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## The enigma of the left atrial septal pouch

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Ischemic strokes of undetermined origin (variously referred to as “cryptogenic stroke” or “embolic stroke of unknown source”) continue to pose a challenge in the field of stroke neurology, comprising more than 30 % of ischemic strokes in some series [1]. The heterogeneous nature of such strokes (which may be attributed to mechanisms such as occult atrial fibrillation, atrial cardiopathies, or non-flow-restrictive carotid atherosclerosis) and the lack of consensus on how aggressively to search for and treat the underlying cause, underscore the need for a deeper understanding of stroke pathophysiology as a whole.

Recent attention has been paid to the interatrial septum – specifically, the left atrial septal pouch – as a potential site for thrombus formation. Discovered in 2010 by Krishnan and Salazar, a left atrial septal pouch is characterized as the kangaroo pouch-like structure that forms when the septum primum and septum secundum do not completely fuse but no interatrial channel remains, in contrast to a patent foramen ovale (PFO) [2]. The result is a blind pouch that may serve as a nidus of stagnant flow, leading to potential thrombus formation and eventual cardiac embolism. Despite intriguing insights from autopsy studies and case reports, the clinical and therapeutic significance of the left atrial septal pouch remains enigmatic [3–6].

In this issue of Trends in Cardiovascular Medicine, Scagliola et al. conduct a comprehensive overview of atrial septal pouches, exploring the embryogenesis, epidemiology, clinical significance, diagnostic methods, and therapeutic implications following the identification of these anatomical variants [7]. They characterize the interatrial septum as subject to continuous remodeling over time due to friction between the septum primum and septum secundum, leading to a spectrum of atrial septal variants. They indicate that septal layers continue to fuse into adulthood owing to fluctuations in left atrial pressures, leading to progressive development from a PFO in young adulthood to a septal pouch later on in life and finally into a completely fused septum. Clinically, the authors draw attention to the growing body of literature describing a significantly increased prevalence of a left atrial septal pouch in patients with ischemic strokes [3]. Following a meta-analysis pub-

lished in 2018 reporting an odds ratio of 1.5 for risk of cryptogenic stroke with left atrial septal pouch [3], two additional positive retrospective studies have been added to the medical literature [5,6].

Some important points emerge from this article. First, identification of the left atrial septal pouch is paramount. The authors address the difficulty of distinguishing the left atrial septal pouch from a prominent rim of a PFO; they emphasize routine use of transesophageal echocardiography (TEE) with appropriate administration of agitated saline contrast and Valsalva maneuvers to diagnose left atrial septal pouch. In addition to obtaining standard views of the interatrial septum, a comprehensive assessment of the septal anatomy utilizing the 2D biplane mode and rotational techniques on 3D TEE should increase the diagnostic yield. Use of 3D TEE will also enable routine reporting of the morphology and depth of the left atrial septal pouch, which could shed light (beyond simple volumetric quantification) on high-risk features predisposing to thrombogenic potential.

Second, once a left atrial septal pouch has been identified in a patient with stroke, there is little consensus on management. Lifelong systemic anticoagulation for these individuals has not been advocated, despite the reports of *in-situ* thrombi identified in the left atrial septal pouch [8,9]. Such case reports often have attributed thrombus formation to additional factors such as spontaneous echo contrast or reduced ejection fraction [8,9]. But as evidence of left atrial septal pouch as a potential risk factor for cryptogenic stroke mounts, whether the overall increased stroke risk with left atrial septal pouch can be explained by these other thrombogenic factors is unclear.

The way forward will require a multifaceted approach. Data on left atrial septal pouch and stroke have been limited by low utilization of TEE in the diagnostic work-up of stroke patients. Guidelines do not clearly support routine use of TEE to make a diagnosis of cryptogenic stroke, but this decision may need to be reconsidered should more data emerge on the left atrial septal pouch and its implication in ischemic stroke [10]. It is unclear how well stroke neurologists understand the actual performance of the TEE procedure, and its risks and benefits. The development of alternate tools to identify the left atrial septal pouch without TEE also merits exploration. CT imaging, which offers spatial resolution superior to any other cardiac imaging modality, is currently unable to reliably distinguish a left atrial septal pouch from a PFO due to het-

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erogeneous contrast enhancement-related artifacts. If methods to overcome such artifacts were developed, the yield for identifying the left atrial septal pouch – and our understanding of its unique pathophysiology and clinical consequences – would be greatly improved. Artificial intelligence-supported screening on TTE to predict presence of a left atrial septal pouch may also be a fruitful route to explore.

Finally, the authors suggest that atrial septal variants may influence transseptal puncture in percutaneous interventions. This is arguable, as most transseptal punctures are confined to the fossa ovalis. The presence of a ridge or pouch, which is typically outside the fossa, is unlikely to complicate such interventions.

In conclusion, this review explores the embryological and clinical significance of interatrial septal variants and advocates for a comprehensive imaging assessment of such findings if discovered. It serves as an important call for collaborative efforts in research, clinical practice, and innovation to navigate the challenges identifying and treating the patient with a left atrial septal pouch. There is good reason to believe that such efforts will lead to advancement in clinical management of strokes of undetermined origin.

#### CRediT authorship contribution statement

**Jennifer Xu:** Writing – original draft. **Jin Kyung Kim:** Writing – review & editing. **Mark Fisher:** Writing – review & editing, Conceptualization.

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