Contemporary Management of Pulmonary Arteriovenous Malformations

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Int J Angiol 2017;26:205–211.

Abstract

Keywords

- pulmonary arteriovenous malformations
- transcatheter embolization therapy
- vascular plug embolization
- coil embolization
- chest CT
- pulmonary angiography
- hereditary hemorrhagic telangiectasia

Pulmonary arteriovenous malformations (PAVMs) are atypical vascular structures involving a direct connection between the pulmonary arterial and venous circulations. While PAVMs are a relatively uncommon disorder, unmanaged cases are at risk for the development of serious complications including embolization and infection. Since their first description in 1897, PAVMs have been identified and treated in a variety of ways. Advancements in diagnostic methods and operative techniques have allowed for more effective treatment of the disease. Most recently, the use of vascular plug transcatheter embolization has been described as an effective therapeutic procedure in the management of PAVMs. In this report, we present our experience with nine cases of PAVMs treated at the University of Kentucky, including special consideration of an exemplary case that illustrates the typical course of treatment for the disease.

Pulmonary arteriovenous malformations (PAVMs) are atypical vascular structures involving a direct connection between the pulmonary arterial and venous circulations causing a right to left shunting of blood within the lungs. These vascular abnormalities result in decreased perfusion of pulmonary tissue and bypassing of alveoli, which prevents the normal exchange of blood gasses within the lungs.¹

PAVMs were first described by Churton in 1897 following the autopsy of a young cyanotic boy. The child had been noted to have a loud pulmonary systolic bruit and suffered from recurrent episodes of hemoptysis.² In 1938, Rodes described the association between PAVMs and hereditary hemorrhagic telangiectasia (HHT).³ The first clinical diagnosis of the disease in a living patient was made in 1939.⁴ An early epidemiological study performed at Johns Hopkins in 1953 found only 3 cases of PAVMs in a series of 15,000 consecutive autopsies for an estimated incidence of 1 in 5,000.⁵

Since these early discoveries, the management of PAVMs has changed in a variety of ways. Many studies have shown that advancements in diagnostic methods and therapeutic approaches have allowed for better understanding for improved management of patients with the disease. Our review of recent cases of PAVMs treated at the University of Kentucky contributes to the current understanding of how to best manage patients with this disease.

Clinical Features

A total of 9 cases from the past 10 years were studied involving the treatment of 10 PAVMs at the University of Kentucky. A summary of the presentation, diagnosis, and management of each patient can be found in ►Table 1. The study population included one male patient and eight female patients with a mean age of 56.3 years. The most common

published online
September 18, 2017

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Tel: +1(212) 584-4662.

DOI <https://doi.org/10.1055/s-0037-1607033>.
ISSN 1061-1711.

Table 1 Patient presentation, diagnosis, and management

Patient no./age/sex	PAVM no.	Presentation	Diagnosis	Management
1/68/F	1	Hypoxemia	CT scan	Coil occlusion
2/55/F	2	Dyspnea	CT scan, echo bubble study	Coil occlusion
3/55/F	3	Transient ischemic attacks, headaches	Echo bubble study	Vascular plug occlusion
4/60/F	4	Incidental finding (asymptomatic)	CT scan	Vascular plug occlusion
5/29/F	5	Transient ischemic attacks, visual changes	Echo bubble study	Coil occlusion
6/55/M	6	Dyspnea	CT scan	Vascular plug occlusion ^a
7/47/F	7	Cerebrovascular accident	Echo bubble study	Vascular plug occlusion
8/60/F	8	Dyspnea	CT scan	Vascular plug occlusion
9/78/F	9, 10	Cerebrovascular accident	CT scan	Vascular plug occlusion

Abbreviations: CT, computed tomography; PAVMs, pulmonary arteriovenous malformations.
^aLobectomy was performed following two failed attempts at vascular plug embolization.

presenting symptoms were dyspnea/hypoxemia and cerebrovascular accident/transient ischemic attack. Diagnosis of PAVM was made via computed tomography (CT) scan and/or echo bubble study. Of the 10 PAVMs treated, 9 were successfully treated using transcatheter embolization therapy, while 1 required surgical resection. Of the PAVMs managed with embolization therapy, six were occluded using vascular plug devices, while three were occluded using coils. The single case managed through surgical resection involved a lobectomy performed following two failed attempts at vascular plug embolization. All patients reporting for follow-up described symptomatic relief (including improvement of dyspnea and increased activity level). Ultimately, all nine cases had successful outcomes. Since 2012, vascular plug embolization has been the primary treatment method for PAVMs at the University of Kentucky.

