Transcranial Doppler Detection of Cerebral Fat Emboli and Relation to Paradoxical Embolism
A Pilot Study

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Background—The fat embolism syndrome is clinically characterized by dyspnea, skin petechiae, and neurological dysfunction. It is associated mainly with long bone fracture and bone marrow fat passage to the systemic circulation. An intracardiac right-to-left shunt (RLS) could allow larger fat particles to reach the systemic circulation. Transcranial Doppler can be a useful tool to detect both RLS and the fat particles reaching the brain.

Methods and Results—We prospectively studied patients with femur shaft fracture with RLS evaluation, daily transcranial Doppler with embolus detection studies, and neurological examinations to evaluate the relation of RLS and microembolic signals to the development of fat embolism syndrome. Forty-two patients were included; 14 had an RLS detected. Seven patients developed neurological symptoms; all of them had a positive RLS (P<0.001). The patients with an RLS showed higher counts and higher intensities of microembolic signals (P<0.05 and P<0.01, respectively) compared with those who did not have an RLS identified. The presence of high microembolic signal counts and intensities in patients with RLS was strongly predictive of the occurrence of neurological symptoms (odds ratio, 204; 95% confidence interval, 11 to 3724; P<0.001) with a positive predictive value of 86% and negative predictive value of 97%.

Conclusions—In patients with long bone fractures, the presence of an RLS is associated with larger and more frequent microembolic signals to the brain detected by transcranial Doppler study and can predict the development of neurological symptoms. (Circulation. 2011;123:1947-1952.)

Key Words: embolism ■ embolism, fat ■ foramen ovale, patent ■ stroke ■ ultrasonography, Doppler, transcranial

The fat embolism syndrome (FES) is characterized by the clinical triad of skin and mucosal petechiae, neurological dysfunction (generally, but not always, encephalopathy), and pulmonary involvement (primarily hypoxemia). Typically, it occurs shortly after long bone fractures, but it has also been described in other settings.2–4 The incidence varies from 0% to 10%, depending on the type of fracture, treatment, and diagnostic method.5–7 Recognized risk factors for the development of FES include a larger number of long bone fractures, femoral shaft fractures, concomitant head injury, intraoperative reaming of the femoral canal, and multiple trauma with blood loss.8–10

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The origin remains uncertain. One of the theories is purely mechanical and was first mentioned in 1873 with one of the earliest reports of FES in humans; the idea was that obstruction of blood flow by embolic material caused the symptoms.11 Another theory considers biochemical changes (free fatty acid peroxidation and release of inflammatory mediators) as causative.12–14 Evaluating brain flow in patients with the syndrome can contribute to a better understanding of this condition.

Transcranial Doppler (TCD) sonography provides a unique diagnostic and monitoring tool, given its capability of detecting particulate and gaseous emboli in real time and in a noninvasive manner.15,16 It also allows the diagnosis of right-to-left shunts (RLSs) with high sensitivity.17

We prospectively studied 42 patients hospitalized with at least I femoral shaft fracture. An RLS-TCD evaluation, daily TCD–embolus detection studies (EDS), and daily neurological examinations were performed to evaluate the relation of RLS and microembolic signals (MESs) to the development of FES.

Methods

All patients who presented to the Ryder Trauma Center at the Jackson Memorial Hospital within 48 hours of the onset of a traumatic femoral shaft fracture were eligible to enter the study.

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Written informed consent was obtained before enrollment. The study design and consent forms were approved by our institutional review board. Patients were excluded if any of the following criteria were present at the time of enrollment: inability to provide informed consent, Glasgow Coma Scale score <12 at the time of arrival at the emergency department, any abnormality on brain computed tomography, and pulmonary contusion on admission chest x-ray or computed tomography scan. Further exclusion criteria included coexisting microembolic sources, such as arterial dissection, known atherosclerotic cerebrovascular disease, current atrial fibrillation, or history of valvular heart disease or cardiomyopathy. The development of deep vein thrombosis, pulmonary thromboembolism, or need for abdominal or chest surgery at any time during hospitalization also resulted in the exclusion of study participants.

All patients were monitored daily for the presence of MES with TCD-EDS until discharge. The first TCD was performed within 48 hours of the trauma and included monitoring of both middle cerebral arteries (MCAs). The highest number of MES was monitored daily for 60 minutes until the extinction of all MESs. All patients had an agitated air-saline contrast TCD study with and without a Valsalva maneuver within 72 hours of fracture to determine whether an RLS was present.

