Transcranial Doppler Detection of Fat Emboli

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Background and Purpose—The fat embolism syndrome (FES) is characterized by the simultaneous occurrence of pulmonary and neurological symptoms as well as skin and mucosal petechiae in the setting of long-bone fractures or their surgical repair. Its pathophysiology is poorly understood, and effective treatments are lacking. We present 5 patients with long-bone fractures in whom in vivo microembolism was detected by transcranial Doppler.

Methods—Five patients with long-bone fractures were monitored with transcranial Doppler for microembolic signals (MESs) after trauma. Two patients also had intraoperative monitoring. A TC-2020 instrument equipped with MES detection software was used. Detected signals were saved for subsequent review. Selected signals satisfied criteria defined previously and were categorized as large or small.

Results—Cerebral microembolism was detected in all 5 patients and was transient, resolving within 4 days of injury. Intraoperative monitoring revealed an increase in MESs during intramedullary nail insertion. The characteristics of MESs after injury varied among patients, with large signals being more frequent in the only patient with a patent foramen ovale.

Conclusions—Cerebral microembolism after long-bone fractures can be detected in vivo and monitored over time. These findings may have potential diagnostic and therapeutic implications. (Stroke. 1999;30:2687-2691.)

Key Words: cerebral embolism ■ embolism, fat ■ trauma ■ ultrasonography, Doppler, transcranial

The fat embolism syndrome (FES) is characterized by the triad of dyspnea, brain dysfunction, and petechiae in the upper body and conjunctivae. Cerebral manifestations include encephalopathy, seizures, and focal neurological deficits.1 The syndrome usually follows long-bone fractures but has also been described in association with diabetes mellitus, pancreatitis, sickle cell disease, and other conditions.2,3 The incidence of FES after single long-bone fractures is estimated to be 0.5% to 3%, even though fat globules can be detected in the blood of almost all patients with fractures.4 Fat embolism, which is most commonly asymptomatic, therefore needs to be distinguished from the fat embolism syndrome, which consists of the symptomatic triad. Factors that determine the development of FES are poorly understood,5,6 and the broad ranges in severity and distribution of these brain lesions are only some of the areas in which questions remain unanswered.

The study of brain embolism has been greatly advanced with the advent of transcranial Doppler (TCD) with embolism monitoring (EM). Transient increases in the Doppler signal are termed microembolic signals (MESs) and are presumed to be caused by an embolus moving through the Doppler sample volume.7 We here describe 5 patients with long-bone fractures who were monitored for MES.

Subjects and Methods

TCD Testing

All TCD with EM tests were performed with a Nicolet Pioneer TC 2020 instrument equipped with microembolus-detection-monitoring software version 2.31, 256-point fast Fourier transform, with sample volumes of 10 mm. Each study lasted 30 minutes. A 2-MHz probe was used to insonate the right, left, or both middle cerebral arteries (MCAs) at a depth of 5.6 cm through the temporal window. In case 1, the basilar artery was insonated by use of an occipital approach. A headband was used to immobilize the probe against the temporal bone window. The same experienced technician performed all studies, and all suspicious signals were saved manually, as well as by the automatic detection software. Two independent blinded observers reviewed all studies. MESs were defined in accordance with the criteria established by the Consensus Committee of the Ninth International Cerebral Hemodynamic Symposium8 as signals that were unidirectional, >3 dB in intensity over background signal, <300 ms in duration, and accompanied by a characteristic chirping sound. Emboli are reported per 30 minutes of insonation. If both the left and right MCAs were insonated, an average for a 30-minute period was calculated. These counts were used to create Figure 3.

Each MES was further classified based on its intensity: those with an intensity of 12 dB or more were arbitrarily classified as “large” (Figure 1).

