

**Clinically Suspected Pulmonary Arteriovenous Malformation
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
1. Cartin-Ceba R, Swanson KL, Krowka MJ. Pulmonary arteriovenous malformations. <i>Chest</i> . 2013;144(3):1033-1044.	Review/Other-Dx	N/A	To present a contemporary overview of the clinical characteristics, diagnosis, treatment, and management of PAVM.	PAVMs are abnormal vascular structures that most often connect a pulmonary artery to a pulmonary vein, bypassing the normal pulmonary capillary bed and resulting in an intrapulmonary right-to-left shunt. The main complications of PAVM result from intrapulmonary shunt and include stroke, brain abscess, and hypoxemia. These malformations may be idiopathic or genetic (eg, HHT) or relate to secondary conditions such as hepatopulmonary syndrome and bidirectional cavopulmonary shunts. The most common cause of PAVM is HHT. The preferred screening test for PAVM is TTCE, and chest CT scan is performed to establish the presence of PAVM. Embolization with the use of transcatheter embolization is the treatment of choice and is safe and effective in experienced hands. Collateralization and recanalization may occur, so lifelong follow-up is important. Antibiotic prophylaxis for procedures with a risk of bacteremia (eg, dental procedures) is recommended in all patients with PAVM.	4
2. Faughnan ME, Palda VA, Garcia-Tsao G, et al. International guidelines for the diagnosis and management of hereditary haemorrhagic telangiectasia. <i>J Med Genet</i> . 2011;48(2):73-87.	Review/Other-Dx	N/A	To develop evidence-informed consensus guidelines regarding the diagnosis of HHT and the prevention of HHT-related complications and treatment of symptomatic disease.	The outcome of the conference was the generation of 33 recommendations for the diagnosis and management of HHT, with at least 80% agreement amongst the expert panel for 30 of the 33 recommendations.	4
3. Rodriguez-Roisin R, Krowka MJ. Hepatopulmonary syndrome--a liver-induced lung vascular disorder. <i>N Engl J Med</i> . 2008;358(22):2378-2387.	Review/Other-Dx	N/A	To review hepatopulmonary syndrome.	The hepatopulmonary syndrome is characterized by defects in oxygenation due to pulmonary abnormalities associated with chronic liver disease. Dyspnea and hypoxemia can be severe and often worsen in the upright position. Gross dilatation of the precapillary and capillary vessels occurs with ventilation-perfusion mismatch. The syndrome usually improves after liver transplantation.	4

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4. Srivastava D, Preminger T, Lock JE, et al. Hepatic venous blood and the development of pulmonary arteriovenous malformations in congenital heart disease. <i>Circulation</i> . 1995;92(5):1217-1222.	Review/Other-Dx	10 patients	To describe patients with congenital heart disease at our hospital who developed PAVMs as diagnosed by cardiac catheterization.	PAVMs after cavopulmonary anastomoses are related to the diversion of normal hepatic venous flow from the pulmonary circulation. In this sense, these PAVMs may be analogous to those associated with liver disease, which have been found to resolve after liver transplantation. Redirection of hepatic flow to the pulmonary bed in some patients with congenital heart disease and PAVMs may lead to reversibility of the PAVMs.	4
5. Cottin V, Plauchu H, Bayle JY, Barthelet M, Revel D, Cordier JF. Pulmonary arteriovenous malformations in patients with hereditary hemorrhagic telangiectasia. <i>Am J Respir Crit Care Med</i> . 2004;169(9):994-1000.	Observational-Dx	105 patients	To retrospectively compare the diagnostic value of noninvasive tests for the screening of treatable (amenable to embolization) PAVMs in a series of patients, using chest CT and/or pulmonary angiography as a “gold standard.”	Patients had assessment of dyspnea, chest radiograph, alveolar-arterial PO2 gradient under 100% oxygen (AaPO2), contrast echocardiography, and radionuclide perfusion lung scanning. Contrast echocardiography in the supine position was the most sensitive test (93%). The sensitivity of self-reported dyspnea (59%), chest radiograph alone (70%), measurement of alveolar-arterial PO2 gradient under 100% oxygen by the 100% oxygen method (62%), or radionuclide lung scanning (71%), was not suitable for efficient screening. A 100% sensitivity and negative predictive value could be obtained when combining anteroposterior chest radiograph and contrast echocardiography.	3
6. Trerotola SO, Pyeritz RE. PAVM embolization: an update. <i>AJR Am J Roentgenol</i> . 2010;195(4):837-845.	Review/Other-Dx	N/A	To provide an update regarding PAVM embolotherapy.	PAVM management in HHT patients has changed a great deal since its introduction and, at the same time, many aspects of this patient population’s care have not changed. Interventional radiology plays a pivotal role in maintaining the health and well-being of these patients, and caring for them and their families is immensely gratifying. The challenge for interventional radiology clinicians and their patients moving forward is to try to approach the many unanswered questions in PAVM management using an evidence-based approach, so that the next set of HHT guidelines can be based on more level 1 evidence.	4

