



Pulmonary Arteriovenous Malformations - A Rare Cause of Cyanosis in the Pediatric Population

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Abstract

Pulmonary Arteriovenous Malformations (PAVMs) are rare aberrant connections between the lung's arterial and venous vascular systems. Although uncommon, PAVMs are associated with significant disease burden attributed to their high mortality and difficult management. PAVMs present with non-specific pulmonary and cardiac symptoms with radiographic findings similar to other common pulmonary diseases such as pneumonia and tumors. This has led to significant underrepresentation of this entity. Herein, we present a comprehensive review of the current literature to better describe this entity and help guide diagnostic and treatment options. We also report a case of a 9-year-old boy that presented to the American University of Beirut Medical Center with dyspnea and cyanosis in the setting of diffuse microscopic PAVMs. Contrast-enhanced transthoracic echocardiography plays a vital role in accurately diagnosing PAVMs and offers better sensitivity and specificity compared to routinely ordered chest radiography. Furthermore, first-line management of this disease includes surgical treatments such as transcatheter embolization, ligation, local excision, segmentectomy, lobectomy, and pneumonectomy. Non-surgical candidates on the other hand may benefit from nifedipine, propranolol, and nighttime oxygen therapy; however, disease recurrence and progression remain common. In short, PAVM is an uncommon and underrepresented lung pathology that requires high clinical suspicion and prompt surgical or medical management to improve patient prognosis.

Received: Nov 30, 2022

Accepted: Dec 19, 2022

Published Online: Dec 21, 2022

Journal: Annals of Cardiology and Vascular Medicine

Publisher: MedDocs Publishers LLC

Online edition: <http://meddocsonline.org/>

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Introduction

Pulmonary Arteriovenous Malformations (PAVMs) are aberrant connections between the arterial and venous vasculature in the lungs that allow direct communication by bypassing the capillary bed [1]. PAVMs are uncommon, with a reported incidence rate of 1-38 in 100,000 [1-9] individuals and a 2:1 female predominance [4]. Ten percent of cases are diagnosed in infancy; however, disease incidence increases in the fifth and sixth decades of life [10]. This led to a gross underrepresentation of the entity in medical curricula and respiratory specialty training programs across the US and the UK [11]. PAVMs were first described in 1897 by Churton et al. in a postmortem investigation on a 12-year-old boy who complained of recurrent epistaxis, hemoptysis, and a pulmonary systolic bruit [4]. The following decades proved to be pivotal for defining, diagnosing, and treating PAVMs. Rhodes et al. first reported their association with telangiectasia in 1938 [4]. Hepburn and Dauphine performed the first successful pneumonectomy for treating PAVM and reported symptomatic improvement in the patient in 1942 [4]. Nevertheless, the direct pathogenetic connection has not yet been elucidated. Suggested theories include embryological defects in the terminal arterial loops causing the dilatation of the thin-walled capillary sacs, incomplete resorption of the vascular septae separating the vascular plexuses, or failure of capillary development in the fetus [12].

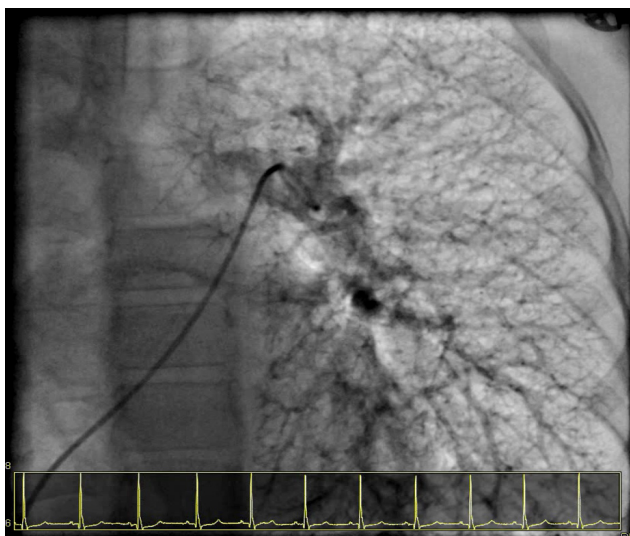


Figure 1: Illustration depicting a normal capillary bed (left) and a capillary bed arteriovenous malformation (right) in the lung.

