Paradoxical Embolism*  
An Underrecognized Problem

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Despite reports of the clinical presentations and devastating consequences of paradoxical embolus (PDE) for more than a century, this diagnosis continues to be frequently missed. Because the prevalence of patent foramen ovale (PFO) is 27 to 35% in the normal population and the presence of deep vein thrombosis or pulmonary embolus may not be clinically obvious, a high suspicion for PDE is needed in the event of unexplained arterial occlusion. While contrast echocardiography and transesophageal Doppler ultrasound have facilitated clinical recognition of PDE, the optimum approach to diagnosis requires clarification. Primary therapy for patients with PDE is anticoagulation, with thrombolytics considered in carefully selected individuals, but there is little published information regarding long-term treatment and outcomes. Prevention remains essential whenever possible. It is not yet defined whether prophylactic treatment of persons with recognized predispositions to PDE (eg, PFO and pulmonary hypertension) is beneficial.

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Key words: cryptogenic stroke; paradoxical embolus; patent foramen ovale; pulmonary embolus; transcranial Doppler; transesophageal echocardiogram

First described by Cohnheim1 in 1877, paradoxical embolism (PDE) was defined as a venous thrombosis causing systemic embolization through a right-to-left shunt. Multiple autopsy-proven cases were described in the French and German literature until 1930 when two patients diagnosed during life were reported.2,3 Since then, over 170 cases have been reported,4-13 with increasing numbers recognized antemortem.5,7,9-17 Recent investigations of patients with peripheral and cerebral arterial emboli of unknown cause suggest that PDE is a potentially treatable problem that occurs more often than usual. We report four patients with PDE, two of whom were diagnosed antemortem, and review the literature.

Case Reports

Case 1

A 30-year-old woman (gravida 2, para 1) was hospitalized while in labor at 40 weeks’ gestation. During delivery, she became cyanotic, apneic, and pulseless. Cardiopulmonary resuscitation was begun and an endotracheal tube was inserted. A viable 9 lb 10 oz infant was delivered via forceps. The patient developed ventricular fibrillation and underwent defibrillation with conversion to sinus rhythm but remained hypotensive. Arterial blood gas values demonstrated a profoundly increased alveolar-arterial O₂ pressure difference with a pH of 7.40, PaCO₂ of 9 mm Hg, and PaO₂ of 168 mm Hg while breathing 100% O₂. Initial chest roentgenogram (CXR) was normal and ECG revealed S-T segment elevation in anterolateral leads. Laboratory studies included a platelet count of 81,000/mm³ and prolonged prothrombin and partial thromboplastin times. A transesophageal echocardiogram (TTE) showed increased echogenicity in the inferior vena cava (IVC) and right atrium (RA), which was believed to represent thrombus, and the patient received thrombolytic therapy.

On transfer to our center the patient remained hypotensive, with persistent coagulopathy, bleeding, and ECG changes. An intraaortic balloon pump was inserted, and cardiac catheterization showed occlusion of the left anterior descending coronary artery. Left ventricular function was reduced and there was no evident thrombus. Coagulopathy and shock continued despite maximal support and the patient died. At autopsy,18 a cervical tear and disrupted muscular wall were found. No atrial or coronary thrombi were seen, but cardiac examination showed necrotic myocardium in the anterior left ventricular wall. The microvasculature in this region and both lungs contained scattered squamous cells consistent with amniotic fluid emboli (AFE) (Fig 1). A pencil-thick 0.8-cm patent foramen ovale (PFO) was found (Fig 2).

Case 2

A 49-year-old woman presented with a pulseless, cold left hand 10 days after open reduction of a left tibia-fibula fracture. She underwent thrombectomy of the left brachial and axillary arteries. The TTE suggested a left atrial thrombus. After heparinization, the patient was transferred to our ICU with an enlarging hematoma of the left arm. Physical examination revealed stable vital signs, a medial incision of the left upper extremity with a large hematoma and a left median nerve palsy. Irrigation and debridement of the arm were performed and anticoagulation was continued. Transesophageal echocardiogram (TEE) with saline infusion revealed a PFO with right-to-left shunt, but no intraatrial thrombus (Fig 3). Lower extremity duplex Doppler showed no deep vein thrombosis (DVT). On the third postoperative day, the patient developed hypoxemia and left-sided pleurisy. Arterial blood gas determination revealed a PaO₂ of 67 mm Hg (FIO₂, 0.6). The CXR showed basilar atelecta-

