Endovascular Closure of a Patent Foramen Ovale in the Fat Embolism Syndrome

Changes in the Embolic Patterns as Detected by Transcranial Doppler

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Background: The posttraumatic fat embolism syndrome (FES) is characterized by petechiae and pulmonary and cerebral dysfunction. A patent foramen ovale (PFO) could worsen the prognosis of FES by allowing larger emboli to reach the systemic circulation. Transcranial Doppler ultrasonography can be used to diagnose and monitor cerebral microembolism in FES.

Objective: To describe a case of successful percutaneous closure of PFO in a patient with posttraumatic FES with excellent clinical outcome.

Patient and Methods: A 17-year-old girl presented with a posttraumatic long-bone fracture complicated by typical severe FES. Transcranial Doppler disclosed multiple microembolic signals over both middle cerebral and basilar arteries. A large PFO was diagnosed by transesophageal echocardiogram. A brain magnetic resonance image with diffusion-weighted sequences showed multiple bilateral areas of abnormal diffusion in watershed territories. Percutaneous PFO closure with a buttoned device was successfully performed.

Results: Closure of PFO was associated with marked reduction in the number and intensity of microembolic signals. Subsequent surgical repair of the fracture with the patient under transcranial Doppler monitoring was uneventful. There was excellent correlation between clinical course and microembolic signal load by transcranial Doppler.

Conclusions: Cerebral fat embolism after long-bone fractures can be detected in vivo and monitored over time with the use of transcranial Doppler techniques. If a PFO is present, its closure before surgical manipulation of the fracture is feasible and could have important protective effects against massive systemic embolization.

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The posttraumatic fat embolism syndrome (FES) is a multisystem disorder characterized by the clinical triad of petechial rash, dyspnea, and signs of cerebral dysfunction. Pathological studies of patients who died after having FES typically show widespread microvascular occlusion by fat emboli, particularly within the lungs and brain. The presence of a patent foramen ovale (PFO) has been suggested to worsen the prognosis of FES by allowing a larger embolic load to reach the systemic circulation, and it has been shown that during bone surgery large fat globules may cross a PFO, causing severe cerebral complications, including death.

Our group recently reported that cerebral microembolism in patients with FES can be diagnosed and monitored in real time with transcranial Doppler (TCD). Two years ago, we began a prospective study in which patients with long bone fractures were monitored with TCD within 24 hours of trauma. Our preliminary results, presented elsewhere, suggest that the presence of a PFO is a risk factor for developing more severe manifestations of FES. If this holds true, it may be helpful to occlude the right-to-left shunt before a critical embolic load has caused irreversible or significant damage.

We describe a patient with severe posttraumatic FES and a PFO who successfully underwent percutaneous closure of the intracardiac shunt followed by excellent clinical recovery.

A 17-year-old girl had a car crash and was brought to our Trauma Emergency Room. No loss of consciousness or head trauma occurred. Her Glasgow Coma Scale score was 15 at the scene of the accident and on arrival to the hospital. Initial evaluation showed a fully alert patient in no sig-
nificant distress who complained only of left thigh pain. Vital signs showed a regular tachycardia of 100 beats per minute, a blood pressure of 120/80 mm Hg, and a respiratory frequency of 16/min. The left thigh was swollen and deformed, but there was no disruption of the skin continuity.

A radiologic survey was performed, including a computerized tomographic scan of the brain, with normal results. An x-ray film of the left femur showed a comminuted, transverse fracture at the junction of the proximal and middle thirds of the shaft, with lateral and posterior displacement of the distal fragment. Routine blood work showed leukocytosis (white blood cell count, 22.7 \times 10^3/µL) and mild anemia (hemoglobin level, 11.9 g/dL; hematocrit, 37%). Prothrombin time was 14 seconds, and activated thromboplastin time, 24 seconds. Initial blood gas values while the patient was breathing room air were as follows: pH 7.41, PCO2 34 mm Hg, PO2 61 mm Hg; bicarbonate, 21 mEq/L; and arterial oxygen saturation, 92%. The patient was placed in skeletal traction and received nonopiate pain medication.

Fourteen hours after admission, she suddenly became confused and agitated. Tachycardia and tachypnea worsened and pulse oximetry showed that the arterial oxygen saturation had dropped to 85% while the patient was breathing room air, improving to 98% when 4 L of oxygen by nasal cannula was administered. Repeat blood gas measurement showed a pH of 7.42, PCO2 of 35 mm Hg, PO2 of 45 mm Hg, bicarbonate level of 22 mEq/L, and arterial oxygen saturation of 83%. The patient was transferred to the intensive care unit and intubated orally. At that time, she was stuporous, responding with eye opening, grimacing, and withdrawing limbs to painful stimuli. Bilateral Babinski signs and bilateral subconjunctival petechiae were noted.