PAVMs are classified based on the number and complexity of the aberrant feeding arteries; simple malformations involve one feeding segmental artery while complex malformations involve multiple [1]. Most cases (83%) appear in the lower lung segments, whereas upper lung segment involvement accounts for only 17% of cases. Moreover, a rare subcategory of PAVMs known as diffuse PAVM (5%) [2] exists and is characterized by aberrant segmental and sub-segmental arterial malformations involving the entire lung lobe [2, 5].

Unlike other systemic AVMs, PAVMs do not alter cardiac hemodynamics; cardiac output, index, heart rate, blood pressure, and pulmonary capillary wedge pressure are all usually preserved [10]. In addition, Rotenberg et. al demonstrated that PAVMs do not affect most mechanical properties of the lung, wherein the presence and size of PAVMs did not influence total lung capacity (TLC), residual volume (RV), vital capacity (VC), forced expiratory volume at 1 second (FEV_1), or FEF_{75} . However, the low resistance pathway supplied by the aberrant arterial-

venous connections in PAVMs allow right-to-left blood shunting across the heart, resulting in an increased A-a gradient [13]. Shunting allows for the mixing of deoxygenated and oxygenated blood, which leads to systemic hypoxemia that cannot be corrected by 100% Oxygen administration [10].

Complications of PAVMs are severe; they range from hypoxemia and cyanosis to paradoxical strokes, brain abscesses, and hemorrhage during pregnancy [7]. This led to significant morbidity and mortality rates of 50% and 55% [4], respectively. Thus, properly diagnosing PAVM becomes crucial as prompt surgical and medical therapy can greatly improve patient outcomes and prognosis. In this review, we highlight the main clinical features and characteristics associated with PAVMs and offer the most up-to-date therapies used to treat this disorder.

Methods

We searched Pubmed, Medline, and Embase using standardized MESH terms and keywords for "Pulmonary arteriovenous malformation", "diagnosis", and "management". We identified heterogeneous studies with a predominance of case reports. In consensus, we selected the relevant studies and case reports to be included.

Our patient

A 9-year-old male patient presented to the Emergency Room at our institution with severe dyspnea of four days duration and was found to have an oxygen saturation of around 70%. His previous medical history was positive for thrombocytopenia diagnosed at three years of age. History was taken from the parents who reported persistent exertional dyspnea that began when the boy was playing basketball 1 year before presentation; the patient's symptoms would often persist at rest as well. Six months before presentation, the patient contracted a relatively uncomplicated case of COVID-19; however, the parents reported severe worsening of his dyspnea and desaturation. Four days before presentation, the patient visited another hospital for a similar complaint of dyspnea and desaturation. Routine complete blood count and metabolic panels with hepatic function tests were taken and were unremarkable except for thrombocytopenia. Echocardiography, chest CT and chest CT angiography were also unrevealing. The patient was then discharged on supplemental oxygen via nasal cannula; however, his oxygen saturation levels never recovered beyond 89%.

In the emergency room, the patient was given supplemental oxygen via facemask 10Lpm, and his saturation improved to 83%. His vitals were otherwise normal. Physical examination revealed central and peripheral cyanosis with digital clubbing, and arterial blood gases showed hypoxemia. The patient was then admitted for further investigation. Echocardiography with bubble testing was done and suggested a clinical picture of pulmonary arteriovenous malformations. The patient underwent chest CT angiography which did not demonstrate PAVMs Cardiac catheterization in addition to the echocardiography findings revealed structurally normal heart. There was no shunting at atrial, ventricular, or arterial levels. LPA and RPA angiography revealed severe diffuse bilateral microscopic pulmonary arteriovenous malformations. Pressure measurements revealed normal PA pressure with a mean PA pressure of 15 mm Hg and mean RA pressure of 11 mm Hg. During his hospital stay, the patient received prednisone and IVIG for presumed immune thrombocytopenic purpura, and supplemental oxygen via facemask was weaned down to 6Lpm. SpO2 levels reached >94%

on facemask which decreased to 88%-90% on room air with no complaints. The patient was then discharged on facemask oxygen supplementation.