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sis, and a ventilation perfusion lung scan was indeterminate. Pulmonary arteriogram demonstrated multiple bilateral pulmonary emboli (PEs) and elevated pulmonary artery pressures (PAPs) (50/19 mm Hg). An inferior vena cavagram was performed, a “bird’s nest” filter was inserted and the patient recovered uneventfully. After 1 week, duplex Doppler studies remained negative, and she was discharged on a regimen of warfarin therapy.

Case 3

A 53-year-old woman with hypertension and obesity with acute respiratory failure was transferred to our institution. She had been hospitalized for 11 days previously with right upper lobe pneumonia and now had vomiting and headache and had trouble keeping her balance. In the emergency room, she developed a left hemiparesis and right facial droop, became progressively dyspneic, and was intubated. Arterial blood gas determination revealed a pH of 7.47, PaCO\(_2\) of 42 mm Hg, PaO\(_2\) of 29 mm Hg while breathing room air, and after intubation fraction of inspired oxygen (FI\(_{\text{O}}\)\(_2\)) 1.0; positive end-expiratory pressure, 10 cm H\(_2\)O, a pH of 7.58, PaCO\(_2\) of 29 mm Hg, and a PaO\(_2\) of 31 mm Hg.

At transfer, examination revealed a blood pressure of 132/65 mm Hg, constricted, reactive pupils, and no papilledema. There were faint bilateral wheezes. The heart had a regular rate and rhythm with a 3/6 systolic murmur along the left sternal border. The patient moved all extremities spontaneously and withdrew extremities when pain stimulus was induced. The ECG showed anteroseptal myocardial ischemia or possible right ventricular strain, and CXR revealed minimal right mid-lung atelectasis. Massive PE was suspected, but anticoagulants were not administered because of neurologic changes. Cranial CT confirmed a large right parieto-occipital, hypodense area adjacent to the atrium of the right ventricle (RV), mass effect, and associated edema. Lumbar puncture showed no infection or bleeding. The TTE revealed an ejection fraction of 60%, RV volume and pressure overload with enlarged RV and RA, paradoxical septal movement, and tricuspid regurgitation, but an atrial septal defect (ASD) could not be excluded. There were no pericardial effusions, intracardiac masses, or thrombi. Broad-spectrum antibiotics were started for possible sepsis, and the patient worsened with fever (38.8°C), hypotension, and progressive hypoxemia. She died within 48 h. Autopsy showed right coronary occlusion by an embolus, multiple PEs with associated infarcts, a cerebral infarct, and a PFO.

Case 4

A 49-year-old man was admitted to our institution with left leg pain and swelling. He had a history of mesenteric arterial emboli with bowel necrosis 2 years earlier, left middle cerebral arterial infarction (with negative carotid ultrasound and TTE) 4 months earlier, right lower extremity DVT, and multiple bilateral segmental defects by perfusion scan 2 months earlier. Medications included phenytoin (Dilantin) and warfarin sodium (Coumadin). The blood pressure was 118/76 mm Hg, heart rate, 80 beats per minute; respiratory rate, 26 breaths per minute; and temperature, 38.0°C. The heart had a fixed, split S-2 without murmurs or gallops. The left lower extremity was warm, swollen, and erythematous with a “cord” palpable in the left medial thigh. Neurologic examination showed hemiparesis. The CXR showed mild cardiomegaly. Arterial blood gas determination showed a pH of 7.48; PaO\(_2\), 60 mm Hg; PaCO\(_2\), 29 mm Hg. A ventilation perfusion scan was unchanged from previous studies. The patient was heparinized, and leg edema improved over 4 to 5 days. The TTE showed RV overload. At right heart catheterization, passage of the catheter tip across the interatrial septum suggested a PFO or a very small ASD. The mean PAP, 44 mm Hg, and right ventricular end diastolic pressures, 10 to 12 mm Hg, were elevated. Hemoglobin oxygen saturations (95%, LA; 65%, RA) did not suggest shunt. Pulmonary arteriogram showed multiple bilateral defects indicating previous embolization with partial recanalization.
After 2 weeks of anticoagulation, he underwent a macroaggregated albumin cardiac study confirming a right-to-left shunt. Subsequently, a caval umbrella was inserted and he was discharged on a regimen of warfarin. It was concluded that the patient had had PDEs from the venous system to his cerebral circulation and also to his bowel 2 years previously. Six years later when hospitalized for pneumonia, the patient developed small-bowel obstruction and died. At autopsy, a PFO was found.