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7. Schneider G, Uder M, Koehler M, et al. MR angiography for detection of pulmonary arteriovenous malformations in patients with hereditary hemorrhagic telangiectasia. <i>AJR Am J Roentgenol.</i> 2008;190(4):892-901.	Observational-Dx	203 patients	To evaluate CE-MRA as a screening procedure for the detection of PAVMs in patients with HHT.	The presence of PAVM was considered definite in 56/203 (27.6%) patients and uncertain in 1 of 203 patients on CE-MRA. Of 156 PAVMs detected on CE-MRA, 124 (49 in 27 males, 75 in 30 females) were detected on first screening CE-MRA and 32 on follow-up CE-MRA. PAVMs on CE-MRA were solitary in 25 patients, multiple in 31 patients, and predominantly small (<5 mm, n = 32; 5–10 mm, n = 45). Significantly ($P<0.0001$) fewer PAVMs were detected on pulmonary angiography (76/96 [79.2%] evaluable PAVMs in 40 patients before first pulmonary angiography; 92/119 [77.3%] PAVMs overall). 3-D maximum-intensity-projection reconstructions permitted improved pulmonary AVM visualization and embolization planning of complex PAVMs.	3
8. Mojadidi MK, Winoker JS, Roberts SC, et al. Accuracy of conventional transthoracic echocardiography for the diagnosis of intracardiac right-to-left shunt: a meta-analysis of prospective studies. <i>Echocardiography.</i> 2014;31(9):1036-1048.	Meta-analysis	13 studies with 1,436 patients	To determine the accuracy of TTE compared to TEE as the reference.	A systematic review of Medline, Cochrane, and Embase was done to look for all the prospective studies assessing for intracardiac right-to-left shunt using conventional TTE compared to TEE as the reference; both TTE and TEE were performed with a contrast agent and a maneuver to provoke right-to-left shunt in all studies. A total of 13 studies with 1,436 patients fulfilled the inclusion criteria. The weighted mean sensitivity and specificity for TTE were 46% and 99%, respectively. Likewise, the positive likelihood ratio and negative likelihood ratio were 20.85 and 0.57, respectively. Using different contrast agents, different microbubble cutoffs for a positive TTE/TEE, and different cardiac cycle cutoffs for a positive TTE/TEE did not affect the accuracy of TTE. In a population of patients with cryptogenic stroke, a TTE that tests positive for right-to-left shunt has a 95% probability of being a true positive.	M

