

Endovascular Treatment of Pulmonary Arteriovenous Malformations: How We Do It

Abstract

Pulmonary arteriovenous malformation (PAVM) is a rare disease disproportionately affecting patients with hereditary hemorrhagic telangiectasia and may be associated with other pulmonary or infectious etiologies. Respiratory symptoms are the most common, including dyspnea, hypoxemia, and hemoptysis. Due to the impairment of normal pulmonary filtration function, patients with PAVM are at risk for embolic events, ranging from ischemic strokes to brain abscesses. More importantly, PAVM can enlarge over time or with physiological changes, which may lead to catastrophic hemorrhages and increased embolization risks. From imaging perspective, echocardiography with contrast bubbles and computed tomography can both be used to diagnose PAVMs with high sensitivity and specificity. Treatment modalities have evolved from invasive surgeries to transluminal catheter-based interventions. In recent decades, the evolution of interventional techniques and equipment has resulted in a high technical success rate for the treatment of PAVMs. Here, we present the interventional PAVM treatment protocol at our institution.

Keywords: *Interventional treatment, multidetector computed tomography, pulmonary arteriovenous malformation, transthoracic contrast echocardiography*

Introduction

Pulmonary arteriovenous malformations (PAVMs) are abnormal vascular connections most commonly between the pulmonary arteries and veins. The aberrant connection bypasses the capillary bed, thereby creating an anatomical right-to-left shunt. The first PAVM was reported in 1897 through the autopsy of a 12-year-old boy.^[1] The advent of noninvasive imaging, particularly computed tomography (CT), has shed light on the true prevalence, which was estimated to be 38 cases per 100,000 individuals in one study.^[2] PAVM-related symptoms manifest between the fourth and sixth decades with female predominance.^[3] The majority of PAVMs occur in patients suffering from hereditary hemorrhagic telangiectasia (HHT), accounting for approximately 90% of PAVM cases. Multiple studies have shown that HHT patients have a PAVM incidence of 18%–58% depending on the genotypes of HHT.^[4,5] Sporadic PAVM can be associated with liver cirrhosis, infection, trauma, Fanconi syndrome, hepatopulmonary syndrome, or bidirectional cavopulmonary

shunts.^[6,7] PAVMs can result in a host of complications, ranging from systemic hypoxemia and neurological manifestations to life-threatening hemorrhage. The therapeutic options for PAVM have evolved from lobectomy and segmentectomy to percutaneous transcatheter interventions. In this article, we review the common clinical manifestations, diagnostic imaging, and therapeutic options of PAVM. We also present our institutional approach on the endovascular treatment of PAVM.

Clinical Manifestations

PAVM can manifest in simple or complex forms. Simple PAVM typically has a single feeding artery and draining vein, while a complex PAVM has multiple feeding arteries [Figures 1-3]. Diffuse PAVMs are rare, affecting approximately 7%–11% of the PAVM patient population and present as numerous small aneurysmal sacs in multiple segmental branches.^[8] Feeding and draining vessels are typically pulmonary arteries and veins. However, in certain cases, systemic connections may occur through a feeding bronchial artery or a direct draining vein into the inferior vena cava or innominate vein. PAVM is typically located in the inferior segments and can

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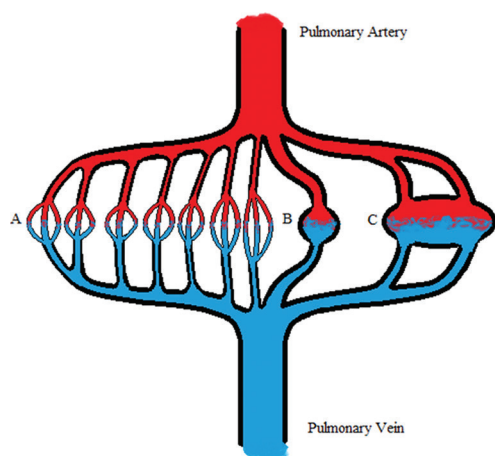