**Discussion**

The courses of these patients exemplify the clinical presentations of PDE and dilemmas in its management. Four elements must be present for PDE: (1) systemic embolism confirmed by clinical, angiographic, or pathologic findings without an apparent source in the left area of the heart or proximal arterial tree; (2) an embolic source within the venous system; (3) an abnormal intracardiac or intrapulmonary communication between right and left circulations; and (4) a pressure gradient that promotes right-to-left shunting at some point in the cardiac cycle. In 1951, Johnson categorized PDE as “presumptive” in the presence of the first three findings and “proved” if thrombus is lodged within an intracardiac septal defect at autopsy.

**Sources of Paradoxical Embolus**

Some restrict their definition of PDE to include only emboli due to thrombotic material, whereas others include emboli of any kind. Most reports cite venous thrombi from branches of the IVC as the major source. In Loscalzo’s review, 20 patients (66%) had PE diagnosed by high-probability ventilation perfusion scans, angiograms, or both, and 13 (43%) had DVT documented at venography. Recently, Stollerberger et al reported that 19 of 29 patients (66%) with PFO and arterial embolism (without evident intraarterial or cardiac sources) had DVT at venography; two thirds of the DVT were clinically silent. Thrombogenesis associated with Swan-Ganz catheters has
been well documented. At least two cases of PDE to a coronary artery have occurred during cardiac catheterization, with thrombus forming along the venous catheter.

Unusual PDE have included two cases of fat embolism after long bone fracture, brain tissue complicating birth injury, tumor emboli from a malignant teratoma, and the current case of AFE. Definitive diagnosis of the latter rare obstetric complication is based on demonstrating fetal squamous cells, mucin, hair, or vernix in the pulmonary vasculature at autopsy. Extrapulmonary AFE have occurred previously in capillaries of the heart, kidney, brain, small intestine, liver, spleen, pancreas, adrenal glands, gallbladder, and the retina, attributed primarily to passage of fetal debris via the pulmonary vascular bed. We suspect that initial increased right-sided pressures due to pulmonary AFE predisposed to PDE via a PFO in case 1.

Eleven cases of paradoxical air embolism have been reported. Accidental introduction of air may complicate intravenous injection, hemodialysis, induction of pneumothorax owing to central line placement, trauma, or any surgical procedure where the wound is above the heart (most often during craniotomies performed with patients in the sitting position). Complications include decreased right heart filling (potentially with cardiac arrest), noncardiogenic pulmonary edema, and PEs. With the latter, increased mean PAP and right-heart pressures might predispose to PDE. The true incidence of PDE due to air is unknown, and it is controversial whether PDE occurs primarily via the pulmonary circulation or owing to an intracardiac defect. Among 11 case reports, 5 had intracardiac defects.

Cardiac and Vascular Communications

Most PDEs have been associated with a PFO, a finding in all our patients. Among 25 cases diagnosed antemortem in whom the interatrial defect was characterized, 18 (72%) had a PFO, 3 had an ASD, 3 had a pulmonary arteriovenous malformation, and one had a ventricular septal defect. There also has been a case with Ebstein’s anomaly and patent truncus arteriosus. The PFO has been known to be a very common finding since 1930, when Thompson and Evans identified a “pencil patent” defect (0.6 to 1.0 cm in diameter) in 6% of unselected autopsies and a “probe patent” foramen (0.2 to 0.5 cm) in 29%. Although most PDE are associated with the former, some have occurred with a PFO smaller than 0.6 cm. Moreover, PFOs have allowed passage of massive emboli that in three cases resulted in aortic occlusion. Hagen et al found PFO in 27.3% of 965 autopsied hearts. The incidence and size of PFO did not differ with gender but varied significantly with age: 34.3% occurred in the

![Figure 4](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21718/) **Figure 4.** Potential strategy for diagnosis of patient with arterial embolus of uncertain cause. TIA = transient ischemic attack.