A TCD examination disclosed multiple microembolic signals (MES) over both middle cerebral arteries (MCAs) and the basilar artery (Figure 1A-B shows MES over left MCA). Two seconds after the injection of agitated isotonic sodium chloride solution in an antecubital vein, numerous MES appeared over both MCAs and the basilar artery, indicating the presence of a right-to-left shunt (Figure 1C-E). A venous duplex scan of the lower extremities and a ventilation-perfusion nuclear scan obtained during the following 12 hours were unremarkable. A transesophageal echocardiogram performed during the third hospital day showed a redundant interatrial septum, confirmed the presence of a PFO, and showed spontaneous passage of aerated microbubbles across the septum (Figure 2A-B). A brain magnetic resonance image with diffusion-weighted images obtained that same day showed multiple areas of abnormal diffusion on diffusion-weighted images, some with high T2 and fluid-attenuated inversion recovery signal intensity, located in the subcortical and periventricular white matter of both cerebral hemispheres in the distribution of the watershed territories (Figure 3).

On the fourth day of admission, after informed consent was signed by proxy, a transcatheter device closure of the PFO was successfully performed with the patient...
under general anesthesia and transesophageal echocardiographic control (Figure 2C–D). A 40-mm buttoned device (Custom Medical Devices, Amarillo, Tex) was placed in the left atrium with the use of a 10F sheath from the femoral vein. The right-to-left shunt was eliminated by adding a 25-mm inverted counter occluder in the right atrium. Treatment with clopidogrel bisulfate and enoxaparin sodium was started.

During the next 36 hours, the patient exhibited progressive improvement, eventually recovering normal mental status. An echocardiogram performed 5 days after the catheterization confirmed that the device remained in place with no passage of microbubbles from right to left. Treatment with clopidogrel bisulfate and enoxaparin sodium was started.

During the next 36 hours, the patient exhibited progressive improvement, eventually recovering normal mental status. An echocardiogram performed 5 days after the catheterization confirmed that the device remained in place with no passage of microbubbles from right to left. On the 10th day of admission, the patient underwent surgical repair of her femoral fracture without complications. Continuous TCD monitoring was performed during surgery. Close clinical follow-up did not show any suggestion that the surgery worsened the patient’s mental status. On the contrary, during the days after the surgery, she continued to improve and was discharged home while receiving warfarin sodium on the 16th hospital day.

**Figure 2.** Transesophageal view of redundant interatrial septum and patent foramen ovale (A) with spontaneous passage of contrast (aerated isotonic sodium chloride solution) from right atrium (RA) to left atrium (LA) (B). After deployment of the occluding device, there is no further passage of contrast from right to left (C and D). T indicates transverse axis; L, longitudinal axis; RV, right ventricle; and LV, left ventricle.

**TCD EXAMINATIONS**

Embolic detection monitoring was performed on admission, intraoperatively, and daily until a 1-hour monitoring period failed to identify MES. All studies were performed with a TCD unit (Pioneer TC 4040; Nicolet Biomedical Inc, Madison, Wis) equipped with microembolus detection software, version 2.31, 256-point fast Fourier transform with a sample volume of 10 mm. Each study lasted 1 hour. A 2-MHz probe was used to insonate the right and left MCAs and the basilar artery through temporal and transforaminal windows. All studies were performed at a depth of insonation between 5 and 5.6 cm for the MCAs and between 8 and 9 cm for the basilar artery. A headband was used to immobilize the probe against the temporal window. Two experienced technicians (including I.C.B.) performed all studies, and any suspicious signals were saved manually. Two independent blinded observers (A.M.F. and S.K.) reviewed all studies.

The initial study on the day after trauma showed 14 MES per hour, with only 2 MES smaller than 12 dB. Daily
studies during the next 2 days demonstrated a similar pattern, with more than 80% of all emboli having an intensity of 12 dB or more. Percutaneous closure of the PFO eliminated all large emboli and decreased the embolic load, so that on day 8 only 1 MES per hour was detected. An increase in the number of emboli to 16 MES per hour was noted during femur surgery, of which 75% were smaller than 12 dB. Postoperative monitoring was continued for 72 hours, when only 1 MES per hour was found (Figure 4).

DETECTION OF RIGHT-TO-LEFT SHUNT

Nine milliliters of isotonic sodium chloride solution was vigorously mixed with 1 mL of air and injected into an antecubital vein, while 1 MCA was monitored. A second injection was performed with the patient performing a Val- salva maneuver 5 seconds after the injection. The study was considered positive with the appearance of embolic signals within 60 seconds of the injection (Figure 1C-E).

COMMENT

The clinical spectrum of the FES ranges from asymptomatic to fulminant cases.\(^2\)\(^,\)\(^6\) The incidence of FES after single long-bone fractures is estimated to be between 0.9% and 3%, even though fat globules can be detected in the venous blood of almost every patient with these fractures.\(^3\) The factors that determine the development and severity of FES remain incompletely understood.