Report of a Case

One particular case included in this review provides an excellent example for the typical management of PAVMs. This case involved a 59-year-old woman who was referred to

the University of Kentucky from an outside hospital for evaluation of her shortness of breath and abnormal chest X-ray (► **Fig. 1A**) and CT scan (► **Fig. 1B**). Specifically, her contrast CT scan revealed a left upper lobe pulmonary nodule of around 0.4 cm in size that had since grown to 1.4 cm over the course of 1 year. The patient was known to have both a personal and family history of PAVM as well as HHT. The patient was scheduled for a catheterization procedure, including angiographic study and embolization therapy. Pre-intervention angiography (► **Fig. 2A**) was performed to visualize the affected vessels. Embolization was then achieved using two vascular plug devices: a 10-mm plug placed into the feeding artery of the AVM and a 16-mm plug placed distally at the neck of the venous sac for further stabilization of the AVM. Post-intervention angiography (► **Fig. 2B**) revealed immediate success of the operation with complete occlusion of the PAVM and stable positioning of the vascular plugs. Upon 1-year follow-up, the patient reported that her shortness of breath had resolved and that she was now asymptomatic. Chest X-ray confirmed resolution of the PAVM and stable positioning of vascular plugs (► **Fig. 3A** and **B**). Overall, the patient

Fig. 1 Presentation of PAVM. Chest X-ray (A) showing left hilar mass. CT scan (B) showing vascular mass within the lingula. CT, computed tomography; PAVMs, pulmonary arteriovenous malformations.

Fig. 2 Angiographic studies. Pre-intervention angiogram (A) identifying shunting of blood. Post-intervention angiogram (B) depicting occlusion of PAVM. PAVM, pulmonary arteriovenous malformation.

experienced significant improvement following embolization therapy with the vascular plug devices.

Discussion

Incidence and Demographics

A recent analysis of data gathered using thoracic CT scanning determined that PAVMs affect 38 individuals out of 100,000 (~1 in 2,600).⁶ PAVMs are about twice as common in women as they are in men, with a male-to-female ratio of ~1:1.5:1.8.⁷ The disease typically has an onset in the third or fourth decade of life with an average age of 36 years.⁸ PAVMs are fairly uncommon in children with only 4% of cases found in patients under 10 years of age.⁹ Around 70% of PAVM cases are associated with HHT, and 15 to 35% of patients with HHT will develop a PAVM.¹⁰ About 80% of PAVMs can be described as structurally simple having a single feeding and a single draining vessel. The other 20% of PAVMs are complex with two or more feeding and/or draining vessels.¹¹

Etiology

Three specific genes have been associated with HHT and the development of PAVMs. HHT1 involves mutations to the *ENG* gene encoding endoglin, while HHT2 involves mutations to the *ACVRL1* gene encoding activin receptor-like kinase

(ALK-1). Mutations to *SMAD4* are associated with juvenile polyposis/HHT, a condition that is less common than HHT1 and HHT2. Patients with mutations to *ENG* and *SMAD4* are more likely to develop PAVMs than are patients with mutations to *ACVRL1*. Two additional genes have been identified in connection with the development of classical HHT (*HHT3* on chromosome 5q and *HHT4* on chromosome 7p); however, little else is known about these genes. Mutations related to HHT result in the production of a nonfunctional allele with subsequent phenotypic expression due to haploinsufficiency. The specific genes affected in HHT code for proteins involved in the transforming growth factor- β (TGF- β) signaling pathway. Typically, the TGF- β signaling cascade promotes cellular growth and differentiation via initial activation of transmembrane receptor complexes. Mutations to the endothelial-specific co-receptor endoglin and receptor complex ALK-1 (along with other components of the TGF- β signaling pathway) are hypothesized to cause atypical maturation of vascular structures and the development of telangiectasias and arteriovenous malformations (AVMs).¹

