**International Journal of Biology and Life Sciences**
ISSN: 2957-9511 | Vol. 5, No. 2, 2024

# A Case of Forming Test for the Diagnosis of PFO Combined Dynamic Left Ventricular Outflow Tract Stenosis after Occlusion

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**Abstract:** This patient was diagnosed with Patent Foramen Ovale (PFO) due to recurrent headaches, and her headaches improved significantly after oval foramen occlusion, but a grade 3/6 coarse murmur was heard in the aortic valve auscultation area, and left ventricular outflow tract stenosis was suggested by cardiac ultrasound. This change may be related to a variety of factors, suggesting that we should do a good preoperative assessment of the patient; intraoperative operation as gentle as possible to reduce the damage to the surrounding tissues; postoperative operation should be strengthened to avoid the progression of the inflammatory process, and at the same time to pay attention to the patient's symptoms, signs and dynamics of the relevant examinations to reduce the incidence of complications.

**Keywords:** PFO; Foaming Test; Occlusion; Complications.

## 1. Case Information

### 1.1. General Information and Complaints

Patient is a 65-year-old female, was admitted to the hospital for "recurrent chest tightness and shortness of breath with headache for 3 years, aggravated for 2 months".

### 1.2. Medical History

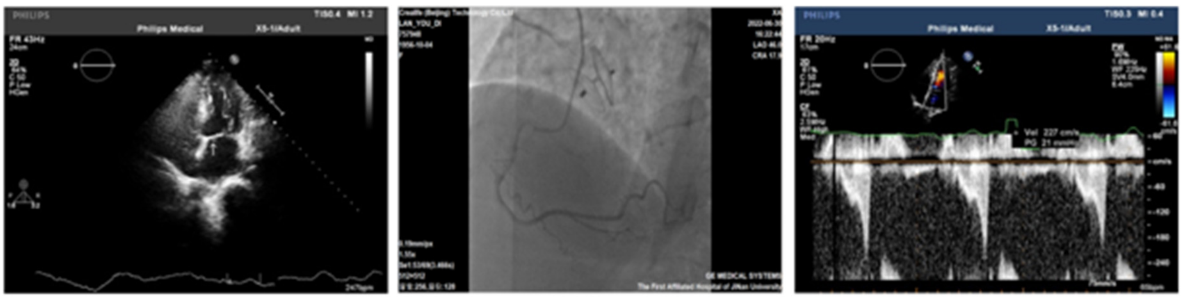
The patient reported experiencing chest pain three years ago, which occurred during sleep at night without any apparent cause. The pain, persistent and located behind the sternum, radiated to the back and was paroxysmal in nature. It was accompanied by shortness of breath and concurrent headaches characterized by a feeling of distension. These symptoms have recurred consistently over the past three years. Additionally, two months ago, the patient experienced another episode of chest pain, shortness of breath, and headache, similar in nature to previous occurrences but with increased severity. The patient's past medical history was unremarkable.

### 1.3. Main Positive Physical Examination and Examination on Admission

1) Positive signs: cardiac auscultation could hear a low-pitched soft systolic murmur of grade 2/6 in the auscultation zone of the pulmonary valve.

2) Main examination: cardiac ultrasound suggests that the foramen ovale is not closed (the size of shunt bundle measured by CD is about 4.3 mm). Complete right heart acoustic imaging: no sign of bubbles in the left atrium with calm breathing; few signs of bubbles could be seen in the left atrium after Valsalva maneuver (<3 per section). Foaming test: positive [Figure 1(A)]. The rest of the examination was unremarkable.

### 1.4. Post-admission Treatment and Outcomes



1 (A) 1 (B) 1 (C)

**1(A)**Positive image of foaming test: A right-to-left shunt is seen in the apical four-chamber section, and the arrows point to the microbubbles that appear in the left atrium after Valsalva's maneuver; **1(B)**After PFO: Angiography showed that the foramen ovale occluder was in a normal position; **1(C)**Murmur occurs after PFO closure, and the left ventricular outflow tract stenosis indicated by ultrasound shows dynamics, and the maximum left ventricular outflow tract velocity of 2.3 m/s and PG 21 mmHg after Valsalva can be dissolved.

