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MEETING REPORT

The 2022 FASEB Virtual Catalyst Conference on the Cardiac Interatrial Septum and Stroke Risk, December 7, 2022

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Abstract

There is emerging evidence that the cardiac interatrial septum has an important role as a thromboembolic source for ischemic strokes. There is little consensus on treatment of patients with different cardiac interatrial morphologies or pathologies who have had stroke. In this paper, we summarize the important background, diagnostic, and treatment considerations for this patient population as presented during the Federation of American Societies for Experimental Biology (FASEB) Virtual Catalytic Conference on the Cardiac Interatrial Septum and Stroke Risk, held on December 7, 2022. During this conference, many aspects of the cardiac interatrial septum were discussed. Among these were the embryogenesis of the interatrial septum and development of anatomic variants such as patent foramen ovale and left atrial septal pouch. Also addressed were various mechanisms of injury such as shunting physiologies and the consequences that can result from anatomic variants, as well as imaging considerations in echocardiography, computed tomography, and magnetic resonance imaging. Treatment options including anticoagulation and closure were addressed, as well as an in-depth discussion on whether the left atrial septal pouch is a stroke risk factor. These issues were discussed and debated by multiple experts from neurology, cardiology, and radiology.

KEYWORDS
interatrial septum, left atrial septal pouch, patent foramen ovale, stroke, transesophageal echocardiography, transthoracic echocardiography

1 | INTRODUCTION

The Federation of American Societies for Experimental Biology (FASEB) Virtual Catalyst Conferences are meetings geared to establish a scientific community around an emerging scientific topic in the field. The FASEB Virtual Catalytic Conference on the Cardiac Interatrial Septum and Stroke Risk was held online on December 7, 2022.

Stroke remains a leading cause of morbidity, mortality, and medical expense worldwide with nearly 12 million new cases diagnosed every year at a yearly cost of $721 billion USD.[1] Ischemic strokes account for greater than 80% of total strokes, and of these, cryptogenic strokes, or strokes where a cause cannot be determined despite a thorough workup, account for as high as 30%.[2–4] Also known is that cardioembolic phenomena account for nearly 25% of ischemic strokes.[3] The cardiac interatrial septum, or the septum that divides the right and left atria from one another, may play a role in thromboembolic phenomena via several mechanisms.[3] Of the anatomic variations in the interatrial septum, patent foramen ovale (PFO) and left atrial septal pouch (LASP) appear to be the most relevant in this context (Figure 1).[3] Understanding how these structures may play a role in causing stroke is critical in order to be able to provide appropriate workup and therapeutic interventions.

During the symposium, experts in cardiology, neurology, and radiology discussed the contribution of various cardiac interatrial pathologies to stroke etiology. Among the many topics presented were the development of the interatrial septum, the definition of LASP and PFO, the proper imaging modalities and techniques used to visualize the interatrial septum, the mechanisms of stroke with varying interatrial septal pathologies, and the pharmacological and transcatheter approaches for the interatrial pathologies implicated in stroke. These presentations were followed by a debate on whether the LASP should be considered an independent risk factor for stroke, and finally, by an open discussion on the current state of research and future directions for the interatrial septum as it contributes to stroke. The purpose of this paper is to summarize these presentations, debates, and discussions for the biomedical community at large.

1.1 | Anatomy of the interatrial septum: PFO and left atrial septal pouch

Jeannette P. Lin (University of California, Los Angeles, Los Angeles, CA, USA).

As the heart develops early on in embryology, the atrium begins as a single common chamber that eventually divides into the right and left atria. The process of division occurs as the septum primum begins to grow from the roof of the common atrium and progresses toward the crux of the heart and the endocardial cushion. The septum primum does not grow linearly, but rather circumferentially with the growing edge forming a circular shaped "hole" called the ostium primum that gradually shrinks in size. As the septum primum continues to grow and the ostium primum continues to get smaller, fenestrations begin to appear in the septum primum, which will collectively form the ostium secundum. The atrial walls will begin to infold and create the septum secundum, which grows and eventually covers the ostium secundum. The septum primum functions as a flap on the left atrial side of the atrial septum. The fossa ovalis is a relatively thin part of the interatrial septum composed of the septum primum. This opening and flap are important in fetal development in that it allow for oxygenated blood to bypass the fetal pulmonary circulation and flow directly from the right to the left atrium. After birth, as pulmonary vascular resistance decreases and the right ventricular compliance increases, the right atrial pressure falls, and the septum primum flap closes due to the higher pressures in the left atrium. In the majority of individuals, the septum primum flap seals closed against the septum secundum. However, at the anterior superior edge of the fossa ovalis, the septum primum and the septum secundum may fail to fuse completely, resulting in a PFO that may continue to allow shunting across the atria.

Two main anatomic variations in the PFO are a probe-patent PFO and a stretched PFO. The difference between these two structures depends upon the degree of fusion between the septum primum and septum secundum. On echocardiography, a stretched PFO appears open and demonstrates flow by color Doppler with a larger gap (Figure 2) between the septum primum flap and the septum secundum. In contrast, a probe-patent PFO appears closed, often without evidence of flow by color Doppler

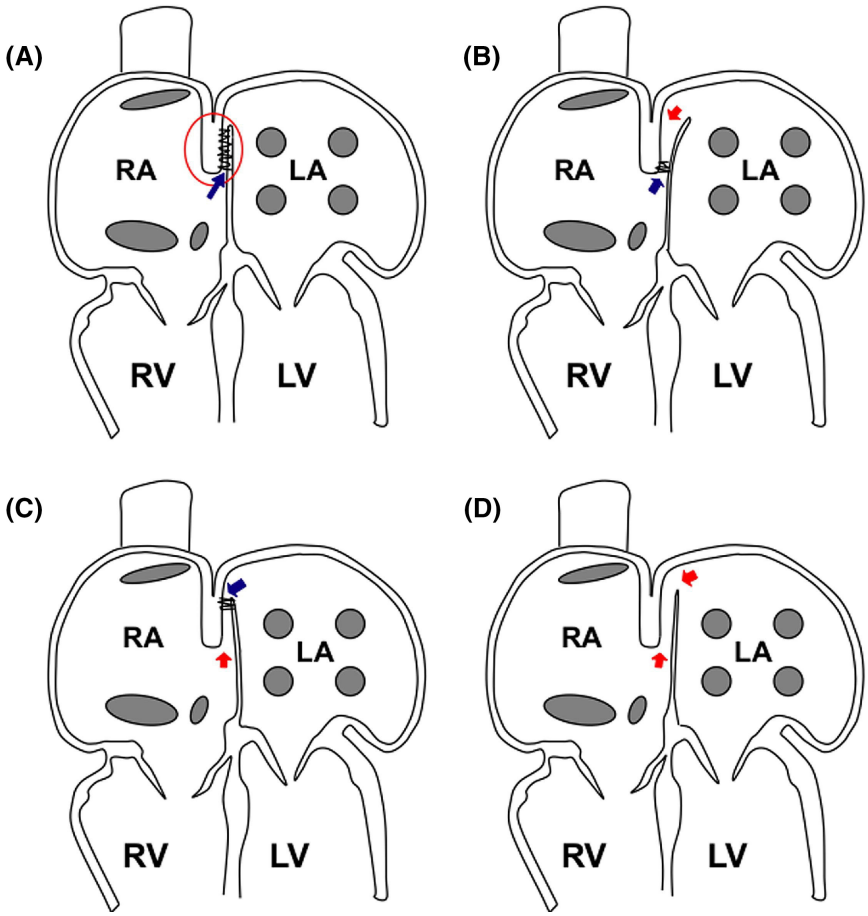

FIGURE 1 Representative cartoon demonstrating variations in the interatrial septum. Panels show four variations in fusion between the septum primum and septum secundum forming the interatrial septum. (A) There is complete fusion, forming a normal interatrial septum (red oval and blue arrow). (B) There is incomplete fusion of the septum at the caudal end (blue arrow), which leaves a pouch accessible to the left atrium, or left atrial septal pouch (red arrow). (C) There is incomplete fusion of the septum at the cranial portion (blue arrow), leaving a pouch accessible to the right atrium, or right atrial septal pouch (red arrow). (D) There is incomplete fusion at any section, leaving a channel connecting the right and left atria and forming a patent foramen ovale (PFO; red arrows). LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. Reprinted from *JACC Cardiovascular Interventions*, Vol. 3, Ed. 1, pp. 98–104, Subramaniam C. Krishnan and Miguel Salazar, Septal pouch in the left atrium: A new anatomical entity with potential for embolic complications, Copyright 2010, with permission from Elsevier.

unless maneuvers are used to increase right atrial pressure and thus "push" the septum primum flap open (Figure 3). The atrial septal pouch is the space that can form in between a remnant of the septum primum and the septum secundum (Figure 3). There may be further anatomical variants of PFO, depending on the length of the tunnel, the presence or absence of an atrial septal aneurysm, and variable thickness and height of the septum secundum. These various anatomic features have been examined in patients with stroke in the published literature to assess whether they may have contributed to those patients who have them.

