Medical Research Archives

European Society of Medicine

OPEN ACCESS

Published: November 30, 2023

Citation: Frizzelli, R, and Frizzelli, A., 2023. Chronic obstructive pulmonary disease with unexplained hypoxemia: what to do? Medical Research Archives, [online] 11(11). https://doi.org/10.18103/mra.v11i11.4648

DOI: https://doi.org/10.18103/mra.v11i11.4648

ISSN: 2375-1924

SPECIAL ARTICLE

Chronic obstructive pulmonary disease with unexplained hypoxaemia: what to do?

Rino Frizzelli[1]*, Annalisa Frizzelli[2]

1 Department of Community Medicine - Cardiology, Viadana Hospital -ASST Carlo Poma - Mantova, Italy
2 Department of Medicine and Surgery, Respiratory Disease and Lung Function Unit, University of Parma, Italy

* frizzelli.rino@gmail.com

ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a slowly progressive disease characterized by inflammation that involves the airways, lung parenchyma, and pulmonary vasculature commonly associated with lung function decline and alveolar impairment of gas exchange. All these alterations can lead to hypoxaemia. In COPD hypoxaemia presenting refractory to very high concentration of inspired O2 with a drop of SpO2 (peripheral saturation) > 5% during the upright position and an improvement on recumbency (platypnea/ortodeoxya syndrome) can be suspect for righ-to-left shunt, e.g. intrapulmonary shunt or most frequently a patent foramen ovale.

Among COPD patients, several studies showed a higher prevalence of patent foramen ovale than in general population (70% versus 35%). Chest imaging and echocardiogram with bubble contrast should be the first clinical assessment to differentiate subjects with intracardiac shunt (such as in Patent foramen ovale) from those with extracardiac (or intrapulmonary) one.

Definitive treatment of right-to-left shunt involves percutaneous closure but literature provides conflicting data about indications and results, particularly regarding selection of COPD patients to be subjected to such intervention. Several key factors should be taken into account from a clinical and ethical point of view: first periprocedural complications, then echocardiographic assessment of right ventricular systolic and diastolic performance should be performed to rule out severe pulmonary hypertension and to avoid further post-procedure clinical deterioration; in addition, quality of life should be assessed.

In our experience, among 12 patients with patent foramen ovale 5 were affected by COPD GOLD III with refractory hypoxaemia. After evaluation of right ventricular performance, only 2 patients were eligible for patent foramen ovale closure with the Amplatzer device; long-term follow-up showed discontinuation of oxygen therapy and improvement in quality of life. Therefore, COPD patients with hypoxaemia refractory to high O2 supplementation must be thoroughly assessed taking into account a careful history and a targeted physical examination. The presence of patent foramen ovale should raise suspicion of a right-to-left shunt. If a patent foramen ovale is identified, evaluation of pulmonary function, right ventricular systolic reserve, and severity of pulmonary hypertension is mandatory for closure.

The development of a multidisciplinary team to conduct a multicenter study is necessary to understand if and when the right-to-left shunt in COPD can benefit from this novel therapy.

Keywords: Chronic obstructive pulmonary disease, hypoxaemia, platypnea-orthodeoxia, right-to-left shunt

Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous lung disease characterised by chronic respiratory symptoms (dyspnoea, cough, sputum and/or exacerbations) due to airway ab-normalities (bronchitis, bronchiolitis) and/or alveoli (emphysema), leading to a persistent, often progressive and not fully reversible obstruction of airflow and damage to the pulmonary vascula-ture, with a decrease in lung function and alveolar impairment of gas exchange leading to hy-poxaemia. Globally, COPD is a leading cause of chronic morbidity and mortality and is currently the fourth leading cause of death. The age-adjusted mortality rate relative to the 1965 mortality rate is 163% (compared with 59% for ischaemic heart disease) (1-2).

The aim of our work was to develop a diagnostic-therapeutic pathway for COPD with hypoxaemia refractory to high-flow oxygen therapy. Based on a literature review and our experience, the possible anatomical-clinical conditions that may cause oxygen-refractory hypoxaemia in COPD are described. Suggestions for therapy are also formulated, which may prove to be crucial for a definitive correction of refractory hypoxaemia.