![Figure 5](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21718/) **Figure 5.** Potential strategy for management of patients with arterial PDE. AVM = arteriovenous malformation; HTN = hypertension.
first three decades, 25.4% in the 4th to 8th decades, and 20.2% in the 9th and 10th decades. The PFO ranged from 1 to 19 mm (4.9 mm, mean) and increased progressively from a mean of 3.4 mm in the first decade to 5.8 mm in the 10th, perhaps because smaller defects seal with age. Among 30 patients diagnosed during life, Loscalzo5 found the mean age to be 44.3±16.1 years, with a 2.1 female-to-male predominance. The precise frequency of PDE complicating PFO is unknown. The PDE occurs in a minority of the 27 to 35% of patients with venous thromboembolic disease who also have a PFO, because normally the foramen ovale is closed by the left atrial pressure-right atrial pressure (RAP) gradient.37

The ASDs are the most common form of congenital heart disease in adults, comprising one third of cases. The direction and severity of shunt depends on ASD size, left ventricular and right ventricular compliance during diastole, and the ratio of pulmonary-to-systemic vascular resistance. Size is not a major determinant for defects more than 1 to 2 cm.3 Patients with thromboembolism and ASD have a small but definite risk of PDE, depending on the degree of right-to-left shunt.38 In patients with left-to-right shunt, dilutional studies also have shown small right-to-left shunt due to streaming of venous blood from the IVC toward the fossa ovalis and across the defect.39 Even in the absence of ventricular hypertension, the pressure gradient may reverse transiently before or during atrial systole.

Hunter41 first hypothesized that PDE would be facilitated by shunting through the low resistance communication of a pulmonary arteriovenous malformation. The latter are very uncommon, with only 3 PDE reported.5 Thrombosis within the fistula is common and 10% are reported to cause bland and septic cerebral emboli.42 However, there is a 37% incidence of neurologic abnormalities ranging from mild sensory and motor deficits to severe hemiplegia, often ascribed to polycythemia and hypoxia.43

Mechanisms of Right-to-Left Pressure Gradients

The PE is the most common cause of acutely elevated RAP and right-to-left shunt in patients with PFO or ASD, and occurs in at least 60% of PDE (5). The frequency with which PDE occurs in patients with PE is unknown. In the investigation of Sharma and colleagues44 concerning acute hemodynamic alterations after PE, PAP rose in proportion to the extent of pulmonary vascular obstruction in 21 patients without preexisting pulmonary vascular disease. Obstruction of 25 to 30% of the pulmonary vasculature was associated with pulmonary hypertension, although no patient had a mean PAP over 40 mm Hg despite massive (>50%) embolic obstruction. The RAP was elevated only occasionally for mean PAP less than 30 mm Hg, but it rose consistently for mean PAP more than 30 mm Hg. Similar observations have been made by other investigators.45-47 Such data suggest that in patients without preexisting pulmonary vascular disease, acute PE may result in PDE if mean PAP increases to at least 30 mm Hg and there is a 35 to 40% pulmonary vascular obstruction and an intracardiac defect such as an ASD or PFO.

When PDE occurs in the absence of PE, chronic lung disease with pulmonary hypertension has usually been present.4 The frequency of PDE in this setting is unknown. In the report of Sharma et al44 on 30 patients with chronic pulmonary vascular disease and acute PE, mean PAP of 40 mm Hg was seen, reflecting preexisting RV hypertrophy. Also, acute elevations of RAP in a Valsalva maneuver or cough have been associated with 15% of PDE cases.5 On release of the Valsalva maneuver, RAP momentarily exceeds left atrial pressure due to a sudden rush of blood into the RV and has been useful in diagnosing intracardiac defects. In some circumstances, superimposed acute respiratory illness and its treatment may accentuate the potential hazard of PDE: patients with acute respiratory failure who receive positive end expiratory pressure may experience shunting across a PFO. Cuje45 et al reported these effects of positive end-expiratory pressure in patients with acute respiratory failure and compared patients with PFO with those without PFO. The TEE showed increased right-to-left shunt in 28% of 46 patients; nearly half of these individuals had a PFO. Other causes of elevated RAP facilitating right-to-left shunt include idiopathic pulmonary hypertension, pulmonary valve stenosis, congestive heart failure, aftermath of an RV infarction, cardiopulmonary bypass, air embolism, and platypnea orthodeoxia.49 Stroke and other neurologic deficits are common in patients with COPD; the role of PDE in those with pulmonary hypertension is unknown.