Study participants were screened daily for the occurrence of neurological and pulmonary dysfunction. Two scales were used to assess neurological impairment: the National Institutes of Health Stroke Scale and Mini-Mental State Examination. Baseline tests were administered within 48 hours of admission and repeated daily until discharge. Daily examinations were performed by a neurologist blinded to the TCD findings, including the presence of RLS. Neurological impairment was defined as a drop of ≥2 points on the National Institutes of Health Stroke Scale or Mini-Mental State Examination in the absence of other obvious causes that could account for the neurological decline such as new or worsening sepsis, sedative effects, or endocrine or electrolyte imbalances.

All patients were treated according to standard protocol in terms of respiratory function. Monitoring was performed clinically, and through either arterial blood gas sampling or continuous pulse oximetry. Respiratory dysfunction was defined as sudden or worsening dyspnea with an alveolar oxygen/arterial oxygen pressure gradient >20 mm Hg in the absence of other respiratory disorders that could explain these findings, such as pneumonia, adult respiratory distress syndrome, or pulmonary edema. A lower-extremity venous Duplex was performed in all patients during the course of hospitalization to rule out deep vein thrombosis as a source of paradoxical embolism.

All patients were monitored intraoperatively for MES with TCD-EDS. All patients were initially placed in skeletal traction until the time of definitive surgery. Reamed, locked intramedullary nails were inserted with both antegrade and retrograde techniques. The medul-

ary canal werereamed 1.5 mm larger than the chosen nail. Venting of the medullary canal was not used. The preoperative intensity and frequency are an average of the intensity and frequency before surgery. Postoperative intensity and frequency are expressed as averages obtained 24 hours after surgery.

Transcranial Doppler: Technical Notes

All TCD studies were performed with a Nicolet Pioneer TC 4040 instrument equipped with microembolus detection monitoring software version 2.31 and 256-point fast Fourier transform with sample volumes of 10 mm. A 2-MHz probe was used to insonate the MCAs at a depth of 5.6 cm through the temporal window, fixed with a headband. The basilar artery was insonated transorally at a depth of 8 cm. The same experienced technician performed all studies, and all suspicious signals were saved manually and by the automatic detection software. All studies were reviewed by 2 observers, 1 blinded to the participant’s clinical course and the presence of an RLS. When there was disagreement between readers on the character of the suspicious signal, it was discarded as artifactual, leaving only the signals with 100% agreement for analysis.

Microembolic signals were defined in accordance with modified criteria established by the Consensus Committee as signals that were unidirectional, >6 dB in intensity over background signal, <300 milliseconds in duration, and accompanied by a characteristic chirping sound. A threshold of 6 rather than 3 dB was chosen to increase the sensitivity of microembolus detection and to explore whether this threshold could be appropriate or clinically relevant in the context of TES. The number of MESs per hour of insonation was recorded for all studies. Additionally, the intensity of all MESs was measured by calculating the difference of the average background signal intensity and the maximal intensity of the MES, as determined by visual inspection of the Doppler spectrum.

Agitated air-saline contrast TCD studies with and without a Valsalva maneuver were performed as follows: 1 mL air was vigorously mixed with 9 mL normal saline and injected into the antecubital vein under TCD monitoring of either MCA for 60 seconds. The appearance of MESs during the first 60 seconds in the insonated MCA territory after contrast injection was considered confirmatory of the presence of an RLS, as recommended elsewhere. If the initial study was negative for the presence of an RLS, the procedure was repeated with a Valsalva maneuver started 5 seconds after contrast injection with monitoring of the MCA for 60 seconds.

Statistical Analysis

The statistical analyses of the continuous variables MESs per hour and MESs were performed with repeated measures ANOVA using the SAS procedure PROC MIXED for a random-effects model. The procedures for deciding which covariance structure to use and whether the repeated measures ANOVA model in PROC MIXED was appropriate were patterned on the material presented by Littell et al. Group comparisons were done using PROC MIXED with 1 repeated measure (day of observation) and 1 random effect (subject). Group differences were then compared within each day using the ESTIMATE procedure within PROC MIXED. The within-day comparisons were based on the Fisher least-significant-difference test. The least significant difference can be applied only when the omnibus F test is significant and is used to find the 1 or more pairs already known to be significant by the overall F test. The experiment-wise error rate is control by the F test. In the Discussion, we also refer to comparisons corrected by the Dunn procedure (Bonferroni adjustment) because this is a very popular approach, but inferences are based on the least-significant-difference comparisons. Other continuous variables were compared by use of the Student t test for independent samples. Categorical variables were analyzed with the χ² test, and predictive markers were analyzed with Mantel-Haenszel stratified odds ratio analyses. The statistical significance was set at P<0.05. The senior author (R.D.) conducted the statistical analyses.