PATHOPHYSIOLOGY OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic obstructive pulmonary disease (COPD) is an inflammatory disease affecting the airways, lung parenchyma and pulmonary vasculature. The main pathophysiological feature is airflow limitation caused by airway narrowing and/or obstruction, loss of elastic recoil, or both; the pulmonary vasculature is also frequently affected.

Tobacco smoking and environmental pollution, especially particulate matter, alone or in combination, are responsible for the damage caused by inflammatory conditions leading to mucus hypersecretion, mucus plugging, mucosal oedema, bronchospasm, peribronchial fibrosis and remodelling of the small airways, or a combination of these mechanisms. The alveolar septa are destroyed, reducing the parenchymatous attachments to the airways and thereby preventing airway closure during exhale. Enlarged alveolar spaces sometimes condense into bullae, defined as air spaces ≥ 1 cm in diameter. Bullae may be completely empty or traversed by strands of lung tissue in areas of localised emphysema; occasionally they occupy the entire hemithorax. These changes lead to loss of elastic recoil and hyperinflation of the lungs (3-4).

Thus, cigarette smoke products and pollution cause both endothelial and epithelial damage leading to vascular remodelling, airway and pulmonary parenchymal abnormalities, all of which can contribute to worsening lung function, alveolar impairment of gas exchange, hypoxaemia, and pulmonary vascular hypertension .

Finally, it is known that chronic hypoxaemia in COPD is not the only cause of increased vascular resistance and pulmonary hypertension, but also of marked morphological changes in the lung parenchyma (5-6-7). When the inflammatory state is particularly severe, the loss of pulmonary capillaries contributes to a mismatch in the ventilation-perfusion (V/Q) ratio in the alveoli, resulting in wasted ventilation (alveolar dead space) and wasted perfusion (venous admixture).

In patients with low $\dot{V}/\dot{Q}$ abnormalities in whom venous admixture leads to hypoxaemia, it is itself a factor leading to increased remodelling of the vascular bed and, over time, structural changes called "remodelling of the pulmonary vasculature", increased vascular resistance and worsening of hypoxaemia (8).

Venous admixture is a physiological shunt, usually about 3% of total cardiac output, as measured in normal individuals breathing room air, but often loosely referred to as a shunt: venous admixture is not a shunt and the hypoxaemia caused by venous admixture is partially reversible at high oxygen flows. In human subjects breathing 100 per cent oxygen on room air, PaO2 rises above 500 mmHg after 30 minutes (hyperoxia test). In the presence of a true right-to-left shunt, there may be no significant improvement in hypoxaemia even if the patient is treated with 100 per cent oxygen and the alveolar-arterial partial pressure (AaD) difference is increased (9).

Clinically right-to-left shunt can vary from minor disease-related symptom to severe dyspnoea and platypnea-orthodeoxia, depending on the extentet of the shunt and severity of pulmonary hypertension.

PLATYPNEA-ORTHODEOXIA SYNDROME

Platypnea-orthodeoxia syndrome (POS) is a rare clinical entity usually associated with interatrial right-to-left shunt due to intrapulmonary arteriovenous malformations and patent foramen ovale. POS is characterized by positional dyspnoea (platypnea) and arterial desaturation (orthodeoxia) (SpO2 < 90% or PaO2 < 60 mmHg) in the upright position). This saturation drop is defined as a drop in SpO2 > 5% or PaO2 > 4 mmHg from supine to an upright position. At POS, both values improve when the change from an upright to a supine position return to normal. The pathophysiology of POS has puzzled clinicians for years, and in some patients the exact mechanisms remain unclear (10).

CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND RIGHT-TO-LEFT SHUNTS

Intrapulmonary arteriovenous malformations (PAVMs) and patent foramen ovale (PFO) are true right-to-left (RTL) shunts. PAVMs are intrapulmonary abnormal connections between pulmonary arteries and pulmonary veins; they are congenital in most cases (approximately 8-20% of healthy adults at rest. Their role after birth remains controversial; most cases are associated with hereditary hemorrhagic telangiectasia, also known as Rendu-Osler-Weber disease. In COPD patients PAVMs are more common than in healthy individuals; and are usually well tolerated because of the attendant low pulmonary vascular resistance, but there is conflicting evidence for the existence of a direct association with condemnation of the lung parenchyma (11-12-13).

The manner of formation of these direct connections or shunts from the pulmonary arteries to veins is not yet clear. It is possible that they resemble the structures described by Tobin (14), which enlarge in patients in advanced stages of chronic obstructive pulmonary disease. It is also possible that they are passageways formed by recanalization of pulmonary arteries and arterioles after thromboembolism. Because of their relatively small size it is not surprising that they have not been observed in the usual examination type of pulmonary artery vessels.

Miller (15) reported that of 27 patients with moderate-to-severe chronic obstructive pulmonary disease, 22 had an anatomic intrapulmonary shunt that was larger than in normal individuals. Blood in the shunt flowed through enlarged pulmonary vessels, as evidenced by particles 10-90 micrometers in diameter. The extend of the shunt correlated with the decrement in lung diffusing capacity. It did not correlate well with pulmonary mechanical abnormalities such as air flows and volumes or resting blood gas data. Nevertheless, shunting through enlarged pulmonary vessels may play a role in the hypoxaemia seen in COPD patients, especially at exercise.

Cameron Norris (16) studied the prevalence and degree of blood flow through intrapulmonary arteriovenous anastomoses at rest and during exercise compared with healthy controls in 43 subjects with COPD >50 years of age; the presence of a cardiogenic shunt was excluded. Under both conditions, blood flow through intrapulmonary arteriovenous anastomoses was present in 26% of all subjects and was significantly higher at rest than in healthy (8%).

DIAGNOSTIC STUDIES OF INTRAPULMONARY ARTERIOVENOUS MALFORMATIONS AND PATENT FORAMEN OVALE

Macroscopic intrapulmonary arteriovenous malformations (PAVMs) typically present themselves on a chest radiograph as a round mass of uniform density that is usually lobulated and sharply defined. Its usual location is in the lower lobes. Transthoracic contrast echocardiography (TTEc) is an ideal screening test for the evaluation of cardiac as well as intrapulmonary shunts. Once the intrapulmonary shunt has been suggested by echocardiography, contrast-enhanced computed tomography (CT) of the chest should be performed to evaluate the exact location and anatomy of the lesions. CT is superior in identifying PAVMs than invasive angiography. However, pulmonary angiography is better at assessing individual PAVMs anatomy and is also used for treatment. Other adjunct tests that can be used in the evaluation of PAVMs include radionuclide perfusion lung scanning as well as magnetic resonance imaging (17).

Like PAVMs, patent foramen ovale (PFO) is a true shunt that occurs in 25-30% of the population (18); most remain without haemodinamic sequelae under normal conditions, and symptoms can vary from little or none to severe dyspnoea and POS, depending on the degree of RTL shunt.

Because cardiac RTL shunt associated with a PFO is the most commonly reported aetiology, an echocardiogram with bubble contrast and intravenous moving saline should be performed both in the supine and upright positions. This examination can help to distinguish patients with an intra-cardiac shunt from those with an extracardiac shunt. The appearance of bubbles in the left atrium within 3 cardiac cycles is suggestive of an intracardiac shunt. Delayed microbubble opacification of the left atrium (after 3 e 6 cardiac cycles) indicates an extracardiac shunt, usually located in the pulmonary vasculature. Transoesophageal echocar-diography (TEE) may be performed for direct visualisation of the cardiac defect or aneurysms if a TTEc is inconclusive. In cases of high suspi-cion and indeterminate echocardiographic examination, cardiac magnetic resonance imaging may be performed to look for a distortion of the cardiac anatomy leading to RTL shunting (19).

CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND PATENT FORAMEN OVALE

Currently, there are few studies examining the prevalence of PFO in COPD. In the United States, COPD affects up to 32 million people, which is 10% of the population. In addition, at least 20% of COPD patients also have a PFO, meaning that more than 6 million patients are affected by both COPD and PFO. More than one million Medicare patients use supplemental oxygen due to COPD, and the annual cost is over $2 billion.

In COPD, the PFO can be a major cause of hypoxaemia and contribute significantly to worsening arterial oxygenation, performance status, and a further increase in pulmonary artery pressure, usually due to the predominant V/Q defects, until the PFO reopens (reopened PFO) (20) .

The presentation of the PFO can be subtle, particularly in the presence of severe dyspnoea associ-ated with respiratory disease. Common signs and symptoms such as dyspnoea or hypoxaemia can easily distort the diagnosis between COPD and COPD with PFO. Thus, the diagnosis of a PFO in COPD requires a high degree of suspicion and clues to the disease can be obtained through a care-ful history.

The relationship between PFO, pulmonary artery hypertension and hypoxaemia in COPD remains complex (21) and the existence of a direct relationship between PFO and hypoxaemia remains contradictory evidence. Soliman and colleagues (22)were the first to describe an association between PFO and COPD in 20 patients with severe COPD GOLD III-IV (Global Initiative for Chronic Obstructive Lung Disease stage III–IV). Using contrast TEE and pressure-generating movements (cough and Valsalva manoeuvres), the researchers found that the prevalence of PFO was twice as high in the COPD group as in the control subjects (70% vs. 35%; $P < 0.05$). More PFOs were detected in their control group than in the control groups of most other population studies, perhaps because they defined a positive shunt as a minimum of 5 microbubbles in the left atrium within 3 cardiac cycles; this was a low cutoff compared to those used in others stadies.

In a Turkish study similar to that of Soliman and colleagues, Hacievliyagil and associates (23) de-tected a 2-fold increase in PFO prevalence in COPD patients with hypoxaemia in comparison with healthy controls. Although Kilic and colleagues (24) found no association between PFO and hy-poxaemia in COPD patients, they did detect higher pulmonary artery hypertension levels in pa-tients with a PFO. Martolini and colleagues (25) found a PFO in 12 of 22 patients with COPD, and more of these patients had hypoxaemia in comparison with their non-PFO counterparts. Shaikh and co-authors (26) were unable to corroborate these findings in their study of 50 patients with COPD and 50 healthy controls; the 2 groups had a PFO prevalence of 46% and 30%, respectively (P=0.15).

CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND TREATMENT OF RIGHT-TO-LEFT SHUNT

Although the natural history of untreated PAVMs has not been optimally described, significant morbidity and mortality exist in some patients. Traditional indications for treatment of PAVMs, should be offered to all symptomatic and asymptomatic patients with lesions less than 2 cm in diameter on chest radiography, their progressive enlargement, paradoxical embolism, and symptomatic hypoxaemia. Treatment options include closure with transcatheter embolization and surgery.

Transcatheter embolization seems preferable in most cases of COPD because it is safe, selective, effective, and less invasive; it avoids major surgery, general anesthesia, and loss of lung parenchyma. However, in COPD some considerations must be made before deciding to treat the RTL shunt with closure, especially since improvement in oxygenation and ventilation status is not always guaranteed. Hypoxaemia in COPD is an indicator of disease exacerbation, and there is a possibility of concomitant pulmonary hypertension, although generally to a moderate degree, so closure may be contraindicated because of a further increase in vascular resistance.

Terry and coworkers (27) reported arterial blood gases and pulmonary function tests in 10 patients before and after balloon embolism. Embolotherapy improved dyspnoea, oxygenation, and shunt fraction, but there was no significant improvement in resting ventilation. The researchers concluded that ventilatory responses in patients with embolized PAVMs were similar to those of people from sea level acclimatised to high altitudes. Other studies of postembolotherapy (28-29) have shown similar improvements in gas exchange and shunt fraction. Although these studies showed significant improvement in shunt fraction after embolotherapy, shunt fraction generally remained elevated after embolotherapy, with mean values ranging from 13 to 24%. It was hypothesised that the remaining shunt represented the shunt through microvascular PAVMs and PAVMs too small to be embolized (ie, those with feeding arteries < 3 mm).