Presenting Symptoms and Complications

Due to the high number of PAVM cases related to HHT, the majority of clinical evidence and knowledge of PAVMs has been gathered in populations also diagnosed with HHT. HHT

Fig. 3 Follow-up radiographic studies. PA (A) and lateral (B) chest X-rays showing resolution of PAVM and secure placement of the vascular plugs. PA, posterior-anterior; PAVM, pulmonary arteriovenous malformation.

is an autosomal dominant disorder that most commonly presents with epistaxis and mucocutaneous telangiectasias, but can be complicated by the formation of AVMs within the lung as well as the brain, liver, and GI tract.¹² According to the Curaçao' Criteria for the clinical diagnosis of HHT, a diagnosis of HHT may be described as definite (three or more criteria present), possible/suspected (two criteria present), or unlikely (zero or one criterion present) with reference to the following criteria: epistaxis (spontaneous and recurrent), telangiectasias (multiple and at characteristic sites, including lips, oral cavity, fingers, and nose), visceral lesions (GI telangiectasias, pulmonary, hepatic, cerebral, or spinal AVMs), and family history (first-degree relative with HHT according to stated criteria).¹³ PAVMs not associated with HHT are largely considered to be idiopathic, but other causes have been described, including infection (schistosomiasis and actinomycosis), trauma, and Fanconi syndrome. PAVMs have also been noted to occur secondary to hepatopulmonary syndrome and bidirectional cavopulmonary shunts.⁷

The most common presenting symptoms of PAVMs include dyspnea on exertion (27–71%), hemoptysis (2.4–20%), and chest pain (1.9–17%). Notably, a large percentage of patients (25–58%) will be completely asymptomatic. Common signs present with PAVMs include bruit/thrill (25–58%), cyanosis (9–73%), and clubbing (6–68%).⁷ Dyspnea has classically been associated with the presentation of PAVMs, but more recent studies have shown that it is not as common as was once thought.¹⁴ Asymptomatic hypoxemia is more likely to be seen at presentation as compared with dyspnea on exertion. Patients with significant hypoxemia ($\text{SaO}_2 < 85\%$) demonstrated the ability to pursue physical activity at a high level.¹⁵ In a study of 165 consecutive patients, only those with a significant co-existing cardiopulmonary disease received a Medical Research Council (MRC) dyspnea grade higher than 3 (dyspnea following ~1 mile walk on flat).¹⁶ Hemoptysis can be attributed to the fragility of the vasculature involved in the PAVM as well as the presence of nasopharyngeal and endobronchial telangiectasias in patients with coexisting HHT. Rarely, hemorrhage of PAVMs leading to hemoptysis or hemothorax can be fatal. However, the patient is at increased risk of this complication if they are pregnant, or if the PAVM is perfused at systemic pressures (due to pulmonary hypertension or increased systemic arterial supply).¹⁴

The impetus for treatment, other than symptomatic relief, is to reduce the possibility of developing serious complications. The risks of embolization (including ischemic stroke and myocardial infarction) and infection (including cerebral abscess formation) pose the greatest threat to patients with PAVMs. Patients have been recorded to have an ischemic stroke rate of 11.3% with adjustment for ascertainment bias.¹⁷ A separate imaging study found cortical or subcortical infarcts present in 51% of patients (median age of 41 years).¹⁸ Similar to ischemic stroke, paradoxical embolization may also result in myocardial infarction.¹⁹ Cerebral abscess formation was noted in 9.05% of patients following the study of 219 consecutive patients with PAVM/HHT, adjusting for ascertainment bias.¹⁷ In some situations, cerebral abscess formation may be the first symptom noted in a patient with an occult PAVM.⁸

