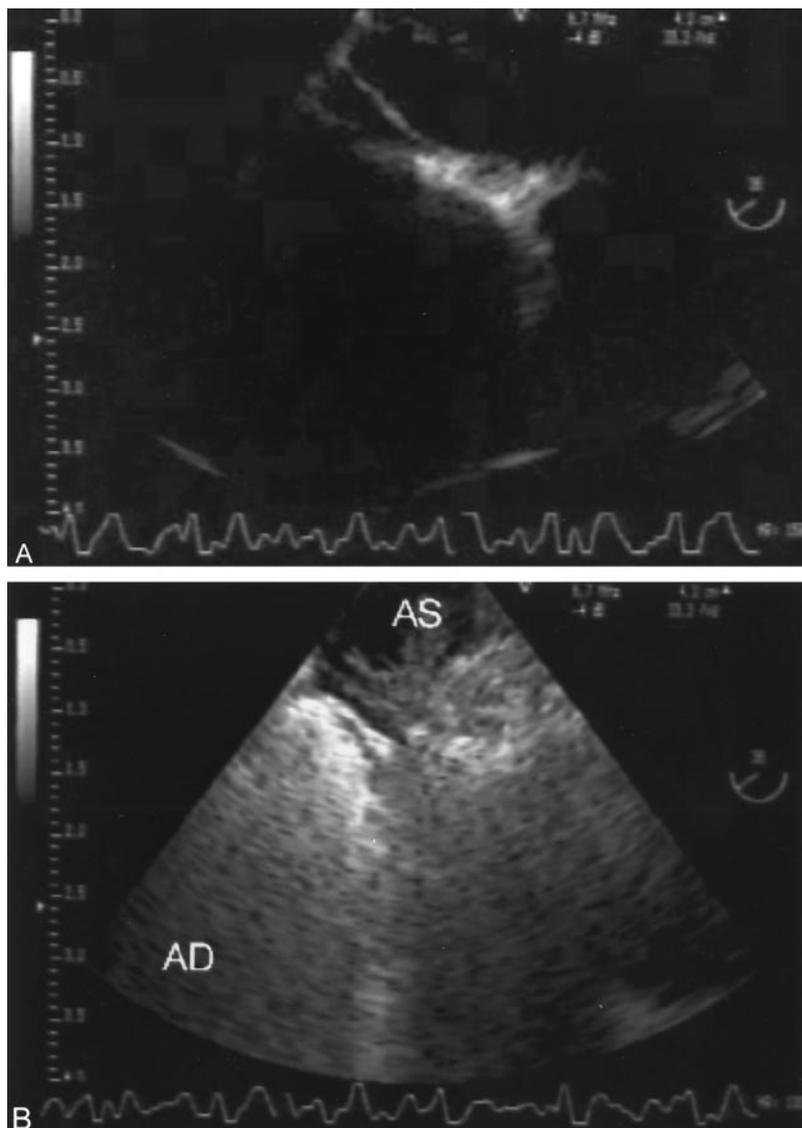


Fig 2. ECG on admission: note ST segment elevation in lead I, VL, V₄, V₅, and V₆. ST segment depression in V₁, V₂, and VR.

venous fistula. It is rare event in childhood. Paradoxical emboli can embolize to every systemic artery, including coronary arteries. There is extensive literature to suggest an association between cryptogenic stroke in young adults and paradoxical embolism, commonly related to a PFO.^{1,2,5} Studies on young stroke victims have shown that there is a significantly higher proportion of these young people who have a PFO.^{3,4} For this reason, the possibility of paradoxical embolism should be considered in young patients with ischemic stroke and PFO, without other causes for stroke.⁵ Although many other causes for stroke are sought in young patients, paradoxical embolization is often neglected.

Similarly, it would be expected that paradoxical embolism to the coronary circulation could explain acute MI that occurs in the absence of coronary artery disease. Crump et al¹⁰ studied the prevalence of PFO in patients with acute MI and angiographically normal coronary arteries. They did not find any increase of prevalence of PFO in these patients when compared with the control group with no history of coronary artery disease. The incidence of PFO was similar to that expected by autopsy studies.¹¹ This may suggest that paradoxical embolism through a PFO is an uncommon cause of acute MI with normal

Fig 3. A, Short axis transesophageal ECG demonstrating the atrial septum. The thin portion in the fossa ovalis and the arrow points to the orifice of the foramen ovale. RA, right atrium; LA, left atrium; A, anterior; L, left. B, During injection of agitated saline contrast into the RA with induced Valsalva maneuver, there is prompt passage of a larger amount of contrast (arrow) across the PFO into the left atrium (LA).



coronary arteries. Indeed, reports of MI as a result of paradoxical embolism are sporadic in the literature.¹²⁻¹⁵

Three criteria for the confident diagnosis of paradoxical embolism are frequently cited: 1) arterial embolism with no evidence of a source in the left heart or arterial circulation, 2) evidence of an abnormal communication between the right and left circulations, and 3) confirmation of deep venous thrombosis or pulmonary embolism. Paradoxical embolism can be considered proved only when the embolus is found located in the abnormal communication between venous and arterial circulation (the so-called impending paradoxical embolism).¹⁶

Recent advances in the knowledge of prothrombotic disorders in children have demonstrated their relevant contribution in the pathogenesis of arterial ischemic events, venous thrombosis, and venous thrombo-embolism.⁷⁻⁹ The prothrombin G20210A mutation has been shown to be associated with an increased risk of venous thrombosis.¹⁷ Regarding the influence of this mutation on coronary artery thrombosis, the results of large case-controlled studies indicates that the importance of the prothrombin