In addition to the anatomic features, cardiovascular physiology determines the amount and direction of shunting across a PFO—shunting may be intermittent or continuous. The direction of the shunt flow may be right to left, left to right, or bidirectional, with variable physiological and hemodynamic consequences. In a right-to-left shunt across a stretched PFO with coexisting right heart pressure or volume increase, as might be seen in patients with moderate–severe tricuspid valve stenosis or regurgitation or right ventricular dysfunction, the agitated saline injected intravenously ("bubble study") during an echocardiogram can help identify the intracardiac right-to-left shunt by the appearance of bubbles in the left atrium after the opacification of the right heart by the agitated saline contrast. In a bidirectional shunt, such as in the case of normal increases in volume in pregnancy, the saline bubble study will also be positive, indicating the right-to-left component of the bidirectional shunt. In contrast, in a left- to-right shunt only, which occurs when the left atrial pressure is greater than the

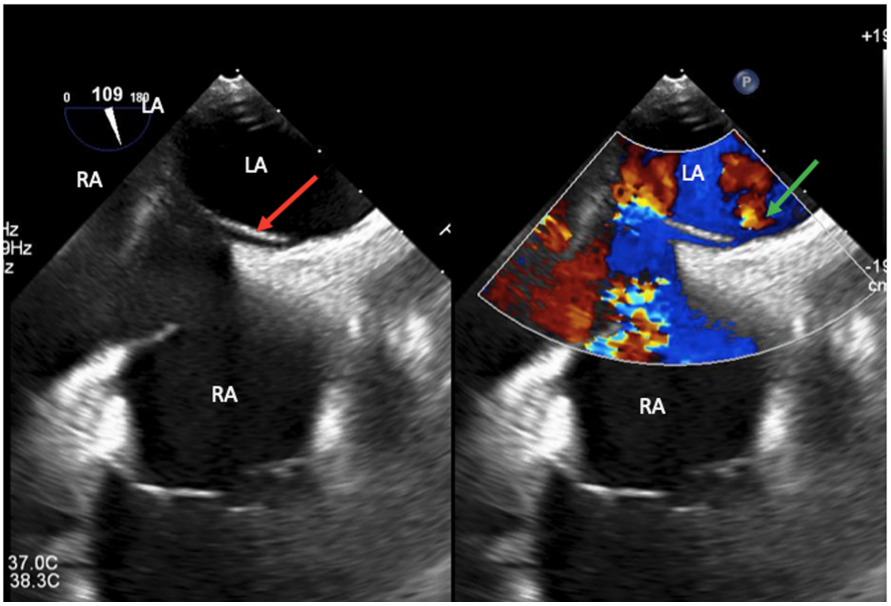

FIGURE 2 Stretched PFO. Transesophageal echocardiographic images show a stretched PFO (left) that is open (red arrow) and with color Doppler (right) demonstrating shunting across the PFO. The shunt is shown with a red color "jet" suggesting flow from the right atrium (RA) to the left atrium (LA), as indicated by the green arrow. Reproduced with permission of Jeannette P. Lin from her FASEB Catalyst Conference lecture.

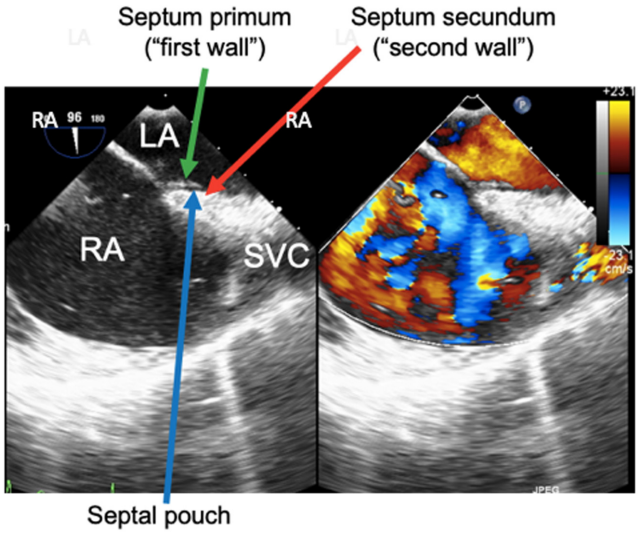

FIGURE 3 Probe-patent PFO showing septum primum remnant, septum secundum, and LASP. Image shows a probe-patent PFO appearing closed (left), with no flow indicated by color Doppler (right). The septum primum (green arrow) and septum secundum (red arrow) are shown with a left atrial septal pouch, indicated by the blue arrow. Reproduced with permission of Jeannette P. Lin from her FASEB Catalyst Conference lecture.

right atrial pressure, the saline bubble study will be negative. In a probe-patent PFO, the shunt is only intermittent and occurs when right atrial pressure is increased with a provocative maneuver. Therefore, the saline bubble study is negative at rest but may become positive with maneuvers to adequately increase the right atrial pressure, such as with coughing, abdominal pressure, or Valsalva release. The presence of a PFO with hemodynamically significant shunting can manifest clinically with platypnea orthodeoxia and thromboembolic complications such as stroke.

1.2 | Imaging the interatrial septum by transthoracic and transesophageal echocardiography

Sunil V. Mankad (Mayo Clinic, Rochester, MN, USA).

The common indication for a transesophageal echocardiogram (TEE) is for the evaluation of a possible cardiac source of embolism in a patient with a stroke.[5,6] Possible cardiac sources include tumors, intracardiac thrombi in the left heart (including left atrial appendage and LASP), paradoxical embolism through PFO (often associated with atrial septal aneurysm), fibrinous stranding, Lambl's excrescences, and vegetations.[7–10] Sixty-seven percent of TEEs are abnormal when performed in patients with stroke.[7]

The PFO is a normal fetal structure that persists in approximately 25% of adult patients. It has historically been associated with an increased risk of stroke, attributed to the paradoxical embolism of venous thrombi that shunt through the PFO directly to the arterial circulation.[11] The indications for PFO closure include cryptogenic stroke with demonstrated right-to-left shunt, a paradoxical embolism, a straddling embolus, and platypnea orthodeoxia syndrome.[11]

Several randomized clinical studies have demonstrated superiority of PFO closure to medical management alone to prevent recurrent strokes.[12–14] The RESPECT trial studied 980 patients with a mean age of 46 and showed a 62% relative risk reduction of recurrent stroke with closure. PFO closure was more effective in patients with

concurrent atrial septal aneurysm and with a large right-to-left shunt.[12] In the Gore REDUCE trial, in which 81% of 664 patients had a moderate-to-large shunt, PFO closure had a recurrent stroke rate of 1.4%, compared to 5.4% with antiplatelet therapy alone.[13] The Analysis of Individual Pooled Patient Data from RCTs of Device Closure of PFO after Stroke examined six randomized controlled trials between 2000 and 2017 with a total number of 3740 subjects and showed benefit for closure of PFO in reducing recurrent stroke.[14] Based on the published data, the British Medical Journal (BMJ) released a practice guideline that supported PFO closure followed by antiplatelet therapy in cryptogenic stroke, while acknowledging that there is a slight increase in device-related atrial fibrillation.[15] A research study led by Kasner et al. examining long-term outcomes of PFO closure versus antiplatelet therapy alone for cryptogenic stroke showed that the number needed to treat to prevent one stroke at 5 years was 25.[16] The guidelines from the American College of Neurology now recommend PFO closure for secondary stroke prevention in patients aged under 60 with a PFO-related stroke, and in patients between the ages of 60 and 65 with a very limited degree of traditional vascular risk factors (i.e., hypertension, diabetes, hyperlipidemia, or smoking) and no other mechanism of stroke detected following a thorough evaluation, including prolonged monitoring for atrial fibrillation.[17] Thorough workup may include neurology consultation, brain MRI or CT, MRA or CTA of the extracranial circulation, thrombophilia testing, TEE, or transthoracic echocardiography (TTE) with bubble study with Valsalva release, and 30 to 90 days of cardiac monitoring.[17] A causal relationship between a PFO and a stroke should be suspected under certain circumstances. In patients who are straining and have a history of immobilization, thrombophilia, or obstructive sleep apnea (OSA), there is a higher likelihood of the PFO being implicated.[18]

Certain anatomic states, such as atrial septal aneurysm, a large shunt, prominent eustachian ridge or valve, and a large Chiari network can be considered "malignant" and can raise the risk of stroke with a PFO (the latter two may even act as a substrate for a transient thrombus to form).[18] In reviewing echocardiographic images of a bubble study, it is important to pay attention to the location where bubbles cross and how many are crossing (Figure 4). This analysis is critical to determine the extent of shunt. Noting where the bubbles cross can differentiate an intracardiac from an intrapulmonary shunt. In the case of the latter, the agitated saline bubbles may be noted to enter the left atrium from the pulmonary veins rather than crossing the interatrial septum. Association of an atrial septal aneurysm with PFO was statistically significant (2.2% of control and 7.9% of cardioembolic stroke patients) and should be considered a high-risk feature (Figure 4).[19] When clinical suspicion for PFO is high, echocardiographic evaluation must be thorough in searching for evidence of the shunt. During the agitated saline contrast injection, there may be a contrast-void area (or "dropout") in the right atrium at the interatrial septum, representing a left-to-right continuous flow (Figure 5). A comprehensive sweep of the septum must be done (Figure 6). If the bubble study does not demonstrate intracardiac shunt at rest, it should be repeated with a provocative maneuver (Figure 7). When the bubble study is positive for a right-to-left shunt, PFO versus intrapulmonary shunting should be differentiated by the location, numbers, and timing of the bubbles entering the left side (Figure 8).

