UNEXPLAINED HYPOXEMIA
Intrapulmonary or Intracardiac shunts

On occasions, after the initial work up, we encounter the situation in which we do not find an explanation for persistent hypoxemia. Rare conditions that we should investigate include but are not limited to presence of intrapulmonary or intracardiac shunts:

- Intrapulmonary shunts
  - Pulmonary arteriovenous malformations (PAVMs)
    - Hereditary hemorrhagic telangiectasia (HHT)
    - Hepatopulmonary syndrome (HPS)
    - Others such as advanced ILD
- Intracardiac shunts
  - Patent foramen ovale (PFO)
  - Atrial septal defect (ASD)

INTRAPULMONARY SHUNTS

Pulmonary Arteriovenous Malformations (PAVMs)

PAVMs are dilated artery or arteries associated with an intrapulmonary shunt

- Right-to-left shunt between the pulmonary and systemic circulation (pulmonary artery-to-pulmonary vein

Etiology

Congenital

- Hereditary hemorrhagic telangiectasia (HHT)

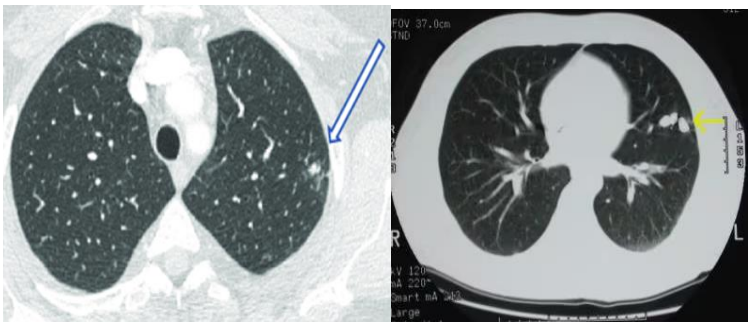
Acquired

- Hepatopulmonary syndrome (HPS)
- Less frequently associated with other conditions such as chest trauma or surgery, mitral stenosis, metastatic cancer, actinomycosis

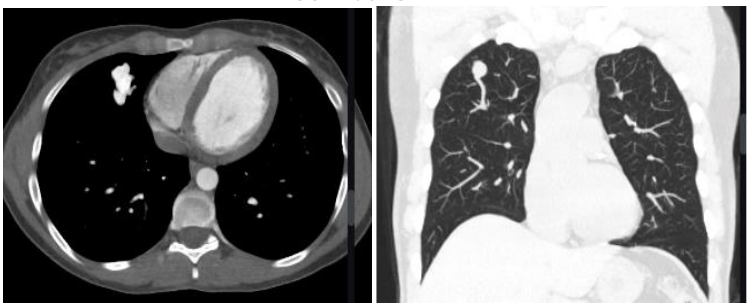
Clinical presentation

Half of the time, PAVMs are asymptomatic and found incidentally in chest imaging studies as a nodular lesion

Non contrast CT



Contrast CT



Most PAVMs remain stable in size and asymptomatic

- Up to 25 percent will enlarge slowly or due to right-to-left shunting and potential paradoxical emboli can become symptomatic
- Common symptoms
    - Dyspnea
    - Symptoms paradoxical embolization across a PAVM
        - Ischemic embolic stroke or brain abscess
    - Other symptoms such as hemoptysis or hemothorax

Diagnosis

Transthoracic echocardiogram (TTE) with bubble contrast is the imaging modality of choice for the initial evaluation and a contrast chest CT scan for confirming the presence and visualization of the PAVMs.

PAVMs should be suspected and a diagnostic evaluation initiated in patients with:

- Unexplained hypoxemia and typical nodules on chest imaging
- Right-to-left shunting symptoms
    - Platypnea – dyspnea in upright position
    - Orthodeoxia - defined as a decrease in PaO2 >4 mmHg or O2 Sat by 3-5% or more when transitioning from the supine to the upright position
- Evidence of paradoxical embolization
    - Embolic stroke of undetermined source or brain abscess
- Unexplained hemoptysis or hemothorax
- Suspected, known, or a family history of HHT

Once PAVM is suspected, the first step is TTE with bubble contrast.