Results

Forty-seven patients met our inclusion criteria. Five patients were subsequently excluded because of documented deep venous thrombosis (n = 3), pulmonary embolism (n = 1), and delayed appearance of subarachnoid hemorrhage in a follow-up computed tomography scan of the brain (n = 1). The final study population consisted of 42 patients. The mean age of the study participants was 29 years (range, 17 to 51 years), and 76% were men. Twenty-eight patients (67%) had isolated unilateral femoral fractures, whereas multiple fractures were present in 14 patients (33%). Femoral fractures were open in 5 patients (12%). The mean Glasgow Coma Scale score was 14.8 (range, 12 to 15), with 37 patients (88%) having a sum score of 15 at the time of admission.

The first TCD-EDS was performed within 24 hours of trauma in 30 patients (71%) and between 24 and 48 hours in 12 patients (29%). The mean number of TCD studies per-
formed during the hospitalization was 6 (range, 3 to 12). All patients had MESs detected in at least 1 study. Agitated air-saline contrast TCD was performed in all cases, and an RLS was detected in 14 patients (33%).

Table 1 summarizes the relationship between the presence of an RLS and the occurrence of pulmonary and neurological symptoms. Twenty patients (48%) developed pulmonary symptoms; 9 had an RLS (odds ratio, 2.78; 95% confidence interval, 0.74 to 10.5; \( P = 0.13 \)). Seven patients (17%) developed neurological dysfunction, and all of these patients had an RLS. The presence of an RLS was significantly associated with the occurrence of neurological symptoms \( (P < 0.001) \). All 7 patients with neurological dysfunction had at least a 2-point drop in the Mini-Mental State Examination; 2 patients also had a drop in the National Institutes of Health Stroke Scale of >2 points associated with focal signs.

The number of MESs detected in each EDS was tabulated. In all patients, the average number of MES decreased over time. Examination of the data indicated that the AR1 covariance structure was appropriate for all analyses with PROC MIXED. Patients with an RLS had significantly higher mean MES counts compared with the patients without an RLS \( (P = 0.0018) \). As shown in Figure 1 the differences between groups were also significant over the first 3 days when compared by the least significant difference \( (P < 0.05) \). (These differences were also each statistically significant at \( \alpha = 0.007 \) using the Bonferroni adjustment for 7 comparisons, except at day 3, at \( P = 0.0230 \).) The intensity of MESs on every EDS was also quantified. With all preoperative EDS included, the median maximal intensity of MES was 13 dB. The intensity of MES also showed a decreasing trend over time in all patients. MESs were significantly more intense overall in patients with an RLS and neurological symptoms compared with patients without neurological symptoms or an RLS \( (P < 0.001) \). This difference remained significant throughout the entire study period by both least-significant-difference and Bonferroni-adjusted comparisons (Figure 2).

Microembolic signals were detected intraoperatively in all but 2 patients, and 2 patients had MESs only during surgery. Both the number and intensity of MESs were greater during surgery than either before or after the intervention (Table 2). However, the difference reached statistical significance only for MES intensity \( (P < 0.05) \). Patients with an RLS had significantly more MESs detected during intraoperative monitoring \( (P = 0.03) \). Although the frequency of the MES was also greater among patients with an RLS, the difference was not significant.

The data were analyzed to identify predictive markers for the development of neurological symptoms. The rationale for this approach is to monitor patients before and on the day of the operation (ie, preoperatively) for patent foramen ovale (PFO), emboli, and size of the emboli (decibels). We found that the joint presence of high maximal posttraumatic MES counts (ie, >4 MESs per hour) and high maximal posttraumatic MES intensity (ie, >13 dB) in patients with an RLS was predictive of the occurrence of neurological symptoms (odds ratio, 204; 95% confidence interval, 11 to 3724; \( P < 0.001 \), Mantel-Haenszel \( \chi^2 \)). The presence of the combination of findings (presence of an RLS, high embolic counts, and high intensity) had a positive predictive value of 86% for the development of neurological manifestations, whereas their absence had a negative predictive value of 97%. When the analysis was restricted to patients with an RLS, the presence of high preoperative MES counts and high preoperative MES intensity remained predictive of the occurrence of neurological symptoms (odds ratio, 36; 95% confidence interval, 2 to 718; \( P = 0.01 \), Mantel-Haenszel \( \chi^2 \)).