Another anatomical variant of the interatrial septum is LASP. The presence of LASP was found to be associated with an increased risk of ischemic stroke in either univariable analysis (17.2 vs. 7.9%, $p = .03$, odds ratio 2.43) or after adjustment for other stroke risk factors using multiple logistic regression analysis (odds ratio 2.45, $p = .036$).[20] LASP can be identified on echocardiography as a blind pouch open to the left atrium along the interatrial septum (Figure 1). There is no shunting across the septum. However, the LASP may be a nidus of stagnant flow, with several case series demonstrating thrombi in the LASP itself. These findings raise concern that LASP may

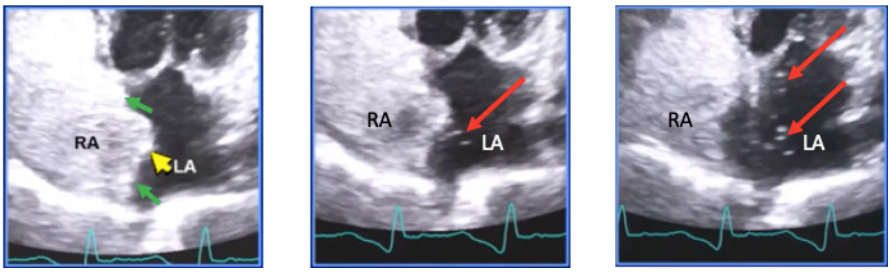

FIGURE 4 Beat-by-beat analysis during transthoracic echocardiography. Image demonstrates the beat-by-beat analysis showing the bubbles (red arrows) crossing into the left atrium (LA) from the right atrium (RA) across the interatrial septum (green arrows) and confirming the right-to-left shunt from a PFO. Also shown is the presence of an atrial septal aneurysm, with the fossa ovalis bulging into the left atrium, as indicated by the yellow arrow. Reproduced with permission of Sunil V. Mankad from his FASEB Catalyst Conference lecture.

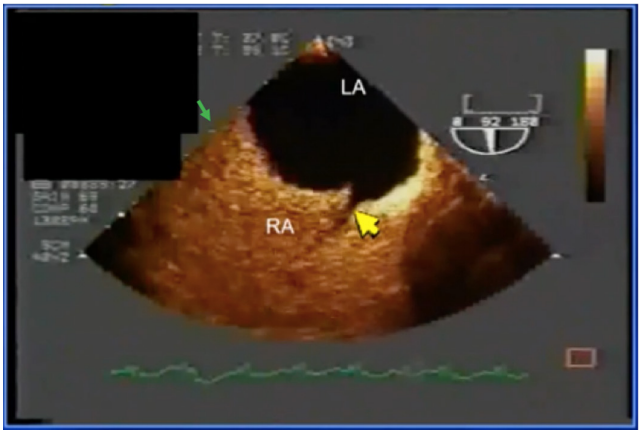

FIGURE 5 Negative contrast effect. Image shows an example of an echocardiographic study where there is a negative contrast effect, indicated by the yellow arrow, showing an area lacking the bubbles in the right atrium (RA) at the septum (green arrow), indicating a constant flow from the left atrium (LA) to the right atrium across a PFO. Reproduced with permission of Sunil V. Mankad from his FASEB Catalyst Conference lecture.

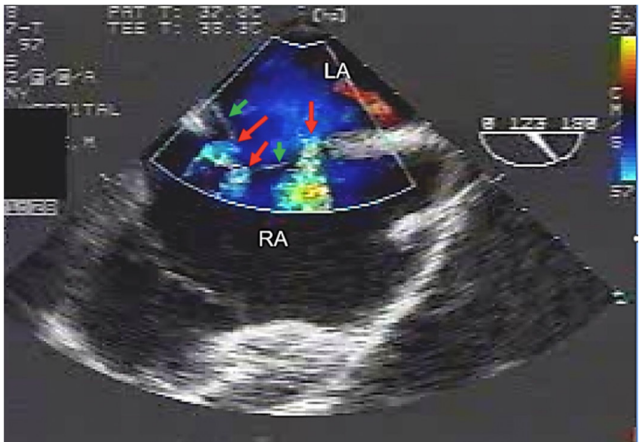

FIGURE 6 Fenestrated interatrial septum. Image shows an example of an echocardiographic image with color Doppler demonstrating flow through a fenestrated interatrial septum from the left atrium (LA) to the right atrium (RA). Red arrows indicate flow; green arrows indicate septa. Reproduced with permission of Sunil V. Mankad from his FASEB Catalyst Conference lecture.

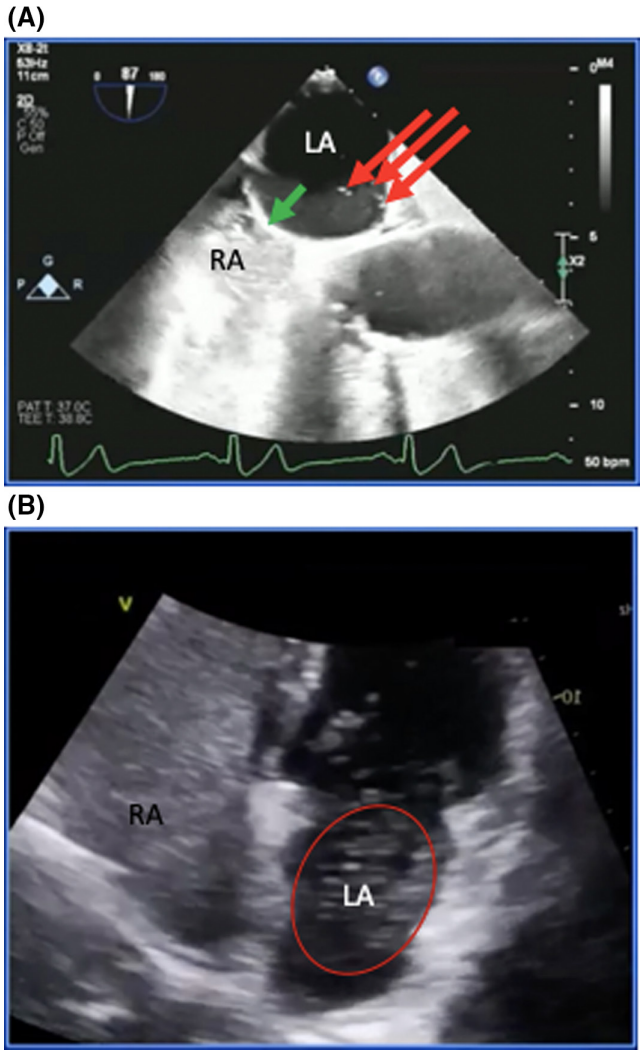

FIGURE 7 Side-by-side comparison of bubble studies on TEE and TTE. Images show a comparison between a TEE (A) and a TTE (B) performed on the same patient. The TEE shows evidence of a small PFO with a few bubbles (red arrows) crossing the septum (green arrow) from the right atrium (RA). The TTE of the patient participating in Valsalva maneuvers demonstrates many more bubbles in the left atrium (LA; indicated by the white dots seen in the area within the red oval), which is evidence of a larger PFO. Reproduced with permission of Sunil V. Mankad from his FASEB Catalyst Conference lecture.

be a source of embolus (Figure 9). Lastly, data have shown that in patients who have a PFO and an implanted cardiac device, such as a pacemaker, the incidence of stroke or TIA is fourfold higher.[21–23]

1.3 | Imaging of the interatrial septum: CT and MR

Mayil S. Krishnam (Stanford University, Stanford, CA, USA).

In cardiac CT, retrospective or prospective EKG-gated technique can be performed to evaluate the heart and coronary arteries. In prospective technique, only a predefined time point of the cardiac cycle, typically the diastolic phase, is acquired and therefore no functional information is generated, but this technique provides volumetric images of cardiac anatomy and also significantly reduces the amount of radiation exposure. In contrast, the retrospective technique will provide the functional information of the heart as the entire cardiac cycle over a certain number of heartbeats is acquired such that reconstructed

cine images would help to assess normal and abnormal myocardial wall and septal motion and also excursion and coaptation of valve leaflets.

Although various strategies, such as low kilovoltage (kV) and iterative reconstruction, can be used to reduce the radiation dose, the retrospective technique results in more radiation to patients when compared to the prospective method. Contrast opacification of the chambers is also needed to clearly demonstrate the anatomy of the interatrial septum, typically 70–100 ml of iodinated contrast can be administered at 3-4 mL/s and a bolus trigger with the region of interest (ROI) placed on the ascending aorta with a triggering threshold of 100–150 Hounsfield units (HU). In certain indications, the field of view (FOV) can be extended to include the whole chest in addition to coverage of cardiac structures to assess extracardiac shunts such as partial anomalous pulmonary venous return (PAPVR), but this extended FOV will also increase the ionizing radiation dose to patients. Cardiac MR results in radiation, and the general protocol includes steady-state free precession (SSFP), T1- and T2-weighted dark blood double inversion recovery, 2D phase contrast for flow, contrast (typically gadolinium-based)-enhanced magnetic resonance angiography (CEMRA), inversion time (TI) Look Locker scout, and IR delayed enhancement.

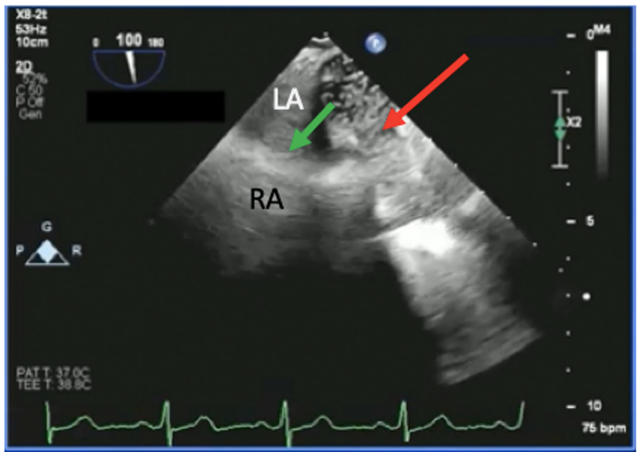

FIGURE 8 Intrapulmonary shunt. Image shows an echocardiographic study with return of bubbles through the pulmonary vein (red arrow), suggesting an intrapulmonary shunt is present rather than a PFO. Septum is indicated by the green arrow. LA, left atrium; RA, right atrium. Reproduced with permission of Sunil V. Mankad from his FASEB Catalyst Conference lecture.