Figure 1: Schematic diagram of the pulmonary arteriovenous malformation. "A" represents the normal pulmonary capillary bed. "B" represents a simple pulmonary arteriovenous malformation with a single feeding artery and drainage vein. A complex pulmonary arteriovenous malformation is illustrated by "C" with multiple feeding arteries and drainage venous vasculature

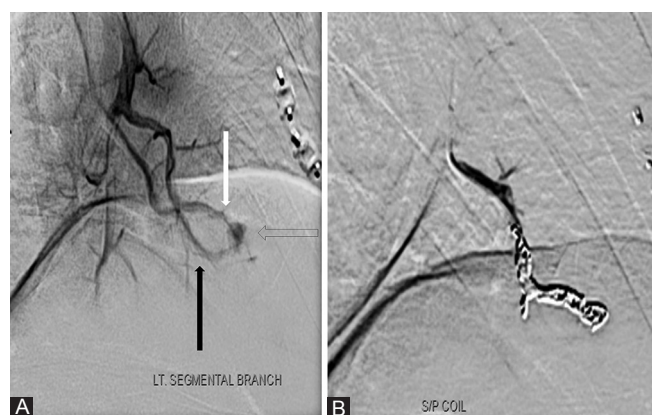


Figure 2: Single pulmonary arteriovenous malformation. Panel A shows a simple pulmonary arteriovenous malformation. Notice the single feeding and draining vessel (white and black arrows, respectively). Also note the aneurysmal shape of the abnormal arteriovenous connection (hollow arrow). Panel B shows the postembolization angiography of the same simple arteriovenous malformation, notice the absence of abnormal arteriovenous connection

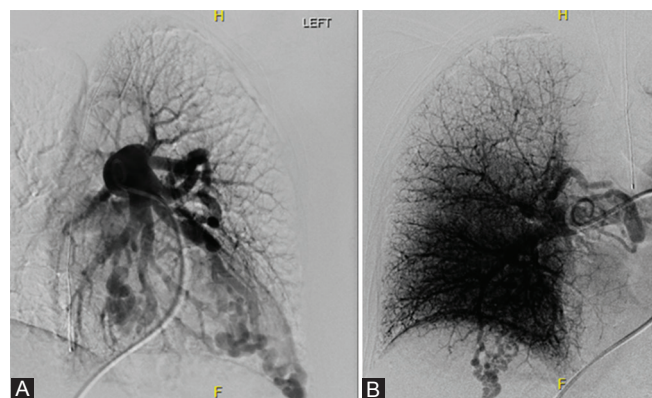


Figure 3: A hereditary hemorrhagic telangiectasia patient with multiple bilateral pulmonary arteriovenous malformations. Panel A demonstrates multiple pulmonary arteriovenous malformations in the left lower lobe. Note the tortuosity of the feeding vessels. Panel B reveals multiple pulmonary arteriovenous malformations in the right lower lobe

manifest bilaterally. In HHT patients, 69% of PAVMs are located in the lower lobes. Histologically, PAVM is composed of a thin-walled aneurysmal sac with a single layer of endothelium.^[9]

