

Mechanisms of platypnea-orthodeoxia syndrome

Mecanismos del síndrome de platipnea-ortodesoxia

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Abstract

Platypnea orthodeoxia syndrome (POS) is a clinical entity described in the middle of the last century. It is characterized by dyspnea and hypoxemia triggered by standing and relieved with recumbency. The diagnosis is predominately clinical. The degree of hypoxemia is variable; however, the diagnostic criteria include the decrease in arterial oxygen pressure more than 4 mmHg or oxygen saturation more than 5%. Even though many diseases cause this syndrome, there are only two responsible mechanisms, intracardiac, and intrapulmonary shunts. The coexistence of diverse structural and physiological abnormalities joined to gravitational forces that induce blood shunt after standing is crucial in each mechanism. The intracardiac mechanism is characterized by right to left blood shunt through atrial septal communications and, the right atrium pressure could be normal or increased. In addition, some patients have one or more coexistent aortic, spinal, or intracardiac alterations. The intrapulmonary mechanism is less frequent and is caused by parenchymal or vascular pathologies. Transthoracic echocardiogram is the first diagnostic modality; however, understanding the pathophysiology is the key for a rational diagnostic approach and subsequent diagnostic studies. Treatment is possible and effective in the majority of intracardiac mechanisms and some intrapulmonary. This review focuses on the pathophysiologic mechanisms of POS and their diagnostic workup.

Keywords: Platypnea. Orthodeoxia. Patent foramen ovale. Atrial septal defect.

Resumen

El síndrome de platipnea ortodesoxia es una entidad clínica descrita a mediados del siglo pasado. Se caracteriza por disnea e hipoxemia que se desencadenan con la bipedestación y se alivia con el decúbito. El diagnóstico es predominantemente clínico. El grado de hipoxemia es variable; sin embargo, los criterios de diagnóstico incluyen disminución de la presión arterial de oxígeno de más de 4 mmHg o saturación de oxígeno de más de 5%. A pesar de que este síndrome es causado por gran cantidad de enfermedades, solo hay dos mecanismos responsables: los cortocircuitos intracardiacos e intrapulmonares. En cada mecanismo es crucial la coexistencia de diversas anomalías estructurales y fisiológicas que, unidas a las fuerzas gravitacionales, inducen un cortocircuito sanguíneo después de la bipedestación. En el mecanismo intracardíaco hay un cortocircuito sanguíneo de derecha a izquierda a través del tabique interauricular y la presión auricular derecha puede ser normal o aumentada; además, algunos pacientes tienen una o más alteraciones aórticas, espinales, o intracardíacas coexistentes. El mecanismo intrapulmonar es menos frecuente y es causado por patologías parenquimatosas o vasculares. El ecocardiograma transtorácico es la primera modalidad de diagnóstico, sin embargo, comprender la fisiopatología es la clave para un enfoque de diagnóstico racional y estudios diagnósticos subsecuentes. El tratamiento es posible y eficaz en la gran mayoría de los mecanismos intracardíacos y en algunos intrapulmonares. Esta revisión se centra en los mecanismos fisiopatológicos del síndrome de platipnea ortodesoxia y su diagnóstico.

Palabras clave: Platipnea. Ortodesoxia. Foramen oval permeable. Comunicación interauricular.

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Introduction

The term platypnea refers to dyspnea development when a patient changes from decubitus to seated or standing posture. Orthodeoxia refers to hypoxemia precipitated with the exact postural change. In the 1960 and '70s, these terms were coined in patients with hepatic and pulmonary diseases, and platypnea-orthodeoxia syndrome (POS) emerged as a new clinical entity after that^{1,2}. In 1984, POS was described in patients with an intracardiac shunt³. At present, POS is defined as postural dyspnea and arterial oxygen desaturation that appears in standing or seated posture and relieve with recumbency. There is no consensus for the magnitude of arterial oxygen desaturation. Still, the cut-point for a decrease in arterial oxygen pressure (PaO_2) more than 4 mmHg and oxygen saturation (SaO_2) more than 5% are accepted⁴. Habitually, the severity of hypoxemia is mild; however, some patients experience severe PaO_2 reduction. Classically, the postural change from decubitus to upright is the known trigger for dyspnea; nevertheless, it has also been reported during right lateral decubitus⁵. Bradley et al. found nausea more than dyspnea as a leading POS symptom, reflecting the broad spectrum of unspecific manifestations potentially related to the same physiological event⁶. Since the first POS report, more than 200 cases have been described. The exact prevalence remains unknown; however, the entity is increasingly recognized between clinicians. Despite that numerous diseases are associated with POS; there are two main causal mechanisms: cardiogenic right-left (R-L) shunt and intrapulmonary shunt. This review emphasizes the pathophysiological mechanisms of POS and their diagnostic approach.