The treatment strategy for this particular clinical condition seems to be a kind of medical dilemma; avoiding invasive procedures may be beneficial for patient survival (30).

There are no data on PFO closure in COPD patients; evaluating the role of a PFO in hypoxaemia is difficult and should include all of the patient's clinical, imaging, and functional data.

The PFO may contribute to the deterioration of arterial oxygenation by further increasing the pressure in the pulmonary artery, which increases the RTL shunt of deoxygenated blood. As a result of this vicious cycle, disease progression is accelerated. Thus the main clinical goal is to interrupt the RTL shunt, control hypoxemia and counteract the worsening of pulmonary hypertension, but no data exists to suggest when PFO closure would be contraindicated .

Otherwise, the PFO was thought to protect patients with pulmonary hypertension from further elevation of pulmonary artery pressure and further deterioration of cardiac function. However, this finding could not be confirmed, and no difference in survival was observed between patients with and without pulmonary hypertension (31-32). In the few available observational studies that have been published, larger and permanently open PFO were the features most commonly correlated with hypoxaemia in various clinical syndromes.

No randomised trials of percutaneous closure of the PFO in desaturation syndromes have been performed. A meta-analysis of observational studies performed before and after closure reported SaO2 or SpO2 for two different hypoxaemia syndromes-POS and strenuous desaturation: a statistically significant increase in SaO2 or SpO2 was found in both clinical states after PFO closure, for exertional desaturation, 9.8% (95% CI: 7.1-12.5%) with strong heterogeneity between studies (I2 : 79%) and for POS 9.6% (95% CI: 5.7- 13.5%), also with strong heterogeneity between studies (I2 :82%) (33-34).

If closure of the PFO is planned, assessment of residual right ventricular output is necessary to prevent further clinical deterioration. Echocardiographic evaluation of pulmonary pressure and right ventricular output is essential to rule out severe pulmonary hypertension and decreased contractile capacity, which could worsen after closure. Accurate assessment of right ventricular function remains difficult: unlike the left ventricle, the right ventricle (RV) does not have a symmetrical, well defined shape and does not lend itself to simplistic formulas. The position of the RV just posterior to the sternum may interfere with adequate visualization of all segments of the RV, and different angles may result in very different measurements. A 2 - dimensional (2D) evaluation of the RV starts with a qualitative and quantitative evaluation (chamber dimensions, systolic and diastolic functions). Measurements of systolic function include tricuspid annulus systolic excursion (TAPSE), RV area fraction changes (RVFAC), peak

tissue systolic velocity at the tricuspid annulus (S'), and RV index of myocardial performance (RIMP); RV diastolic function is assessed by pulsed Doppler of tricuspid inflow, tissue Doppler of the lateral tricuspid annulus, pulsed Doppler of the hepatic vein, and measurements of IVC size and collapsibility. The E/A ratio, deceleration time, E/e' ratio, and RA size are recommended (35).

In our experience, of 12 patients with PFO, 5 were affected by COPD GOLD III and hypoxaemia refractory to high-flow oxygen. After evaluation of RV performance, only 2 patients were eligible for PFO closure with the Amplatzer device; those excluded after admission had severe pulmonary hypertension and impaired RV function. Long-term follow-up of patients admitted to closure showed preserved right-sided function, discontinuation of oxygen therapy and improvement in quality of life (36).

Conclusion

COPD is a chronic respiratory disease characterized by progressive structural remodeling due to an inflammatory process affecting both the airways and the vessels of the lungs.
The damage leads to hypoxaemia due to an altered V/P ratio, which can usually be corrected with oxygen therapy. In COPD patients, if the hypoxaemia cannot be corrected even with high oxygen flow (unexplained hypoxaemia), the physician must extend the diagnostic hypotheses by ruling out the RTL shunt either pulmonary or cardiac.
Therefore, COPD patients with unexplained hypoxaemia must be thoroughly investigated, taking into account a careful history and a focused physical examination; the presence of a PFO should raise suspicion of an RTL shunt.