Discussion

Etiology

Previous studies have shown that 80% of PAVM cases are congenital [14]. PAVMs are also tightly associated with Hereditary Hemorrhagic Telangiectasia (HHT) (or Osler-Weber-Rendu disease), wherein 80-90% of PAVMs occur in the setting of active or not yet diagnosed HHT [1-4, 13, 14]. Recent genetic HHT analyses have reported that the two main germline mutations, endoglin (ENG) and activin A receptor type II-like 1 (ACVRL1) play critical roles in developing abnormal connections between pulmonary arteries and veins. These genes belong to the transforming growth factor-beta pathway in HHT [1, 3]. 62% of patients with ENG mutation, also known as the HHT1 gene, and approximately 10% of patients with ACVRL1 mutation, known as the HHT2 gene, develop PAVMs [1,3,13,15]. Moreover, mutations in the SMAD4 (Mothers against decapentaplegic homolog 4) gene, commonly seen in juvenile-polyposis-HHT syndrome, are thought to also be associated with PAVMs [5, 13, 16].

Recently, single nucleotide variants (SNVs) of Growth Differentiation Factor 2 (GDF2) gene were identified. GDF2 encodes various ligands that bind TGF- β that subsequently activate the SMAD-family transcription factors [16]. GDF2-SNVs play a role in PAVMs pathogenesis by triggering aberrant angiogenesis. Topiwala et al described a case of PAVMs with underlying GDF2-SNV; however, the patient had isolated PAVMs with no reported arteriovenous malformations elsewhere.

Acquired PAVMs are less common than their congenital counterparts. Causes of secondary PAVMs include chest surgery, trauma, schistosomiasis, actinomycosis, metastatic carcinoma, and hepatopulmonary syndrome. Of note, secondary PAVMs have been reported in up to 25% of patients who undergo the Glenn procedure, where the superior vena cava is connected directly to the pulmonary artery. Furthermore, studies have shown that PAVMs occur in lung tissue deprived of hepatic venous blood [7]. This may be explained by the lack of hepatic factors that inhibit the formation of the PAVM connections [17]. PAVMs secondary to polysplenia syndrome, periportal fibrosis, and dyskeratosis congenita with ataxia also exist [18].

Clinical presentation

Most patients (13-55%) with PAVMs are asymptomatic [2]; however, patients with multiple or large PAVMs most commonly present with dyspnea [10]. Cyanosis may also be present. Orthodeoxia and platypnea also occur as most PAVMs are localized to the lower lung segments. Rarer manifestations include hemoptysis, chest pain, cough, migraines, dizziness, vertigo, diplopia, dysarthria, and syncope, the cause of which remain unclear; however, they may be partly explained by hypoxemia, polycythemia, or paradoxical embolization [10].

Most PAVMs are reported in the adult population; however pediatric and neonatal cases have also been documented. Trivedi et al. reported a neonate who had persistent central cyanosis with an otherwise normal examination and normal echocardiography findings. However, eight days after birth, a persistent murmur was detected over the right lower chest and a large PAVM involving the right middle and lower lobes was detected on pulmonary arterial angiography [19].

Other pediatric cases have been reported with the classical triad of cyanosis, dyspnea, and digital clubbing. Of note, Dokumcu et al. described a PAVM case wherein the patient initially presented with unresolving pneumonia [12].

Jiang et al. reported an ischemic stroke in a 17-year-old female. She presented with sudden speech failure accompanied by right limb weakness for 1.5 hours [15]. Upon further investigation, a left middle cerebral artery embolism was revealed, suggesting the presence of vascular malformation. A subsequent pulmonary artery CT angiography showed bilateral diffuse PAVMs of varying sizes [15].

Even though PAVMs are uncommon, their natural course is not benign. PAVMs progressively enlarge with age and lead to a plethora of life-threatening complications, including heart failure, stroke, cerebral abscesses, pulmonary hemorrhage, hemothorax, and rupture [12]. Myocardial infarction and increased pregnancy-related deaths have also been reported [7].