**Discussion**

All our patients with femoral shaft fractures had MESs detected by TCD regardless of whether they developed symptoms of the
FES triad. Therefore, the mere detection of MESs in the brain arteries after a femoral fracture seems to be a very common phenomenon, and does not predict the occurrence of clinical manifestations of FES. However, the presence of an RLS (likely representing a PFO) detected by TCD, the embolic count, and the intensity of the emboli over time did predict which patients would develop neurological dysfunction. In fact, all patients who developed neurological dysfunction had an RLS, and no patient without an RLS developed neurological dysfunction. The lack of transesophageal echocardiogram confirmation of the PFO raises doubts, but TCD-RLS has shown a sensitivity and specificity comparable to transesophageal echocardiogram\(^9\),\(^{21}\)\(^{,}\)\(^{22}\) and has the advantage of being less invasive, especially in unstable patients.

Supporting our findings, previous reports have associated PFOs with neurological dysfunction in FES.\(^{11,\,23\, -\, 27}\) However, FES can occur without a PFO, as previously reported by us and others.\(^{11,\,24\, ,\, 28\, ,\, 29}\) This could mean that another mechanism must be involved in the pathophysiology of FES besides paradoxical embolism through a PFO. Our findings suggest that patients with an RLS may have more frequent and severe neurological symptoms than those without an RLS, but this possibility needs to be confirmed in future studies.

The intensity and number of the MESs were higher in patients with an RLS. Higher MES intensity and higher loads were significantly associated with the development of neurological dysfunction. The intensity stratification in Figure 2 suggests a dose-response effect for the development of neurological symptoms. The presence of MESs of \(>13\) dB, a frequency of \(>4\) per hour, and an RLS was a very good predictor of development of neurological symptoms, with a very strong negative predictive value and a good positive predictive value. The relationship of larger and higher loads of MESs with RLS was preserved during the follow-up. The \(5\) dB threshold chosen to capture significant signals was determined in part on the basis of previous results that considered that MESs \(>5\) dB are likely to be solid instead of gaseous, and the suggestion that the intensity of the MES is disease specific. We wanted to explore this particular value of \(5\) dB in the context of MESs.\(^{30\, -\, 32}\) Our results suggest that in the context of FES, the threshold can be set to \(9\) dB without increasing the false-negative rate.

Higher MESs were also detected during the fracture repair, suggesting increased MES load when the injured bones are manipulated. The association of higher MES during the surgical intervention to repair fractures has been documented in other studies.\(^{8\, ,\, 15}\) Because different surgical techniques exist, depending on the type and extent of fracture, and we did not control them systematically, our study is limited in the scope of conclusions in terms of differences among techniques and fractures with the amount of MESs observed.

Our study has several limitations. The lack of neuroimaging, such as magnetic resonance imaging, could potentially introduce attribution bias. Nevertheless, the probability of bias is likely to be low, because only 2 neurologically impaired patients developed focal findings. The exclusion of other causes of encephalopathy, such as metabolic insults, an initial unenhanced brain computed tomography, and the baseline normal Glasgow Coma Scale argue against pretraumatic or posttraumatic secondary causes of encephalopathy. The second limitation refers to the lack of validation of either the National Institutes of Health Stroke Scale or the Mini-Mental State Examination in the context of FES. Both scales have been used to quantify focal neurological symptoms and cognitive decline, respectively. The fact that the Mini-Mental State Examination was abnormal in all patients with neurological symptoms is likely related to its sensitivity to detect global cerebral dysfunction, typical of the FES. Finally, the presence of RLS in our group is somehow higher than in previous population-based studies.\(^{33\, ,\, 34}\) However, we believe that the transpulmonary shunting could account for a proportion of the RLS and that the younger and male-predominant population studied in our cohort is expected to have a higher prevalence of PFO.

Our results are in line with previous data derived from animal and human models. It has been shown that the first event in FES is the lodging of fat particles in the lung with a transient increase in pulmonary artery pressure.\(^{35\, -\, 39}\) This transient pulmonary hypertension opens arteriovenous shunts that allow fat particles to bypass the lungs and disseminate systemically.\(^{38}\) In our cohort, all patients had MESs, regardless of the presence of an RLS. The smaller fat droplets could have bypassed the lung by arteriovenous shunts, or as demonstrated elegantly by Byrick et al,\(^{39}\) the fat particle can deform to cross through the arterioles and capillaries themselves, then reaching the systemic circulation. The small fat particles reaching the brain are less likely to cause neurological symptoms, as shown by our results.