G20210A mutation is restricted to individuals who have additional major cardiovascular risk factors (eg, age, smoking, diabetes, hypertension).^{18,19}

In our case, MI occurred in a young patient who is homozygous for prothrombin G20210A mutation, has angiographically normal coronary arteries, and has a PFO with echo contrast evidence of right-to-left shunting during the Valsalva maneuver. The only pathogenetic explanation that we have found is that MI was caused by paradoxical embolization into the coronary circulation in this patient with inherited thrombophilia with associated increased risk of venous thrombosis and a PFO. We could not demonstrate either impending paradoxical embolism or venous thrombosis, but the sensitivity of ultrasound examination of this lower echo Doppler is known to be a suboptimal method to detect small thrombi, especially those located below the knee. Moreover, even in patients with proven pulmonary embolism, deep venous thrombosis is often not found despite appropriate investigations. However, in adults, current clinical management of PFO in patients with demonstrated thrombophilia would include PFO closure. In addition, we believe that children and ado-

lescents with echocardiographically defined PFO or small atrial septal defects unlikely to require closure should be screened for thrombophilia.

To avoid additional paradoxical embolization in this homozygous patient, we closed the PFO with a 25-mm PFO Amplatzer occluder. As opposed to patients who do not have thrombophilia and undergo transcatheter closure of PFO or atrial septal defect in whom we recommend aspirin (single dose of 5 mg/kg/day) for 6 months, in this patient, we advised warfarin anticoagulation treatment for 6 months to limit the potential thrombogenic effect of the intracardiac device.

CONCLUSION

MI is a rare disease in children. It is often difficult to find the cause, and every possibility has to be considered carefully. We speculate that the cause of MI in our case was paradoxical embolism via a PFO in a patient with inherited thrombophilia. Thus, it should be stressed that in the young patients who present with MI without coronary abnormalities, PFO and prothrombotic disorders should always be investigated.

REFERENCES

1. Chant H, McCollum C. Stroke in young adult: the role of paradoxical embolism. *Thromb Haemost.* 2001;85:22-29
2. Di Tullio M, Sacco RL, Gopal A, Mohr JP, Homma S. Patent foramen ovale as a risk factor for cryptogenic stroke. *Ann Intern Med.* 1992;117:461-465
3. Lechat P, Mas JL, Lascault G, Loron P, et al. Prevalence of patent foramen ovale in patients with stroke. *N Engl J Med.* 1988;318:1148-1152
4. Webster MWI, Chancellor AM, Smith HJ, et al. Patent foramen ovale in young stroke patients. *Lancet.* 1988;2:11-12
5. Mas JL. Patent foramen ovale, atrial septal aneurysm and ischemic stroke in young adults. *Eur Heart J.* 1994;15:446-449
6. Jungbluth A, Erbel R, Darius H, Rumpelt HJ, Meyer J. Paradoxical coronary embolism: case report and review of the literature. *Am Heart J.* 1988;116:879-885
7. Chalmers EA. Heritable thrombophilia and childhood thrombosis. *Blood Rev.* 2001;15:181-189
8. de Veber G, Monagle P, Chang A, et al. Prothrombotic disorders in infants and children with cerebral thromboembolism. *Arch Neurol.* 1998;55:1539-1543
9. Chan HKC, de Veber G. Prothrombotic disorders and ischemic stroke in children. *Semin Pediatr Neurol.* 2000;7:301-308
10. Crump R, Shandling AH, Van Natta B, Ellestad M. Prevalence of patent foramen ovale in patients with acute myocardial infarction and angiographically normal coronary arteries. *Am J Cardiol.* 2000;85:1368-1370
11. Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. *Mayo Clin Proc.* 1984;59:17-20
12. Gersony DR, Kim SH, Di Tullio M, Fard A, Rabbani L, Homma S. Acute myocardial infarction caused by paradoxical coronary embolization in a patient with a patent foramen ovale. *J Am Soc Echocardiogr.* 2001;14:1227-1229
13. Uchida S, Yamamoto M, Masaoka Y, Mikouchi H, Nishizaki Y. A case of acute pulmonary embolism and acute myocardial infarction with suspected paradoxical embolism after laparoscopic surgery. *Heart Vessels.* 1999;14:197-200
14. Meier-Ewert HK, Labib SB, Schick EC, Gossman DE, Stix MS, Williamson CA. Paradoxical embolism in the left main coronary artery: diagnosis by transesophageal echocardiography. *Mayo Clin Proc.* 2003;78:103-106
15. Tillett A, Hartley B, Simpson J. Paradoxical embolism causing fatal myocardial infarction in a newborn infant. *Arch Dis Child Fetal Neonatal Ed.* 2001;88:F137-F138
16. Meacham RR III, Headley AS, Bronze MS, Lewis JB, Rester MM. Impending paradoxical embolism. *Arch Intern Med.* 1998;158:438-448
17. Poort SR, Rosendaal FR, Reitsma PH, Bertina RM. A common variation in the 3'-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. *Blood.* 1996;88:3698-3703
18. Doggen CIM, Cats VM, Bertina RM, Rosendaal FR. Interaction of coagulation defects and cardiovascular risk factors: increased risk of myocardial infarction associated with factor V Leiden or prothrombin G20210A. *Circulation.* 1998;97:1037-1041
19. Gardemann A, Arsic T, Katz N, Tillmanns H, Hehrlein FW, Haberbosch W. The factor II G20210A and factor V G1691A gene transitions and coronary heart diseases. *Thromb Haemost.* 1999;81:208-213

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