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Patent Foramen Ovale and Stroke in Intermediate-Risk Pulmonary Embolism

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BACKGROUND: Patent foramen ovale (PFO) in pulmonary embolism (PE) is associated with an increased risk of complications. However, little is known about PFO and ischemic stroke prevalence, particularly in acute intermediate-risk PE. In addition, in this context, the so-called "gold standard" method of PFO diagnosis remains unknown. We aimed to evaluate PFO and ischemic stroke prevalence and determine which of transesophageal echocardiography (TEE) or transthoracic echocardiography (TTE) is the best PFO diagnostic method in this context.

METHODS: We conducted a prospective monocentric study of consecutive patients with intermediate-risk PE in whom a TEE and TTE with contrast were performed. Brain MRI was used to confirm clinically obvious strokes or to diagnose subclinical ones.

RESULTS: Forty-one patients with intermediate-risk PE were identified over a 9-month period. Contrast TEE revealed PFO in 56.1%, whereas contrast TTE showed PFO in only 19.5% ($P < .001$). Of note, all PFOs observed with TTE were also diagnosed by TEE. Ischemic stroke occurred in 17.1% and was always associated with PFO and large shunt.

CONCLUSIONS: PFO and related ischemic strokes are frequent in intermediate-risk PE. TEE is much more efficient than TTE for PFO diagnosis. Considering the high risk of intracranial bleeding with thrombolysis in PE, which may be partly due to hemorrhagic transformation of subclinical strokes, screening PFO with TEE should be considered in intermediate-risk PE when thrombolytic treatment is discussed. CHEST 2014; 146(4):967-973

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ABBREVIATIONS: ASA = atrial septal aneurysm; ICH = intracerebral hemorrhage; PE = pulmonary embolism; PFO = patent foramen ovale; TCD = transcranial Doppler; TEE = transesophageal echocardiography; TTE = transthoracic echocardiography

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Pulmonary embolism (PE) is a frequent and serious condition associated with high mortality.[1] The presence of patent foramen ovale (PFO) in PE correlates with a high incidence of paradoxical embolism, especially brain embolism. PE-related mortality increases in the presence of PFO.[2] With transthoracic echocardiography (TTE), PFO has been found in up to 25% of PE and identified as an independent predictor of silent brain infarcts.[3] However, this prevalence has mainly been found in patients with low-risk PE without transesophageal echocardiography (TEE).[3] The best method to identify PFO is still being discussed. We sought to evaluate PFO and ischemic stroke prevalence in intermediate-risk PE and to determine the best PFO diagnostic method between TEE and TTE.

Materials and Methods

Study End Points

We aimed to evaluate PFO and ischemic stroke prevalence. We sought also to determine whether TEE or TTE is the best PFO diagnostic method in this context.

Patients

We performed a prospective monocentric observational study between October 2011 and June 2012 at the cardiac ICU of Pasteur University Hospital (Nice, France). Consecutive patients hospitalized for acute intermediate-risk PE were included. All PEs were confirmed with multidetector CT angiography. Intermediate risk was defined according to European Society of Cardiology guidelines[1] and based on at least one of the following criteria: systolic pulmonary arterial pressure > 40 mm Hg, right ventricular dilation (defined on the apical four-chamber view as a right-to-left ventricular telediastolic diameter ratio > 0.6), right ventricular systolic dysfunction (defined on the apical four-chamber view as a tricuspid annular plane systolic excursion < 16 mm or a systolic tricuspid annular velocity < 11 cm/s), or elevated cardiac biomarkers (B-type natriuretic peptide level > 100 pg/mL [Beckman Triage method] or troponin I level > 0.06 ng/mL [Beckman Access method]). Patients aged < 18 years, pregnant or breastfeeding, contraindicated for MRI, or not consenting to the study were excluded from this protocol. Approval by ethics committee (Agence Nationale de Sécurité du Médicament et des Produits de Santé; project approval number: 2014-A00253-44) was obtained. Each patient gave written informed consent.