Normal variant anatomy of the interatrial septum can be demonstrated using cardiac CT or MR to include the left atrial septal pouch (Figure 10), right atrial septal pouch, double interatrial septum, and PFO (Figure 11).[24] If the goal of the imaging study is to provide the most comprehensive assessment of the interatrial septum including flow assessment, cardiac MRI is a preferred modality of choice despite the ability to obtain better spatial resolution data on CT; however, it is dependent on the center's capabilities, imaging equipment, and expertise of the radiologist and availability of cardiac technologists. The quality of the study is important to guide potential interventions, and the size of both the septal defect and the rim must be considered; for example, for an atrial septal defect (ASD), the size of the rim must be at least 5 mm for a closure device to be placed (Figure 12). It is important that these clinical needs be taken into consideration when protocoling, performing, and interpreting imaging studies. In patients with atrial septal aneurysms, in addition to assessment of excessive bulging of the septum into the atrial chambers, defined as >1 cm, cardiac imagers should carefully evaluate cine images for a coexisting thrombus or PFO. In this regard, a time-resolved magnetic resonance angiography (MRA), phase contrast flow MRA, and 4D flow MRA may be helpful in assessing shunt within the atrial septal aneurysm.[25]

Differentiation between tumor types and thrombus at the interatrial septum can also be evaluated with cardiac MR or CT. In general, a thrombus that is avascular should not take up contrast, while a tumor such as an

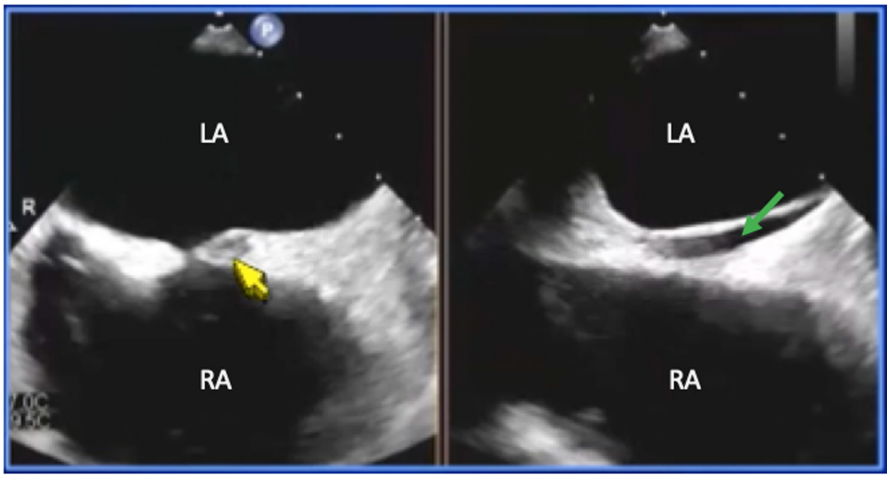

FIGURE 9 LASP with thrombus. Image demonstrates the presence of a left atrial septal pouch in a patient without a PFO that also has a thrombus within it, as indicated by the yellow arrow. The LASP cavity is indicated by the green arrow. LA, left atrium; RA, right atrium. Reproduced with permission from Sunil V. Mankad from his FASEB Catalyst Conference lecture.

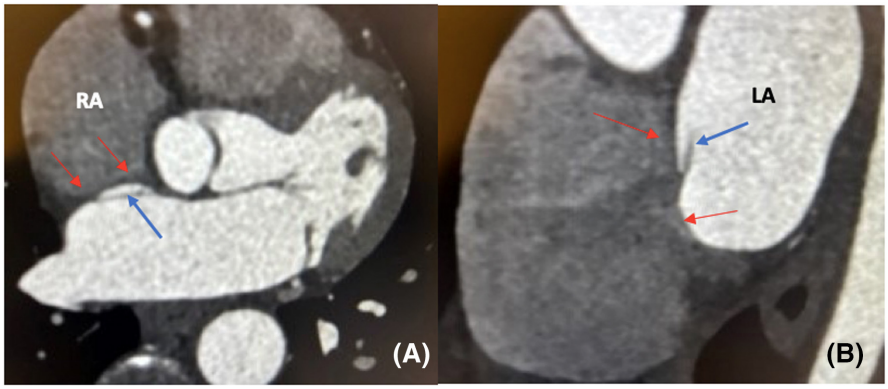

FIGURE 10 CT imaging of the heart showing a left atrial septal pouch. (A) Image shows a thin membrane (blue arrow) along the interatrial septum, indicated with red arrows. (B) Image shows an opening at left atrial side without a contrast-filled channel crossing the septum to right atrium (RA); findings are consistent with an incidental LASP. No thrombus is seen. LA, left atrium.

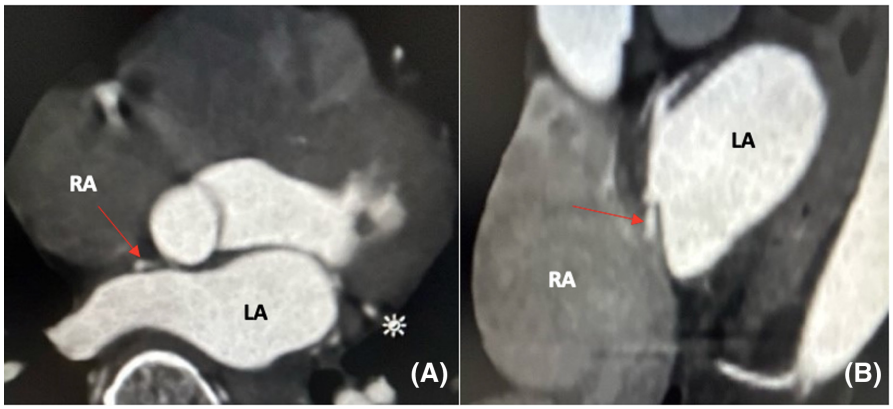

FIGURE 11 Patent foramen ovale (PFO) on CT. (A) Image shows a subtle thin contrast-filled channel (red arrow). (B) This sagittal image better shows the communication between the left atrium (LA) and right atrium (RA) through a defect at the fossa ovalis (red arrow) consistent with a PFO.

atrial myxoma, sarcoma, metastasis, or tumor thrombus should take up contrast, with the exception of benign tumors such as a cardiac lipoma that involves the septum. Incidentally noted intracardiac masses on echocardiography are therefore better assessed using MR or CT, but MR is the preferred choice to better characterize a cardiac mass, especially if the size is 10 mm or greater. Cardiac MR protocol with bright blood, dark blood, first-pass contrast perfusion, and phase-sensitive inversion recovery delayed enhancement, including with long TI sequences, would help. Cardiac CT and MR on patients with known anaphylactic contrast reaction may be challenging; however, MR can be performed using noncontrast sequences, such as SSFP for anatomical and functional information and 2D phase contrast for flow quantification; additionally, 3D free-breathing noncontrast-enhanced MRA and real-time SSFP cine images can be performed in the diagnostic workup of challenging patients who have difficulty holding their breath.[26]

In ASD and PFO patients status post-closure device, cardiac CT can be performed to evaluate closure device position and for any residual shunt, which can be seen as contrast leak across the device. In summary, cardiac CT and MR imaging provides useful information in the assessment of interatrial septal diseases. Therefore, understanding the CT and MR imaging protocol is important to demonstrate normal and abnormal septal morphology, including LASP, and also various interatrial septal diseases.

1.4 | Mechanism of stroke with PFO

MingMing Ning (Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA).

The mechanism of PFO-related stroke may seem simple, with the PFO merely acting as a conduit through which peripheral clots enter the brain; however, PFO stroke is a complex multiorgan disease. The brain and heart communicate through the blood via atrial septal shunting, which is a concept essential to understanding the mechanism of PFO stroke.[27] In addition to serving as a "back door" for clots, PFO right-to-left shunting directly exposes the brain to injury by allowing procoagulable and oxidative harmful factors to bypass the lung's detoxification.[28–30]

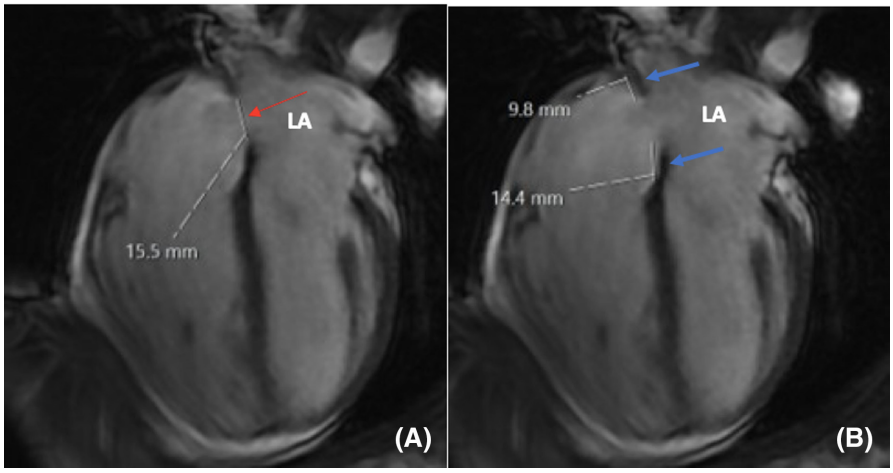

FIGURE 12 Atrial septal defect (ASD) on cardiac MR. (A) Image shows a snapshot of a four-chamber cine steady-state free precession (SSFP) with a 16 mm defect (red arrow) at the midseptum, consistent with a secundum type of ASD. LA, left atrium. (B) Image shows adequate rims (blue arrows) greater than 5 mm to the defect shown. Precontrast 2D phase contrast imaging to assess flow quantification at the ascending aorta and main pulmonary artery (not shown) demonstrated a shunt ratio of greater than 1.5, suggesting a significant shunt from the ASD. Although 4D flow was performed in the patient, this technique is usually performed after IV contrast and currently is not widely practiced in other centers.