- No shunt: no bubbles in the LV at baseline or after Valsalva maneuver
    - Failure to demonstrate transient leftward bowing atrial septum with Valsalva release indicates insufficient performance of the maneuver and should be repeated
- Delayed shunt: bubbles appears in the LV after 3 to 8 cardiac cycles after its appearance in the RA
- Immediate shunt: bubbles appears in the LV within 1 cardiac cycle after its appearance in the RA
- Indetermined shunt: bubbles appears in the LV within 1–3 cardiac cycles

Next step depends on the findings of TTE with bubble contrast:

- ***If no shunt*** present, no further investigation is needed
- ***If delayed shunt*** present consistent with intrapulmonary shunt, proceed with noncontrast CT chest with thin cuts (ie, 1 to 2 mm collimation) or contrast enhanced CT chest or CTA chest
    - If CT chest findings are consistent with PAVM, diagnosis is confirmed
        - The feeding artery diameter (FAD) should be measured
    - If the CT chest does not detect PAVMs, microscopic PAVMs may be the cause of the shunt as seen in conditions such as HPS
- ***If immediate shunt*** present consistent with intracardiac shunt, proceed with cardiac work up
- ***If indetermined shunt*** **present**, proceed with transesophageal echocardiogram (TEE)
    - Indetermined shunt bubbles appears in the LV within 1–3 cardiac cycles

Contrast induced allergies or contrast associated acute kidney injury (CAAKI) in the present era using iso-osmolar contrast are very rare and overestimated. So, my view is to proceed with contrast enhanced CT chest once delayed shunt is confirmed followed by CTA chest if embolization is considered.

Treatment

The treatment options of PAVMs include:

- Embolization by IR aiming at improving symptoms and hypoxemia and preventing complications such as embolic strokes and brain abscesses, or
- Watchful observation

The decision to offer treatment depends on the FAD and the presence of symptoms attributed to the PAVM (neurovascular complications can occur with PAVMs of any size

- If the CT scan shows one or more PAVMs with a FAD of ≥2 to 3 mm or the patient has symptoms suggestive of a treatable PAVM (platypnea or orthodeoxia, hemoptysis or hemothorax, or evidence of embolic stroke or brain abscess):
    - Perform CTA chest to define the vascular anatomy of PAVMs and refer to IR for pulmonary angiography and potential embolization
    - If the CT scan shows PAVMs with a FAD <2 mm and patient has no symptoms suggestive of a treatable PAVM:
        - Watchful observation with yearly clinical evaluation and CT chest every five years

Potential benefits of embolization therapy

- Immediate: relief from symptoms and improvement of oxygenation
- Long-term: reduce the incidence of complications such as embolic strokes and brain abscesses.

Complications of embolization:

- Pleuritic chest pain: common and self-limiting complication
- Stroke: less common
    - Transient ischemic attack
    - Air embolization: typically transient and managed medically