If a PFO is identified, pulmonary function, right ventricular systolic reserve and severity of pulmonary hypertension are mandatory for closure; this implies a non-invasive echocardiographic examination of the right heart. The complex geometry of the right ventricle remains controversial and leaves some questions about the management of right ventricular dysfunction. However, an integrated multimodal assessment with clinical and haemodynamic parameters may provide a more comprehensive way to select the most appropriate treatment for patients with COPD.

We, therefore, believe that in selected COPD patients with refractory hypoxaemia, closure of the RTL shunt may be critical for patient survival, but preserved right ventricular systolic function must be a "conditio sine qua non" for its correction. The establishment of a multidisciplinary team to conduct a multicentre trial is necessary to understand if and when the RTL shunt in COPD can benefit from this novel therapy.

Declaration of competing interest

The authors report no conflict of interest.

Authors' contributions

All authors expressed their consent for the publication of this article.

Cover Letter

Chronic obstructive pulmonary disease (COPD) is a progressive inflammatory disease of airways, lung parenchyma, and pulmonary vasculature with alveolar impairment of gas exchange that leads to hypoxemia. In COPD patients with hypoxaemia refractory to high concentration of inspired O2 and platypnea/ortodeoxya can be suspect for right-to-left shunt, e.g intrapulmonary or most frequently a patent foramen ovale.
Chest imaging , echocardiogram with bubble contrast and a multidisciplinary clinical evaluation are fundamental to adopt the measure useful for the patient's survival: closing right-to-left shunt or excluding any invasive treatment.]

References

1. Celli B, Fabbri L, Criner G, et al. Definition and Nomenclature of Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med. 2022 Dec 1; 206(11): 1317–1325. doi: 10.1164/rccm.202204-0671PP PMCID: PMC9746870 PMID: 35914087.

2. Global Strategy for the diagnosis, management, and prevention of COPD (GOLD 2023), available on the GOLD website: www.goldcopd.org

3. Bagdonas E, Raudoniute J , Bruzauskaite I, Aldonyte R. Novel aspects of pathogene sis and regeneration mechanisms in COPD. Int J Chron Obstruct Pulmon Dis . 2015 Jun 2;10:995-1013. doi: 10.2147/COPD.S82518. PMID: 26082624 PMCID: PMC4459624

4. Kaur M, Chandel J, Malik J. et al. Particulate matter in COPD pathogenesis: an overview. Published online 2019 Oct 26. doi: 10.15326/jcopdf.6.5.2019.0149

5. Brashier BB , Kodgule R. Risk factors and pathophysiology of chronic obstructive pulmonary disease (COPD). J Assoc Physicians India. 2012 Feb; 60 Suppl:17-21. PMID: 23155808

6. Barbera` JA, Peinado V.I, Santos S. Pulmonary hypertension in chronic obstructive pulmonary disease. Eur Respir J 2003; 21: 892–905 DOI: 10.1183/09031936.03.00115402

7. Kovacs G, Agusti A, Barbera`JA, Celli B, Criner G, Humbert M, et al. Pulmonary Vascular Involvement in Chronic Obstructive Pulmonary Disease. Is There a Pulmonary Vascular Phenotype? American Journal of Respiratory and Critical Care Medicine Volume 198 Number 8 | October 15, 2018.

8. Cooper CB, Celli B. Venous admixture in COPD: pathophysiology and therapeutic approaches COPD. 2008 Dec;5(6):376-81. DOI: 10.1080/15412550802522783 PMID: 19353352 PMCID: PMC2645850

9. Said SI, Banerjee CM. Venous admixture to the pulmonary circulation in human subjects breathing 100 per cent oxygen. J Clin Invest. 1963;42(4):507-515. https://doi.org/10.1172/JCI104739

10. Agrawal A, Palkar A, Talwar A. The multiple dimensions of Platypnea-Orthodeoxia syndrome: A review . Respir Med . 2017 Aug;129:31-38. doi: 10.1016/j.rmed.2017.05.016. Epub 2017 May 31.