Contrast Echocardiography Technique

Within 3 days of patient admission, contrast TTE and TEE were performed consecutively within the same hour by a single experienced echocardiologist. Two different echocardiologists participated in the study. TEE was performed systematically after TTE using a matrix array transducer (X7-2t, Philips iE33 ultrasound system; Philips Healthcare Nederland). Local anesthesia for the orolarynx was delivered by 5% lidocaine pump spray without sedation. TTE was performed using a variable frequency harmonic phased-array transducer (S5-1) and a Philips iE33 ultrasound system. Harmonic imaging modality was used to improve imaging quality. Acoustic windows used for contrast TTE were of both the four-chamber and the subcostal views. Agitated saline contrast was injected into a peripheral vein during the strain phase of the Valsalva maneuver. The atrial septum was imaged during the release phase of the maneuver. All patients were submitted to a carefully standardized Valsalva maneuver. First, they were asked to contract abdominal muscles, and the echocardiologist checked for effective contraction with his hand. Second, Valsalva efficiency was defined by a 20 cm/s decrease in transmitral E-wave velocity and atrial septal bulging visualization.[4] The presence of PFO was defined by the visualization of contrast (at least three bubbles) in the left-side cavities within the first three cardiac cycles after opacification of the right atrium during the maneuver. Two injections were performed for each acoustic window (TEE, TTE four-chamber and subcostal transthoracic views). A large shunt was considered when > 20 bubbles appeared in the left atrium.[5] Atrial septal aneurysm (ASA) was defined by a 10-mm excursion of the atrial septum into the left or right atrium or both.[6]

Contrast Echocardiography Analysis

Two trained observers blinded to each other and to the patients' clinical status evaluated the images off-line. In case of discrepancy, a third interpretation was required, and consensus was obtained.

General TTE Analysis

Right ventricular dysfunction was assessed according to American Society of Echocardiography guidelines.[7] The mitral Doppler inflow E velocity/annular tissue Doppler e′-wave velocity ratio was obtained with the average of early diastolic lateral and medial velocities according to American Society of Echocardiography guidelines.[8]

Brain MRI

To diagnose ischemic stroke, a diffusion-perfusion MRI was performed during the hospitalization using echoplanar imaging on a 1.5-T magnet (OPTIMA MR450w 1.5T with GEM Suite; GE Healthcare). The number of cerebral lesions and their topographies were reported. Images were analyzed by a single experienced neuroradiologist blinded from any other clinical or paraclinical data. An ischemic lesion was considered to be recent if hyperintense on diffusion-weighted images and associated with a decrease of the apparent diffusion coefficient.[9] To confirm clinical suspicion of stroke, a neurologist blinded to the MRI results examined every patient the very same day the brain MRI was performed.

Carotid Duplex Ultrasound

To rule out carotid stenosis, which could possibly be the cause of stroke, duplex ultrasound of the supraaortic trunks was performed during the hospitalization with a 9.0-MHz transducer on a Philips iE33 ultrasound system. According to North American Symptomatic Carotid Endarterectomy Trial criteria, a significant carotid stenosis was defined by a reduction of the lumen of ≥ 60% without neurologic symptoms and ≥ 50% in the presence of neurologic symptoms.[10]

Cardiovascular Monitoring and ECG Analysis

Every patient was monitored with continuous ECG throughout the ICU stay to determine the potential for cardioembolic arrhythmias. ECG signs of right ventricular strain were defined with the presence of at least one of the following according to European Society of Cardiology guidelines[1]: inversion of T waves in leads V1 to V4, a QR pattern in lead V1, the classic S1Q3T3 type, new incomplete or complete right bundle branch block, and tachycardia (sinus tachycardia or atrial arrhythmias).

Statistical Analysis

Statistical analysis was performed with SPSS version 19 (IBM) software. Data are presented as mean ± SD for normally distributed data or median and 25th-75th percentile for skewed data. Fisher exact test was used for comparison of percentages. Mann-Whitney *U* and Student *t* tests were used for other comparisons. Differences between parameters diagnosed with TTE and those diagnosed with TEE (prevalence of PFO, ASA, and large shunt) were compared using the Wilcoxon paired test. Differences were considered statistically significant at $P < .05$.