In cases 1 and 2, daily TCD studies were done; case 3 was studied at days 2, 5, 7, and 10; case 4 at days 3, 4, 5, and 6; and case 5 at days 2, 3, 4, 5, and 7. All patients were studied until no further MESs were detected.
All patients had an agitated saline TCD study with and without the Valsalva maneuver, with the exception of case 1, who could not cooperate with the Valsalva maneuver because of his neurological status. The procedure was performed in the following fashion: 1 mL of air was vigorously mixed with 9 mL of normal saline and injected into the antecubital vein. A Valsalva maneuver was started 5 seconds after the injection. The left MCA was then monitored for 60 seconds, and the appearance of 1 MES was considered to confirm the presence of a right-to-left shunt.

Case Reports

Case 1
A 49-year-old healthy male pedestrian was struck by a motor vehicle. No head injury was sustained. On arrival at the trauma center, his neurological examination was normal. Bilateral displaced fractures of the middle third tibial diaphysis with segmental fibular fractures were found. Cranial CT was normal. Nine hours after the accident, he had bilateral insertion of 10-mm-diameter unreamed, locked intramedullary tibial nails without complications. Twenty-two hours after the accident, the patient became unresponsive. He had normal blood pressure and was tachypneic and tachycardic, with a low-grade temperature. Deep tendon reflexes were normal in all 4 extremities, but both plantar responses were extensor responses. He had normal blood pressure and was tachypneic and tachycardic, with a low-grade temperature. Deep tendon reflexes were normal in all 4 extremities, but both plantar responses were extensor responses. Bilateral subconjunctival petechiae were noted. An arterial blood gas measurement taken while the patient was breathing room air showed pH 7.5, PCO$_2$ 34 mm Hg, and PO$_2$ of 54 mm Hg. Repeat cranial CT at that time showed bilateral occipital lobe hypodensities extending to the cerebral convexities. An extracranial vertebral and carotid duplex ultrasound study was normal. During a TCD examination 36 hours after trauma, multiple MESs were observed in the basilar artery and left MCA. The detection of MESs led to a further search for an embolic source: intravenous injection of agitated saline showed numerous MESs over both MCAs within seconds, which suggested the presence of a right-to-left shunt. A contrast enhanced transesophageal echocardiogram (TEE) confirmed a large patent foramen ovale (PFO). A duplex scan of the lower extremities, performed 72 hours after trauma, did not reveal deep venous thrombosis (DVT). A ventilation-perfusion pulmonary scan showed low probability for pulmonary embolism. MRI of the brain 3 days after the injury showed striking T2 and fluid attenuated-inversion recovery (FLAIR) signal hyperintensities in a watershed distribution (Figure 2). Forty-five days after the accident, the patient remained quadriplegic, followed simple commands, and was only able to say a few words.

The initial TCD with EM, performed 36 hours after trauma, showed 71 MESs during 30 minutes of insonation of the left MCA and 8 MESs during 10 minutes of insonation of the basilar artery. The right MCA was not monitored during that study. Thereafter, MESs were detected in both MCAs, and daily studies were obtained over the next 7 days, with an additional study performed on day 13 after the accident. Figure 3 shows the decay in the number of MESs over time.

Case 2
A healthy 26-year-old man was involved in a motor vehicle accident. No head trauma occurred, and the neurological examination was normal on his arrival at the emergency room. Brain CT was normal. Radiographic studies revealed a comminuted transverse fracture of the right mid-distal third of the tibial diaphysis with 50% lateral offset and a displaced fracture of the right fibular shaft at the same level. Forty hours after the accident, the patient became agitated and severely disoriented. Vital signs revealed a temperature of 39.8°C, blood pressure of 90/60 mm Hg, tachypnea, and regular tachycardia. Numerous petechiae were found in his axillae and conjunctivae. Funduscopic examination showed scattered soft retinal exudates. Neurological examination was remarkable for disorientation, agitation, and inability to follow commands. An arterial blood gas measurement taken while the patient was breathing room air showed pH 7.5, PCO$_2$ 26 mm Hg, and PO$_2$ 51 mm Hg. Blood cultures failed to show any growth after 5 days, and urinalysis results were normal, as was a chest radiograph. A duplex examination of the lower extremities did not reveal deep venous thrombosis (DVT).
extremities showed no evidence of DVT 48 hours after trauma. A noncontrast MRI of the brain was normal. A contrast-enhanced TEE and an agitated saline TCD study, both performed with and without the Valsalva maneuver, failed to show a PFO or other right-to-left shunt. Supplemental oxygen administration by face mask corrected the hypoxemia but failed to reverse the neurological symptoms. His course was one of gradual improvement, and his mental status cleared over the ensuing 48 hours. During this time, a transient fluent aphasia became apparent, which resolved within 24 hours. Eight days after the accident, an unreamed 9-mm-diameter locked tibial intramedullary nail was inserted without complications. Four days after surgery, the patient was discharged without neurological sequelae.