**Figure 1.** Pictures related to patient case data

On the fourth day after admission, coronary angiography and PFO closure was performed under local anesthesia. Immediately after surgery, the atrial level occluder was well positioned, and there was no shunt at the atrial level (Fig.

1(B)). No effusion was found on pericardial ultrasound. On postoperative examination, the patient had a grade 3/6 rough murmur in the auscultation area of the aortic valve, and the echocardiography showed that the occluder was in good position and the left ventricular outflow tract was stenosis (Fig. 1(C)). The patient's headache symptoms were significantly improved after occlusion surgery.

# 2. Case Study of PFO

## 2.1. PFO Definition and Epidemiological Data

The foramen ovale, a small opening situated at the center of the atrial septum in the heart, plays a pivotal role during fetal development. In the early stages of fetal growth, owing to low pulmonary blood flow and high pulmonary vascular resistance, blood necessitates passage through the foramen ovale from the right atrium to the left atrium to ensure adequate oxygen and nutrient supply to fetal tissues and organs. As gestation progresses, the foramen ovale typically undergoes gradual closure over weeks to months after birth. This closure is facilitated by the establishment of pulmonary circulation, which reduces the pressure disparity between the right and left atria, leading to compression of the tissue overlying the primitive septum and eventual closure of the foramen ovale. Nevertheless, in some cases, the foramen ovale fails to close entirely during infancy, resulting in the condition known as Patent Foramen Ovale (PFO). This condition is prevalent globally, and in many individuals, PFO may be linked to neurological issues such as migraine headaches—a common neurological disorder with a significant impact on patients' daily lives and activities [1]. Besides migraine, PFO is strongly associated with other clinical ailments and symptoms, including cerebral thrombosis and cerebral infarction. Hence, early and thorough evaluation and treatment of individuals suspected of having PFO are imperative. Treatment modalities for PFO encompass medications, surgical interventions, or closure of the unclosed foramen ovale through interventional methods like transcatheter sealing. These approaches aim to alleviate symptoms associated with PFO and mitigate potential complications.

## 2.2. Pathological Mechanisms

PFO stands as the most prevalent type of congenital heart disease, affecting between 20% and 34% of the adult population worldwide [2]. Conversely, studies indicate that migraine represents one of the characteristic manifestations of PFO, with a high degree of co-morbidity between the two [3].The current pathophysiological mechanism is attributed to the activation of the trigeminal-cerebrovascular system due to PFO-related substances, thus triggering migraine. Presently, no consensus exists, and mainstream theories are divided into two hypotheses:the venous microthrombus paradoxical embolism hypothesis and the vasoactive substance hypothesis.1)Venous microthrombus paradoxical embolism hypothesis: This theory posits that PFO can facilitate the passage of emboli (such as blood clots, gas emboli, and fat emboli) from the venous system into the left atrium via an abnormal pathway (such as an unclosed patent foramen ovale). These emboli can then enter systemic and cerebral circulation, precipitating a migraine aura attack. 2) Vasoactive substance hypothesis: This hypothesis suggests that vasoactive substances, such as 5-HT, which are typically metabolized in the lungs by the enzyme monoamine oxidase (MAO), evade metabolism in the lungs due to the presence of an unclosed patent foramen ovale. Instead, these substances enter systemic circulation through the patent foramen ovale, consequently triggering migraine headaches.

