

Arrested Morphogenesis: The Cellular Failure of Septal Fusion in Patent Foramen Ovale

By:-

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INTRODUCTION

The central objective of this research is to deliver a comprehensive analysis of the Patent Foramen Ovale (PFO), tracing its

trajectory from embryonic morphogenesis to its clinical manifestations in adulthood. Specifically, this paper seeks to:

- **Elucidate Morphogenesis:** Examine the intricate cardiac development during the embryonic phase, focusing on how the failure of the *septum primum* and *septum secundum* to fuse results in PFO persistence.
- **Analyze Pathophysiology:** Investigate the cellular, genetic, and biomechanical determinants—such as defective fibrogenesis, morphological mismatches, and chromosomal anomalies—that underlie this septal fusion failure.
- **Bridge Embryology and Clinical Pathology:** Explore how this developmental anomaly functions as a conduit for paradoxical embolization, with particular emphasis on its contribution to cryptogenic strokes.
- **Evaluate Clinical Management:** Review current diagnostic protocols (including neuroimaging) and therapeutic interventions (from pharmacological antiplatelet therapy to transcatheter or surgical closure) utilized to manage PFO-associated risks.

Heart:-Heart is a powerful fist sized muscular organ located between the lungs in a central cavity called the mediastinum protected by the sternum and the rib cage, bordered by oesophagus trachea and thoracic vertebrae that rests on the flat surface of diaphragm, it is a highly complex organ that pumps roughly 100,000 times a day just to keep us living. The heart contains three important layers that are

1. **The outer Epicardium:-**responsible for vanishing all the friction that might destroy the internal structure or necessary cells of the heart. This is also necessary for embryonic development and action towards an injury.
2. **The Middle Myocardium:-** This is the main layer that contains all necessary muscles that helps in proper rhythmic contractions of the heart. It contains nerve endings of the bundle of his, also called as purkinjee fibres, that is connected to the Arterio ventricular node that acts as a natural pacemaker. This is connected with the brain for maintaining and regulating the pulse, although it creates a heartbeat by generating electric signals on its own.
3. **The Inner Endocardium:-**It is also a lubricating layer that prevents small blood thrombus to stick onto the heart's wall and cause larger clots. this is the layer which turns in on its own to form septums, That are :-
 - a) **Interatrial septum:-**This is a wall-like structure that separates the two atriums, and prevents intermixing of deoxygenated and oxygenated blood. The Interatrial septum contains two structures that are developed during the embryonic development that are :-
 - i) **Septum Primum:-**This wall grows down from the top of the atria toward the ventricles. Before it closes completely, a hole forms in its upper section, called the foramen secundum.
 - ii) **Septum secundum:-**A second, thicker wall then grows right next to the septum primum. It stops short of covering the entire space, leaving an opening called the foramen ovale.
 - b) **Interventricular Septum:-**This is also a wall-like structure that separates the two ventricles to prevent intermixing of unlike blood. It can be subdivided into 4 parts that are-
 - i) **Inflow Septum:** This segment is characterized by smooth musculature situated in the region immediately below the mitral and tricuspid valvular structures.

ii) **Muscular (Trabecular) Septum:** This constitutes the primary, most robust segment defined by its irregular surface of fleshy ridges.

iii) **Outflow (Infundibular) Septum:** This region is composed of smooth muscular tissue positioned immediately inferior to the aortic and pulmonary semilunar valves.

iv) **Membranous Septum:** This constitutes a diminished, delicate fibrous region situated in close proximity to the core of the cardiac fibrous skeletal framework.