A single PAVM with an aneurysmal diameter <2 cm does not cause significant symptoms.^[10] In fact, the majority of PAVM patients may be asymptomatic. In a study of 305 patients, 79.5% of the patients did not experience significant clinical symptoms and were diagnosed incidentally.^[11] Patients suffering from bilateral diseases and multiple PAVMs are more likely to present earlier with more severe symptoms. Respiratory manifestations are the most common, owing to the anatomical shunt created by the PAVM. Asymptomatic hypoxemia is a common clinical presentation, with resting oxygen saturations as low as 78.5%. Remarkably, patients were able to pursue strenuous activities with a low resting oxygen saturation due to compensatory hematological responses. Studies have shown that there was an increase of hemoglobin by 0.82 g/dl for every 1% fall in resting oxygen saturation in the PAVM population.^[12] In addition, PAVM patients had higher resting and exercise cardiac output and maintained good maximum exercise capacity despite the profound decrease in arterial oxygen saturation during the exercise.^[13] In addition, PAVM patients may present with symptomatic dyspnea at rest. In a review of more than 1000 patients, the prevalence of dyspnea was 44% among HHT patients with PAVM. In addition, the odds ratio for dyspnea among HHT patients with and without PAVM was 3.45.^[14] More interestingly, since the majority of PAVM is located in the lower lung segments, patients may experience orthodeoxia (increased dyspnea upon standing) and platypnea (relief of dyspnea upon lying down). The dependent perfusion of PAVM increases with gravity, thereby exacerbating the right-to-left shunt. Conversely, resuming a supine position leads to the re-distribution of blood flow into the upper lobes where PAVMs are less abundant, thereby increasing the ventilation/perfusion ratio. Other respiratory signs and symptoms may include cyanosis and clubbing of the digits.

Apart from the physiological shunt, the thin-walled aneurysmal sac carries a small risk of rupture. It is a relatively rare phenomenon, since PAVM is perfused by the low-pressure system of the pulmonary circuit. However, if the PAVM is perfused by the systemic circulation, i.e., the bronchial artery, the risk of bleeding is higher. Patient may then present with hemoptysis and hemothorax.^[15,16] In addition, pregnancy carries a significantly higher risk of PAVM hemorrhage likely attributed to the increased cardiac output and blood volume during pregnancy. It is worth noting that PAVMs often increase in size and number during the pregnancy. In a retrospective review, the risk of PAVM hemorrhage during pregnancy and delivery was 1.4%, while the risk during the postpartum period was 0.6%.^[17]

The pulmonary circuit serves as a filter for the systemic circulation. The compromised filtration function puts patients at higher risk of paradoxical emboli of both infectious and embolic etiologies. Cerebral abscess affects 7.8%–12.8% of the patients.^[11,18] In addition, the incidence of cerebral abscess is 155 cases per 100,000 individuals per year in HHT patients, while the rate is 0.4 cases per 100,000 individuals per year in the general population.^[8] The risk of cerebral abscess formation has been directly related to the number of PAVMs (11.5 vs. 6.2 untreated PAVMs in patients with and without brain abscess), while the risk for strokes has been directly related to the size of the feeding artery (4.9 mm vs. 3.2 mm in patients with and without ischemic stroke).^[19] Embolic events can lead to transient ischemic attack or ischemic stroke. In one study, 33% of PAVM patients suffered from an ischemic stroke while 18% endured a transient ischemic attack.^[20] The risk of ischemic stroke decreases after endovascular treatment of PAVMs.

Imaging Diagnosis

Due to the high incidence of PAVMs in HHT patients and the significant morbidity and mortality, screening for PAVMs in patients with HHT is warranted. Transthoracic contrast echocardiography (TTCE) has become the initial screening modality for PAVMs due to its high sensitivity and negative predictive value. On TTCE, agitated saline is injected while the heart is monitored on the four-window view. In a normal individual, gas rapidly diffuses down the concentration gradient in the pulmonary capillary. Therefore, saline bubbles quickly shrink and rupture. On the contrary, in a PAVM patient, saline bubbles will not undergo destruction due to the right-to-left shunt. Therefore, the TTCE test is considered positive if saline bubbles are visualized in the left chambers [Figure 4]. To differentiate between cardiac and pulmonary shunts, contrast bubble visualization after four cardiac cycles is considered positive for a pulmonary shunt. TTCE can be used to assess the right-to-left shunt size as well.^[21] One to 29 bubbles were indicative of a grade 1 shunt, while 30 to 100 bubbles and more than 100 bubbles were considered positive for grade 2 and 3 shunts, respectively.^[21,22] Grade 3 shunts have a 92.5%