Diagnosis

Symptoms associated with PAVMs are ubiquitously present in other common pulmonary pathologies, and their appearance on chest radiographs is uncharacteristic. They classically appear as round or oval sharply defined masses with uniform densities which make them resemble, and thus misdiagnosed as, pneumonia or tumors [12].

Nevertheless, chest radiography with frontal and lateral projections provides rapid, easily available, and inexpensive imaging modalities to screen for PAVMs [17]; however, they have a low sensitivity of approximately 66% [2] and their findings are nonspecific. Simple PAVMs may appear as nodules since chest radiography fails to demonstrate the feeding and draining vessels. Complex PAVMs are more ill-defined and can appear as generalized areas of opacities. Therefore, chest radiography fails to exclude other common diagnoses [17]. A more sensitive screening tool is contrast-enhanced transthoracic echocardiography which offers a sensitivity of 98.6% [2]. Agitated saline or contrast is injected peripherally while the patient is undergoing TTE. The presence of the agitated saline or contrast in the left heart within three to eight heart cycles (known as a positive bubble test) indicates the existence of right-to-left shunting [20].

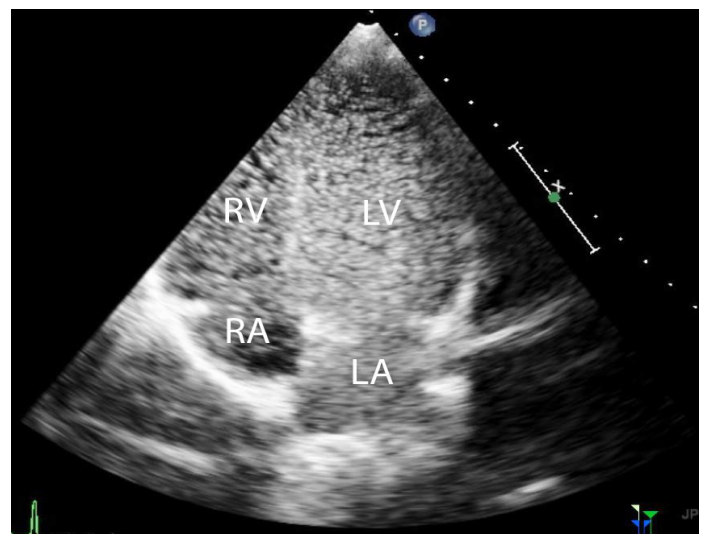


Figure 2: Contrast-enhanced transthoracic echocardiography performed on our patient showing a positive bubble test. Bubbles of agitated saline visible in all chambers of the heart. RA: Right Atrium, RV: Right Ventricle, LA: Left Atrium, LV: Left Ventricle.

In 1998, Wang et al. found that using the then-advent Doppler ultrasound was reliable for diagnosing PAVMs. Using Doppler ultrasound, they were able to verify the vascular nature of PAVMs and avoid bleeding associated with biopsies of misinterpreted PAVMs [21]. Doppler ultrasonography has also been shown to be beneficial in the antenatal detection of PAVMs [20].

Nevertheless, pulmonary angiography remains the gold standard for diagnosing PAVMs [20]. It allows for detecting and illustrating the angioarchitecture of the pulmonary tree. Pulmonary angiography also offers a superior assessment of the PAVMs, their feeding and draining vessels, and any aneurysmal dilations that may be present.

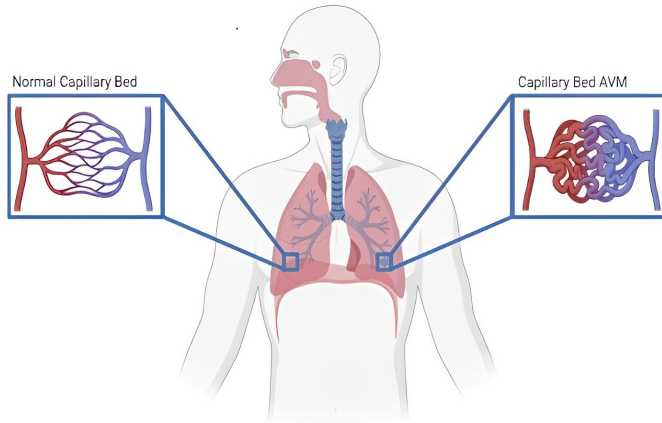


Figure 3: Image of right and left cardiac catheterization done on our patient showing the right lung after pulmonary angiography. Contrast forms a ground glass appearance typical of diffuse microvascular PAVMs.