The first TCD with EM was obtained 48 hours after the accident. During the next 7 days, MESs persisted in both MCAs (Figure 3). On the eighth day, the fractures were corrected surgically under TCD monitoring. During the 2-hour 50-minute procedure, 36 MESs were detected in the left MCA. The right MCA was not monitored. The number of MESs was highest during the fracture-reduction (8/36) and nail-insertion (16/36) phases of surgery.

Case 3
A previously healthy 47-year-old woman was involved in a motor vehicle accident. No head injury occurred, and on arrival at the hospital, the neurological examination was normal. A brain CT was normal. A grade II liver laceration and fractures of the midshaft and diaphysis of the right femur, left tibial plateau, right ulna and radius, and the C5 and C6 vertebral bodies were diagnosed. A contrast CT of the chest was normal and showed no pulmonary contusions or aortic dissection. Twenty-four hours after the accident, she developed confusion and respiratory distress requiring endotracheal intubation. An arterial blood gas measurement taken while the patient was breathing supplemental oxygen through a face mask showed pH 7.34, PaCO₂ 39 mm Hg, and PaO₂ 39 mm Hg. Because the patient was at high risk for the development of DVT, and because it was believed that prophylactic antithrombotic medications were contraindicated in view of the liver laceration, a Greenfield filter was placed 48 hours after the accident. A venogram of the patient's inferior vena cava at that time showed no thrombosis. On the same day, a TCD with EM detected 13 MESs over the left MCA. Ten days after the accident, the patient was successfully weaned off ventilatory support, and her mental state improved. She was subsequently discharged to a rehabilitation facility. Three months after discharge, an outpatient contrast-enhanced TEE and agitated saline TCD, both performed with and without the Valsalva maneuver, failed to show a PFO or right-to-left shunt.

The first TCD with EM was performed shortly before surgery, 48 hours after the accident, and showed 13 MESs per 30 minutes over the left MCA. The right MCA was not monitored at that time. Repeat studies showed only 1 MES per 30 minutes of insonation on days 5 and 7 over both the right and left MCAs (Figure 3). Two days after the accident, this patient underwent closed reduction and intramedullary nailing of the right femur fracture, monitored intraoperatively with TCD. During this procedure, a total of 43 MESs were observed. The number of MESs was highest during fracture reduction (10/43) and nail insertion (22/43).

Case 4
A previously healthy 21-year-old man was involved in a motor vehicle accident. No head injury occurred, and the neurological examination performed in the emergency ward was normal. A cranial CT was normal. He was found to have a right comminuted midshaft femur fracture. He underwent an uncomplicated intramedullary femoral nail insertion on the day of the accident. Fourteen hours after surgery and 24 hours after trauma, he developed dyspnea, tachycardia, confusion, and a low-grade fever. An arterial blood gas examination with the patient breathing room air showed pH 7.5, PaCO₂ 31 mm Hg, and PaO₂ 34 mm Hg, with a blood O₂ saturation of 72%. A chest radiograph was normal. A ventilation-perfusion scan showed a low probability for pulmonary embolus, and a lower-extremity duplex scan done 72 hours after the accident was normal. The patient received oxygen via a face mask, and his arterial O₂ increased to 55 mm Hg without significant improvement of his mental status. Fat embolism was suspected. A TCD with EM showed MESs in both MCAs. The oxygen requirements decreased over the next 7 days, and he was discharged without any sequelae other than the femur fracture. An agitated saline TCD with and without the Valsalva maneuver performed 4 months later failed to reveal a right-to-left shunt.