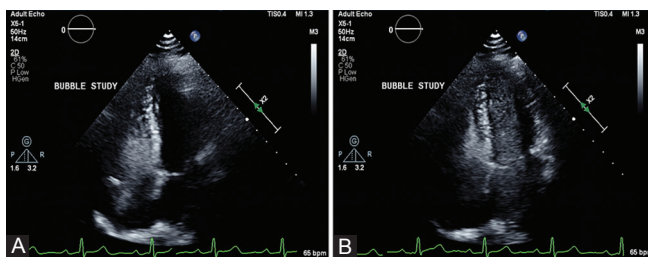


Figure 4: Transthoracic contrast echocardiography. Panel A shows enhancement in the right atrium, representing contrast saline bubbles. Panel B shows enhancement in both left and right atria, indicative of an underlying shunt. The bilateral enhancement may also indicate a severe right-to-left shunt

positive predictive value for PAVM detectable on CT angiography.^[23]

HHT patients with negative initial TTCE should undergo repeated testing every 5 to 10 years. Repeated screening should also be considered after puberty and before pregnancy due to the increased risk of PAVM enlargement during this period.^[24] Patients with positive TTCE should be evaluated with CT angiography as the noninvasive modality of choice. CT can demonstrate the size and location of the PAVM for treatment planning purposes. On CT imaging, a simple PAVM appears as a well-defined peripheral nodule with a clear feeding artery and drainage vein.^[25] In comparison, a complex PAVM will show multiple feeding and drainage vessels on CT. The emphasis is on the visualization of both feeding and drainage vessels since other pulmonary process, such as granuloma, can resemble the appearance of PAVM [Figure 5].^[26,27] If CT scan appears to be normal, repeat CT scan may be considered at 6–12 months after the initial scan in high-risk population such as HHT patients.^[23] It is worth noting that there is no consensus guideline on diagnosing and treating PAVM, clinical practice varies widely among institutions.^[28]

Catheter-directed angiography may also serve to diagnose and treat PAVM. Until recently, invasive angiography was the gold standard for evaluating the pulmonary arterial system. Angiogram follow-up may also be necessary to assess treatment response and need for further endovascular treatment sessions.^[23,29] Other imaging modalities include perfusion scan, although it has largely been replaced by the state-of-the-art CT and magnetic resonance imaging for both morphological and perfusion assessment. Perfusion scan may still have a role in assessing shunt ratio in the correct clinical context^[30] [Figure 6].



Figure 5: Maximum intensity projection of a computed tomography image of a simple pulmonary arteriovenous malformation. Note the single feeding artery (notched arrow), draining vein (hollow arrow), and aneurysmal fistulous communication sac (white arrow). Image courtesy of Dr. Amit Gupta, MD

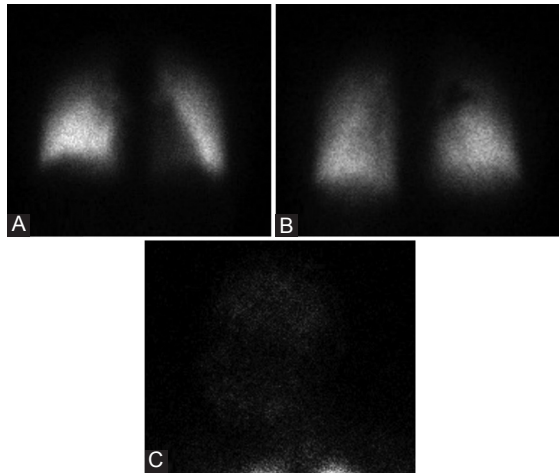


Figure 6: Perfusion lung scan. Panels A and B show several perfusion defects in the bilateral upper lobes. Panel C depicts abnormal radiotracer uptake, indicating an underlying right-to-left shunt. In this patient, the shunt is caused by the bilateral pulmonary arteriovenous malformations. This particular patient has undergone previous embolization for pulmonary arteriovenous malformation. Recanalization was suspected and perfusion scan confirmed the recanalized pulmonary arteriovenous malformation by demonstrating abnormal right-to-left shunt