Search strategy

We conducted a literature search of PubMed under the terms “platypnea” and “orthodeoxia” and identified relevant articles written in the English language from 1949 up to May 2020. A total of 231 articles were examined. Most articles were case reports, small patient series, and reviews. We gave weight to publications from the past 20 years describing pathophysiology, diagnostic approach, and treatment modalities.

Pathophysiology

The critical pathophysiological phenomenon in POS is the admixture of deoxygenated venous blood with

arterial blood. In the intracardiac mechanism, deoxygenated blood is shunted from the right to the left atrium through a patent foramen ovale (PFO), atrial septal defect (ASD), or fenestrated atrial septal aneurism (ASA). Vascular abnormalities, capillary lung dilatation, and ventilation/perfusion (V/Q) mismatch give origin to the intrapulmonary mechanism as is observed in pulmonary arteriovenous malformations (PAVM), hepatopulmonary syndrome (HPS), and a broad range of pulmonary parenchymal disorders, respectively^{7,8}.

In the circulatory system, there are physiological R-L shunts of negligible magnitude and without hemodynamic repercussion. In healthy subjects, the bronchial arteries receive 2-3% of cardiac output and, two-thirds of this flow return by bronchial veins directly to pulmonary veins⁹. The other shunt is constituted by drainage of thebesian veins into the left ventricle; however, this only accounts for 0.3% of cardiac output¹⁰. In POS, deoxygenated blood reaches the systemic arterial circuit directly and the magnitude of symptoms and hypoxemia are proportionally related to the amount of blood shunted. The shunt fraction is the proportion of blood entering the arterial system without going through ventilated areas of the lung. The shunt fraction required to reduce arterial oxygen pressure below 70 mmHg is approximately 20-25%; for severe hypoxemia ($\text{PaO}_2 < 40$ mmHg), is needed a shunt fraction of 50%¹¹. Figure 1 shows the mechanisms of POS.

Intracardiac Shunt

The intracardiac mechanism is present in more than 80% of patient's with POS. Assuming this shunt is produced by the passage of blood from the right to the left atrium, at first glance, this mechanism is relatively simple. However, a detailed review reveals more complex interactions. The interplay of multiple complex structural and physiological alterations is needed to develop intracardiac POS, which is indicated by the high prevalence of PFO in the general population (around 25-30% depending on age) and the low prevalence of this syndrome¹². In first place, the structural mandatory condition required for POS is an anatomical interruption of the interatrial septum caused by PFO, ASD or, fenestrated ASA. In second place, another anatomical abnormality is necessary in some patients, such as prominent Eustachian valve, ascending aortic dilatation or aneurism, ascending aorta elongation or horizontalization, thoracic spine kyphosis, and hemidiaphragm paralysis, among others⁴. In third place, the right atrial pressure (RAP) must be considered. Elevated RAP is