Because the classic triad of pulmonary distress, mental status changes, and petechial rash is most frequently incomplete, and might take 24 to 48 hours to develop, TCD constitutes an important tool for early diagnosis and early intensive management. Moreover, in our study, TCD-EDS predicted neurological dysfunction in still-asymptomatic pa-

### Table 2. Characteristics of Microembolic Signals Before, During, and After Surgery for Femoral Fracture

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Preoperative</th>
<th>Intraoperative</th>
<th>Postoperative</th>
<th>Preoperative</th>
<th>Intraoperative</th>
<th>Postoperative</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n=42)</td>
<td>2.6±0.48</td>
<td>3.5±0.69</td>
<td>3.1±0.98</td>
<td>8.0±0.85</td>
<td>11.5±1.10</td>
<td>8.1±0.98</td>
</tr>
<tr>
<td>RLS absent (n=28)</td>
<td>1.6±0.33</td>
<td>2.1±0.37</td>
<td>3.1±1.46</td>
<td>7.0±0.95</td>
<td>11.1±1.07</td>
<td>7.6±1.39</td>
</tr>
<tr>
<td>RLS present (n=14)</td>
<td>4.5±1.15</td>
<td>6.3±1.74</td>
<td>3.1±0.49</td>
<td>10.0±1.62</td>
<td>12.5±2.56</td>
<td>8.9±0.95</td>
</tr>
<tr>
<td>RLS present and ND (n=7)</td>
<td>6.6±1.91</td>
<td>7.5±2.72</td>
<td>3.3±0.87</td>
<td>12.7±2.08</td>
<td>14.2±4.96</td>
<td>8.6±1.65</td>
</tr>
<tr>
<td>RLS present without ND (n=7)</td>
<td>2.4±0.78</td>
<td>5.1±2.31</td>
<td>3.0±0.53</td>
<td>7.3±2.13</td>
<td>10.8±1.64</td>
<td>9.3±1.07</td>
</tr>
</tbody>
</table>

MES indicates microembolic signal; RLS, right-to-left shunt; and ND, neurological dysfunction.
tients, raising the potential role for early PFO closure, especially if large fat embolisms are detected. Several therapeutic attempts have been attempted to modify the natural history of FES with only modest results and no clear benefit. With earlier detection of the syndrome by TCD, treatment could possibly be started quicker. Mechanical attempts to decrease the load and intensity of emboli (early surgery and/or PFO closure) and medications to suppress the prominent inflammatory response may prevent damage if started early.

Our present results strongly support a role for PFOs in facilitating brain injury in the FES. In a previous report, our group was unable to establish such a role in an elderly population of patients undergoing joint replacement surgery. The reasons for the discrepancy are likely multiple and related to different age group, different mechanisms causing the bone trauma, and the much longer and larger exposure time/load to fatty brain embolism in patients with acute fractures than in scheduled surgeries.

If our findings are confirmed, they would strengthen the body of evidence associating paradoxical embolism after bone fracture with neurological dysfunction. The potential for changes in the standard of care of patients with long bone fractures is substantial.

Conclusions
From these findings, we suggest that TCD shunt/EDS demonstrating an RLS and high loads and/or intensity should be used as a screening test and as a predictor of increased risk of developing FES with neurological dysfunction in patients with long bone fractures. Early surgical correction seems reasonable. Preoperative PFO closure could be further investigated.

Disclosures
None.

References
5. Assal M, Zanone X, Peter RE. Osteosynthesis of metastatic lesions of the bone fracture with neurological dysfunction. The potential for acute fractures than in scheduled surgeries. Early surgical correction seems reasonable. Preoperative PFO closure could be further investigated.

None.

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Fat Embolism Syndrome Associated With PFO
1951

degree of lung dysfunction after femoral nailing following severe trauma?

**CLINICAL PERSPECTIVE**

The fat embolism syndrome is a relatively common complication of long bone fractures. The classic triad of the syndrome includes petechiae, respiratory distress, and neurological dysfunction in the absence of other alternative explanations. The origin of the syndrome is related to the embolization of particulate matter, probably bone marrow, to different organs like skin, lungs, and brain. The risk factors to develop this syndrome are not yet clearly defined. In theory, the presence of an intracardiac right-to-left shunt (RLS), for example, a patent foramen ovale, can allow larger particles to bypass the lung and reach the brain. In an observational prospective study using transcranial Doppler, we observed that patients with long femoral fractures and intracardiac RLS were more likely to develop fat embolism syndrome compared with those without the RLS. The size and frequency of microembolic signals also predicted the occurrence of fat embolism syndrome in the context of RLS. Additionally, we monitored the patients intraoperatively, observing that during the surgical manipulation of the bones, there was an increase in the number and size of the microembolic signals. The clinical implications of the study are enormous if our findings are confirmed. The relatively easy identification of RLS with transcranial Doppler in the emergency room for patients with long bone fractures could become routine. In those in whom the RLS is identified, alternatives like closure of the RLS before surgery could be a potential treatment that needs to be explored with clinical trials.
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