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9. Porter TR, Abdelmoneim S, Belcik JT, et al. Guidelines for the cardiac sonographer in the performance of contrast echocardiography: a focused update from the American Society of Echocardiography. <i>J Am Soc Echocardiogr.</i> 2014;27(8):797-810.	Review/Other-Dx	N/A	The paper updates sonographers on developments in these 4 areas: understanding of microbubble physics and ultrasound instrumentation, recognition of indications for the use of contrast media, establishment of intravenous access privileges if necessary, and development of written policies for contrast agent infusion or injection.	N/A	4
10. Velthuis S, Buscarini E, van Gent MW, et al. Grade of pulmonary right-to-left shunt on contrast echocardiography and cerebral complications: a striking association. <i>Chest.</i> 2013;144(2):542-548.	Observational-Dx	1,038 patients	To evaluate the potential relation between pulmonary shunt grade on TTCE and prevalence of cerebral manifestations in patients screened for HHT.	A pulmonary right-to-left shunt was present in 530/1,038 patients (51.1%; mean age, 44.3 +/- 15.6 years; 58.6% women). The presence of a cerebral manifestation (n = 51) differed significantly among pulmonary shunt grades on TTCE: 1.4%, 0.4%, 6.5%, and 20.9% for grades 0, 1, 2 and 3, respectively. A pulmonary shunt grade 1 was not associated with an increased prevalence of cerebral manifestations (OR, 0.44; 95% CI, 0.05–4.13; <i>P</i> =0.47), whereas pulmonary shunt grade 2 (OR, 4.78; 95% CI, 1.14–20.0; <i>P</i> =0.03) and grade 3 (OR, 10.4; 95% CI, 2.4–45.3; <i>P</i> =0.002) were both independent predictors for the prevalence of a cerebral ischemic event or brain abscess.	3
11. Zukotynski K, Chan RP, Chow CM, Cohen JH, Faughnan ME. Contrast echocardiography grading predicts pulmonary arteriovenous malformations on CT. <i>Chest.</i> 2007;132(1):18-23.	Observational-Dx	155 patients	To determine the positive predictive value of TTCE grades for the presence of PAVMs on CT.	Of 155 patients screened for PAVMs, 104 had positive TTCE results. Complete data were available for 90 patients (87%). Mean age was 45 years; 62% were female. 17% of patients screened and 27% of patients with positive TTCE results had CT detectable PAVMs. There was a significant association between TTCE grade and presence of PAVMs on CT (<i>P</i> <0.0001). The positive predictive value of grades 1, 2, 3, and 4 were 0.02 (95% CI, 0.00 to 0.06), 0.25 (95% CI, 0.06 to 0.44), 0.56 (95% CI, 0.23 to 0.88), and 1.0 (95% CI, 1.0 to 1.0), respectively.	2

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12. van Gent MW, Post MC, Luermans JG, et al. Screening for pulmonary arteriovenous malformations using transthoracic contrast echocardiography: a prospective study. <i>Eur Respir J.</i> 2009;33(1):85-91.	Observational-Dx	317 patients	To prospectively establish the diagnostic value of TTCE as a screening technique for PAVM using chest high resolution CT as the gold standard for PAVMs.	TTCE was positive in 87 (58.8%), 12 (16.7%) and four (6.7%) patients, and chest high resolution CT was positive in 54 (36.5%), three (4.2%) and zero (0%) patients with a definite, possible and negative clinical diagnosis of HHT, respectively. Two patients with a negative TTCE were diagnosed with PAVMs after computed tomography; in both cases the PAVMs were too small to be treated by embolotherapy. The sensitivity of TTCE was 97% (95% CI, 93.6–98.3) and negative predictive value 99% (95% CI 96.9–99.8). The other diagnostic tests showed a considerable lower diagnostic value.	1
13. Lee WL, Graham AF, Pugash RA, et al. Contrast echocardiography remains positive after treatment of pulmonary arteriovenous malformations. <i>Chest.</i> 2003;123(2):351-358.	Observational-Dx	68 patients	To determine the effect of the successful performance of transcatheter embolotherapy on the performance of contrast TTE, specifically, in what proportion of patients the findings of contrast TTE normalized or remained positive after the performance of transcatheter embolotherapy.	39 patients underwent contrast TTE prior to undergoing transcatheter embolotherapy, and 29 patients underwent contrast TTE both prior to and after undergoing transcatheter embolotherapy. In all patients, TTE findings were positive prior to transcatheter embolotherapy. All PAVMs with feeding vessels ≥ 3 mm were successfully occluded based on completion angiography. After transcatheter embolotherapy, 48% of patients had no detectable residual PAVMs, and the remainder had small (ie, < 3 mm) residual PAVMs. Of the 29 patients, 90% had positive contrast TTE findings after undergoing transcatheter embolotherapy. In the subset of patients who had no residual PAVMs on the completion angiography, 80% had positive contrast TTE findings after undergoing transcatheter embolotherapy.	4
14. Manawadu D, Vethanayagam D, Saqqur M, Derksen C, Choy J, Khan K. Screening for right-to-left shunts with contrast transcranial Doppler in hereditary hemorrhagic telangiectasia. <i>Stroke.</i> 2011;42(5):1473-1474.	Observational-Dx	12 patients	The authors hypothesized that contrast transcranial Doppler, shown to be highly sensitive for detecting right-to-left shunts in patent foramen ovale, will be as comparable to TTCE for screening HHT patients.	Both TTCE and transcranial Doppler had 100% sensitivity in detecting underlying PAVM; the specificity was 25% and 38%, respectively. The agreement in detecting right-to-left shunts between TTCE and transcranial Doppler was high ($\kappa=0.76$). Transcranial Doppler was well-tolerated with no immediate adverse or embolic events over the next 3 months.	3