Three days after injury, the first TCD with EM showed 1 MES over the left MCA and 1 MES over the right MCA. MESs continued to be detected up to day 5 (Figure 3).

Case 5
A 39-year-old healthy male pedestrian was hit by a car. No head injury was sustained, and a cranial CT was normal. Comminuted left midshaft tibial and fibular fractures were found. Three hours after the accident, he became confused and disoriented; the neurological examination was otherwise normal. The confusion was associated with a drop in arterial oxygen saturation from 95% to 85% as determined by pulse oximetry. A chest radiograph was normal. He was treated with supplemental oxygen, and his mental status returned to normal. On the next day, a TCD with EM showed multiple MESs. An agitated saline TCD, with and without the Valsalva maneuver, performed during this time showed no right-to-left shunt. Six days after the accident, an uncomplicated tibial intramedullary rod was placed. He was discharged 3 days after surgery.

The first TCD with EM was performed ≈48 hours after the accident and detected 10 MESs over the left MCA. One MES was detected on day 3 and none thereafter (Figure 3). The right MCA was not monitored at any time.

Results
MESs were detected in all 5 patients. In the first 4 cases, MESs were detected in both MCAs, and in case 1, MESs were also detected in the basilar artery. Case 5 was monitored only over the left MCA.

The amplitude of the MESs observed ranged from 6 to 22 dB, and their duration ranged from 6 to 48 ms. Sequential TCD studies showed MESs as early as 36 hours after a long-bone fracture, and microembolism persisted over a period of several days (Figure 3). No monitoring was performed during the first 36 hours. In each patient, however, a decaying effect was observed, with the disappearance of MESs within 4 days of injury or surgery. When all 149 MESs

Figure 3. The relation between number of MESs and days after trauma is depicted, as well as the day of surgery. All cases were studied 2 days after injury, except for case 1, who was studied at 36 hours.
from the 5 patients were considered together, 131 (87.9%) were observed in the first 3 days after injury. Case 2 was the exception, with persistent embolism until 10 days after trauma; surgery was delayed until the eighth day after his injury.

In the only patient with a PFO (case 1), 96 (95%) of 101 MESs observed during the first 3 days after trauma were classified as large. Only 11 (37%) of 30 MESs observed in the same period in all other patients (without PFO) met the criterion for large MESs ($\chi^2 = 52.685, P=0.001$).

**Discussion**

FES has been referred to as a “microembolic state.” In patients who die of complications of FES, diffuse petechiae are seen on gross examination of the brain, particularly in the white matter; these are hemorrhagic microinfarcts caused by small vessel occlusions from fat emboli. Our finding of in vivo cerebral microembolism in all 5 monitored patients shows that this is a very common phenomenon after long-bone fractures and provides insight as to how the microembolic state may develop.

Although all 5 patients studied had ultrasonic evidence of microembolism, only cases 1, 2, 3, and 4 satisfied the classic clinical criteria for FES. In case 5, the neurological symptoms were associated with hypoxemia. Transient hypoxemia not necessarily leading to complete FES is frequently observed after long-bone fractures, and its causes are not fully understood, although a similar pathophysiology to that of FES is the accepted explanation.

In vivo detection of fat emboli has been reported previously. Kelly and colleagues used Doppler ultrasonography to monitor the ipsilateral femoral vein in 42 patients with long-bone fractures; FES subsequently developed in 8 of 12 patients with and in only 4 of 30 without emboli. Gurd showed that fat globules can be detected in venous blood immediately after a long-bone fracture and that they disappear from the peripheral circulation 48 hours after trauma. A second wave of fat emboli was detected ~35 hours after injury in patients who developed FES. Our data suggest that embolism is a more continuous process and that its course extends up to 96 hours after injury. This discrepancy between our findings and those of previous studies may be explained by the different techniques used in the detection of emboli. Ultrasound monitoring appears to be more sensitive than spot venous blood analysis, because a larger volume of blood is surveyed over a longer period of time. However, not all of our patients were studied with TCD on a daily basis, and an undetected surge in microembolism on days on which no study was performed cannot be excluded.