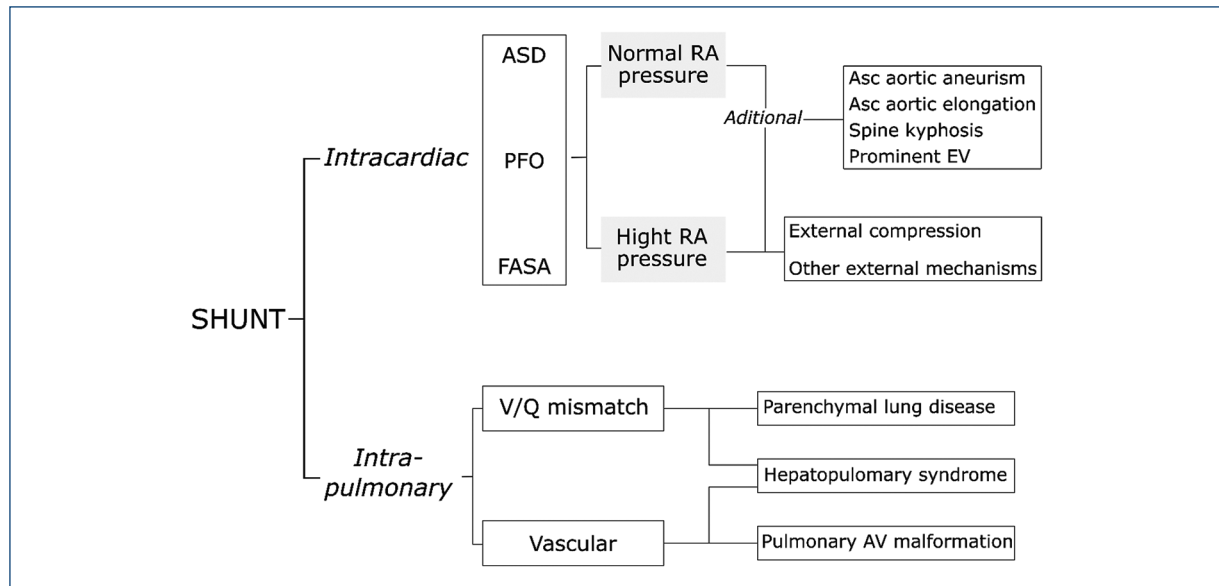


Figure 1. The mechanisms of POS are broadly divided into intracardiac and intrapulmonary. In intracardiac mechanisms, mandatory atrial septal communication is required. In addition, other structural abnormalities such as aortic root or spinal pathologies sometimes occur. High pressure in the right atrium is associated with external compression from masses or fluids or complex mechanisms such as after pneumonectomy. In the intrapulmonary mechanism are implicated purely vascular, parenchymal, or mixed abnormalities. Asc: ascending; ASD: atrial septal defect; AV: arterio-venous; EV: Eustachian valve; FASA: fenestrated atrial septal aneurysm; PFO: patent foramen ovale; V/Q: ventilation/perfusion.

the result of pulmonary hypertension (by left heart or pulmonary diseases), pneumonectomy, and less frequently, pericardial disorders¹³⁻¹⁶. Patients with POS and normal RAP generally have accompanying anatomical modifications in the ascending aorta or spine. If the previous anatomic-functional abnormalities have coexisted in the same patient, the mechanism for blood flow redirection must still be considered in response to postural change. Hypothetically the gravitational effects of upright posture modify the relationship of intracardiac structures and occur alignment between blood inflow from the inferior vena cava and interatrial septum¹⁷. The upcoming paragraphs describe the main diseases and structural alterations related to POS.

In the case of POS with ascending aorta pathologies, Bertaux et al. performed an elegant echocardiographic study in which showed the abnormal spatial configuration of the interatrial septum caused by the dilated aortic root complex¹⁸. Dilated aorta reduces the distance between the aortic root and the posterior atrial wall; thus, decreasing the interatrial septum length, which facilitates the opening of the fossa ovalis flap valve, enabling R-L shunt (Figure 2). The authors hypothesized loosening of tautness and decreased length of the interatrial septum as main mechanisms. The

dilated and angled ascending aorta reduces the atrial septum's space, increasing atrial septum oscillation amplitude. In addition, the mean aortic root diameter was 43 ± 9.1 mm in patients with PFO, and the ascending aorta was angled to 123° regarding the horizontal plane.