Treatment of Pulmonary Arteriovenous Malformations

From the 1940s to 1970s, surgery used to be the only treatment option for PAVM. Ligation, segmentectomy, lobectomy, and pneumonectomy were performed. The postoperative PAVM recurrence rate was low. In a small case series, nine patients underwent surgical excision of PAVMs. At a mean follow-up period of 12 years, none of the patients experienced recurrence.^[31] Lung transplantation is a last resort option for patients who are suffering from diffuse, bilateral diseases.^[32]

Apart from surgery, transcatheter embolization enables minimally invasive management of PAVM. In 1977, the first embolization procedure using steel coils for the treatment of PAVM was performed.^[33] Since then, transcatheter embolization has gradually become the mainstay treatment option. Surgery is now reserved for patients with failed embolization or life-threatening hemorrhage. The goal of embolization is to embolize the fistula close to, or at the junction of the feeding artery and the aneurysm.^[6] Historically, a 3-mm feeding artery was thought to be a significant risk factor for paradoxical embolization and was chosen as the threshold indication for interventional treatment. However, evidence has shown that as high as 13.5% of the patients with untreated below-threshold PAVM suffered from paradoxical embolization as well.^[11,34,35] Further, case reports have shown that untreated PAVM could gradually grow in size.^[36] Therefore, interventional therapy may be considered in feeding arteries <3 mm if subselection is technically feasible. Different strategies, techniques, and embolizing agents have been described, such as detachable balloons,

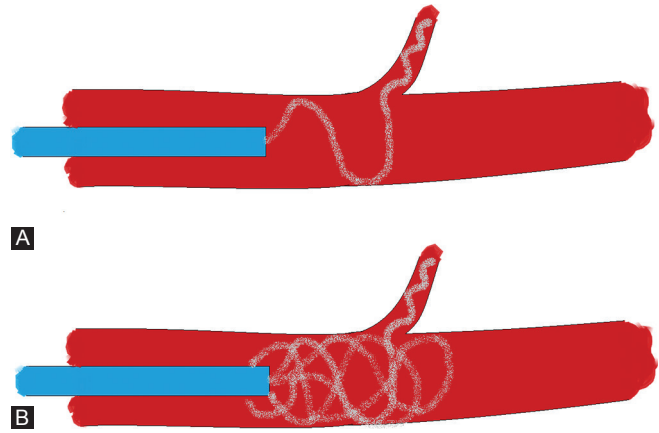


Figure 7: Anchoring techniques. Catheter may advance toward a side branch of the feeding artery. The 1st or 2 cm of the coil may be anchored in the small feeding artery. Then, the catheter can be pulled back and the rest of the coil deployed in the main feeding artery

pushable fibered coils, vascular plugs, and detachable coils. Here, we would like to present the PAVM protocol at our institution.

How We Do It

In some other institutions, interventional radiologists advocate giving a 3000–5000 U of heparin bolus after the catheter introduction as a safety measure against thrombus formation in or around the catheter, eventually preventing inadvertent paradoxical thromboembolism. We personally elect not to heparinize patients because 67%–83% of HHT patients also have telangiectasia in the oral or nasal mucosa and lips. Giving heparin might provoke nasal and/or oral bleeding which could compromise the airway.

All catheter and guidewire manipulations or exchanges should be performed in a manner that prevents air from entering the catheter, causing inadvertent air embolism across the PAVMs. Our preferred method to address this issue is to perform all exchanges and catheter manipulations while the catheter hub is submerged in a saline-filled bowl. In addition, frequent catheter flushing with bubble-free solution is a critical technique in this procedure.

We usually perform PAVM embolization procedures through a right common femoral vein approach under moderate sedation and local anesthesia, which results in increased stability for embolization. It is worth mentioning that oversedation should be avoided since patient cooperation and respiratory maneuvers are imperative for adequate imaging and treatment planning. In addition, patients with PAVMs are generally young and nervous about their diagnosis which can lead to a hyperdynamic state. Pulmonary angiography in this population may require higher flow rates (30–35 ml/s for 2 s) than the typical older patients with thromboembolic disease.