The occurrence of fat microembolism has been solidly documented in vivo,\(^1\)\(^,\)\(^6\)\(^,\)\(^10\) and the prevailing theory in posttraumatic cases of FES proposes that damaged intramedullary veins allow the intravasation and subsequent embolism of marrow fat.\(^11\) Fat emboli are suspected to be able to modify their shape to reach the systemic circulation either through pulmonary capillary shunts or directly across the pulmonary-capillary bed.\(^12\)\(^-\)\(^14\) However, presence of a PFO has been shown to be responsible for the occurrence of paradoxic embolism in some patients with FES,\(^3\)\(^,\)\(^6\) and it may be associated with a worse outcome. By blocking the lumen of pulmonary capillaries, fat emboli could lead to an increase in right ventricular filling pressures, thereby favoring right-to-left shunting in patients with PFO.

Our patient presented with a typical clinical picture of posttraumatic FES. The elements of the diagnostic clinical triad were present: acute respiratory distress, petechiae, and signs of cerebral dysfunction. Embolus monitoring showed the presence of numerous MES in the absence of any evidence of deep venous thrombosis in the lower extremities. Magnetic resonance imaging of the brain showed multiple areas of abnormal diffusion suggesting acute ischemia distributed throughout watershed regions. This pattern of magnetic resonance imaging findings has been previously reported in patients with FES.\(^6\)\(^,\)\(^15\)\(^,\)\(^16\)

The embolic load and the intensity of the emboli as assessed by TCD were significantly reduced after our patient underwent successful percutaneous closure of her PFO, but the emboli did not disappear immediately, rising again during the surgical repair of the fracture (Figure 4). Our results suggest that the endovascular closure of the PFO stopped large emboli from being shunted through the heart, but small emboli continued to reach the brain (although in smaller numbers) for several days, possibly crossing through intrapulmonary shunts.\(^12\)\(^,\)\(^13\) Progressive clinical improvement followed this procedure, and subsequent surgical repair of her femoral fracture did not alter this favorable course.

Our case brings out issues with both clinical and pathophysiologic implications. Several aspects of the case reaffirm the concept of FES as a microembolic state.\(^3\) Microembolic signals were clearly demonstrated throughout the course of the disease and were maximal at the time of worst clinical status. Their clinical relevance was

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**Figure 3.** Brain magnetic resonance images showing fluid-attenuated inversion recovery signal changes in the deep anterior and posterior watershed areas (A and B) and abnormal diffusion on diffusion-weighted images (C and D).

**Figure 4.** Daily embolus detection monitoring demonstrating large emboli from the day of injury until patent foramen ovale (PFO) closure, with a small increase the day of femur surgery. Gray bars indicate emboli of 12 dB or more; black bars, emboli less than 12 dB. MES indicates microembolic signals.
further supported by the appearance in the magnetic resonance image of the brain of multiple areas of abnormal diffusion along the watershed distribution. Furthermore, after closure of the PFO, the reduction of MES reaching the systemic circulation was associated with a clear and persistent clinical improvement.

Presence of a PFO has previously been implicated as a poor prognostic factor in patients with FES. The severity of the clinical presentation in our case and the improvement after correction of the intracardiac shunt add further credence to this notion. The presence of a PFO allows the passage of larger and therefore more dangerous fat particles, as suggested by the MES detected before and after PFO closure in Figure 4. In fact, our decision to close the PFO in this case was based on the experience with a previous patient with FES and PFO who ultimately developed severe neurologic sequelae.

This case also illustrates the value of TCD monitoring and magnetic resonance imaging with diffusion-weighted images in the evaluation of patients with long-bone fractures and early neurologic symptoms. We believe that the presence of numerous and particularly of large MES as well as the evidence of areas of abnormal diffusion should prompt the search for a correctable intracardiac shunt, such as a PFO. This is especially important, since intraoperative monitoring with transesophageal echocardiography may detect fat embolism in approximately 40% of patients undergoing major orthopedic procedures, and intraoperative transesophageal echocardiography has been proposed as a useful diagnostic tool to monitor these patients.

The periprocedural complication rates of percutaneous PFO closure vary with the method and device used, and they have ranged between 0% and 10%. Complications may include damage to the peripheral vessels with ensuing retroperitoneal hematoma, perforation of the right atrium with pericardial tamponade, intra procedural stroke presumably due to air embolism, and embolization of the device. Success rates as defined by trivial or no residual shunt seen on echocardiography have ranged between 86% and 98%. Follow-up for up to 5 years showed an incidence of recurrent thromboembolic events of 3.2% to 3.4%, and these events were more frequent in cases of suboptimal closure. How this transcatheter percutaneous technique compares with surgical closure remains to be determined.

In summary, we present a provocative case of severe posttraumatic FES in a patient with PFO who was successfully treated by percutaneous closure of the intracardiac shunt. This case reaffirms that cerebral fat embolism after long-bone fractures can be detected in vivo and monitored over time with the use of TCD. If a PFO is present, its closure before the surgical manipulation of the fracture could have important protective effects against massive systemic embolization.

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