It is important to understand how the brain and heart communicate and influence each other through bidirectional signaling via blood. Without blood supplied from the heart, during an ischemic event such as stroke, nearly 1.9 million neurons die per minute.[31] Conversely, through emotional stress, the brain has been shown to influence the heart during stress cardiomyopathy, which can result from a surge in circulatory catecholamines.[31–37] Overall, more than 30% of all ischemic strokes may involve the heart.[38]

Studies also show that blood procoagulable states and conditions that promote venous clotting, such as May–Thurner pathology, long-distance travel, and pregnancy, can all result in substantial risk for stroke.[27,39] A predisposition to form clots is key in the mechanism of PFO-related stroke. Hypercoagulability increases recurrent stroke risk, and anticoagulation can reduce this risk by about half. Various hypercoagulable states can affect the efficacy of anticoagulation, and in those patients who have multiple hypercoagulable factors, these tend to have a multiplying, rather than additive, effect on risk.[40,41] In a prospective study with 591 hypercoagulable PFO stroke patients with long-term follow-up, patients with hypercoagulable state had significantly higher risk of recurrent events (hazard ratio [HR]: 1.85; 95% confidence interval [CI]: 1.09–3.16; p ¼ .024).[40] The choice of therapy matters for these high-risk patients such that PFO closure was better compared to medical therapy (HR: 0.16; 95% CI: 0.09–0.30; $p < .001$), and for those on medical therapy, anticoagulation was superior compared to antiplatelets (Figure 13).[40]

According to Special Coagulation Laboratory, the cost of checking a hypercoagulable panel is about $1200 USD, which is similar to daily morning routine complete blood count (CBC) and electrolyte monitoring in an inpatient setting. However, the cost of a recurrent stroke far exceeds $80 000 USD.[42] Thus, it is both prudent and cost-effective to check for a hypercoagulable state.

The success of several well-executed randomized controlled trials, such as RESPECT, CLOSE, and REDUCE, has helped to establish better clinical guidelines for PFO stroke treatment.[12,13,43] However, all major trials excluded patients with known hypercoagulable states.[12,13,43] Due to such significant exclusion criteria, a major challenge remains, as data from these trials are not generalizable to more than 70% of our clinic population in the real-world setting. Future studies need to include patients with hypercoagulable states, as they have the highest risk of recurrent stroke, and stand to benefit most from appropriate treatment.

In order to better understand how to treat individual patients who would have been excluded from the trials, the key is understanding the mechanism of injury from the heart to the brain. PFO's right-to-left anatomical shunting physiology is central to clot formation and neurovascular injury. We learned from pivotal clinical trials that the number needed to treat has also decreased from the 40s to around 17 as a result of larger shunt size selection.[12,13,43] And in 1078 patients who underwent a PFO closure, those who had residual right-to-left shunting after endovascular closure had a fourfold increased incidence of recurrent stroke or TIA.[12,13,43,44] This indicates that both shunting and residual shunting physiology matter in stroke recurrence.

PFO shunting does not only enable clots to go through: its physiology helps to form clots, too. In analyzing blood

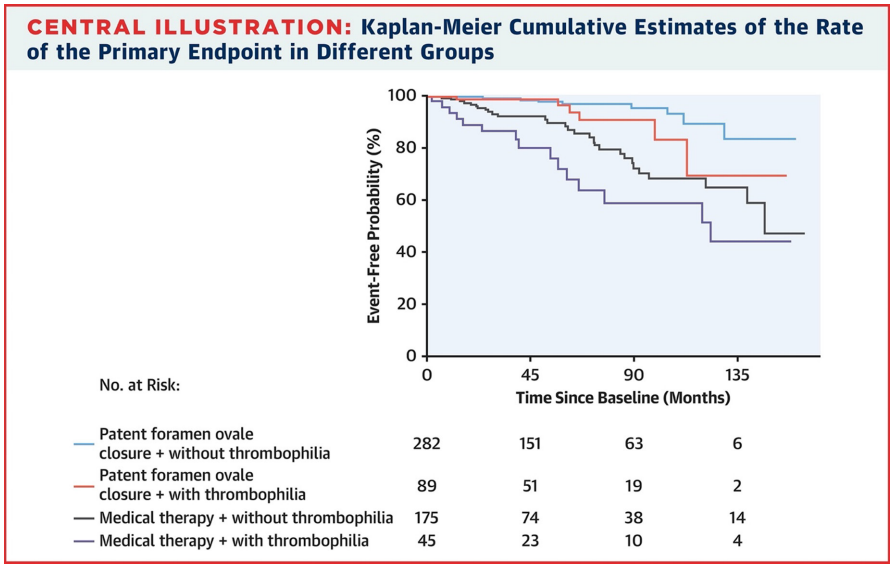

FIGURE 13 Kaplan–Meier survival curve comparing PFO closure, medical therapy, and anticoagulation groups. The illustration demonstrates superiority in patients with hypercoagulable states who underwent PFO closure as compared to those who were treated with medical therapy alone in terms of a Kaplan–Meier curve with event-free probability in percent. Reprinted from *JACC Cardiovascular Interventions*, Volume 13, pp. 2745–2752, Kai Liu, Bo Song, Igor F. Palacios, Ignacio Inglessis-Azuaje, WenJun Deng, David McMullin, XiaoYing Wang, Eng H. Lo, YuMing Xu, Ferdinando S. Buonanno, and MingMing Ning, Patent foramen ovale attributable cryptogenic embolism with thrombophilia has higher risk for recurrence and responds to closure; Copyright 2020, with permission from Elsevier.

in the cardiac atria pre- and post-PFO closure, it was noted that PFO closure lowers procoagulable factors, such as homocysteine, serotonin, and oxidized cholesterol (Figure 14).[28–30] The lungs can act as a detoxification organ that helps to remove many procoagulant factors, including homocysteine. When a PFO with significant right-to-left-sided shunt is present, these procoagulant factors can bypass the lungs, and this can result in a procoagulable state even in patients without any known genetic hypercoagulable condition.[28–30]

Since PFO-related stroke is a multiorgan systemic disease involving the brain, heart, lung, and blood, multidisciplinary collaborative efforts are key to understanding the mechanism and tailoring therapy. While the PFO anatomy can act as a clot conduit, over the past decade, emerging data clearly show that atrial septal shunting physiology itself can cause blood hypercoagulability and augment ischemic risk. Therefore, understanding the mechanism of PFO-related stroke through blood chemistry is crucial for individualizing treatment.

1.5 | PFO closure: A cardiologist's approach

Pranav M. Patel (University of California, Irvine, Irvine, CA, USA).

First and foremost, it is imperative that the cardiologist and the neurologist collaborate with one another for their patient. Cryptogenic stroke is a common problem and occurs in the absence of any identifiable cardiac event, without large vessel stenosis or atherosclerosis, in a pattern not consistent with small vessel disease as might be seen with a lacunar infarct.

Approximately 200,000 strokes per year in the United States are cryptogenic.[45] In patients diagnosed with a cryptogenic stroke, half will have an incidental finding of PFO, and in those patients, half are thought to be pathogenic, in which an embolus may cross and travel to the brain.[45]

In addition to PFO, LASP may be a source of a thromboembolic event and should be in the differential diagnosis. However, currently, there is no clinical practice guideline on how to treat it, given that it is a relatively new finding. Clinicians may treat it with anticoagulation or antiplatelet medications, but evidence is lacking to help guide therapy. Although it is plausible that LASP causes cryptogenic stroke, there is not enough evidence on how to manage these patients. More data and research are needed to this end.

Initially, trials such as the PC and CLOSURE I did not show that PFO closure was superior to medical therapy with anticoagulation or antiplatelet therapy. However, more recent studies, including the CLOSE, RESPECT, and DEFENSE trials, with longer follow-up, did show superiority of closure compared to medical therapy.[12,13,43,46,47] As a result, there has been a trend toward performing more PFO closures. Reasons for the discrepant results between the older studies and more recent trials are unclear.