Sequelae of Paradoxical Embolus

As seen in our patients, PDE can have catastrophic sequelae. In the review of 30 patients by Loscalzo,5 sites of arterial embolii included 20 peripheral (40%), 15 cerebral (37%), 4 coronary (9%), 1 renal (1%), and 1 splenic (1%). In addition, PDE have been reported to cause brain abscess.43 The relationship of PDE to embolic stroke, present in two of our patients, merits particular attention. Forty percent of cerebral infarcts are of undetermined cause despite comprehensive evaluation.50 The PDE via a PFO has been suggested as a potential cause in such persons. In 1988, Webster et al44 found that half of 40 stroke patients less than 40 years of age had a PFO, in contrast to only 15% of control subjects. Among 34 patients with cryptogenic stroke, 56% had PFO. Lechat et al51 found PFO in
The prevalence of Patent Foramen Ovale (by transthoracic echocardiogram with contrast and Valsalva maneuver) in stroke patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Investigation Reference</th>
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<tbody>
<tr>
<td>Age, yr (x±SD)</td>
<td></td>
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<tr>
<td>Patients, No.</td>
<td>Webster et al14</td>
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<tr>
<td>&lt;40 (31±6)</td>
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<tr>
<td>&lt;55 (36±10)</td>
<td>60</td>
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<tr>
<td>&lt;5</td>
<td>45</td>
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<td>=≥</td>
<td>101</td>
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<tr>
<td>Overall, No. (%)</td>
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<tr>
<td>Stroke, determined origin</td>
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<tr>
<td>Stroke, cryptogenic controls with risk factors for stroke</td>
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<tr>
<td>Stroke, cryptogenic</td>
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</tr>
<tr>
<td>Control subjects</td>
<td>6/40 (15)</td>
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*N1—not identified.

?Risk factors in this study included mitral valve prolapse, atrial fibrillation, use of contraceptives. None presented with hypertension or diabetes.

 Patent foramen ovale was inversely associated with the presence of hypertension and diabetes, but the number of cryptogenic stroke patients with combination of risk factors and PFO was not specifically provided.

40% of 60 patients aged less than 55 years with stroke vs 10% of control subjects. In the first PFO prevalence report in older persons with stroke, Di Tullio et al16 evaluated 146 stroke patients of all ages with contrast TTE and found PFO in 18%. Thirty-one percent of strokes were cryptogenic; these were associated with higher frequencies of PFO in both younger (<55 years; 48 vs 4%; p=0.001) and older (≥55 years; 38 vs 8%; p<0.001) patients when compared with those with identifiable causes of stroke. The differences remained significant after controlling for hypertension and diabetes. These associations of PFO with cryptogenic stroke suggest that a larger proportion of such events may be secondary to PDE than is generally appreciated (Table 1).

Paradoxical coronary embolism is a rare diagnosis first reported by Marchand in 1894.51 In the recent review of 27 cases by Jungbluth et al.69 were diagnosed antemortem. Of the 18 thrombotic PDE, the right-to-left communication was via PFO in 13, an ASD in 4, and a patent truncus arteriosus in 1. The remaining eight cases were caused by air embolism, and an abnormal intracardiac defect was found in only three. Five air emboli involved the left coronary artery, perhaps related to its anterogranial position.