There are increasing numbers of case reports describing POS in patients with thoracic spinal kyphosis. The mechanism is not entirely clear^{19,20}. In kyphosis, the thoracic cage decreases in vertical diameter and increases the anteroposterior. Furthermore, the cardiovascular structures modify their orientation. The cardiac apex deviates upward and base downward, giving to the heart a more horizontal position (Fig. 2)²¹. The pericardium is attached to the sternum, diaphragm, and posterior mediastinal structures²². The spinal column deviation pulls intracardiac structures throughout their pericardial attachments to both atriums, great arteries, pulmonary, and cava veins. The tensile forces stretch the septum Secundum superior limbic band and pull apart the foramen ovale boundaries producing its opening. As seen in severe biatrial enlargement cases, atrial remodeling and dilatation open the foramen ovale by exerting traction over the interatrial septum.

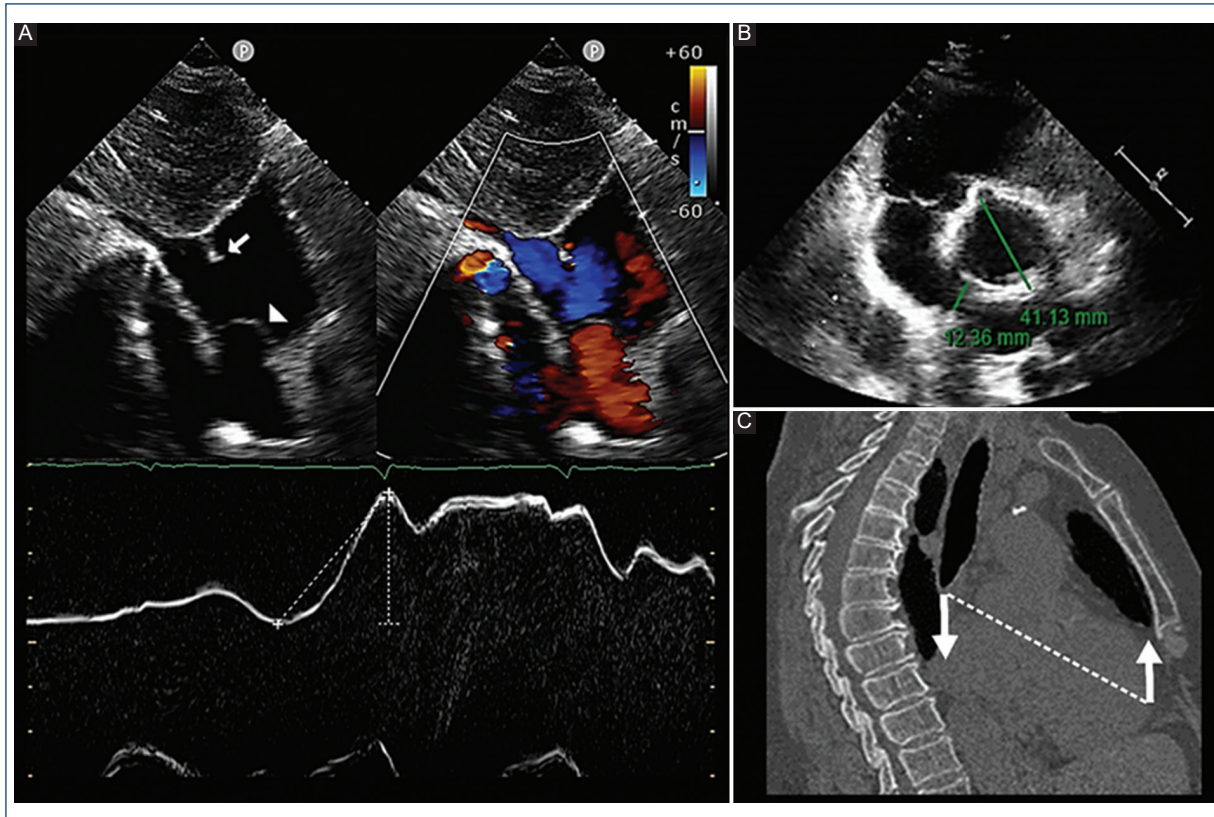


Figure 2. Intracardiac mechanisms of POS. **A:** the upper image depicts a comparative echocardiographic B mode and color Doppler subcostal view of fenestrated atrial septal aneurysm (arrowhead) with blood shunted from left to right; also, is observed the Eustachian valve redirecting blood flow toward the interatrial septum (arrow); lower image, atrial septal bulging in transesophageal M mode echocardiography. **B:** echocardiographic view at great vessels parasternal short axis view shows decreased atrial septal length due to ascending aortic dilatation. **C:** the anteroposterior heart axis orientation is modified in spine kyphosis.