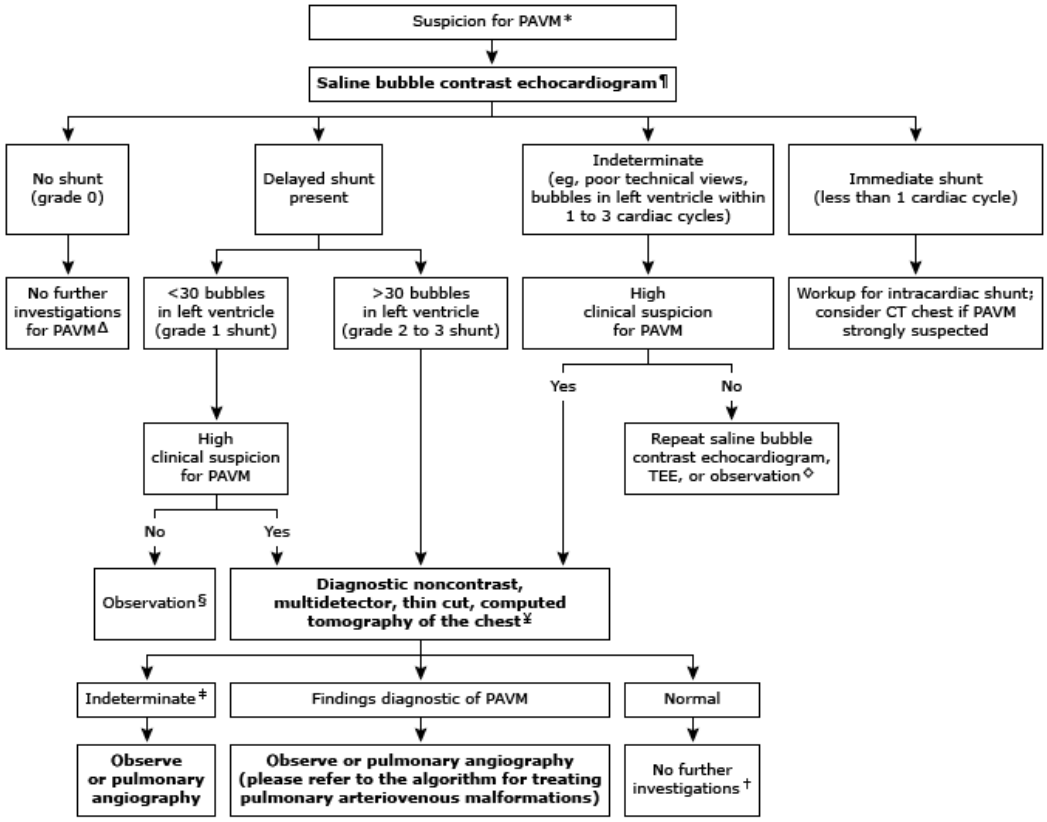
Follow-up postembolization

- Contrast CT chest and TTE to confirm closure of the PAVMs is recommended at 3 to 6 months

Adjunctive Therapy

- Supplemental oxygen to keep O2 Sat 90-96%
- Anticoagulation for stroke prevention when there is a risk of paradoxical embolization
- Lifelong antibiotic prophylaxis is recommended before dental or surgical procedures even after embolization therapy

In UpToDate there is an excellent algorithm summarizing the diagnostic approach for PAVMs



Hereditary Hemorrhagic Telangiectasia (HHT)

- Type 1 (endoglin gene mutation) and type 2 (*ACVRL1* gene mutation, can be combined juvenile polyposis)
- The vascular lesions include **telangiectasias and AVMs**
    - Telangiectasias occur on the skin and mucous membranes
        - Can result in epistaxis and GI bleeding with consequent anemia
    - AVMs most commonly occur in the lung, liver, and brain
- All patients with possible or confirmed HHT should undergo screening for AVMs in the lungs and in the brain
    - **Pulmonary AVMs** may result in right-to-left shunt:
        - Hypoxemia
        - Embolization of clot or bacteria to the cerebral circulation
            - Strokes
            - Cerebral abscesses
    - The initial screening for pulmonary AVMs is a TTE with bubbles. If the echocardiogram is positive
        - CT chest (noncontrast with thin cuts, or with contrast, or CTA depending on individual cases)
        - Brain MRI with and without contrast
- The Curaçao diagnostic classification involves four criteria with three positive criteria required for a definite clinical diagnosis of HHT
    - Recurrent and spontaneous epistaxis
    - Multiple telangiectasias on the skin of hands or face, or inside the nose or mouth
    - AVMs or telangiectasias in one or more organs, including lungs, brain, liver, intestines, stomach, and spinal cord
    - Family history of HHT in a first-degree relative
- Embolization is recommended for all AVMs that reasonably can be embolized, especially those with feeding vessels 3 mm or larger
- Follow up with periodic chest CT angiograms for the development of new AVMs

Hepatopulmonary Syndrome (HPS)

HPS is defined as hypoxemia due to pulmonary vascular dilatation in the setting of liver disease with or without portal hypertension.

Clinical presentation

Dyspnea on exertion or rest in patients with liver disease is the most common presenting symptom of HPS

- The presence of platypnea and orthodeoxia are specific for HPS, but not pathognomonic

Diagnosis

HPS is diagnosed based on the combination of hypoxemia and documentation of intrapulmonary shunt in patients advanced liver disease

- Hypoxemia
    - To determine the presence of hypoxemia, O2 Sat and or ABGs should be drawn with the patient sitting and upright at rest on RA
        - PaO2 <80 mmHg or A-a gradient corrected for age on RA
            - >15 mmHg or >20 mmHg if ≥65 year old
- Intrapulmonary vasodilatation
    - Confirmed by echocardiography with bubble contrast
- Portal hypertension with or without cirrhosis

Classification of HPS based on pulmonary vessels dilatation

- Type I HPS – dilatation of vessels causing V/Q mismatch
- Type II HPS – larger dilatation of vessels causing PAVMs

Once hypoxemia is confirmed

- The next step is echocardiography with bubble contrast
- In patient with refractory hypoxemia perform a CTA chest for consideration of embolization
    - CTA chest can show minimal abnormalities consistent with arterial vasodilation or PAVMs
- PFTs findings