A Human Heart has double circulation, It means the blood enters the heart two times in a cardiac cycle. The double circuit is segregated into 2 distinct pathways that are

- **Pulmonary Circulation:** -The Heart(Right atrium) encounter Deoxygenated blood from superior vena cava and inferior vena cava (from the upper and lower body respectively), and directs it to the lungs via pumping by Right Ventricle by the pulmonary artery

- **Systemic Circulation:** -After Oxygenation the blood from lungs enters the Left atrium and is pumped to the whole body by Left Ventricle via Aorta

The Embryonic development of a Human Heart takes place during the 3rd week of Gestation. The Splanchnic mesoderm is induced by the underlying endoderm when epiblast cells move to the primitive streak to form the splanchnic layer. The Visceral Endoderm Secretes proteins like Bone Morphogenic Protein and Fibroblast Growth Factor. Simultaneously the Endoderm secretes WNT inhibitors which block the antagonist WNT signals from the neural tube. The precise overlap of these conditions causes the activation of NKX2.5 which creates the primitive heart field which is a horseshoe like structure also called the heart crescent. Simultaneously, the process of lateral body folding facilitates the ventromedial migration of the embryonic disc's peripheral borders, merging the bilateral aspects of the cardiogenic crescent at the median plane. Embedded within the primary heart field, specialized progenitor populations consolidate into bilateral endothelial strands, which subsequently canalize to establish a pair of discrete endocardial tubes.

Propelled by the mechanism of lateral body folding near day 21, these parallel structures are brought into mid-sagittal proximity, undergoing a cranial-to-caudal fusion to manifest as a solitary, integrated cardiac conduit.

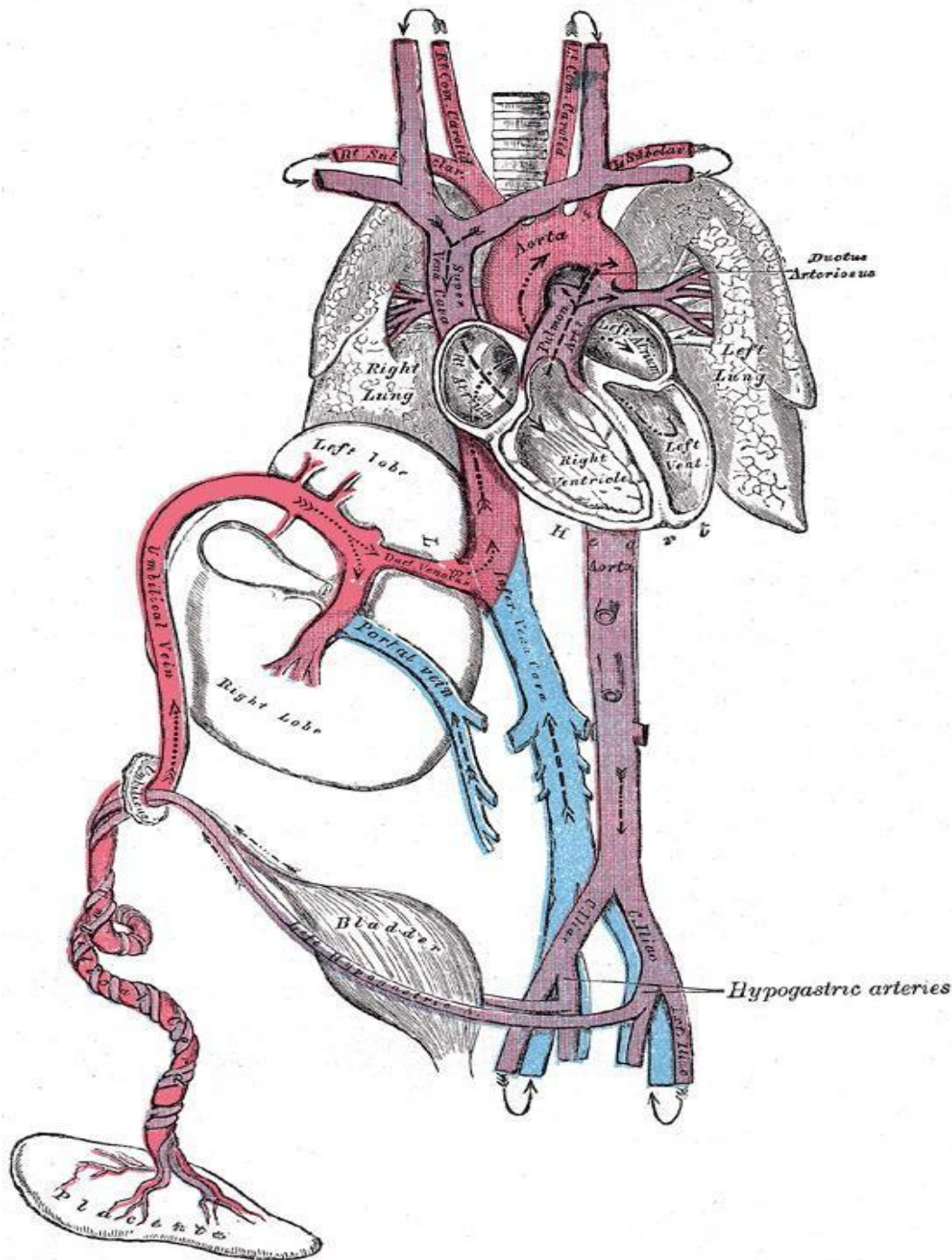
The peripheral splanchnic mesoderm further matures into the myocardial mantle, facilitating the secretion of a dense extracellular matrix layer designated as cardiac jelly; this intervention between the endocardium and myocardium prepares the primitive heart for its initial rhythmic contraction by the 22nd day. Between the days 23 to 28 the heart loop goes under D looping. The second heart field adds important progenitor cells for elongation of the edges. Next, the Septum Primum acts as a thin flexible valve whereas the Septum Secundum provides rigidity and is thicker.