Diagnosis of Paradoxical Embolism

Because of the potentially devastating effects of PDE, early diagnosis and treatment are essential in order to manage the current event and to prevent recurrence. The high prevalence of anatomic (eg, PFO) and hemodynamic (eg, pulmonary hypertension due to acute or chronic respiratory illness or both) predispositions to PDE present unresolved diagnostic and therapeutic dilemmas. The PDE should be suspected in any patient with unexplained arterial embolism. Although clinically obvious, simultaneous pulmonary and systemic embolism should strongly suggest PDE, but it is not prerequisite for the diagnosis. The PE may go undiagnosed, and as noted previously, DVTs are often asymptomatic.17,52 Diagnosis also is hindered by the variable manifestations of systemic emboli, which also may be asymptomatic,53 and the presumptive nature of the diagnosis of PDE when it occurs. Moreover, right-to-left shunt may be transient and occur only during Valsalva or other inciting maneuvers; if the patient is studied after the acute event, both the PE and the right-to-left shunt may have resolved.9 The weight to assign to coexisting carotid disease in the decision whether or not to pursue PDE as a diagnostic consideration is also unclear.

The differential diagnosis of arterial embolism in patients with temporally associated PE or DVT includes (1) cardiomyopathy with right ventricular and left ventricular mural thrombi; (2) emboli from biliary myxomas; (3) mitral and tricuspid valve disease (with or without atrial fibrillation); (4) myocardial infarction with a left ventricular thrombus and congestive heart failure predisposing to DVT; (5) emboli via right- and left-sided infective endocarditis; and (6) emboli related to prosthetic replacement of both mitral (and/or aortic) and tricuspid valves.9 In patients with cyanotic congenital heart disease and arterial embolism, PDE is likely; in other settings, the diagnosis may be difficult to establish. Because of the importance of DVT as origin of PDE, vigorous exclusion of DVT (eg, with contrast venography) assumes special importance in patients with unexplained stroke or other embolic events. Stroke patients with COPD and pulmonary hypertension also should have vigorous assessment for coexisting intracardiac communication and venous disease.

Diagnostic Techniques

Before availability of contrast TTE and TEE, many approaches were used to demonstrate right-to-left shunt. Following the use of oximetry to document a drop in oxygen saturation during the Valsalva maneu-
ver, in the study by Lee and Gillette, various indicators including ascorbate, hydrogen, krypton, freon, and indocyanine green were injected into the right side of the circulation, with their early systemic appearance signifying a right-to-left shunt.\textsuperscript{4,21,55,56} Accurate antemortem diagnosis has been facilitated greatly by contrast echocardiography.\textsuperscript{57} Six cases of impending PDE (with the clot visualized within the intracardiac defect), "embolism interruptus," have been reported during life, three each by TTE\textsuperscript{5,7} and TEE.\textsuperscript{9,13}

The contrast effect is achieved by microcavitation bubbles produced during rapid injection of 10 mL \mbox{of agitated contrast solution (eg, 9 mL of saline and 1 mL of air)} into a peripheral vein. Various contrast agents may be used, including indocyanine green, dextrose water, normal saline solution, or autologous blood. Usually, contrast TTE is obtained using an apical four-chamber view. At least four saline injections are performed in quiet breathing and after the Valsalva maneuver. The study is considered positive if microbubbles appear either in the LA or left ventricle no later than two to three cycles after their initial appearance in the RA.\textsuperscript{58} Another maneuver, the cough test, has been reported to be superior to the Valsalva maneuver in diagnosis of PFO in TEE.\textsuperscript{59} Three to five rapid, successive coughs are performed immediately after opacification of the RA with contrast. In 73 consecutive patients, PFO was detected during the cough test in 32 (43.8\%), significantly more often than in the Valsalva maneuver (32.9\%) or quiet breathing (24.7\%).

Contrast TTE is more sensitive than oximetry and dye curves, but its sensitivity is only 64\%.\textsuperscript{60} Technical limitations relate to spontaneous variations in right-to-left shunt during normal breathing, the quality of the Valsalva maneuver, uneven distribution of contrast solution, and missing the sampling site of the M-mode beam. Contrast shunting is apparent immediately in patients with cyanotic heart defects but is often subtle in patients with uncomplicated ASD. Contrast shunting may become evident during the Valsalva maneuver, but this part of the tracing often is technically unsatisfactory and difficult to interpret. The most important moment is thus the first diastole following the Valsalva maneuver release. The TTE also frequently demonstrates echo dropout because the ultrasonic beams do not generally hit the interatrial septum with a perpendicular orientation and may result in false-positive appearances of ASDs. Since the degree of contrast shunt is independent of defect size, TTE cannot reliably differentiate ASD from PFO.\textsuperscript{60} By contrast, TEE is unrestricted by lung tissue or thoracic malformations, providing superior imaging of the atrial septum and a clear view of the foramen ovale.\textsuperscript{61}