Magnetic resonance imaging (MRI) and angiography (MRA) detect PAVMs effectively without the use of ionizing radiation. Currently, these techniques are recommended as pre-embolization planning adjunct modalities [17].

Management

Between 1942 and 1977 surgery was the only curative treatment for PAVMs while conservative treatment was offered to asymptomatic patients [22]. Surgical treatments include ligation, local excision, segmentectomy, lobectomy, and pneumonectomy. In 1978, Taylor et al. reported a successful percutaneous transcatheter embolization, thus introducing a new treatment modality [9]. Current practice largely favors embolization of PAVMs; the type of which varies based on the number and size of present PAVMs. A single embolization session is sufficient to treat four or fewer PAVMs. However, multiple lesions require several sessions.

Current guidelines recommend treating symptomatic and asymptomatic adults as well as symptomatic children. Cases of asymptomatic children must be judged based on clinical sense and deliberation [23]. In principle, embolotherapy works by occluding the feeding artery as close as possible to the communicating fistula to maintain maximal lung perfusion [23]. Multiple studies reported favorable results and have highlighted its safety and efficacy. Embolotherapy has also been shown to decrease shunt fractions and increase oxygen saturation [24, 25], which led to success rates of over 99%. Symptomatic relief can be immediate in many cases, and the risk of neurological complications decreases considerably (0–2% vs. 2.6–25%). Recanalization and reperfusion of embolized PAVMs may occur in 17–20% of cases; however, repeat embolization has demonstrated favorable outcomes as well [26].

Nevertheless, the defect size poses a challenge for embolotherapy. Previous studies recommend embolization of PAVMs with feeding arteries with diameters greater than 3mm; however, paradoxical emboli and strokes can still occur when the feeding arteries are smaller than 3mm [27]. Thus, appropriate materials and techniques are required to treat small defects safely and effectively. Mahdjoub et al. showed that microvascular plugs are safe and effective treatments for small PAVMs [27]. Large defects pose different challenges such as incomplete occlusion, recanalization, detachment, and coil migration. Kong et al. demonstrated that Amplatzer Vascular Plugs are efficacious and safe modalities for treating large defects [14]. Diffuse PAVMs on the other hand require coil packing with endovascular technique to eliminate blood flow through the PAVMs [28].

Surgery is a viable option in cases where embolotherapy is not possible [9]. Surgical approaches include wedge resection, segmentectomy, lobectomy, and pneumonectomy. Nevertheless, the surgical approach is not devoid of complications as all surgical approaches carry risks; however, when properly performed on well-selected patients, minimal morbidity and mortality rates have been reported [22].

Of note, despite the overwhelming evidence pointing to the favorable outcomes following endovascular PAVM repair, no randomized control trials (RCTs) have assessed the exact role of embolization in treating PAVMs. Currently, most available data on the topic is derived from retrospective observational studies [5].

In cases of failure of embolotherapy and classical surgical procedures, lung transplantation becomes a viable approach. Two case reports described successful unilateral and bilateral lung transplantation procedures for managing and curing PAVMs [29,30]. Patient survival was documented 3 years post-procedure [29].

Another promising interventional modality is radiofrequency ablation. It was shown to be efficacious in treating and controlling life-threatening hemorrhages in complex diffuse PAVM cases [31].

On the other hand, medical management has a limited role in treating pulmonary AVMs. Nevertheless, Sands et al. described cases of diffuse microvascular PAVMs whereby surgical and transcatheter interventions were impractical. Nifedipine was administered to induce pulmonary vasodilation and increase blood flow through physiologic capillary beds. These trials were successful at decreasing cyanosis and increasing resting O₂ saturation (>90%) [32]. In cases of combined polysplenia and PAVMs, nighttime oxygen therapy was found to decrease cyanosis and return oxygen saturation levels to normal. Oxygenation remained at normal levels years after discontinuation of therapy [unpublished observation]. It is theorized that oxygenation caused blood to pool in the physiologic vasculature away from the anomalous AVMs [18].