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15. American College of Radiology. ACR Appropriateness Criteria®: Hemoptysis. Available at: https://acsearch.acr.org/docs/69449/Narrative/ . Accessed September 30, 2015.	Review/Other-Dx	N/A	Evidence-based guidelines to assist referring physicians and other providers in making the most appropriate imaging or treatment decision for a specific clinical condition.	N/A	4
16. Remy J, Remy-Jardin M, Giraud F, Wattinne L. Angioarchitecture of pulmonary arteriovenous malformations: clinical utility of three-dimensional helical CT. <i>Radiology</i> . 1994;191(3):657-664.	Review/Other-Dx	37 PAVMs	To determine the clinical utility of 3D helical CT in pretherapy evaluation of the angioarchitecture of PAVMs.	A reliable analysis of the angioarchitecture of 28 PAVMs (76%)—25 simple and 3 complex—was provided by 3D reconstructions; combined interpretation of 3D images and transverse sections led to accurate evaluation of 35 PAVMs (95%). Positioning of the target anatomy in the reconstructed volume, threshold value, number of stacked sections, and section thickness influenced the diagnostic information.	4
17. Nawaz A, Litt HI, Stavropoulos SW, et al. Digital subtraction pulmonary arteriography versus multidetector CT in the detection of pulmonary arteriovenous malformations. <i>J Vasc Interv Radiol</i> . 2008;19(11):1582-1588.	Observational-Dx	18 patients	To compare digital subtraction pulmonary arteriography with 16-detector row CT in the detection of suspected PAVMs in patients with HHT.	Whole-lung analysis (ie, correct identification of a lesion anywhere in the lung) showed 16-detector row CT readings to have a mean sensitivity of 83% and specificity of 78% and pulmonary arteriography readings to have a mean sensitivity of 70% and specificity of 100%. Lobar analysis (ie, correct identification of a lesion in a given lobe) showed 16-detector row CT readings to have a mean sensitivity of 72% and specificity of 93% and pulmonary arteriography readings to have a mean sensitivity of 68% and specificity of 100%.	2
18. Boussel L, Cernicanu A, Geerts L, et al. 4D time-resolved magnetic resonance angiography for noninvasive assessment of pulmonary arteriovenous malformations patency. <i>J Magn Reson Imaging</i> . 2010;32(5):1110-1116.	Observational-Dx	7 patients	To assess the capability of 4D time-resolved MRA to assess PAVMs patency by analyzing pulmonary arterial and venous enhancement kinetics.	Mean image quality was 3.2 +/- 0.9. dTTPav was significantly smaller in PAVMs (0.15 +/- 0.76 sec) than in reference vessels (3.75 +/- 1.62 sec), $P < 0.001$.	3
19. Shimohira M, Kawai T, Hashizume T, et al. Reperfusion Rates of Pulmonary Arteriovenous Malformations after Coil Embolization: Evaluation with Time-Resolved MR Angiography or Pulmonary Angiography. <i>J Vasc Interv Radiol</i> . 2015;26(6):856-864 e851.	Observational-Dx	16 patients	To assess reperfusion rates after coil embolization for PAVMs using time-resolved MRA or pulmonary angiography.	Reperfusion rates at 3, 6, 12, and 24 months were 8%, 27%, 36%, and 49%, respectively, for the 12 untreated PAVMs (primary embolization) and 50%, 50%, 92%, and 100%, respectively, for the 12 reperused PAVMs (repeat embolization) ($P = .0062$). No significant differences were observed in the other parameters measured.	3