Partial involution of the caudal region of the sinus venosus right valve gives rise to three remnants: Chiari network, Eustachian, and thebesian valves. In fetal life Eustachian valve (EV) redirects oxygenated blood inflow from the inferior vena cava to the left atrium through the foramen ovale²³. Contemporary imaging studies and autopsy series have found that EV is a common finding in postnatal life, persisting until 50% of the general adult population²⁴. The dimensions of EV are variable; however, a prominent EV has a length more than 10 mm, measured from the implantation to their free edge²⁵. The mechanisms that conduce to EV persistence are unknown. Several authors have described the association between prominent EV and POS^{26,27}. As in intrauterine life, in adult patients with POS, the EV directs blood flow toward the interatrial septum (Figure 2). In the presence of atrial septal communication (ASD, PFO or, fenestrated ASA) along with other structural abnormalities such as kyphosis or

aortic aneurysm, a postural R-L shunt could be established.

The intracardiac mechanisms previously described are characterized by normal right atrium pressure. However, some patients have elevated right atrium pressure secondary to pulmonary hypertension or extrinsic atrium compression. Hemodynamic complications seen after pneumonectomy or in pericardial effusion are among the most frequent causes of POS in the setting of elevated right atrium pressure. In a cohort study of 546 patients that underwent pneumonectomy, only five developed POS¹⁵. The mechanism was multifactorial. After surgery, reduction in pulmonary vascular bed leads to increased pulmonary pressure that joined to positional change in the left atrium reopen the foramen ovale. Right atrium inflow obstruction is also a significant contributor caused by liver dislocation into the right hemithorax due to diaphragm relaxation. Vascular or parenchymal lung disorders with elevated pulmonary

artery and right heart pressures have also been associated with POS.

Intrapulmonary shunt

There is physiological inequality of perfusion distribution in the normal lung. Blood flow and intravascular pressure increase from nondependent to dependent lung regions, originating a pressure gradient of approximately 23 mmHg. This difference is determined gravitationally by interactions between alveolar, arterial, and venous pressures. According to this principle, the lung divides into three West zones. In Zone 1, located in the apical regions, blood flow is present only during systole because alveolar pressure is higher than arterial and venous pressures. Next down is Zone 2, where arterial pressure is higher than alveolar pressure and flow is almost continuous. In Zone 3, arterial pressure dominates over venous and alveolar pressures, and blood flow is constant²⁸. Because gravity is the most crucial determinant in lung perfusion heterogeneity, decubitus position almost abolishes these differences, and practically the entire lung behaves like Zone 3²⁹. In this way, the postural change from decubitus to seated or standing increases the flow in lower lung regions. This principle explains POS in pulmonary diseases with anatomical and functional abnormalities involving predominantly basal lung regions. The following paragraphs describe the main etiologies of the intrapulmonary shunt in POS.

HPS is a particular and underreported type of acquired intrapulmonary shunt observed in advanced liver disease. HPS occurs in 5-32% of patients with cirrhosis. It is characterized by liver disease, portal hypertension, and intrapulmonary vascular dilatation that originates abnormal oxygenation with an elevated alveolar-arterial oxygen gradient³⁰. HPS is asymptomatic in the early stages; however, platypnea and orthodeoxia emerge and become incapacitating in advanced settings³¹. Gómez et al. coined the operational definition of orthodeoxia in HPS as a fall in $\text{PaO}_2 > 5\%$ or > 4 mm Hg at upright (AUC 0.96; sensitivity, 80%; and specificity, 93%). Pulmonary vasodilatation plays a critical, as pulmonary capillaries increase their diameter until 10 times the baseline. The increased vascular diameter increases the distance for oxygen diffusion from the erythrocyte to the tissues. Furthermore, in HPS has been demonstrated by tomography that dependent lung zones have more pronounced vascular dilatation, and postural change increases their perfusion by trigger blood flow redistribution³². The above

shows that preexisting V/Q mismatch aggravation in zones with a low V/Q ratio produces orthodeoxia in HPS.