Sildenafil and inhaled nitrous oxide have also been utilized in cases of PAVMs. A 6-year-old patient presented with multiple PAVMs and oxygen saturation levels (SaO₂) between 30% and 60%. His breathing status greatly improved following inhaled nitrous oxide was used wherein his SaO₂ stabilized at 90%. He was gradually weaned off nitrous oxide and was eventually discharged on oral sildenafil therapy with a stable oxygen saturation between 86% and 93% [33].

Propranolol has also been explored for arteriovenous malformations in organs other than the lung. Propranolol was effective in treating right lower limb arteriovenous malformation, whereby its administration induced significant remission and growth regression. The therapy was well tolerated and reported to be effective at the 5-month follow-up. Nevertheless, recurrence was reported after discontinuation of propranolol [34], and thus the use of propranolol in the setting of PAVMs needs to be further explored.

No current study has accurately described bronchodilator therapy efficacy in treating PAVMs and associated hypoxemia. However, a 2013 case report described PAVM as difficult-to-treat asthma. In this report, an 11-year-old boy presented with asthma and hypoxemia refractory to fluticasone and salmeterol 250µg/50µg twice daily, montelukast

five mg once daily, and salbutamol [35]. This case highlights the futility of bronchodilator therapy in treating PAVM; however, larger studies are needed before making definitive clinical decisions.

Future studies aimed at investigating the relationship between COVID-19, PAVMs, illness severity, and progression will prove vital in understanding the underlying pathophysiological mechanisms of this disease. Our patient's condition reportedly began deteriorating shortly after COVID-19 infection as the infection might have affected the pulmonary physiology leading to the worsening of the patient's condition.

Conclusion

PAVM is a rare lung parenchymal disorder associated with significant health burden due to its high morbidity and mortality rates. High clinical suspicion of this entity is required as it is commonly misdiagnosed as pneumonia or tumors [12] due to their resemblance on chest radiography. Thus, other imaging modalities are preferred, such as contrast-enhanced transthoracic echocardiography, or MRI and MRA for pre-embolization planning [17]. Surgical treatment modalities include ligation, local excision, segmentectomy, lobectomy, and pneumonectomy; however, transcatheter embolization is preferred due to its high success rate and low recanalization rates. Nevertheless, medical therapy may be used to prevent PAVM progression in non-surgical candidates. Current effective medical treatments include Nifedipine, propranolol, and nighttime oxygen therapy. Trials analyzing their efficacy noted markedly improved resting oxygen saturation and an improved clinical profile. In the case of our patient, oxygen therapy showed some efficacy in recovering oxygen saturation levels. Long-term outcomes remain under observation as the patient's clinical progress has not fully unfolded. Close follow-up for any arising changes is needed. Moreover, the patient's history suggests a possible interplay between PAVMs and COVID-19 infection which warrants future investigation.

Table 1: Summarizing select case reports of pulmonary arteriovenous malformation in the pediatric population, interventions performed, and reported outcomes.