The prevalence of PFO detected by TEE has ranged from 8 to 63\% because of varying study populations, techniques, and defining criteria.\textsuperscript{14,58-64} In the first report validated by catheterization or operative results, Chen and coworkers\textsuperscript{58} documented PFOs with contrast TTE and TEE in 32 patients. A right-to-left shunt was seen by TEE in 14 in normal breathing and 20 with the Valsalva maneuver and by TTE in 8 with normal breathing and 12 with the Valsalva maneuver. All PFOs seen by TTE were also seen by TEE, and all but one of the PFOs seen by TEE were confirmed by catheterization or surgery. The false-positive patient had a right atrial myxoma, the highest RAP of the group; presumably, right-to-left shunt was accentuated by "communications other than PFO." The diagnostic sensitivity (100 vs 63\%) and accuracy (97 vs 78\%) of TEE were higher than with TTE. Although such initial observations suggest that TEE provides superior imaging, even in the strain phase, and higher sensitivity in the detecting PFO, TEE has the disadvantages of semiinvasiveness, higher cost, and limited availability.

Transcranial Doppler (TCD) ultrasound of the middle cerebral artery in contrast injection is another noninvasive method that may enhance detection of interatrial right-to-left shunt.\textsuperscript{65} Nemec et al\textsuperscript{66} compared TTE, TEE, and TCD in 32 patients, 21 of whom had unexplained arterial emboli; TEE showed interatrial shunt in 13 and intrapulmonary shunt in 6. Using TEE as the gold standard, TCD had a sensitivity and specificity of 100\% and identified 3 of the intrapulmonary shunts. Thus, TCD provides a useful alternative for excluding interatrial right-to-left shunt when TEE is unavailable. This role of TCD warrants further investigation because of its wide availability.\textsuperscript{66,67}

**Diagnostic Approaches**

**Evaluation**

Integrated use of these tools in diagnostic evaluation of an arterial embolus varies considerably with institutional resources and clinicians' preferences. Because arterial emboli most often originate in the heart or proximal arteries, evaluation often begins with M-mode two-dimensional TTE, arteriogram or abdominal aortic ultrasound (for abdominal or lower extremity peripheral emboli),\textsuperscript{5,9} or carotid ultrasound (for stroke or transient ischemic attack [Fig 4]). If no source is found, or if DVT or PE or both are associated, then contrast TTE with Valsalva maneuver or cough test or contrast TEE (if TTE is negative) are performed to rule out right-to-left shunt. If TEE cannot be performed, TCD is considered. These approaches focusing upon the embolus and possible intracardiac communications should be coordinated with vigorous exclusion of associated venous disease. The optimum, most cost-effective means of detecting PFO requires further clarification.
Management Issues and Challenges

Various therapeutic strategies have been used in patients with PDE (Fig 5). A multifaceted approach is necessary since no single algorithm is appropriate for all individuals; the heterogeneity and complexity of patients, together with their acuity of illness, makes management highly individualized. There are no published investigations comparing patient outcomes or showing the superiority of any one strategy. Most authorities agree that anticoagulation should be initiated immediately on diagnosis of arterial emboli unless there are major contraindications. Interestingly, anticoagulation strategies for long-term management of patients with PDE or for these diverse issues related specifically to PDE are seldom addressed. Although the long-term courses and risk of recurrent embolization in patients with PDE are unknown, it seems reasonable that such patients should have lifelong anticoagulation in the absence of contraindications. Even more difficult is the approach to persons with DVT and a documented intracardiac communication or that to patients with other combinations of predispositions to PDE (eg, PFO and pulmonary hypertension). Prophylactic anticoagulation appears reasonable in such individuals but data documenting its benefit are unavailable. In this regard, the risk posed by echocardiographically detected PFO in the absence of PDE requires delineation. Without the benefit of large clinical trials, it is unclear whether long-term anticoagulant therapy would benefit stroke patients with PFO and no cardiac source of embolism, particularly in the presence of COPD and pulmonary hypertension.