Surgery for fracture repair is also associated with fat migration into the blood stream. During hip-replacement surgery, Herndon and colleagues used Doppler ultrasound to monitor the common femoral vein of the leg that was being operated on. Emboli were consistently detected, and specific surgical stages were associated with high embolic loads, which suggests that modifications of the surgical procedure might decrease the number of MESs recorded. Edmonds et al detected cerebral emboli by TCD during total hip arthroplasty in 40% of their patients. Our limited experience monitoring 2 patients during surgery suggests that intramedullary nail insertion is associated with a particularly large release of fat globules.

Intraoperative monitoring with TEE during fracture reduction has shown that emboli as large as 7 cm can pass through a PFO into the systemic circulation; the presence of a PFO may be associated with a worse prognosis because more (and presumably larger) fat particles enter the arterial system. Our findings support this hypothesis, and we propose that the difference in the characteristics of cerebral microembolism and the clinical manifestations of FES between our patients may be related to the presence of a PFO. Larger and more numerous MESs were observed in the only patient with a PFO, which possibly explains the severity of the neurological deficits. However, this patient also had more fractures, which has been associated with a higher incidence and more severe manifestations of FES. In addition, he was studied 12 hours earlier than the other cases, and this may have had an influence on the size and number of microemboli detected.

The brain MRI of this patient (Figure 2) revealed extensive signal abnormalities in the watershed areas. Similar MRI findings have been described recently in FES and in other states of diffuse microembolism, such as atheromatous embolic showers.

The presence of a PFO in case 1 raises the possibility of paradoxical embolism with particles different from fat. Nicholls et al described the detection of embolic signals in lower-extremity veins of patients with DVT. Although the presence of a DVT in our case 1 could have led to a mistaken identification of fibrin and platelet emboli, erroneously considered by us to be fat emboli, our case 1 had a normal lower-extremity duplex ultrasound examination 72 hours after injury, and it was precisely at this time that he exhibited the highest MES counts. Nicholls et al also noted that if a venous lower-extremity duplex ultrasound examination is negative, the likelihood of finding venous emboli is only 3%. In the rest of our patients, a right-to-left shunt was excluded, which makes paradoxical embolism unlikely.

How did the fatty emboli actually reach the brain? Fatty emboli are thought to be able to change their shape and traverse the pulmonary vasculature to reach the systemic circulation. In addition, in patients with FES, histological brain sections have predominantly shown fat globules and have shown fibrin and leukocyte emboli only in a minority of lesions.

Trauma patients frequently develop alterations in mental status. Cerebral contusion and metabolic derangements may be present simultaneously in this setting and may confuse the clinical picture. Embolus monitoring by TCD after long-bone fractures may serve as a diagnostic tool in the evaluation of these patients. Identification of microemboli after long-bone fractures may also be of prognostic value as a predictor of the development of FES. At present, such prediction has not been reliable by other methods. In support of this, the presence of fat globules in peripheral blood is an almost universal phenomenon, present in patients with long-bone fractures even without FES. Similarly, urinary detection of fat globules and the presence of fatty droplets in bronchoalveolar
lavage samples are too nonspecific to be of diagnostic value in FES.\textsuperscript{21,22}

In addition, intraoperative monitoring with TCD may identify particularly emboligenic surgical maneuvers. This may lead to modification of surgical technique, as has already occurred in cardiopulmonary bypass and carotid endarterectomy.\textsuperscript{23,24}

In summary, this is the first description of brain microembolism detected by TCD after long-bone fractures and in the FES itself. Our study shows that cerebral microembolism occurring in this context can be detected in vivo and monitored over time. Furthermore, a time decay of the phenomenon of brain microembolism was observed, with more microemboli detected closer to the time of trauma. A relation between the presence of a PFO and the development of worse brain injury in the FES is suggested.

References
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Stroke. 1999;30:2687-2691
doi: 10.1161/01.STR.30.12.2687

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