Diagnostic Methods

PAVMs are most commonly diagnosed through the use of chest radiographs and CT scans, but may be supplemented with additional methods as needed. While chest X-rays may be used to identify most malformations, not all PAVMs can be visualized using X-ray. In one study, 10 to 40% of clinically significant cases of PAVM were reported to have normal radiographic findings.²⁰ CT scanning represents a more valuable imaging modality as compared with X-ray. CT is much more useful for determining the size and extent of the malformation—information that is critical in therapeutic decision making. Due to the extensive capabilities of CT to image pulmonary angiographic anatomy, diagnostic angiographic studies are usually limited to the lung in which the PAVM has already been identified. Most often, fluoroscopic angiography is performed just prior to embolization therapy during the same catheterization procedure to visualize the affected vessels. Following intervention, angiography may once again be used to determine the success of the procedure.¹⁴

Due to the anatomic right-to-left shunting of blood produced by PAVMs, pulmonary arterial blood that flows through a malformation will bypass alveolar ventilation. The severity of this shunting phenomenon can be evaluated using gas exchange and contrast echocardiography studies. Gas exchange studies classically involved the measurement of arterial PaO_2 breathing 100% oxygen; however, it is now more common to assess arterial PaO_2 and/or SaO_2 breathing air.¹⁴ While more invasive than gas exchange studies, contrast echocardiography represents a more sensitive method for evaluating patients with PAVMs and is more commonly used today. This procedure involves the measurement of microbubbles generated upon intravenous injection of contrast material. Gaseous microbubbles are expected to rapidly diffuse through the alveolus when circulating to the pulmonary capillaries. Increased numbers of microbubbles visualized in the left heart or systemic circulation indicate the presence of a pulmonary vascular malformation.²⁰ However, due to the high number of false positive results (especially during exercise or in other high cardiac output states), it is important to specifically note the grade of the shunt by counting the number of microbubbles visible within the left ventricle. One study on the utility of contrast echocardiography found that grade 3 shunts (>100 microbubbles per frame) were associated with a positive predictive value of 92.5% for CT-evident PAVMs, while grade 1 shunts (<30 microbubbles per frame) had a positive predictive value of only 13.4%.²¹

Treatment Methods

The first successful surgical treatment of PAVMs involved a pneumonectomy performed in 1942.²² With further advancements in thoracic surgery, local excision became the preferred therapeutic option by 1959.²³ While surgical resection has proven to be an efficacious option in the treatment of PAVMs, the invasiveness of the procedure along with the loss of viable lung tissue prompted the development of transcatheter embolization therapy.¹⁰ First described in 1977, embolization therapy has been considered the gold standard in the treatment of PAVMs since 1983.^{24,25} Due to ethical concerns, there have been no randomized controlled

trials specifically examining the efficacy of embolization therapy for PAVMs. However, data collected from observational studies indicate that embolization reduces morbidity.²⁶ Following a single dose of prophylactic antibiotics 1 hour prior to operation, the procedure is performed via a femoral venous approach under local anesthesia. Fluoroscopic pulmonary angiography allows for visualization of the affected vessels prior to occlusion at the artery/venous sac junction.¹ Precise placement of the embolization device is critical to prevent unwanted occlusion of blood flow to normal adjacent tissue as well as to minimize the chances for recanalization of the malformation.

Since its introduction, a variety of different devices have been utilized for transcatheter embolization therapy including silicone balloons, coils, and most recently vascular plug devices. Silicone balloons were most commonly used to occlude PAVMs composed of vessels less than 9 mm in diameter, but are no longer available for use today.⁸ Coil devices are deployed one at a time to fill the vessel lumen and are designed to promote the formation of a platelet plug via attached microfiber molecules.⁷ The use of up to 10 coils to occlude a single PAVM has been reported.²⁷ The more recently developed vascular plugs have several advantages over coils. Most notably, a single vascular plug may be used to occlude a large diameter-feeding artery, which can allow for the embolization of multiple PAVMs in a single session (reducing fluoroscopic radiation time). Vascular plugs are also capable of occluding PAVMs over a shorter vessel length as well as at the neck of the venous sac—both of these characteristics lower the chances of occluding blood supply to normal adjacent tissue.²⁰