- Isolated decreased DLCO with normal spirometry and lung volumes unless there is coexisting obstructive or restrictive lung disease

Treatment

- The only definitive therapy for patients with HPS is liver transplantation
- Supplemental O2 to maintain O2 Sat 90-96%
  - Improve oxygenation in HPS type 1 but usually not helpful in HPS type 2
- Embolization by IR for patients with type 2 HPS with refractory hypoxemia
  - It can be done before or after transplantation

INTRACARDIAC SHUNTS

Etiology

In adults are usually due to atrial septum abnormalities including:

- Patent foramen ovale (PFO)
- Atrial septal defect (ASD)
- Atrial septal aneurysm (ASA) associated with PFOs and/or atrial septal defects (ASDs)

Ventricular septal defects (VSDs) in adults are usually small with an orifice dimension of ≤25 percent and not hemodynamically significant

- Small left-to-right shunts (pulmonary to systemic flow ratio (Qp/Qs <1.5:1)
- No LV volume overload
- No pulmonary hypertension

Clinical presentation

- Left-to right intracardiac shunting
  - Pulmonary hypertension (PH)
- Right-to left intracardiac shunting
  - Hypoxemia (platypnea-orthodeoxia)
  - Paradoxical embolization – embolic ischemic strokes
  - Eisenmenger syndrome - PH
- Atrial arrhythmias

Diagnosis

Transthoracic echocardiogram (TTE) with bubble contrast is the accepted diagnostic test for atrial septum abnormalities.

- If TTE is technically suboptimal or fails to show an atrial septum abnormality in a patient in whom is suspected, transesophageal echocardiogram (TEE) is recommended

Treatment

- The decision to close an atrial septum abnormality with intracardiac shunt (Qp/Qs, pulmonary-to-systemic blood flow) depends on:
- Net direction of the shunt
  - Left-to-right versus right-to left
- Hemodynamic significance of the shunt
- Development of PH and its severity
- Symptoms attributed to the shunt
  - Dyspnea and hypoxemia (platypnea-orthodeoxia)
  - Evidence of paradoxical embolization – embolic ischemic strokes

PFO or ASD and net left-to-right shunt

- Without hemodynamic significance defined as Qp/Qs <1.5:1 without RA and/or RV enlargement
  - Asymptomatic
    - Watchful clinical observation and TTE with bubble every three years if patient remains asymptomatic as recommended by American College of Cardiology/American Heart Association adult CHD guidelines
  - Symptomatic
    - With platypnea-orthodeoxia attributed to the shunt
      - Closure of the PFO/ASD is recommended

        - With embolic stroke of undetermined source (ESUS)
            - Antiplatelet therapy
            - Closure of the PFO/ASD after a comprehensive evaluation to rule out other stroke etiologies in patients who meet the following criteria using the PASCAL classification system which incorporate the RoPE score and high-risk features of the PFO/ASD:
                - Age ≤60 years
                - RoPE score >6
                - PFO/ASD with a large shunt or ASA
                - No indication for anticoagulation therapy otherwise

- With hemodynamic significance defined as Qp/Qs ≥1.5:1 and RA and/or RV enlargement
    - Proceed with RHC
        - In patients with mild to moderate PH who meets all the three criteria stated below, closure of the PFO/ASD can be considered along with medical management of PH:
            - pSAP less than 50% of the systemic SAP
            - PVR less than one-third of the SVR
            - No cyanosis at rest or on exercise
                - Hemodynamics assessment in the cath lab before and after balloon occlusion, may help to determine the suitability for closing the PFO/ASD
                    - Decrease in cardiac output and/or increase in LVEDP or PCWP suggests that the closure will not be tolerated
        - In patients with moderate to severe PH, medical management of PH is recommended with serial reassessment

PFO or ASD and right-to-left shunt

Proceed with RHC to confirm the shunt direction and the presence of PH and its severity

- If right-to-left shunt and or severe PH *are* confirmed, closure of the PFO/ASD is contraindicated and medical management of PH is recommended
    - Severe PH defined as:
        - pSAP more than two-thirds of the systemic SAP
        - PVR more than two-thirds of the SVR
    - RHC reassessment after medical management of PH for consideration of closure only if hemodynamics improve and meet the threshold criteria stated above

- If right-to-left shunt and/or severity of PH *are not* confirmed, reassess the direction of the shunt

In UpToDate there is an excellent algorithm summarizing the therapeutic approach for ASD