These septums overlap and join to form the foramen Ovale, a defect in the precise overlapping of this causes Patent Foramen Ovale.

The Foramen Ovale

The Development of the fetal cardiovascular system requires a very complex orchestrated series of anatomical shunts to bypass the dormant phase of pulmonary circuit. Starting off with the development of Patent Foramen Ovale.

A Patent Foramen Ovale is a congenital disease that develops during the Embryonic Stage of development of Heart. During Gestation the hydrostatic pressure of the left atrium is significantly higher than the hydrostatic pressure in right atrium as to bypass the non functional lung in the mother's uterus, The Ductus Arteriosus is a duct that helps bypass the lungs and directly supply the oxygenated blood to the aorta from the pulmonary artery. As soon as the child takes the first breath the pressure difference is reversed as the hydrostatic pressure in the left atrium increases that causes the Septum Primum and Septum Secundum to seal and close down the foramen ovale. Thus the left and right atrium are separated



(Picture taken from National Library of Medicine, *The Study of Anatomy, Thorax, Heart Ductus Arteriosus*)(by: Trevor Huff; Raheel Chaudhry; Yingyot Arora; Kunal)

The Patent Foramen Ovale

The Patent Foramen Ovale is a Congenital Disease that is caused due to fail in sealing the septum primum and septum secundum after birth and the first inhalation by the lungs which swaps the hydrostatic pressure in the atriums that causes the shut of the foramen ovale in normal humans. Many anomalies causes the disruption for proper sealing of this foramen and thus disrupts the normal functioning of the heart. More than half of infants have PFO at 6 months of age. The causes of the following can be

1. **Defective Fibrogenesis:** Normally the Epithelial cells lining the septa undergo a transition to fuse together permanently with fibrous connective tissue. This failure of adhesion is caused in a PFO.
2. **Morphological Mismatch:** If the foramen secundum is excessively large or the septum secundum is excessively small, then the overlap required for a stable tissue fusion is absent.