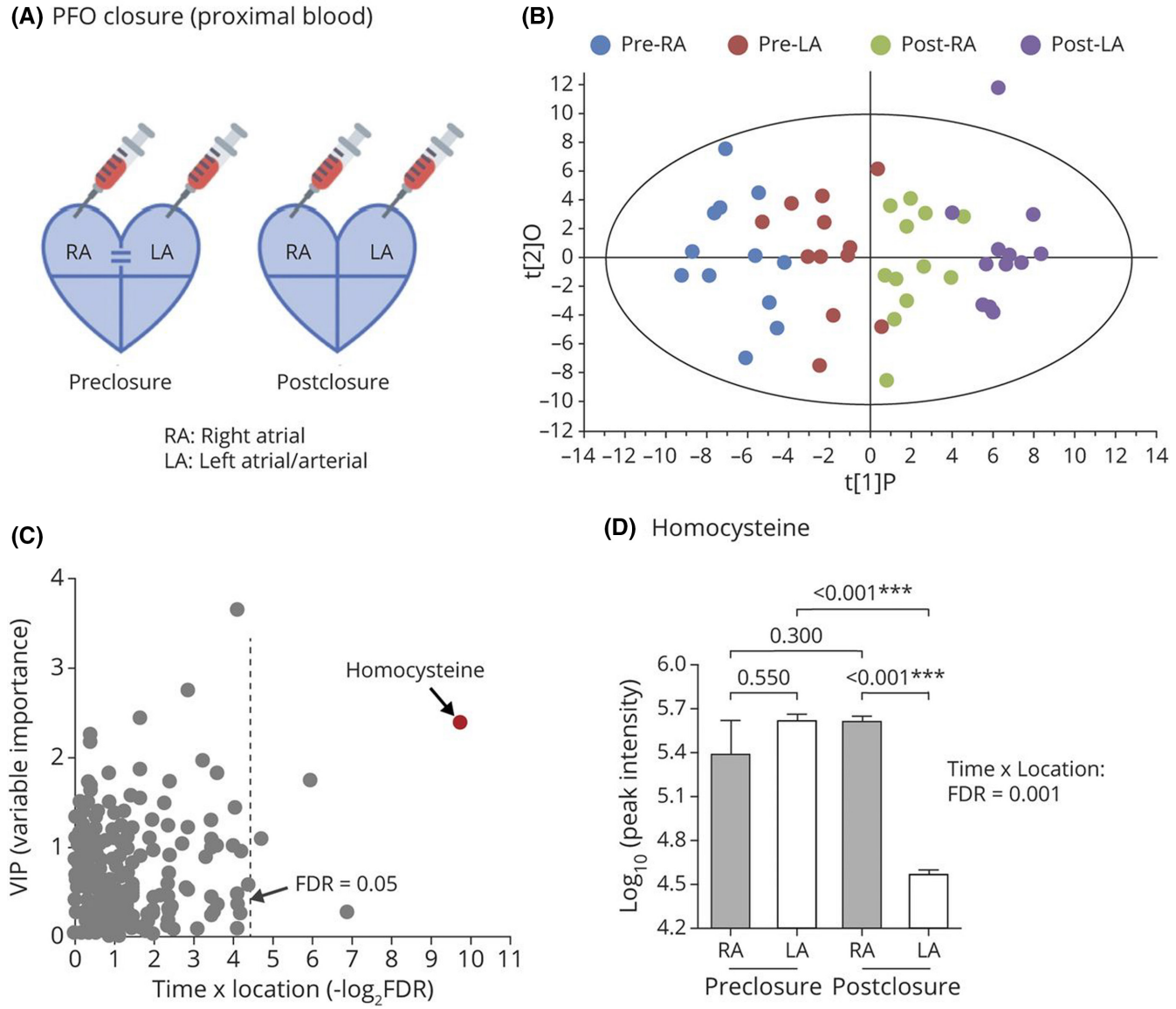

FIGURE 14 Metabolite profiles in patients who underwent PFO closure. Composite image shows (A) an illustration of blood sampling during PFO closure; (B) a scatterplot of orthogonal projections to latent structures discriminant analysis (OPLS-DA) score for the metabolites identified in pre–right atrium (RA), pre–left atrium (LA), post-RA, and post-LA; (C) a scatterplot of variable importance for projection (VIP) values from OPLS-DA versus log-transformed false discovery rate (FDR) from two-way repeated-measures analysis of variance; and (D) peak intensity of homocysteine with pairwise comparisons, $*p < .05$; $**p < .01$; $***p < .001$. Homocysteine is a metabolite associated with prothrombotic state. Reproduced with permission from Wolters Kluwer Health, Inc., with credit to Wenjun Deng, David McMullin, Ignacio Inglessis-Azuaje, Joseph J. Locascio, Igor F. Palacios, Ferdinando S. Buonanno, Eng H. Lo, and MingMing Ning, Effect of patent foramen ovale closure after stroke on circulatory biomarkers, *Neurology*, Volume 97, Issue 2, pp. 203–214, https://n.neurology.org/content/97/2/e203.

Looking more carefully at these, the initial studies used varying inclusion criteria, while more recent ones used stricter inclusion criteria aimed at patients whose initial strokes were more likely to be related to embolism from a PFO.[48] The more recent trials also looked at different types of occluders, and it should be noted that not all PFOs were completely closed with a particular device, which may have influenced some earlier data.[48] The REDUCE trial and subanalysis demonstrated the benefit of PFO closure, particularly in younger patients.[13] It demonstrated a relative risk reduction of 77% and an absolute risk reduction of 4%.[13] The safety profiles between medical management and PFO closure were comparable, including the incidence of atrial fibrillation that can occur post-PFO closure.[13] The atrial fibrillation was most often transient, usually resolving within 30 days.[13]

As more data become available, practice advisories shift in response. In 2020, the American Academy of

Neurology (AAN) released a new practice advisory for PFO closure, stating that in patients younger than 60 years who have evidence of PFO and embolic infarct and no other mechanism of stroke identified, PFO closure should be discussed.[17] This represents a significant shift since their previous practice advisory in 2016, which stated that PFO closure was not recommended.[17]

The decision to proceed with PFO closure should be made in a collaborative fashion among cardiology and neurology, and consultations with other services, such as hematology, may be warranted. As a part of the workup when considering PFO closure, the interventional cardiologist may consider a neurology consult, brain imaging, extracranial imaging, hematology consult for thrombophilia, and hypercoagulability testing. Other essential testing includes TTE and TEE. Each can be performed with a bubble study with or without Valsalva maneuvers.

Additionally, identification of underlying atrial arrhythmia with monitoring for 30–90 days depending on age and risk should be considered. Another consideration is the implementation of the Risk of Paradoxical Embolism (RoPE) score, which may help evaluate the risk of a paradoxical embolism and could be helpful in identifying patients more likely to benefit from closure.[49] Clinicians could also consider the modified Rankin score.[50]

Once the decision to close a PFO has been made, there are several devices to choose from, such as the Gore Cardioform septal occluder and the Amplatzer device.[12,13,43] TEE and intracardiac echocardiography (ICE) can be used to guide PFO closure, and as the quality of ICE improves, it may ultimately become the preferred imaging guidance modality. These are relatively simple procedures in which initially the PFO is crossed with the self-expanding closure device loaded on the catheter. The left atrial side of the device expands when positioned in the left atrial space, at which point it is pulled back to the septum, and the second disk for the right atrial side opens up, with the interatrial septum flanked by the two disks. Once the optimal positioning of the implant is confirmed, the device can be disconnected from the catheter. Over time, the device will be epithelialized, with no communication across the septum. Of note, it is still possible to perform future transseptal punctures through the device if needed. The procedure is generally tolerated well, and most patients are discharged from the hospital the same or the following day. Data suggest that PFO closure and medical therapy combined may not only reduce the risk of stroke but also reduce cost (after 2.5 years) and improve quality of life in terms of physical vitality, mental health, general health, and social functioning.[51,52] The number needed to treat is improving as more data become available and is now under 30.

1.6 | PFO and stroke etiology: Culprit or an innocent bystander?

Chi Kyung Kim (Korea University College of Medicine, Seoul, South Korea).

When evaluating a patient who has been diagnosed with a cryptogenic stroke, it is important to consider all other potential causes before being able to judge whether an incidentally noted PFO is likely to be the cause, or if it is an unrelated finding. In order to do this, the clinician may consider acting a bit like a police detective and "profiling" the PFO while also examining the "scene of the crime." Profiling the PFO would be to thoroughly evaluate the behavior of the PFO, while imaging would be the evaluation of the scene.

To help illustrate the importance of this evaluation, consider two clinical cases. The first is a 34-year-old woman with transient left hemiparesis 2 weeks prior, and dysarthria and facial palsy 3 days ago, whose brain imaging shows a small infarction in the corona radiata area and no occlusion or stenotic regions in vessel imaging, which was suggestive of small vessel disease. The patient had hypertension, Type 2 diabetes with hemoglobin A1c of 9.1, and obesity with BMI of 39.8. In this patient, a PFO seemed to be unlikely, so no imaging for PFO was performed. The second case is a 35-year-old woman with sudden-onset vertigo 6 h prior to presentation and no risk factors. She had a cerebellar lesion, seen on brain imaging, suggestive of an embolic source with no vascular occlusion or stenosis and a transcranial Doppler suggesting a possible shunt. TEE was then performed, showing a large bidirectional shunt, and further imaging noted a deep vein thrombus in her lower extremities. In the latter case, the PFO was deemed to be the most likely cause. In these two cases, the characteristics of the imaging (or evaluation of the scene) and the clinical characteristics of the patient were integrated to make the final determination regarding pursuing a PFO. While the RoPE score is an important tool to help decide on the PFO, it does not take into consideration the imaging findings, but only the clinical characteristics, and both imaging and clinical information are necessary to make the best determination.[49]

There are several limiting factors to consider when evaluating these patients. While it is true that many studies have shown that PFO closure is superior to medical therapy alone, it is important to remember that the risk of worsening stroke or debility was not significantly different and that was likely because the type of stroke itself does not usually cause extensive disability to begin with.[11] There is also no direct consensus on how to determine the high-risk stroke patients based on the number of bubbles seen on the bubble study component of an echocardiogram, but it seems to be around 20–25.[14] Concerns also

exist surrounding the classification system of stroke being related to stenosis because both atherosclerosis and plaque burden play an important role; in the future, these should also be included.[53] Finally, imaging findings need to be incorporated in the evaluation of these patients, as there are stroke patterns that vary from a PFO-associated stroke to an atrial fibrillation-associated stroke.[54,55] For example, there is evidence that posterior circulation strokes are more likely to arise from a PFO than another cause;[54,55] a study from China demonstrated that cortical lesions are associated more with non-PFO strokes, and PFO-related strokes seem to be more associated with the posterior circulation.[54,55] Taken altogether, it is imperative that clinicians take both the patient's clinical factors and imaging factors into consideration in a multidisciplinary team approach when evaluating a PFO as a potential cause of cryptogenic stroke.