We usually place a 9 Fr short vascular sheath in the right common femoral vein. Then, we place a pulmonary

angiographic catheter coaxially through the sheath over a guidewire. Our preferred method to select the pulmonary artery is by using a 7 Fr pulmonary angiographic catheter to allow for high-contrast injection rates (i.e. >20–25 ml/s). The most used catheter is the Grollman pulmonary artery catheter (Cook Inc., Bloomington, IN, USA). Such catheter usually has a preformed pigtail and a 90° reversed secondary curve 3 cm proximal to the pigtail. The pigtail catheter is placed in the right atrium. The anteromedial portion of the right atrium is probed to facilitate catheter entry into the right ventricle. The catheter is then slightly withdrawn and rotated counterclockwise to allow for entry into the right ventricular outflow tract and main pulmonary artery. If the catheter tip becomes lodged in the right ventricular outflow tract, a soft-tipped J guide wire may facilitate catheter entry into the main pulmonary artery.

In patients with right atrial enlargement, the right ventricle may be difficult to probe with the standard Grollman catheter because the distal end of the catheter may be too short to allow for direct passage. In such cases, the 90° angle of the distal tip may be enlarged by introducing a manually bent guide wire. The Van Aman (7 Fr APC, Cook Inc., Bloomington, IN, USA) catheter is a 7 Fr polyurethane-modified Grollman catheter with a 90° reversed secondary curve 6 cm (rather than 3 cm) proximal to the pigtail and has been successfully used for pulmonary artery catheterization in patients with right heart enlargement.

Following successful pulmonary artery catheterization, complete pulmonary angiography with multiple views of both lungs should be obtained to identify all pulmonary vascular lesions. Small PAVMs may be missed on CT, and angiographic detection is important for planning long-term follow-up. AVMs are identified by one or more large feeding arteries and a large draining vein that opacifies before pulmonary parenchyma and the remainder of the pulmonary veins. The actual arteriovenous communication is frequently saccular or aneurysmal in appearance.

After obtaining the planning angiogram, we exchange the pulmonary angiographic catheter for the Cook® White LuMax® guiding catheter, which is long enough to stabilize the system in the pulmonary artery and consists of a 7 Fr multipurpose guiding catheter and a corresponding 5 Fr inner coaxial catheter. There is a short distal angle on both guiding and inner coaxial catheters. This guiding catheter system helps in selective embolization of PAVMs. Microcatheters can sometimes also be used coaxially through the 5 Fr catheter if needed.

In the past, only PAVMs with feeding pulmonary arteries 3 mm or greater in diameter were embolized, because they were thought to be most likely to permit paradoxical emboli. In our practice, however, we embolize any PAVM that can be catheterized, because

even small lesions can lead to strokes. The intended site of occlusion is the feeding artery, not the actual fistula or draining vein. After selection of the feeding artery, hand injection of contrast in multiple views maybe necessary to define the anatomy. The guiding catheter is then advanced as close to the actual shunt as possible. Occlusion of the feeding artery can be accomplished with detachable or pushable coils, or detachable plugs. We prefer to perform the embolization in the feeding artery as close as possible to the fistula using detachable coils, which have a diameter at least 20% larger than the target vessel, in order to avoid iatrogenic paradoxical emboli. If detachable coils are not available, a technique for secure placement of the first coil is to anchor the first centimeter or two of the coil in a small side branch of the feeding artery near the fistulae. As the coil is deployed, the delivery catheter is pulled into the feeding artery so that the majority of the coil is delivered in this location [Figure 7]. Additional coils or plugs more closely sized to the artery are then deposited until there is no longer filling of the shunt.

These procedures can be time-consuming, so we usually stage cases with multiple bilateral PAVMs to avoid radiation and contrast-induced complications. Our limit for radiation per session is a total air krama of 5 Gy and a total contrast load of 200 ml.