# 3. Diagnostic Methods for PFO

## 3.1. Transthoracic Right Heart Sonography

In clinical diagnosis, right heart echocardiography holds significant value in detecting shunt congenital heart diseases [4], and its execution is relatively straightforward. However, when the degree of right-to-left shunt (RLS) in PFO is low, it can be challenging to detect solely through cardiac color Doppler ultrasound, potentially leading to missed diagnoses. The foam test combined with agitated saline contrast echocardiography (ASCE) offers a novel approach to PFO diagnosis, boasting higher accuracy than traditional transthoracic ultrasound. According to the "Chinese Expert Consensus on the Standardized Application of Transthoracic Echocardiography (2024 Edition)," ASCE is indicated for [5]: 1)screening suspected cardiac conditions involving left-to-right or right-to-left shunts, such as PFO; 2)diagnosing congenital vascular anomalies like permanent left superior vena cava and pulmonary arteriovenous fistulae; 3)assessing parameters such as the internal diameter of the right heart chamber, endocardial border contour, and ventricular wall thickness. However, clinical contraindications for ASCE include [5]: 1) severe cyanosis and high intracardiac shunt volume; 2) severe pulmonary hypertension; 3) history of embolism; 4) severe emphysema, respiratory insufficiency, and severe anemia; 5) acidosis and severe cardiac and renal insufficiency; 6) acute coronary syndromes.

## 3.2. Foaming Experiment

### 3.2.1. Foaming Experimental Procedure


Foaming test items: Foaming test article: 6 pieces of vitamin B6 2ml solution, 1 piece of 5% sodium bicarbonate 10ml solution, 1 piece of 50ml syringe and 5ml syringe.

**Figure 2.** Items for the diagnosis of PFO by foaming test

The foaming test, as its name suggests, aids in clinical diagnosis by producing small bubbles. Various methods exist for generating microbubbles in the clinical setting. A study [6], involving 108 individuals undergoing transthoracic echocardiography of the right heart (c-TTE), compared a mixture of vitamin B6 and sodium bicarbonate with stirred saline. It concluded that the mixture of vitamin B6 and sodium bicarbonate outperformed stirred saline in right heart contrast echocardiography. Using vitamin B6 and sodium bicarbonate as a contrast agent is thus considered a favorable choice. In our practice, we utilized vitamin B6 + 5% sodium bicarbonate as the acoustic contrast agent [Figure 2]. We left an intravenous needle in the patient's elbow vein, then extracted 12 ml of vitamin B6 solution using a 60 ml syringe (30 ml or more would be sufficient), and subsequently mixed it with 10 ml of 5% sodium bicarbonate solution before administering it silently.

### 3.2.2. Foaming Experimental Principle

The two solutions swiftly neutralize, resulting in a rapid reaction that generates a significant number of $CO_2$ microbubbles (with an average diameter ranging from 16-38 μm). These microbubbles are then slowly injected into the elbow vein. Given that the average diameter of pulmonary capillaries is approximately 7-8 μm, the microbubbles are unable to traverse the intrapulmonary circulation and reach the left heart within a single cardiac cycle [7]. Following this principle, the detection of microbubble presence in the left cardiac system indicates the existence of an intracardiac shunt.

In the resting state, only a left-to-right shunt at the foramen ovale is typically visualized in normal subjects, with a right-to-left shunt being nearly impossible to observe. In such cases, an excitation test is necessary to better visualize the presence of a right-to-left shunt in the atria. The well-known Valsalva maneuver is the most commonly used excitation test. (The Valsalva maneuver involves the patient inhaling deeply, tightly closing the vocal folds, and then forcefully exhaling against the tightly closed epiglottis, thereby increasing intrathoracic pressure to affect blood circulation. Subsequently, the patient is instructed to close the vocal folds and exhale forcefully for 15-20 seconds before returning to normal exhalation.) The principle behind this maneuver is that upon cessation of the Valsalva maneuver, both intrathoracic pressure and left atrial pressure drop abruptly. Consequently, blood flow back to the right atrium significantly increases, leading to a rise in right atrial pressure and subsequent opening of the patent foramen ovale. This opening allows observation of microbubbles passing through the channel, aiding in a clear diagnosis when combined with right heart acoustic angiography. In addition to the Valsalva maneuver, the foramen ovale can also be prompted to open by abdominal compression, compression of the inferior vena cava, coughing, deep inhalation, forceful exhalation, and tilting of the bedpan, all through the same mechanism. By observing the time and number of microbubbles in the left atrium during both resting and stimulation tests (e.g., the Valsalva maneuver), the source of the microbubbles and right-to-left shunt can be determined, aiding in the diagnosis of PFO.