Because PE is a major problem likely to accompany PDE, its management is another important related issue. In the special circumstance of combined PDE and PE, the greatest danger of further PDE seems to occur in the few hours after the initial episode, when RAP is highest. Thus, thrombolytic agents might be considered in carefully selected patients with suspected PDE and significant RA hypertension due to PE even when systemic hypotension is absent, in an effort to reduce RAP and the likelihood of recurrent PDE. Evidence of cerebral emboli may be a contraindication to thrombolytic therapy, although use of lytic therapy for such cases has been reported. Thrombolytics and, occasionally, embolectomy are considered when peripheral arterial obstruction jeopardizes limb viability. The role of caval interruption in patients with PDE is also unclear. If thrombolytics or anticoagulation are contraindicated, then placement of an IVC filter is recommended in the presence of DVT. Occasionally, pulmonary embolectomy is considered. In the rare case of an “impending” PDE discovered at echocardiography, intracardiac embolectomy may be attempted, together with correction of the intracardiac defect and placement of an IVC filter. If PDE occurs via an unresectable pulmonary arteriovenous malformation or in the presence of inoperable, irreversible intracardiac right-to-left shunt, then an IVC filter is considered. Long-term anticoagulant administration generally is recommended as well because of the potentially devastating effects of even very small PDE. Usually, closure of the PFO is unnecessary after PDE, particularly if RA hypertension and right-to-left shunt are thought to be temporary. Surgical repair of isolated ASD has been advocated when the ratio of pulmonary to systemic blood flow is 1:5:1. In persons with Eisenmenger’s complex (irreversibly elevated mean PAP and right-to-left shunt), surgery is contraindicated because the severe pulmonary hypertension causes heart failure upon closure of the ASD. If an ASD patient has a right-to-left shunt due to an acute PE, RA hypertension may be self-limited and surgical repair may still be possible.

Comment

Most reports of PDE have been descriptive, providing little information about its natural history, outcomes, and effects of various therapeutic approaches. The long-term management of survivors of the acute PDE is unclear from the literature. More epidemiologic data are needed to delineate these issues. The 27 to 35% prevalence of PFO in the general population, and the association of cryptogenic strokes with PFOs suggests that PDE is frequently missed. This impression is supported by the review of AbuRahma et al of 41 cases of arterial embolism: 20 (49%) had a cardiac thrombus or other cardiac disease, 7 (17%) had a proximal arterial thrombus by arteriogram or abdominal aortic ultrasound, 5 (12%) had “possible” or “probable” PDE, and another 9 individuals (22%) had emboli of unknown source after negative or incomplete evaluations. Five of 9 patients (56%) less than 50 years old had “probable” or “possible” PDE. To improve recognition of PDE, clinicians should maintain a high suspicion for this event whenever neurologic changes complicate cardiovascular events, DVT or PE, or any unexplained arterial occlusion occurs (particularly in young or postoperative patients). When the source of an embolus is not identified by M-mode and two-dimensional echocardiogram, abdominal ultrasound, or arteriogram, contrast TTE with cough test or Valsalva maneuver should be considered, followed by a TEE or TCD if necessary. The most cost-effective diagnostic strategy remains to be determined, and approaches will vary with the institutional resources available to the clinician. Anticoagulation is the mainstay of therapy. Unless contraindicated, a lower threshold for use of thrombolytics may be considered in selected cases. It seems reasonable that an-
ticoagulation for patients predisposed to PDE should continue as long as the predisposition is present. For many patients (eg, individuals with COPD-induced pulmonary hypertension, PFO) this recommendation would be lifelong. The benefits of this approach are undocumented and require definition before making firm guidelines.

Prevention of PDE is especially desirable. Although there is no information regarding specific measures to reduce PDE risk, improved application of already validated prophylaxis when predispositions to DVT occur in patients with known PFO or other intracardiac communications would appear especially worthwhile. Even less is known if prophylactic anticoagulation of persons with recognized risks for PDE (eg, PFO and chronic pulmonary hypertension) is beneficial. If future reports confirm that PDE occurs as often as the high frequency of predispositions might suggest, then major adjustments of current thresholds and anticoagulation strategies will be necessary. In the absence of contraindications, lower thresholds for anticoagulating patients at risk might be needed, but documentation of benefits of this approach may be difficult.

REFERENCES

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