POS is described in a small variety of pulmonary parenchymal disorders; in all these, the lower pulmonary regions were predominantly affected. In patients with interstitial lung disease/idiopathic pulmonary fibrosis³³, chronic obstructive pulmonary disease³⁴, cryptogenic fibrosing alveolitis³⁵, and bronchogenic carcinoma³⁶ presented with POS, the lower lobes were involved. Two reports of viral pneumonia by cytomegalovirus and *Pneumocystis jirovecii* showed a similar anatomical location³⁷. Despite different etiological substrates and distinct structural alterations, the common pathophysiological mechanism potentially is severe V/Q mismatch (zone 1 phenomena). The clinician must tailor a careful investigation to exclude cardiogenic or pulmonary vascular shunt.

PAVM are congenital or acquired anomalies that cause direct communication between pulmonary arterial branches and pulmonary veins without an intervening pulmonary bed. Until 80% of PAVM are congenital in origin, and more than a half are associated with Osler-Weber-Rendu disease. PAVM are located more frequently in the lower lobes, subpleural, or embedded in the lung parenchyma. The pathophysiology involves the direct right to left shunt, and the amount of blood shunted determines the symptoms. Manifestations as hypoxemia, cyanosis, and clubbing arise if the shunt is more than 20% of cardiac output³⁸. In general, in the initial stages, cardiac hemodynamics is not affected, and patients maintain intact cardiac structure and function; however, in the long term, some untreated patients develop severe cardiac remodeling, and high output heart failure. In our literature review, only were found few cases of vascular lung shunts manifested with POS^{2,39,40}. Robin et al. reported the first². Ohara et al. reported a case of PFO with minimum R-L interatrial shunt and PAVM³⁹. In initial PAVM reports, the platypnea component was absent. Similarly, a recent case series of 258 patients with PAVM found orthodeoxia ubiquitously distributed; however, platypnea was absent⁴¹. In this way, the complete POS clinical picture (platypnea and orthodeoxia) is scarce in patients with PAVM. Some clinicians claim to reconsider the diagnostic criteria for POS in the presence of PAVM. The lack of platypnea is unknown but could be related to an absence of hemodynamic impairment and cardiac structural modifications in the early stages. The pathophysiological mechanism in POS from cardiac origin is entirely different from that present in PAVM. Some

unidentified differences must be present for trigger platypnea in cardiac patients. Dyspnea is a complex symptom involving multiple sensations that entail neuroanatomic pathways, circulatory and bronchial mechanoreceptors, central, and peripheral chemoreceptors. The signals have central neural processing and evoke autonomic and motor responses⁴². Deserve special attention juxta-pulmonary capillary receptors (J receptors) located near alveolar capillaries that respond to increased interstitial fluid. The abrupt rise in the left atrium preload seen in intracardiac POS induces sudden atrial wall stretch with the retrograde transmission of pressure to pulmonary capillaries activating J receptors⁴³.

Diagnosis

Once that platypnea and orthodeoxia have been confirmed a comprehensive diagnostic workup must be implemented. The intracardiac shunt must be ruled out in first place given its high prevalence. In second place are PAVM. Parenchymal lung disease and other etiologies are less frequently observed. **Figure 3** describes the diagnostic algorithm proposed in the assessment of patients with POS. Some clinical features can be helpful in the differential diagnosis. In the intracardiac shunt associated with ASD, a systolic murmur in the pulmonary valve area, fixed and wide splitting second heart sound, and right bundle branch block could suggest the diagnosis⁴⁴. In patients with PAVM common findings are cyanosis, clubbing, and pulmonary bruit⁴⁵. The suspicion of HPS must arise in a patient with a history of liver disease, stigmata of chronic liver disease, and postural hypoxemia.