Posttreatment Follow-up

Embolization has a high technical success rate. In a recently published study, the technical success rate

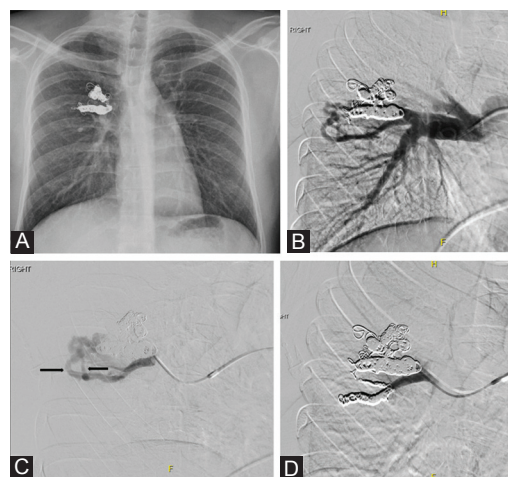


Figure 8: Recanalized complex pulmonary arteriovenous malformation. Panel A with chest X-ray demonstrating status postendovascular coil placement in pulmonary arteriovenous malformation. Panels B and C depict contrast opacification of an arteriovenous connection, consistent with recanalization of the previously embolized pulmonary arteriovenous malformation. Panel C demonstrates the two feeding arteries of the recanalized pulmonary arteriovenous malformation (black arrows), consistent with a complex pulmonary arteriovenous malformation. Panel D shows status post re-treatment with coil embolization of the recanalized pulmonary arteriovenous malformation. Previously visualized contrast opacification of the aneurysm is no longer seen, indicating treatment success

was 100%. Follow-up CT scan showed successful treatment of 97% of PAVMs. Nearly 65% of PAVMs showed complete disappearance.^[37] Other studies have shown a similar immediate technical success rate of 97%–100%, although several embolization procedures were necessary in certain cases.^[38,39] Endovascular embolization reduces physiological shunting and prevents paradoxical embolization and hemorrhage. Despite the technical success rate, endovascular embolization has technical limitations. 8%–25% of the PAVM persisted postprocedurally, mostly due to recanalization. Other causes include previously untreated feeding vessels, systemic-to-pulmonary reperfusion, and pulmonary-to-pulmonary reperfusion.^[40] Postembolization recanalization puts patients at risk of future paradoxical embolization, even as late as 15 years postprocedure.^[41] Persistent PAVM should be treated if it becomes symptomatic (paradoxical embolization, progressive enlargement, and persistent patency of the aneurysmal sac)^[37] [Figure 8]. Technical success rate has been shown to be higher in treating recanalized PAVM as opposed to reperfused PAVM. Apart from persistent PAVM, other complications after transcatheter embolization include transient pleurisy, paradoxical device migration, and nontarget embolization.^[23] Patients should be assessed in the interventional radiology outpatient clinic after embolization. As per the 2011 guidelines, postembolization patients should undergo CT scan at 6–12 months posttranscatheter embolization and then every 3 years after.^[24] In addition, at the time of the follow-up CT scan, a dedicated assessment at the interventional radiology outpatient clinic should be warranted.^[42]

Conclusion

PAVM is a rare disease entity that creates an aberrant capillary-free arteriovenous connection. It most commonly presents in HHT patients and can result in significant morbidity. Paradoxical embolization, respiratory symptoms, and hemorrhage are common complications. Patient death is the most consequential sequelae of PAVMs, especially during pregnancy. From an imaging perspective, CT and TTCE are used to diagnose PAVM with high diagnostic yield. Angiography-guided transcatheter embolization has largely replaced surgery as the mainstay treatment option. Here, we presented the techniques employed at our institution. Endovascular treatment has a high technical success rate. However, small PAVMs will enlarge over time. Therefore, PAVM patients should be followed up closely in the interventional radiology outpatient clinic posttreatment.

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Conflicts of interest

There are no conflicts of interest.

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