2 | THE DEBATE

2.1 | Pro: LASP is a stroke risk factor

Ruchi Kapoor (University of Washington, Seattle, WA, USA): During embryological development, the septum primum and secundum approach each other, and a shunt forms across this site through the foramen ovale.[56] The foramen ovale closes after birth and eventually fuses, leaving most of the population with a fused septum; however, in about a quarter of the population, it fails to fuse and can open with maneuvers such as Valsalva.[56]

In a subset of patients, there is partial fusion of the septa, such that the foramen ovale is not patent (i.e., no shunt across the septum), but the partial fusion leads to the formation of a blind pouch with the unfused edge of the septum open to either atrium.[56] In the original case series by Dr. Krishnam, the septal pouch open to the left atrium (LASP) was found to be more prevalent than PFO, and although this has not been completely supported by subsequent imaging studies, it has been seen in around 40% of patients.[56] There is a concern that the LASP can be a nidus for thrombus formation and thus a cause of stroke.[57] Many case series since have reported thrombi seen at the LASP, and it is easy to imagine how these thrombi might dislodge and embolize.[58–67] While many of these cases were patients with other prothrombotic cardiac conditions, one of the subjects (Case 5) in a case series was a 54-year-old man with no prior cardiac history or arrhythmias who suffered an ischemic stroke and was found to have a thrombus associated with the LASP.[67] This patient was treated with anticoagulation, and follow-up imaging showed that the thrombus had resolved.[67]

The following studies all report a positive association between stroke and LASP. The first is a study by Wong et al., who examined the LASP prevalence among cryptogenic and noncryptogenic stroke subtypes based on the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification and reported an odds ratio of 2.7 for association of LASP with cryptogenic stroke.[68] A Chinese study by Sun et al. reported an odds ratio of 2.4 for cryptogenic stroke, as compared to no stroke for LASP prevalence.[20] Another study by Holda et al. demonstrated an odds ratio of 2.0 for LASP prevalence in cryptogenic stroke.[69] A 2018 meta-analysis noted an odds ratio of 1.52, supporting the association between cryptogenic stroke and the LASP.[70] A more recent study conducted by Kapoor et al. showed an odds ratio of 2.4 for cryptogenic stroke in patients with LASP, compared to noncryptogenic stroke.[57]

Similarly, another group, Steyaert et al. in Brussels, analyzed TEEs in patients with ischemic strokes using stricter criteria for embolic strokes of undetermined source (ESUS), and showed an increased prevalence of the LASP in the ESUS group, with an odds ratio of 1.6, and who were more likely to be younger and less likely to have traditional risk factors such as diabetes and hypertension.[71]

Currently, the understanding of the LASP may be in its infancy, analogous to the earlier years when the role of PFO in stroke was being elucidated. It is known that in cryptogenic stroke, there is an odds ratio of 2.9 in favor of an association with a PFO, and that the odds ratio for the LASP ranges between 1.5 and 2.4 comparable to that of smoking and diabetes, two of the well-acknowledged risk factors for stroke.[72] Given these data, it may be posited that the LASP may be considered an important risk factor for stroke and warrants further discussion on how to manage it when it is present in a patient with ESUS or cryptogenic stroke. Just as screening for a PFO is now routine in the evaluation of stroke, consideration should be given to screening patients with cryptogenic strokes for the presence of a LASP.[72] Barriers to this screening include the invasive nature of TEE, a lack of awareness in echocardiographers of this structural entity, and challenges in ruling out a PFO.

2.2 | Against: LASP is a stroke risk factor

Marco R. Di Tullio (Columbia University, New York, NY, USA): The LASP can be considered a risk factor in particular patients and under specific circumstances, but it is not a definite independent risk factor for stroke. The frequency of LASP in patients is approximately 40% in autopsy.[56] Of the three case studies that were given as examples during the pro side of the argument earlier, two had spontaneous echo contrast, which is a procoagulable

condition, or other cardiac conditions, such as a severely reduced left ventricular ejection fraction, that could in and of themselves serve as stroke risk factors.[58–66] In the aortic plaque and risk of ischemic stroke (APRIS) study, our group performed TEEs in 187 patients with stroke and 157 controls and noted that LASP prevalence was similar in both groups.[73] Between cryptogenic stroke patients and controls, there was no difference in atrial septal aneurysm or the prevalence of a LASP.[73] Predictors of stroke in a multivariable analysis were age, diabetes, and hypertension, but not LASP.[73] Thus, this study did not support an association between the presence of a LASP and ischemic stroke.[73] In the following years, three studies supported the role of LASP as a stroke risk factor, two with very low LASP frequencies and one with very high LASP frequency instead, which suggests different diagnostic criteria; two other studies, however, were against it.[57,68,69,74,75] Then, the results of two meta-analyses were also discordant, leaving uncertainty about the real role of LASP as a stroke risk factor.[70,76]

Contrasting the APRIS study and Dr. Kapoor's study, notable differences include patients' age (the average age 70 vs. 58, respectively) and the frequency of LASP in the cryptogenic stroke subgroup (32% vs. 43%, respectively). The LASP frequency was similar between the two studies in noncryptogenic strokes and controls.[57,73] Therefore, the cryptogenic stroke group alone drove the final differences between the studies, and the age differences between the studies may have been involved.

From the standpoint of embolic potential, the LASP may be somewhat reminiscent of the left atrial appendage (LAA). Morphologically, there are four main types of LAA, with the most favorable anatomic version, called "chicken wing," being associated with the lowest stroke rate.[77,78] The other morphologies, found in 50% of the population, were shown to be associated with a much higher frequency of stroke history.[78] Despite this, clinicians would not regularly think about anticoagulating all of these patients just on the basis of their LAA morphology; a similar argument can be made for LASP. In a patient with an LAA that has thrombus or spontaneous ECHO contrast, the risk of embolus is high. This risk is due to the thrombus or prethrombotic stagnant flow that may lead to the formation of the thrombus, not to the LAA morphology itself. Similarly, clinicians should look for underlying risk factors for thrombus formation when a LASP is present, rather than attributing the stroke risk to the LASP itself.

There are similarities and differences between a PFO and a LASP. Both are highly prevalent in the population and more frequently observed in younger patients. Both are diagnoses of exclusion as an etiology for stroke, and neither will cause stroke on their own but rather require cofactors like blood stasis, hypercoagulability, or circulating thrombi. It is possible to have a stroke in a completely normal heart with a PFO via paradoxical embolism, but so far, LASP has mostly been related to stroke in abnormal hearts, suggesting that other conditions may be responsible for the stroke risk rather than LASP alone, although those conditions may also contribute to make LASP a predisposing factor. Notably, PFO has been implicated in recurrent stroke risk consistently, but this has not been demonstrated in LASP. Also, the treatment considerations for LASP are limited, and only related to coexisting conditions, such as prothrombotic states.

In summary, the evidence regarding the role of LASP as a risk factor for ischemic stroke remains controversial, with most data having been obtained in case–control studies that were limited by heterogeneity in study design and study populations. While it is possible that LASP, in theory, may act as a potential nidus for thrombus formation and subsequent embolization, such a postulation also applies to other structures within the left atrium, such as left atrial appendage, and does not place LASP itself as a specific stroke risk factor. Longitudinal studies would be needed to assess the real stroke risk associated with LASP and inform preventative strategies.

3 | REBUTTALS

Ruchi Kapoor: While it is true that more robust and prospective studies are needed, the odd ratios in the retrospective studies to date are consistently greater than one in favor of the LASP as an independent risk factor for stroke.[20,57,62,68,70,71,79–81] Based on the data that have been compiled so far, the LASP does not appear to require other cofactors to increase the risk of stroke. To this end, two case reports demonstrated the LASP associated with stroke without other risk factors. Admittedly, there is a need for more rigorous studies to standardize differentiation of a PFO from a LASP and better prospective studies to evaluate the LASP and stroke risk. LASP will likely evolve from being an incidental finding to playing a more important role in the evaluation of stroke. The role the LASP plays in thrombus formation remains to be seen, but there are more data being published to address this issue. One proposed mechanism by Gurudevan is a possible promotion of stasis in the flow and thrombogenesis between the right superior pulmonary vein and the adjacent LASP.[60]

Marco R. Di Tullio: With regard to the mechanism related to the pulmonary venous flow raised by Dr. Kapoor, again this would seem to support the idea that, in the absence of irregular blood flow, the LASP is unlikely to form a thrombus. Only if that abnormal flow is present, the LASP will act as a nidus for thrombus formation, which reinforces the fact that the LASP by itself is not the

risk factor for stroke, but rather it is the flow within the heart or some other similar factor that makes the LASP relevant or increases its risk of forming a thrombus. Many other structures, such as a certain shape of the left atrial appendage or the presence in it of pectinate muscles (normal structures that might, however, become a nidus for thrombus in the presence of blood stasis), could similarly be considered risk factors. A PFO can lead to a stroke in a perfectly normal heart through paradoxical embolization, while a LASP may do so only in abnormal hearts that have conditions predisposing to thrombus formation. There is therefore a difference between conditions such as a PFO, where there is a direct contribution to stroke, and a LASP. That being said, there certainly is a need for more studies that investigate LASP and the risk of incident stroke.