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20. Whyte MK, Peters AM, Hughes JM, et al. Quantification of right to left shunt at rest and during exercise in patients with pulmonary arteriovenous malformations. <i>Thorax</i> . 1992;47(10):790-796.	Observational-Dx	19 patients	To report measurement of shunt by the microsphere method and by the 100% oxygen method in patients with PAVMs and in 6 normal subjects at rest.	The mean (SD) shunt at rest as measured by the microsphere method was 23.2% (15.6%) in the patients and 2.7% (1.2%) in the normal subjects. When these values were compared with those of the 100% oxygen method the difference in mean values was 1% and the limits of agreement between the two methods -32% to +45%. The microsphere method is less invasive (arterial blood gas sampling is not required), quicker, and more comfortable for patients than the 100% oxygen method. In 5 of the normal subjects the mean (SD) 99mTc microsphere shunt increased from 2.9% (1.3%) at rest to 5.1% (2.9%) during exercise. In the 12 patients studied during exercise the shunt increased from 33.7% (12.7%) at rest to 41.7% (13.3%) during exercise in 8 but decreased from 22.6% (2.4%) at rest to 17.6% (2.2%) during exercise in 4. Arterial desaturation during exercise correlated with change in the size of the right to left shunt during exercise ($r = +0.80$).	4
21. Thompson RD, Jackson J, Peters AM, Dore CJ, Hughes JM. Sensitivity and specificity of radioisotope right-left shunt measurements and pulse oximetry for the early detection of pulmonary arteriovenous malformations. <i>Chest</i> . 1999;115(1):109-113.	Observational-Dx	66 patients	To assess the effectiveness of pulse oximetry and radioisotope measurement of right-to-left shunt for the early detection of PAVMs in patients with HHT.	Of the 66 patients included, 40 had small PAVMs remaining postembolization. Using univariate logistic regression, radioisotope shunt and erect saturation showed a significant relationship with the presence of residual PAVMs ($P=0.001$, 0.005 , respectively). Erect SaO ₂ $\leq 96\%$ had 73% sensitivity and 35% specificity for detecting PAVMs. Radioisotope shunt $>3.5\%$ of cardiac output had 87% sensitivity and 61% specificity for detecting PAVMs.	3

Evidence Table Key

Study Quality Category Definitions

- *Category 1* The study is well-designed and accounts for common biases.
- *Category 2* The study is moderately well-designed and accounts for most common biases.
- *Category 3* There are important study design limitations.
- *Category 4* The study is not useful as primary evidence. The article may not be a clinical study or the study design is invalid, or conclusions are based on expert consensus. For example:
 - a) the study does not meet the criteria for or is not a hypothesis-based clinical study (e.g., a book chapter or case report or case series description);
 - b) the study may synthesize and draw conclusions about several studies such as a literature review article or book chapter but is not primary evidence;
 - c) the study is an expert opinion or consensus document.
- M = Meta-analysis

Dx = Diagnostic

Tx = Treatment

Abbreviations Key

CE-MRA = Contrast-enhanced magnetic resonance angiography

CI = Confidence interval

CT = Computed tomography

HHT = Hereditary hemorrhagic telangiectasia

OR = Odds ratio

PAVM = Pulmonary arteriovenous malformation

SD = Standard deviation

TEE = Transesophageal echocardiography

TTCE = Transthoracic contrast echocardiography

TTE = Transthoracic echocardiography