Transthoracic echocardiogram (TTE) is the initial diagnostic modality. The American Society of Echocardiography provides comprehensive guidelines for ASD and patent foramen ovale assessment⁴⁵. In patients with ASD, TTE achieves adequate anatomical and hemodynamic characterization and visualizes blood shunt direction. In patients with fenestrated ASA or PFO, the shunt is often undetectable by color flow or pulsated Doppler. With the Valsalva maneuver and using contrast with agitated saline, the diagnostic performance increase. With an agitated saline bolus, intracardiac R-L shunt is found if within 3-6 beats of opacification of the right atrium microbubbles are observed in the left atrium. In patients with intrapulmonary shunt, the bubbles are observed after 3-6 beats⁴⁶. It is necessary to acquire the echocardiogram in habitual decubitus and then in a seated position. Inadequate right atrium

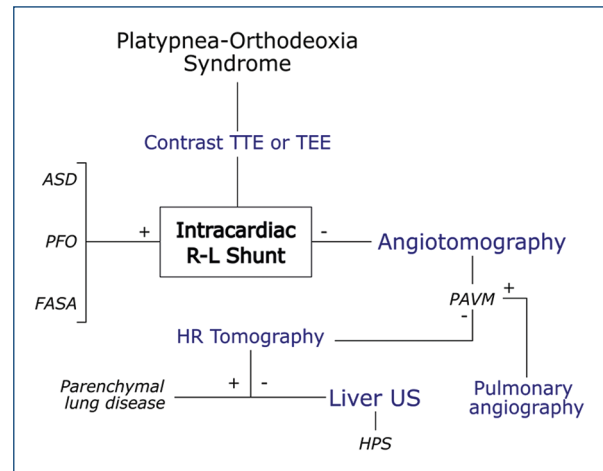


Figure 3. POS diagnostic algorithm. Once POS has been confirmed, the first diagnostic modality is TTE with agitated saline. If an intracardiac shunt is not found but the diagnostic suspicion persists, TEE is recommended. After ruling out an intracardiac shunt, lung angiotomography is the next step in the search for PAVM. High-resolution tomography identifies parenchymal lung disease in PAVM-negative cases. Liver ultrasound recognizes chronic hepatic damage and abnormal flow patterns in cases of HPS. ASD: atrial septal defect; FASA: fenestrated atrial septal aneurism; HR: high resolution; HPS: hepatopulmonary syndrome; PAVM: pulmonary arteriovenous malformation; PFO: patent foramen ovale; TEE: transesophageal echocardiogram; TTE: transthoracic echocardiogram; US: ultrasound.

opacification and left atrium hypertension cause false-negative results. Optimally executed agitated saline injection (some centers use a mix of 8 mL normal saline with 1 mL of air and 1 mL of patient's blood) and adequate Valsalva maneuver overcome these limitations⁴⁷. If results of TTE are inconclusive or negative but a high index of suspicion remains, transesophageal echocardiography (TEE) is recommended. TEE defines with greater detail interatrial septum and neighbor structures anatomy as well suitability for device closure⁴⁸.

If workup for the intracardiac shunt is negative, it is necessary to search for intrapulmonary sources. In PAVM, chest radiography shows alterations in 98% of patients; a lobulated radiopaque mass of variable size is observed in lower lobes in two-thirds of patients⁴⁹. TTE shows shunt with microbubbles in the left atrium after 3-6 beats. Some patients with ipsilateral PAVM saline contrast TTE can show microbubbles entering the left atrium through a single pulmonary vein. The main limitation of TTE is the inability for shunt quantification⁵⁰. In general,

cardiac structure and function are normal in the initial stages. The 100% oxygen calculation method allows shunt fraction quantification more accurately; a shunt fraction $\geq 5\%$ is considered abnormal⁴⁵. Radionuclide perfusion lung scan has the same efficacy that 100% oxygen method in shunt quantification but does not provide anatomical information⁵¹. The standard in PAVM diagnosis is pulmonary angiography which additionally provides a characterization of angioarchitecture for treatment planning, either catheter embolization or surgical resection⁵². Contrast-enhanced computed tomography has an increasing role in PAVM diagnosis and has better performance than angiography in selected cases given the absence of superimposition of lesions⁵³.