The most prominent vascular plug device used in the embolization of PAVMs is the Amplatzer Vascular Plug (AVP) produced by St. Jude Medical (Plymouth, MN). Originally introduced in 2004 as single device for peripheral vascular embolization procedures, the AVP is now available in four distinct models—each with particular utilities and indications for use. Each model is composed of nitinol braids that expand upon deployment to form the vascular plug. Radiopaque platinum markers are present at each end of the device to facilitate visualization under fluoroscopy. Only the AVP and AVP II models are approved by the Food and Drug Administration (FDA) for clinical use. Both of these vascular plug devices have been utilized for transcatheter embolization of PAVMs. The AVP has a single-lobe structure and a single layer of nitinol braids, whereas the AVP II has a three-lobe structure and multiple layers of nitinol braids. The AVP II theoretically has improved occlusive properties compared with the AVP due to its multiple lobes and layers of nitinol mesh, making it preferred in cases requiring rapid vessel occlusion. However, the AVP II is also larger than the AVP and may be more difficult to deploy in smaller landing zones.²⁸ To ensure stability of an AVP, the manufacturer recommends oversizing the device by 30 to 50% compared with the diameter of the target vascular structure. Oversizing of the AVP ensures stability of the device following deployment, but does not significantly improve the thrombogenic capacity of the plug.²⁹ Some studies have described the placement of coils proximal to an AVP to further safeguard against reca-

nalization. It has been demonstrated that the placement of a second AVP proximal to the primary AVP is superior to the placement of coils in terms of time, ease, and rate of occlusion of the vascular malformation.³⁰

Embolization therapy can be limited by the size of the feeding vessels with a vessel diameter lower limit of around 3 mm. PAVMs of diameter 3 mm or greater that are detected by CT scan should be considered for embolization regardless of patient symptoms.³¹ In situations where embolization is technically possible yet the vessel diameter is <3 mm, therapy is indicated regardless of feeding vessel diameter. In such circumstances, embolization should be performed to reduce the risk of paradoxical embolism, especially in patients who have experienced a previous paradoxical embolic event.¹⁷ For cases that fail or are not amenable to embolization therapy (due to small vessel size and/or risk of occluding larger proximal vessels), surgical treatment remains a viable option. Elective surgical procedures have been performed in patients experiencing persistent ischemic strokes or transient ischemic attacks despite maximal embolization of PAVMs. Emergencies related to massive hemoptysis have also been managed with lobectomy or pneumonectomy.³² Lung transplantation, while described in certain situations, remains a controversial option.^{14,33}

Medical management of PAVMs focuses on relieving the symptoms of hypoxemia and iron deficiency along with minimizing risk of infection and providing special consideration for patients who are pregnant. Patients may be prescribed supplementary oxygen for symptomatic relief of hypoxemia; however, its prophylactic use to prevent hypoxic pulmonary hypertension is not supported.^{15,34} Patients suffering from iron deficiency (especially those with HHT and significant epistaxis) may experience exacerbated hypoxemia.³⁵ Hypoxic patients require an elevated hemoglobin concentration to maintain a normal CaO_2 .¹⁵ However, patients with low iron levels will have decreased hemoglobin synthesis and erythrocytosis. Iron-rich diets or iron supplementation may therefore be beneficial in some patients with PAVMs. Cerebral abscess formation via infection by oral bacteria has long been noted as a potential complication of dental procedures in patients with PAVMs. For this reason, use of prophylactic antibiotics prior to dental procedures as well as thorough attention to dental hygiene are recommended.³⁶ Patients who become pregnant have been noted to develop increases in both size and number of PAVMs.^{37,38} In a study of 484 pregnancies in 199 women with HHT and PAVMs, the majority of women underwent a normal pregnancy. Although, a small proportion of the patients developed serious complications, including 1% of pregnancies ending in maternal and fetal death. If an emergency is avoided, but intervention is indicated, PAVM embolization should be delayed until the third trimester.³⁹ Urgent embolotherapy for hemoptysis or hemothorax may be performed as early as at 16 weeks' gestation, at which point limited radiation exposure to the fetus is acceptable.⁴⁰

Success of Treatment

As previously stated, there have been no randomized controlled trials performed to compare the efficacy of surgical

treatment directly to embolization therapy in the management of PAVMs.²⁶ However, a review of observational studies involving the two forms of treatment may be used to compare the relative success of each. Similarly, the results of observational studies involving the use of coil embolization versus vascular plug embolization may also be compared.