3. **Chromosomal Abnormalities (Aneuploidy):** Errors in cell division (nondisjunction) that result in an abnormal number of chromosomes frequently derail early cardiogenesis.

a. **Trisomy 21 (Down Syndrome):** Representing a frequent syndromic etiology of cardiac anomalies, the inheritance of a redundant 21st chromosome precipitates the pathologic overexpression of genetic regulators like DSCAM and COL6. Such molecular dysregulation specifically impairs the ontogeny of endocardial cushion central cardiac tissues essential for septal anchoring and subsequent fusion. While frequently manifesting as comprehensive Atrioventricular Septal Defects (AVSD), this chromosomal condition also yields a high prevalence of isolated PFO.

b. **Turner Syndrome (45, X0):** Arising from the total or partial absence of a singular X chromosome in female subjects. Although primarily correlated with left sided anatomical pathologies, such as aortic coarctation, the pervasive disruption of vascular and lymphatic morphogenesis similarly hinders the requisite fusion of septal layers.

c. **Edwards Syndrome (Trisomy 18) and Patau Syndrome (Trisomy 13):** These profound chromosomal aberrations catalyze systemic failures throughout embryonic maturation, culminating in significant structural cardiac malformations where the physiological closure of the septa is frequently arrested.

4. **Single-Gene Pathogenesis (Pleiotropic Effects)**

Isolated point mutations within highly conserved genetic sequences often suffice to precipitate a Patent Foramen Ovale. These genetic aberrations typically involve transcription factors—specialized regulatory proteins responsible for the precise temporal activation of downstream morphogenetic programs.

a. **Holt-Oram Syndrome (TBX5 Mutation):** As a classic autosomal dominant pathology, this condition manifests through concurrent dysmorphology of the upper skeletal limbs and the atrial septa. The TBX5 regulator is fundamental to the embryonic induction of these disparate structures; its disruption prevents the septal leaflets from achieving the critical longitudinal growth required for overlapping and subsequent fibrous fusion.

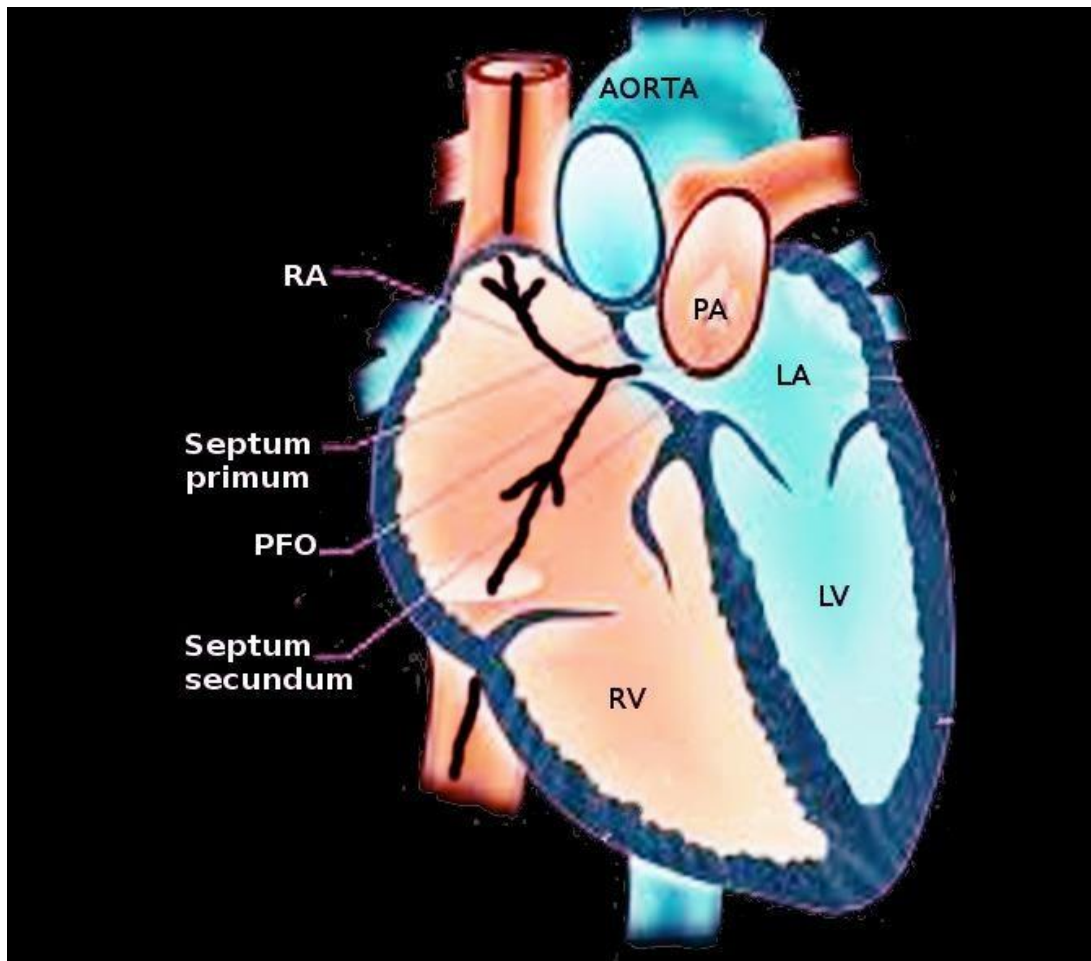
b. **NKX2-5 and GATA4 Dysregulation:** Independent of multisystemic syndromes, mutations in these primary cardiac regulators are strongly correlated with hereditary PFO and atrial septal defects. Serving as "master regulators" for cardiogenesis, their dysfunction uncouples the orchestrated apoptosis and cellular proliferation necessary for septal patterning, resulting in a permanent anatomical mismatch between the valvular components.