11. Gossage JR, Kanj G. Pulmonary Arteriovenous Malformations. A State of the Art Review. Am J Respir Crit Care Med .Vol 158. pp 643–661, 1998.

12. Lovering AT, Riemer RK , Thébaud B. Intrapulmonary Arteriovenous Anastomoses. Physiological, Pathophysiological, or Both? Ann Am Thorac Soc Vol 10, No 5, pp 504–508, Oct 2013 DOI: 10.1513/Annals ATS.201308-265ED

13. Balchum OJ, Jung RC, Franklin Turner A, Jacobson G. Pulmonary Artery to Vein Shunts in Obstructive Pulmonary Disease. American Journal of Medicine Vol. 43, 178-185, August 1967.

14. Tobin CE , Zariquiey MO. Bronchopulmonary segments and blood supply of the human lung; a radiographic and anatomic study. Med Radiogr 26,38–45 (1950).

15. Miller WC,]ohn G, Heard JG, Unger KM. Enlarged Pulmonary Arteriovenous Vessels in COPO. Another Possible Mechanism of Hypoxemia. CHEST / 86 / 5 / November. 1984 704-706.

16. Cameron Norris H, Mangum TS, Kern JP, Elliott JE et al. Intrapulmonary arteriovenous anastomoses in humans with chronic obstructive pulmonary disease: implications for cryptogenic stroke? Exp Physiol 101.8 (2016) 1128–1142.

17. Sharma S. Pulmonary Arterovenous Malformation (PAVM): Imaging and Diagnosis. Radiology Updated: Dec 07, 2020.

18. Hagen PT , Scholz DG, Edwars WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. Mayo Clin Proc, 59 (1984), 17-20.

19. Bernard S, Churchill TW, Namasivayam M, Bertrand PB. Agitated Saline Contrast Echocardiography in the Identification of Intra- and Extracardiac Shunts: Connecting the Dots. J Am Soc Echocardiogr . 2020 Oct 23; S0894-7317

(20) 30615-5. DOI: 10.1016/j.echo.2020.09.013 PMID: 34756394

20. Michael E, Layou ME, Aboulhosn JA, Tobis JM. Potential Role of Patent Foramen Ovale in Exacerbating Hypoxemia in Chronic Pulmonary Disease. Tex Heart Inst J. 2017 Jun; 44(3): 189–197.doi: 10.14503/THIJ-16-6027 PMCID: PMC5505397 PMID: 28761399

21. Bancal C. Patent foramen ovale and hypoxaemia with or without elevated right heart pressures. Rev. Mal. Respir. 28 (8) (2011) 967–977, https://doi.org/ 10.1016/j. rmr.2011.07.001. Oct.

22. Soliman A, Shanoudy H, Liu J. Increased prevalence of patent foramen ovale in patients with severe chronic obstructive pulmonary disease, J. Am. Soc. Echocardiogr. 12 (1999) 99–105, https://doi.org/10.1378/chest.113.1.91.

23. Hacievliyagil SS, Gunen H, Kosar FM, Sahin I, Kilic T. Prevalence and clinical signifi-cance of a patent foramen ovale in patients with chronic obstructive pulmonary disease, Respir. Med. 100 (5) (2006) 903–910, https://doi.org/10.1016/j.rmed.2005.08.015

24. Kilic H, Gülsoy GK. Patent foramen ovale among patients with mild chronic obstructive pulmonary disease and unexplained hypoxia, Echocardiography 27 (6) (2010) 687–690, https://doi.org/10.1111/j.1540-8175.2009.01105.x. Jul.