### 3.2.3. Advantages of Foaming Experiments

The bubbles generated by this acoustic contrast agent are uniformly distributed and of high density, persisting for an extended duration, thereby allowing ample time for concurrent ultrasound visualization. In a study conducted by Jing Wu [8] involving 46 patients with foramen ovale lesions, the efficacy of transthoracic ultrasound was compared with that of the foam test combined with right heart acoustic contrast. The findings revealed a significantly higher detection rate of PFO using the foam test combined with acoustic imaging, both in the resting state and during the Valsalva maneuver. Additionally, the maximum diameter of PFO observed during the Valsalva maneuver was notably greater than that detected by transthoracic ultrasound. Moreover, the procedure is straightforward, utilizing vitamin B6 + 5% sodium bicarbonate as an acoustic contrast agent, which generates $CO_2$ microbubbles that can be rapidly absorbed by pulmonary capillaries and exhaled, making it safer compared to other gas-producing acoustic contrast agents. Furthermore, the technical complexity and requirements for this procedure are relatively low, with a simple process and easy accessibility to the drug source, devoid of toxic side effects. These factors contribute to the convenience and feasibility of promoting the utilization of this drug in grassroots hospitals and even community settings. Thus, its widespread adoption in primary healthcare facilities and communities is highly convenient and feasible.

## 4. Foramen Ovale Closure

An unclosed foramen ovale may, in some instances, result in abnormal blood flow through the heart, potentially increasing the burden on the cardiovascular system and leading to other health complications. Hence, clinical interventions become imperative, primarily consisting of pharmacological and blocking therapies. Pharmacological treatment typically involves antiplatelet therapy, such as aspirin or clopidogrel, which may be recommended as the treatment of choice for patients lacking clinical risk factors. Conversely, blocking therapy appears necessary for patients with risk factors. The German Society of Cardiology, the German Society of Neurology, and the German Stroke Association have jointly published recommendations strongly advocating for interventional PFO closure in such cases [9]. Absolute indications for this intervention include [10]: 1) Presence of one or more anatomical risk factors for PFO. 2) Moderate-to-massive right-to-left shunt (RLS) combined with one or more clinical risk factors. 3) PFO-associated cerebral infarction/transient ischemic attack (TIA) with confirmed deep vein thrombosis (DVT) or pulmonary embolism, where anticoagulation is not feasible. 4) PFO-associated cerebral infarction/TIA persisting despite antiplatelet or anticoagulation therapy. 5) Cryptogenic stroke or peripheral embolism accompanied by a PFO, with a thrombus on the surface of the right heart or implanted device. 6) Age over 16 years (with definite evidence of paradoxical embolism, age relaxation may be considered appropriate).

The occluder procedure offers several advantages. Firstly, it serves as a preventive measure by halting abnormal blood flow through the heart, thereby reducing the burden on the cardiovascular system and minimizing the risk of complications such as infections, cardiac arrhythmias, and thrombosis. Secondly, it significantly enhances patients' quality of life post-procedure by alleviating symptoms associated with heart conditions, such as breathlessness, fatigue, and chest pain, enabling them to engage in daily activities and exercise more effectively. Additionally, occlusion plays a crucial role in averting long-term effects, as an unsealed PFO may have detrimental effects on the heart and vascular system over time, including increased cardiac load, cardiac hypertrophy, and elevated blood pressure, consequently heightening the risk of cardiovascular events such as heart attacks and strokes. Moreover, occlusion treatment may offer some defense against infectious diseases, as an open PFO can elevate infection risk by providing a pathway for pathogen entry into the heart and vascular system via bloodstream circulation.