c. **MYH6 Structural Anomalies:** This locus encodes the alpha-myosin heavy chain, a pivotal contractile protein within the myocardium. Pathogenic variants here introduce subtle biomechanical weaknesses within the atrial parenchyma, rendering the tissue insufficient to sustain the permanent fibrous adhesion necessary following the postnatal hemodynamic transition.

5. **Synthesis and Structural Degradation:** The physiological adhesion and subsequent permanent fusion of the septum primum and septum secundum rely heavily on a highly organized extracellular matrix framework. Fibroblasts within the septal interstitium must synthesize sufficient quantities of structural collagen fibers and adhesive glycoproteins to seal the foramen postnatally. When collagen synthesis is genetically impaired or when fibroblasts fail to infiltrate and establish an adhesive cellular matrix, the structural integrity of the tissue bridging the foramen becomes compromised. Consequently, the extracellular matrix remains structurally weak or underdeveloped, failing to withstand mechanical pressure and preventing the permanent fibrous closure of the patent foramen ovale.

6. **Insufficient cell Migration:** The cells required to form the septum secundum fail to migrate to the correct position and this formation of the septum secundum is very short for covering the full foramen ovale, thus leaving a smaller foramen that still intermixes the blood

ETIOLOGY



Characterized as a conduit-like aperture situated between the overlapping laminae of the septum secundum and septum primum, the foramen ovale achieves permanent fibrous fusion in approximately 75% of the neonatal population. During the intrauterine phase, this anatomical shunt is indispensable for facilitating the transatrial migration of blood. Highly oxygenated blood returning via the inferior vena cava is directed across this patency, effectively bypassing the pulmonary circuit to enter the systemic vasculature. However, in nearly 25% of individuals, this physiological closure is arrested, resulting in a persistent PFO that endures into adulthood. Such patencies are frequently identified in conjunction with various anatomical redundancies and remnants, including:

1. **Atrial Septal Aneurysms:** A localized redundancy and abnormal excursion of the interatrial septal tissue.
2. **Eustachian Valves:** Persistent embryonic remnants derived from the primitive sinus venosus valve.
3. **Chiari Networks:** Reticulated, filamentous strands situated within the right atrial chamber.

The clinical significance of a persistent PFO manifests through two primary pathologic mechanisms that precipitate adverse cardiovascular events:

1. **Paradoxical Embolization:** The defect serves as a direct communication facilitating the transit of venous thrombi into the systemic arterial circulation.
2. **In Situ Thrombogenesis:** Due to the elongated, tunnel-like morphology and the propensity for hemodynamic stasis, the aperture itself may function as a nidus for local clot formation.