HPS diagnosis is suspected in patients with advanced liver disease, hypoxemia, and elevated alveolo-arterial gradient (>20 adjusted for age). Intrapulmonary vascular dilatation and shunt are confirmed with micro-bubble contrast TTE, lung perfusion scanning, high resolution computed tomography, or pulmonary angiography. In healthy individuals, the diameter of capillaries is $15\text{ }\mu\text{m}$; while in HPS can reach as much as $500\text{ }\mu\text{m}$, affecting predominately the lower lung zones³⁰.

Parenchymal lung disease is the least common etiology in POS. The diagnosis is of exclusion. In a patient presenting with POS, without intracardiac shunt in contrast TTE, absence of PAVM in contrast angiotomography, and normal liver function, the presence of structural abnormalities in lower lung lobes could suggest the diagnosis.

Treatment

Definitive treatment of intracardiac shunts involves surgical or percutaneous closure of the primary anomaly. Contemporary trends in the treatment of interatrial communications favor closure of amenable defects percutaneously. According to Rodrigues et al. in POS approximately 61% of intracardiac shunts are closed percutaneously, whereas 19% require surgical closure⁷. The anomaly most frequently closed by percutaneous devices is PFO (88%), followed by ASD and perforated ASA. The benefits of percutaneous compared with open surgical techniques are faster post-procedural recovery and lower cost. Patients with large, complex, or fenestrated ASD are more amenable candidates for surgery. After treatment, symptoms resolve in 95% of patients and, concomitantly, upright oxygen saturation increase; however, in 5% closure is ineffective due to residual shunt. In a single-center cohort study by Ashish et al. PFO closure achieved full symptoms and hypoxemia

resolution in all 52 treated POS patients. They carefully selected the closure device based on PFO and interatrial septum characteristics⁵⁴. Patients that required non-PFO devices (almost 25%) had more frequent ASA, more septal angulation and, shorter septum primum overlap with septum secundum. This demonstrates that careful device selection is of paramount importance in successful defect closure. It is essential to take into account the amount of blood shunted. In some cases, the R-L shunt is minimal throughout PFO, and its closure will not resolve the symptoms. It is necessary to investigate other shunt sources in these patients³⁹.

Untreated PAVM enlarges over time, and in the long term, 50% of individuals develop neurological complications, progressive hypoxia, or high output heart failure⁵⁵. Percutaneous embolization is the current preferred therapy over the surgical procedure. The overall success rate of percutaneous embolization with coils or balloon is high, 99% reported by several series. The complications rate was 13%, mainly pleuritic chest pain. No fatal events occurred^{56,57}. Surgical PAVM resection is indicated in failed embolization, intrapleural rupture, or in patients who develop severe bleeding.

In patients with HPS no effective medical therapy is available. Discordant results have been observed in reports using a transjugular intrahepatic portosystemic shunt^{58,59}. The only efficacious treatment is liver transplantation, which resolves blood gases abnormalities in more than 80% of patients. The 3-year mortality rate after liver transplantation in HPS ranges from 5 to 40%⁶⁰.

Conclusions

POS is a complex clinical entity with relatively low prevalence. It is underdiagnosed in some clinical scenarios. At present, clinicians recognize POS more frequently, and the prevalence has risen in the last two decades. The pathophysiology is complex and involves intracardiac and intrapulmonary mechanisms. Multiple diseases with distinct anatomical or physiological alterations participate from common mechanisms and produce this clinical syndrome. Intracardiac POS is given by R-L blood shunt through atrial septal communications; some patients have increased RAP, whereas others with normal RAP have isolated or coexistent aortic, spinal or intracardiac alterations. Intrapulmonary POS is less frequent and is caused by parenchymal or vascular abnormalities. Once POS has been identified, a comprehensive and ordered diagnostic approach allows the correct characterization of the pathophysiological mechanism. Treatment modalities have a high

success rate in POS from intracardiac or PAVM origin; however, only supportive treatment is warranted in other diseases. Understanding the mechanisms of this complex syndrome will guide the clinician towards a rational diagnostic approach and offer some patients a curative treatment option.

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Conflicts of interest

The author declares no conflict of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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