| Author(s) | Case | Intervention | Outcome |
|-----------------------------|---|---|---|
| Jiang et. al 2021 [15] | 17-year-old female presenting for sudden speech failure and right limb weakness. Cerebral artery CT showed left middle cerebral artery embolism. MRI showed acute cerebral infarction beside the left ventricle body and left external capsule. Pulmonary CT angiography showed diffuse PAVMs. | Mechanical thrombectomy. Coil embolization of PAVMs | Patient recovered well. discharged after 3 days and followed up in 3 months with CTA showing no abnormal vessels. |
| England and Weiss 2020 [38] | 14-year-old male presenting for well-visit found to have blue nails, finger clubbing, low O2 saturation (75%). CT chest showed multiple PAVMs. | Embolotherapy with Amplatzer plugs | At 2-year follow-up patient had 10 embolotherapy procedures. full resolution of symptoms and saturation went back up to 97% |
| Dokumcu et. al 2015 [12] | I. 15-month-old boy treated for misdiagnosed pneumonia with no clinical improvement. Serial X-rays detected an unchanged infiltrative lesion. Patient presented with cyanosis and 93-97% saturation with supplemental oxygen therapy. Echocardiogram showed cardiac failure and CT angiography detected a giant PAVM extending from the upper to the middle lobe of the right lung. | I. Right thoracotomy with right upper lobectomy and lateral segmentectomy of the middle lobe. | I. Postoperative course was uneventful. Child was acyanotic and thriving at 6 months follow-up |
| | II. 17-month-old boy with history of cyanosis and clubbing. Mucous membranes showed telangiectasias. Pulse oximetry saturations showed 70-75%. Chest Xray showed a soft tissue mass in the middle lobe of the right lung. Chest CT angiography showed PAVM of the middle lobe of the right lung. | II. Right thoracotomy with middle lobectomy | II. Uneventful postoperative period. No recurrence at 4 months follow-up. |
| Cirstoveanu 2013 [36] | 20 days of age girl presenting with cyanosis at three days of age. Oxygen saturation 75-90%. Normal clinical exam. PAVM suspicion due to positive "bubble test". Diagnosis was made with CT angiography. | Inhaled NO with little improvement. Left pneumonectomy. | After ligation of the left pulmonary saturation increased from 80% to 100%. Complications: Pulmonary HTN requiring NO and sildenafil. Eventual right ventricular dysfunction and death at 48th day of life |
| Navratil et. al 2013 [35] | 11-year-old boy with history of difficult-to-treat asthma. Asthma was refractory to systemic steroids and bronchodilator therapy. Chest CT angiography revealed two PAVMs, one on each side of the lungs. Saturation 92% at rest | Percutaneous transcatheter embolization of both AVMs | No residual flow in the PAVMs. Pulse oximetry increased to 97% on room air. Follow-up in 6 months revealed an increase in exercise tolerance. |

| | | | |
|--------------------------------------|--|--|--|
| Pantaleoni et. al 2013 [33] | 6-year-old boy presenting with hemangioma of the upper lip and maxilla. Cardiac examination revealed a grade II murmur and SaO ₂ of low to mid 90s. While undergoing sclerotherapy for the hemangioma, SaO ₂ dropped to 85%. Chest CT demonstrated numerous soft tissue densities consistent with PAVMs | Failed coil embolization with SaO ₂ dropping to 50-60%. Inhaled NO and oral sildenafil. | Increase of SaO ₂ to 90% on oxygen therapy 2 Lpm and eventually 92% on room air. |
| Sharifah et. al 2009 [20] | 12-year-old female presenting with intermittent breathlessness, clubbing, marfanoid features and cyanosis. Pulse oximetry 73%. CT chest showed large PAVM of the right lower lobe. | Coil occlusion | Normalization of SaO ₂ 94% on RA, resolution of breathlessness. |
| Bhate et al. 2008 [37] | I. 41-month-old girl presenting with cyanosis and O ₂ saturations of 82-89%. Cardiac catheterization demonstrated PAVF. after cavopulmonary shunting saturation dropped to 36-69%. | I. Sildenafil | I. gradual increase in saturation until stabilization at 97%. Sildenafil was ceased |
| | II. Neonate presenting with double inlet left ventricle, L-transposition of the great vessels and aortic coarctation with hypoplastic transverse arch, Cardiac catheterization demonstrated PAVM. Post Fontan procedure saturation was 70% which improved on high-flow oxygen. Eventually saturation dropped significantly necessitating intubation. | II. Inhaled NO and sildenafil | II. Significant increase in oxygenation with saturation levels reaching 95% at 14 months follow-up |
| Zain 2004 [39] | 9-month-old female delivered by C section presenting for unprovoked fetal distress with cyanosis that is exacerbated with crying and SpO ₂ 65-75% CT chest showed diffuse AVMs with no anomalous vascular involvement of other organs. | NA | NA |
| Trivedi and Sreeram 1996 [19] | Neonate at 30 minutes of age with persistent central cyanosis despite normal structure of the heart. Failure of oxygenation led to mechanical ventilation. Pulmonary angiography revealed large PAVM of the right middle and lower lobes. | Right middle and lower lobectomy | Patient was well at 9 months follow-up |