Symptoms of PFO

1. **Asymptomatic:** Approximately 25% of the patients feel no symptoms and are unaware of their disease
2. **Cryptogenic Stroke:** A sudden stroke in adults particularly under 60 where the primary cause is not immediately apparent through standard diagnosis evaluation
3. **Migraines with Auras:** Severe migraines associated with sensory disturbances called as an aura
4. **Decompression Sickness:** Many Scuba Divers with PFO phase decompression sickness after underground activity
5. **Platypnea Orthodeoxia Syndrome:** A person experiences shortness of breath while standing or sitting whereas feels normal after lying down
 - **Platypnea-Orthodeoxia Syndrome (POS)** manifests through a positional right-to-left interatrial communication, precipitating a systemic deoxygenation as blood bypasses the pulmonary capillaries upon assuming an erect posture. The manifestation of this clinical anomaly necessitates the concurrent presence of two distinct pathogenic components:
 - **Anatomical Shunt Infrastructure:** A requisite structural aperture must exist to facilitate the transit of deoxygenated blood into the systemic circuit.
 - **Cardiac Etiology:** Primarily involving a persistent Patent Foramen Ovale (PFO) or more extensive Atrial Septal Defects (ASD).
 - **Pulmonary Etiology:** Arising from pulmonary arteriovenous malformations that establish a direct vascular bridge bypassing the gas-exchange interface.
 - **Hemodynamic Positional Trigger:** Since left-sided pressures typically predominate, POS requires a secondary biomechanical alteration to redirect blood flow during orthostatic transitions. Gravity-induced distortions of the cardiac parenchyma facilitate the shunting of oxygen-depleted blood. Key catalysts include:
 - **Aortic Pathologies:** Ectatic or elongated aortas that exert mechanical pressure against the right atrium, unsealing the PFO valve.
 - **Thoracic Skeletal Anomalies:** Conditions such as severe kyphoscoliosis that fundamentally alter the heart's spatial orientation within the mediastinum.
 - **Pulmonary Interventions:** Pneumonectomies or emphysematous changes that shift the cardiac axis.
 - **Hypertrophied Eustachian Valve:** An exaggerated embryonic remnant that functions as a funnel, misdirecting inferior vena cava flow toward the atrial defect.
 - **Right-Sided Compliance Deficits:** Pathologies that increase right atrial pressure peaks during postural adjustments.

Cryptogenic Stroke due to PFO

A Cryptogenic Stroke in a patient having PFO is due to a process called paradoxical embolism, when the thrombus bypasses the natural barrier for a clot that is lungs and directly attacks the carotid artery.

Thrombus mostly arise from the deep veins of the legs or knees and as referred to as deep vein thrombosis.

The lungs have thin capillaries which filter out the thrombus from pulmonary artery, in a patent foramen ovale this process is bypassed and the thrombus directly enters the left atrium by the shunt from the right atrium and gets pumped into the aorta, the carotid artery due to its funnel like shape catches the thrombus and the artery is then restricted from the oxygenated blood, this causes the stroke which wouldn't have been the case in a normal heart

Patient Characteristics in cases with and without PFO (n=2680)

Variable	Non-PFO n=1539		PFO n=1141	
	%	n with data	%	n with data
Age in years, mean	57.5	1538	50.3	1141
Male	59.2	911	59.6	1141
Coronary Artery Disease	12.3	1224	6.8	872
Diabetes	18.2	1536	8.6	1136
Hypertension	51.9	1534	30.9	1138
Hypercholesterolemia	31.6	1177	22.5	733
Current Smoker	36.3	1517	32.4	1130
History of Stroke	7.5	1527	4.2	1136
History of TIA	8.0	1530	6.2	1137
History of Stroke or TIA	14.4	1530	9.7	1137
Event Type, Stroke	89.9	1539	88.8	1141
Statins	16.8	285	7.8	193
Antiplatelets	14.4	1021	8.6	842
Anticoagulants	1.4	808	0.8	533