In conclusion, sealing the PFO is imperative to prevent complications, enhance quality of life, mitigate long-term effects, and reduce the risk of infection, thereby positively impacting patients' health and overall quality of life.

## 5. Case Evaluation and Reflection

The patient's diagnosis was clear, and following clinical evaluation and exclusion of contraindications, we proceeded with the occlusion treatment. Preliminary medical investigation post-occlusion revealed a new grade 3/6 coarse murmur in the aortic valve auscultation area, with color echocardiography confirming stenosis of the left ventricular outflow tract. While olecranon occlusion may precipitate various complications such as arrhythmia, cardiac tamponade, residual shunt, and coronary air embolism [11], reports of concurrent left ventricular outflow tract stenosis are relatively uncommon. A single-center retrospective analysis by He Lu [12] and colleagues evaluated major complications in 1336 patients undergoing transcatheter closure of unclosed PFOs. They concluded that transcatheter closure of PFOs is a safe and effective treatment option with low trauma, high success rates, and a minimal complication rate.

For the occurrence of left ventricular outflow tract stenosis in this patient, several hypotheses are considered: 1) Some patients may be born with congenital malformations leading to left ventricular outflow tract stenosis. This anomaly may arise from abnormal development of cardiac structures during fetal development, resulting in abnormal morphology or narrowing of the left ventricular outflow tract. The unique anatomy of the left ventricular outflow tract due to structural changes caused by this atrial septal defect may render it more susceptible to stenosis. This narrowing could be associated with factors such as abnormal length of the left ventricular outflow tract, anomalous papillary muscle position, or underdevelopment of the outflow tract itself. Such structural alterations can result in a smaller angle between the mid-axis of the ascending aorta and the long axis of the interventricular septum, thereby affecting blood flow through the left ventricular outflow tract. 2) Patients undergoing surgical procedures to seal an unclosed foramen ovale may encounter manipulation of structures related to the left ventricular outflow tract, such as the aortic valve or the aorta. Surgical intervention may inadvertently cause damage or compression to these structures, resulting in postoperative narrowing of the left ventricular outflow tract. Additionally, following occlusion, changes in atrial pressure due to cavity closure may lead to decreased pressure within the left atrium, thereby altering pressures in various cardiac chambers and affecting the anatomy of the left ventricular outflow tract. This pressure alteration may induce deformation of the left ventricular outflow tract, potentially resulting in a murmur. 3) Inflammation or fibrosis may also contribute to left ventricular outflow tract stenosis. Postoperative inflammatory reactions or fibrosis could lead to hyperplasia or scar formation in the surrounding tissues of the left ventricular outflow tract, thereby narrowing the tract and impeding blood flow. 4) Other postoperative complications, such as thrombosis and infections, may occur, affecting the patency of the left ventricular outflow tract and potentially leading to stenosis or obstruction.

Overall, postoperative left ventricular outflow tract stenosis may result from a combination of factors, including congenital malformations, surgical complications, inflammation, or fibrosis. Patients presenting with left ventricular outflow tract stenosis may necessitate further clinical evaluation and treatment planning to enhance cardiac function and blood flow, thereby effectively managing symptoms and preventing complications. This underscores the importance of conducting thorough preoperative assessments, performing intraoperative procedures with utmost care to minimize peripheral tissue damage, and implementing comprehensive postoperative protocols to mitigate the progression of inflammation. Additionally, close monitoring of patients' symptoms, signs, and inflammatory markers, along with dynamic review of cardiac ultrasound and other relevant tests, is essential to minimize the incidence of complications.

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