Table 2: Summarizing select case reports of pulmonary arteriovenous malformation in the adult population, interventions performed, and reported outcomes.

| Author(s) | Case | Intervention | Outcome |
|----------------------------------|--|---|---|
| Sueyoshi et al. 2021 [28] | 31-year-old male presenting for hemoptysis, hypoxemia (SpO ₂ 70-80%) and secondary polycythemia. Contrast enhanced chest CT revealed multiple PAVMs of the right lower lobe. | Coil embolization of the diffuse PAVMs. A total of 46 coils used. | Resolution of hemoptysis, hypoxemia (SpO ₂ rose to 90%), and polycythemia. |
| Topiwala et al. 2020 [16] | 43-year-old female presenting for right-arm numbness, weakness and transcortical motor aphasia. History is negative for epistaxis, GI bleed, visceral AVMs, or family with HHT. Positive bubble test. MRI brain showed acute infarction of the left frontoparietal and insular cortices. Cardiac MRI showed PAVM in the medial right upper lobe. | coil-embolization. | Follow up at 12 months no residual shunting follow up at 18 months no further TIA |
| Takao et. al 2019 [40] | I. 65-year-old woman presented previously with brain abscess. Diagnosed to have PAVM of left lower lobe of the lung by CT scan. | I. Coil embolization in 2004 | I. Recanalization of the embolized PAVM 13 years later, in 2017. Presented as aphasia and right frontal cortical infarction. Diagnosed by contrast CT with shunt flow present in the previously embolized PAVM. repeat embolization was successful. |
| | II. 75-year-old woman presented previously with cerebral infarction | II. Coil embolization in 1987 | II. Recanalization of embolized PAVMs 30 years later. Presented in 2017 with left hemiparesis and 50% blindness. Contrast CT showed shunt flow in the previously embolized PAVMs. Repeat embolization of recanalized PAVMs was successful. |
| Sandal et. al 2019[41] | 34-year-old male otherwise healthy presenting for recurrent headaches and shortness of breath. He was found to have digital clubbing. SpO ₂ 82%. Pulmonary CT angiography showed bilateral lower lung PAVMs. | Planned lower lobe lobectomy | Did not undergo procedure. Loss to follow up. |

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|---|--|---|--|
| Gunawardene and Galvin 2018 [42] | 52-year-old female previously healthy presenting for biliary colic incidentally found to have saturation of 90%. Chest Xray found an enlarged inferior right hilum. CT chest detected PAVM in the anterior segment of the right upper lobe. Case was complicated by right hemiparesis thought to be due to paradoxical emboli to the cerebral circulation. | Right upper and middle lobectomy. | Recovery was uneventful. |
| Svetliza et. al 2002 [29] | 39-year-old female known to have HHT who presented with functional dyspnea, cyanosis and digital clubbing. She had been previously diagnosed with multiple PAVMs and had undergone left upper lobectomy and lower left lobe PAVM embolization. Catheterization revealed PAVMs of the right upper and lower lung lobes. | Single right lung transplantation | Post-operative period is only significant for mild upper respiratory infections. The patient was alive and active at 2 year and 10 months follow up. |
| Reynaud-Gaubert et. al 1999 [30] | 27-year-old diagnosed with diffuse PAVMs since the age of 25 years. Presented exertional dyspnea, epistaxis, neurological complications. Trial coil occlusion was not successful. SaO ₂ was as low as 69%. | Sequential bilateral lung transplantation | Patient was well at 8 months follow-up |

Limitations

PAVMs are rare entities and therefore not commonly encountered making them difficult to explore. PAVMs are also underreported, underdiagnosed, and neglected in the medical curricula. Current studies describing this entity mostly involve case reports. Large scale RCTs are needed to accurately explore PAVMs and their treatment modalities

Funding

This research did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors

Conflict of interests

There are no conflicts to declare.

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