4 | FINAL REMARKS

Ruchi Kapoor: There are a few examples of clot-bearing LASP in an otherwise normal heart. However, additional studies are needed to further evaluate potential causes of this and whether other yet undefined factors could play a role in cardiogenic stroke in the context of LASP. A more complete set of studies looking at left atrial appendage velocities, TTE, TEE, and maybe even cardiometabolic factors should all be looked at to help elucidate a more complete mechanism for the LASP as a risk factor for stroke.

Marco R. Di Tullio: Additional studies are definitely needed. It would also be interesting to see the outcomes of the APRIS patients who were not treated with anticoagulation and had a LASP. It is likely that in longer follow-up of patients with a LASP, there would not be any significant difference between them and patients without LASP with regard to stroke incidence unless other coexisting conditions were present that increase the risk of thrombus formation. This hypothesis needs to be tested.

5 | THE ROUND TABLE DISCUSSION

Jinman Jung (Korea University Ansan Hospital, Seoul, South Korea): Additional studies on this topic are needed. Currently, the hospital in Korea where I work and six additional affiliated stroke centers in Korea, as well as the University of California, Irvine, are all working on a multidisciplinary LASP study looking at ischemic stroke patients who underwent TEE. The study is currently in progress with long-term follow-up and may be able to help address some of the concerns and findings voiced earlier during the conference.

Mark J. Fisher (University of California, Irvine, Irvine, CA, USA): We have a question about whether LASP and PFO could be treated similar to a pulmonary embolism, where a course of anticoagulation is prescribed while other potential causes such as hypercoagulability or heart dysfunction can be explored and potentially addressed. Could this be a potential strategy for stroke prevention?

Marco R. Di Tullio: The use of anticoagulation in pulmonary embolism is motivated by the presence of documented emboli in the pulmonary arterial bed, a circumstance that may not always be documented in the cerebral circulation in the case of a stroke. Coming to other conditions that may present some similarities with LASP, our group and others are conducting a study called ARCADIA (Atrial Cardiopathy and Antithrombotic Drugs in Prevention after Cryptogenic Stroke) where patients with atrial cardiopathy are randomized to apixaban or aspirin and will be followed up to the effect of these treatments on recurrence rate of stroke. The risk of stroke in atrial cardiopathy may not necessarily be related to atrial fibrillation, which makes the testing of systemic anticoagulation in patients with suspicion of atrial cardiopathy an interesting one. Also, there is very little data on the use of anticoagulation to prevent stroke in patients with PFO. The treatment to prevent recurrent stroke is usually PFO closure with antiplatelet treatment or just antiplatelet treatment alone, with recent data favoring the first approach in selected patients; regarding anticoagulation, there are no studies that have looked at nonvitamin K oral anticoagulants (NOACs) in preventing stroke in PFO patients, but only older studies that looked at warfarin as a preventive option, which has issues both with patient compliance and with maintaining a therapeutic range; if the patient is not in the therapeutic range for a sufficient time, the risk of thromboembolic phenomenon is about the same as patients not taking warfarin. Therefore, while there are good studies on PFO closure, there are no clear guidelines for the treatment of those patients who do not want or cannot undergo PFO closure or patients who are over the age of 60, for whom closure is currently not recommended in the guidelines. The role of anticoagulation in secondary stroke prevention in PFO is undefined right now; it sounds like a reasonable option, but more information is needed.

MingMing Ning: Tailoring therapy is key. The benefit and risk profile of anticoagulation must be clearly assessed before initiation. For example, a patient with a true hypercoagulable state with low bleeding risk should get anticoagulation, but anticoagulation would not necessarily preclude PFO closure. In a prospective cohort of 591 patients, those with hypercoagulable states with large shunts have the highest stroke recurrence.[40]

If medication compliance is an issue, or anticoagulation therapeutic range is difficult to achieve (like those with antiphospholipid syndrome), these ultra-high-risk patients may need both anticoagulation and PFO closure to prevent future events. In high-risk patients, clinical decisions need to be made on a case-by-case basis, aiming at the underlying mechanism.

Pranav M. Patel: From a clinical provider's perspective, telling a stroke patient that there is not enough evidence to close a PFO when the patient has a PFO can be difficult, especially when as a part of the conversation they are also told that if they are on anticoagulation and they have another stroke, then the provider will close it. Many patients may take issue with this approach.

Jin Kyung Kim (University of California, Irvine, Irvine, CA, USA): There seems to be a higher prevalence of LASP in the younger patient population, which may suggest possible plasticity of cardiac tissue in which the layers of the septum continue to fuse into adulthood, eventually leading to complete fusion and thus lower prevalence of the LASP in older adults. Is there any evidence that suggests this happens?

Jeannette P. Lin: It is a very good question, but there are not enough good data to say with any certainty.

Marco R. Di Tullio: There was a landmark study in the 1980s at the Mayo Clinic that showed that PFOs in the elderly are less frequent than they are in younger patients, and tend to be larger. There is some indication that smaller PFOs may spontaneously close during life and only larger ones stay open. This is likely the case for the LASP, where smaller ones may disappear over time. It is surprising that in the database of studies on LASP, there are 30% or more of the patients undergoing TEE who have a LASP, whereas on routine daily TEEs, its frequency seems to be lower; this may depend on how we define LASP, and especially its size. Large pouches like the ones presented today during the conference are not frequently seen. There is a definite difference in LASP sizes and smaller ones may in fact close over time.

Jin Kyung Kim: Given the data for the association between ischemic stroke and LASP, how can clinicians diagnose LASP better, especially if it has treatment implications? Sometimes a TEE is semi-invasive, can be difficult to do, and not all views may be obtained to define the presence or absence of a LASP. What other imaging modalities, other than TEE, are recommended first line to evaluate the LASP?

Mayil S. Krishnam: Given the high spatial resolution of CT, I would recommend a CT for that. MR is good, but since there is no functional assessment needed, the study that is needed would be something that has high spatial resolution to really evaluate the thin membrane.

Ruchi Kapoor: What is the smallest septal structure that can be seen on CT?

Mayil S. Krishnam: The thinnest structure that can be visualized is between 0.5 mm and 0.6 mm on CT, which is very thin, and this thin structure cannot be imaged using MR.

Mark J. Fisher: There is a question from the audience with regard to the lecture given by Dr. Ning, whether the reduction in homocysteine levels correlated with shunt size and septal aneurysm after PFO closure?

MingMing Ning: The homocysteine level reductions did correlate with the PFO closure, with a reliable dose–response effect in which the larger the PFO shunting, the larger the reduction in homocysteine level. This evidence supports PFO right-to-left shunting physiology contributing to clot formation.

Mayil S. Krishnam: Is there a society recommendation or this panels' recommendation on seeing so many PFO structures on routine imaging, sometimes four to five per week, regarding what should be done if one is found?

Sunil V. Mankad: There was a Cleveland Clinic observational study that showed that if incidentally noted PFOs were closed during another cardiac operation, there was a higher incidence of adverse events. A multidisciplinary team must work together to decide if these PFOs are significant and that ultimately the neurologist will need to help guide the cardiologist and interventional cardiologist regarding further intervention.

Mayil S. Krishnam: What features on imaging or risk score may help to guide intervention?

Sunil V. Mankad: High-risk features on echocardiography are having a large atrial septal defect, degree of shunting, and other right atrial structures, such as a Chiari network or long tunnel PFO. But the anatomy by itself would not cause you to close it. An atrial septal aneurysm probably increases risk of stroke in and of itself; if a PFO is also present in this setting, antiplatelet therapy was demonstrated to be inadequate in a study in the *New England Journal of Medicine*.[43]

MingMing Ning: That older study was well done and still valid. The cardiac features are very important, and other new risk factors need to be considered as well, including older age and risks that promote clotting, such as May-Thurner's, long travels, sleep apnea, Valsalva, divers, astronauts, and the list goes on and on. The input and collaboration between neurologists, cardiologists, and other longitudinal providers are important regarding the dynamic nature of PFO, and the challenges surrounding its identification are humbling. PFO is opportunistic, and many new factors that increase clotting, for example COVID, augment risk.

Pranav M. Patel: Another thing to consider is that in the initial admission of patients with strokes, about 2%

were noted to have atrial fibrillation in the first 24 h of telemetry monitoring. If you followed these patients, the incidence of atrial fibrillation became even higher, around 15–18%, so these patients may benefit from a monitor before PFO closure or other interventions.

Marco R. Di Tullio: There was an old study from France on atrial septal aneurysm and PFO that showed that patients who had these conditions may have greater atrial irritability, and therefore possibly more atrial fibrillation episodes and that the stroke risk may arise from that circumstance as well; this observation suggests that these are all legitimate questions, patients may have other underlying stroke risk factors and we therefore have to ask these questions.

Ruchi Kapoor: When we say ESUS, it is implied that we have ruled out other potential causes of stroke, like atrial fibrillation. Patients who have strokes are evaluated for these things. For example, at the University of Washington, patients would have been evaluated with a cardiac monitor and a TTE with a bubble study. At what point do clinicians say there is a need for TEE because they have reliably ruled out other causes, or should a TEE be a routine part of the stroke evaluation for LAA and the atrial septum?

Mark J. Fisher: That question represents a good place to stop and reflect, as the answer will undoubtedly prompt a long and involved discussion.

AUTHOR CONTRIBUTIONS

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DISCLOSURES

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article, as no datasets were generated or analyzed.

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