While surgical resection of PAVMs involves at least the same amount of risk as any other thoracic surgery, when this form of therapy is performed in the appropriate patient population, there is very low operative risk and only a small rate of recurrence.¹⁰ Surgical resection is reserved for PAVMs that are localized to a particular area within the lung, are very small for embolization, or have failed embolization therapy causing the patient to remain symptomatic (persistent ischemic strokes or transient ischemic attacks). In a combination of five contemporary studies reporting on consecutive patients treated for PAVMs via surgical resection, there was no perioperative mortality reported in any of the 99 cases.^{41–45} Postoperative follow-up reported in five studies for a total of 320 patients determined that there was recurrence or enlargement of PAVMs in 0 to 12% of cases.^{41–43,45,46} Ultimately, surgical treatment of PAVMs should only be considered in a specific patient population due to the invasive nature of the procedure as well as the relative expenses and extended recovery time as compared with embolization therapy.

An observational study published in 2006 by Andresen and Kjeldsen examined the long-term follow-up (mean 67 months) of 35 consecutive patients (14 male, 21 female, and mean age 49 years) with a total of 106 PAVMs treated with embolization therapy using coil devices. Due to suspected pulmonary shunt upon clinical follow-up, 10 (29%) of the 35 patients received repeat pulmonary angiography. Of the 10 patients reexamined, 8 (23%) were found to have PAVMs that were either insufficiently embolized or that had recanalized (this represented 7.6% of the 106 total PAVMs that had been treated). Following treatment, patients of the study were asked to complete a questionnaire regarding their opinions on their personal symptomatic improvement. Of the 31 patients that responded to the survey, 24 (77%) felt symptomatic improvement, and 23 (71%) felt increased physical performance following therapy.⁴⁷

An observational study published in 2010 by Hart et al examined the long-term follow-up (mean 9.6 months) of 69 consecutive patients (28 male, 41 female, and mean age 44.6 years) with a total of 161 PAVMs treated with embolization therapy using primarily vascular plug devices (total of 120 PAVMs or 75% with vascular plugs, all others with coils due to small vessel size). Clinical follow-up data were collected for 51 of the 69 patients (74%). Following post-operative examination, 11 of the 69 patients (16%) received repeat pulmonary angiography. In the patients reexamined, all of the PAVMs previously treated with vascular plugs had remained occluded. Follow-up CT was performed for five patients at a mean of 12.4 months following embolization. For all of these patients, complete occlusion was demonstrated in the feeding vessels embolized with vascular plugs. There were ultimately no reported cases of insufficient embolization or recanalization

of PAVMs treated with vascular plug devices during this study. Prior to treatment, 26 patients reported dyspnea or impaired exercise tolerance. Following vascular plug embolization, all but 1 of those 26 patients expressed an improvement in their symptoms, and an additional 2 patients who had not previously noted impaired exercise tolerance also described an improvement in their symptoms.⁴⁸

Conclusion

The contemporary management of patients with PAVMs has been influenced by observational studies and reviews demonstrating the most efficacious diagnostic and therapeutic techniques. Patients are typically diagnosed using chest X-ray and CT scan, with CT providing a more complete and detailed picture of the malformation. The precise imaging of the pulmonary vasculature captured via CT often limits the use of diagnostic angiography to intraoperative studies performed just prior to embolization therapy. The degree of right-to-left shunting of blood caused by PAVMs is best evaluated using contrast echocardiography. As demonstrated by several observational studies as well as our own clinical review, transcatheter embolization therapy is currently the preferred procedural technique in the management of PAVMs. Surgical approaches are now reserved for a small percentage of patients in specific clinical situations. Vascular plug devices have been proven to provide a variety of benefits over other embolization devices, and their use is preferred in most cases of PAVMs. Patients treated with transcatheter embolization therapy using vascular plug devices experience better overall outcomes than those treated with coils both in terms of symptomatic improvement as well as need for repeat embolization therapy following recanalization of the PAVM.

Conflict of Interests

None.

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