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At Index Event

(table taken from THE NATIONAL LIBRARY OF MEDICINE; Neuroimaging Findings in Cryptogenic Stroke Patients with and without PFO)

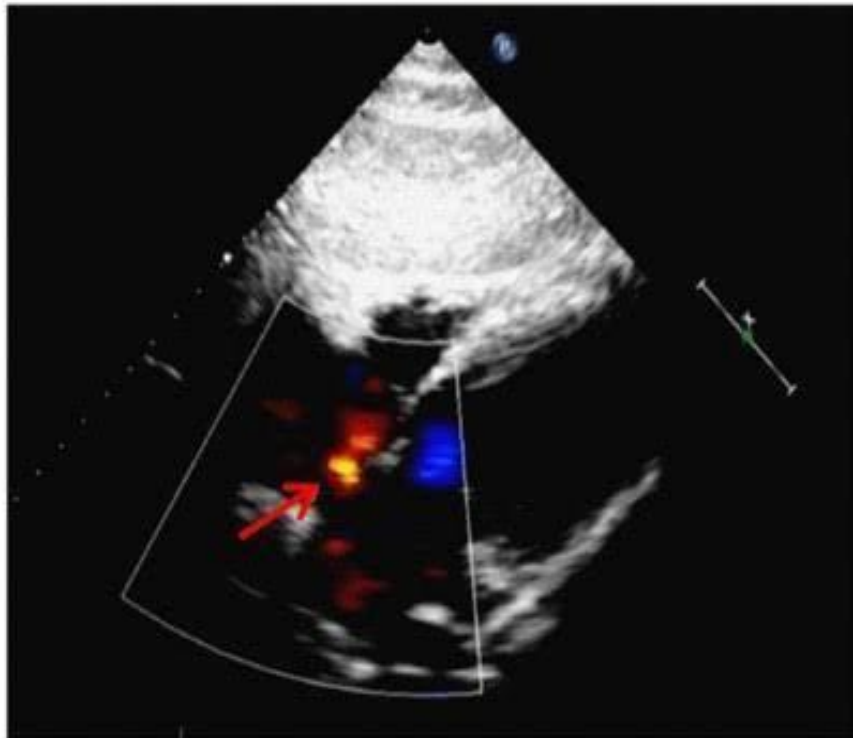
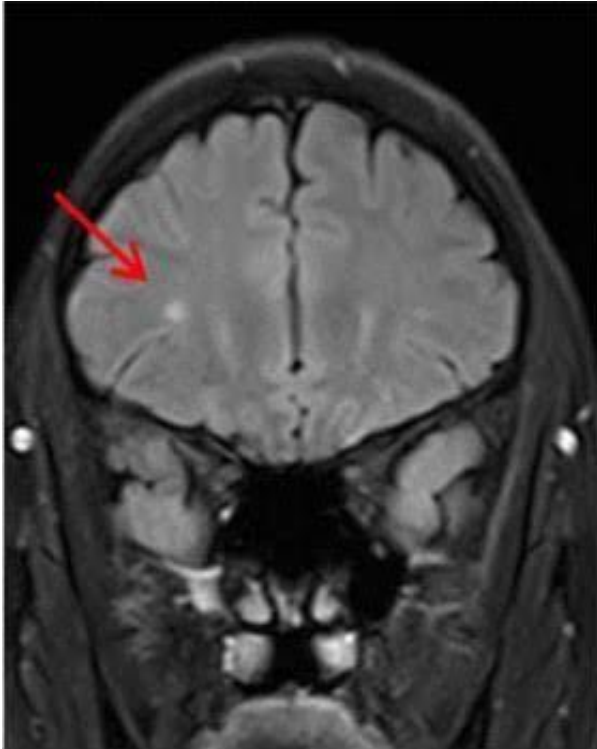
Diagnosis Through Neuroimaging

- **Magnetic Resonance Imaging (MRI):** Diffusion-Weighted Imaging (DWI) is the best test for quickly spotting a stroke. It provides a detailed map of exactly where and how large the damaged brain tissue is.
- **CTA and MRA:** These scans check the brain's blood vessels. They are used to rule out common causes of blockages, such as plaque buildup or damaged arteries.