25. Martolini D, Tanner R, Davey C, Patel MS, Elia D, Purcell H. Significance of patent fora-men ovale in patients with GOLD Stage II chronic obstructive pulmonary disease, J. COPD F. 12 (2014) 185–192, https://doi.org/10.15326/jcopdf.1.2.2013.0003.

26. Shaikh ZF, Kelly JL, Shrikrishna D, de Villa M, Mullen MJ, Hopkinson NS. Patent fora-men ovale is not associated with hypoxemia in severe chronic obstructive pulmonary dis-ease and does not impair exercise performance . Am. J. Respir. Crit. Care Med. 189 5 (2014) 540–547, https://doi.org/10.14503/ THIJ-16-6027.

27.Terry PB, White RI, Barth KH, Kaufman S L, Mitchell SE. Pulmonary arteriovenous mal-formations: physiologic observations and results of therapeutic balloon embolization. N. Engl. J. Med. 308198311971200.

28. Chilvers ER, Whyte MK, Jackson JE, Allison DJ, Hughes JM. Effect of percutaneous transcatheter embolization on pulmonary function, right-to-left shunt and arterial oxygenation in patients with pulmonary arteriovenous malformations. Am. Rev. Respir. Dis.1421990420425

29. Pennington DW, Gold WM, Gordon RL, Steiger D, Ring EJ, Golden JA. Treatment of pul-monary arteriovenous malformations by therapeutic embolization: rest and exercise physi-ology in eight patients. Am. Rev. Respir. Dis.145199210471051.

30. Chiau-Suong L, Jong-Kai H, I-Tseng C. Pulmonary Arteriovenous Fistula with Pulmonary Hypertension - To Close or Not to Close? Acta Cardiol Sin. 2016 Jan; 32(1): 116–119. doi: 10.6515/ACS20150424F PMCID: PMC4804951 PMID: 27122941

31. El Tahlawi M, Jop B , Bonello B, Dragulescu A, Rouault F , Habib G , et al. Should we close hypoxaemic patent foramen ovale and interatrial shunts on a systematic basis? Arch. Cardiovasc. Dis., 102 (11) (2009 Nov), 755-759, 10.1016/j.acvd.2009.09.009 Epub 2009 Nov 14 Volume 104, Issue 6, December 1993: 1673-1675.

32. Nootens M, Laurence A, Berarducci D, Kaufmann E RN , Devries S, Rich S. The Prevalence and Significance of a Patent Foramen Ovale in Pulmonary Hypertension https://doi.org/10.1378/chest.104.6.1673 CHEST Volume 104, Issue 6, December 1993:1673-1675.

33. Guérin P, Lambert V, Godart F, Legendre A, Petit J, Bourlon F, De Geeter B, Petit A, Mon-rozier B, Rossignol AM, Jimenez M, Crochet D, Choussat A, Rey C, Losay J. Transcatheter closure of patent foramen ovale in patients with platypnea-orthodeoxia: results of a multi-centric French registry. Cardiovasc Intervent Radiol 2005;28:164-885.

34. Shah AH, Osten M, Leventhal A, Bach Y, Yoo D, Mansour D, Benson L, Wilson WM, Horlick E. Percutaneous Intervention to Treat Platypnea-Orthodeoxia Syndrome: The To-ronto

Experience. JACC Cardiovasc Interv 2016;9:1928-38.

35. Zaidi A, Knight DS, Augustine DX, Harkness A, Oxborough D, Pearce K,et al. and the Education Committee of the British Society of Echocardiograph. Echocardiographic assessment of the right heart in adults: a practical guideline from the British Society of Echocardiography .Echo Res Pract. 2020 Mar; 7(1): G19–G41. doi: 10.1530/ERP-19-0051 PMCID: PMC7077526 PMID: 32105053

36. Frizzelli R, Lettieri C, Caiola S , Maulucci L, Pinzi C, Agostini F, Frizzelli A. Unex-plained hypoxemia in COPD with cardiac shunt. Respir Med Case Rep . 2022 May 5;37:101661. doi: 10.1016/j.rmcr.2022.101661. eCollection 2022. PMID: 35585906 PMCID: PMC9108509