Stroke Patterns Suggestive of a PFO

When a blood clot travels through a PFO to the brain, the resulting stroke often looks different from typical strokes caused by long-term vascular disease:

- **Multiple Affected Areas:** Clots from the veins often break apart, causing scattered damage in different parts of the brain.
- **Surface Damage:** The clot is often carried to the smaller, outer branches of the brain's arteries, damaging the brain's surface layer (cortex).
- **No Small Vessel Disease:** Strokes linked to PFOs rarely look like "lacunar" strokes, which are typically caused by long-term high blood pressure affecting tiny, deep brain arteries.
- **Healthy Arteries:** Imaging usually shows that the main arteries in the neck and brain are clear of plaque, suggesting the blockage came from somewhere else (like the heart).



(MRI of Brain after a stroke due to PFO vs an 2D echo of a heart with PFO)

Treatment of PFO

1. Antiplatelet Treatment: Most patients are given anticoagulants like aspirin, apixaban to thin blood and prevent formation of clots

2. Transcatheter Device Closure: In patients with severe issues or potential stroke conditions, a thin catheter is inserted from the femoral vein in groin and is navigated up to the right ventricle of the heart, a specialised closure device typically having two self expanding wire mesh discs is used (Amplatzer PFO Occluder or Gore cardio form is used) is deployed through a catheter, one disc open in the left atrium and other in right atrium finally shutting of the foramen tightly between the two discs. Over the next 3 to 6 months Heart tissues the endocardium start to grow covering the shunt. This process is called endothelialization.

3. Surgical Closure: In severe cases where the shunt is too large to cover with a wire mesh disc the foramen ovale is either shut by sewing or by covering it by either the patient's part of its own pericardium tissue or by a synthetic closure like Darcon or PTFE (polytetrafluoroethylene)

Regardless of the closure method used endothelialization (regeneration of heart tissue layer of endocardium) occurs even if its synthetic closure

Conclusion

Patent Foramen Ovale (PFO) represents a significant clinical manifestation of arrested cardiac morphogenesis, arising from the fundamental failure of the septum primum and septum secundum to achieve permanent fibrous fusion following the postnatal hemodynamic transition. While indispensable during fetal development to facilitate the bypass of the dormant pulmonary circuit, the persistence of this interatrial conduit into adulthood introduces substantial risk for adverse cardiovascular events. The clinical significance of PFO is primarily underscored by its role in facilitating paradoxical embolisms, whereby venous thrombi circumvent the pulmonary filtration mechanism to enter the systemic arterial circulation, frequently culminating in cryptogenic strokes.

Advanced neuroimaging and diagnostic modalities remain vital in identifying specific stroke patterns such as multiple, scattered cortical infarcts in the absence of small vessel disease that are indicative of a PFO related etiology. As our diagnostic precision improves, so too does our ability to distinguish between benign, incidental patencies and those with high embolic potential. This paradigm shift requires a multidisciplinary approach, integrating cardiology and neurology to tailor management strategies for each patient.

Ultimately, the management of this condition through diverse therapeutic interventions, including pharmacological antiplatelet regimens and mechanical closure via transcatheter or surgical methods, has proven effective in restoring physiological hemodynamic separation and significantly mitigating the risk of recurrent embolic phenomena. While current clinical trials have provided robust evidence supporting closure in carefully selected populations, the long-term optimization of these treatments remains a dynamic field of study. Continued research into the molecular and biomechanical drivers of septal adhesion, as well as the long-term impact of PFO closure on quality of life and cognitive health, is essential. By synthesizing embryonic understanding with adult clinical pathology, we move toward a future of personalized medicine that can effectively manage the consequences of these early developmental anomalies.

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