

Obstructive Sleep Apnea and Pulmonary Hypertension

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Objectives

- Discuss pathophysiology of OSA and PH
- Explain diagnosis and treatment for OSA and PH

Obstructive Sleep Apnea (OSA)

- OSA – effects estimated 15 mil. Adult Americans

Types

- Obstructive Sleep Apnea – Repetitive interruption of ventilation during sleep caused by collapse of the pharyngeal airway. A ≥ 10 sec. pause in respiration
- Central Sleep Apnea – Prevalent in comorbid conditions of heart failure, stroke, and late life aging. The cause is not completely understood.

Mechanisms of disease and Assoc. CVD

- Severe intermittent hypoxemia and CO₂ retention during sleep
- O₂ sat decrease of $\leq 60\%$
- Repetitive apnea – sympathetic activity - consequent vasoconstriction
- BP can reach levels as high as 240/130 mmHg
- Severe hypoxemia, hypercapnia and adrenergic activation

Mechanisms contributing to CVD risk

Sympathetic Activation

- ↑ sympathetic drive continues during day
- ↑ HR

Treatment

- 100% O₂ ↓ sympathetic activity, HR, and BP during daytime wakefulness

Mechanisms contributing to CVD risk

Vasoactive substances

- Hypoxemic stress – in severe sleep apnea lasting several hours
↑ endothelin levels

Treatment

- After 4 hours of CPAP endothelin levels fall

Mechanisms contributing to CVD risk

Inflammation

- Hypoxemia triggers systemic inflammation ↑ levels of interleukin-6
- ↑ CRP
- Combination sleep deprivation, hypoxemia ↑ cytokines, adhesion molecules, serum amyloid A and CRP
- ↑ leukocyte activation, monocyte binding

Treatment

- CPAP attenuates monocyte binding

Mechanisms contributing to CVD risk

Endothelial dysfunction

- Inflammation, sympathetic activation, pressor surges, oxidative stress contribute to endothelial dysfunction

Treatment

- CPAP may improve endothelial function

Mechanisms contributing to CVD risk

Insulin Resistance

- ↑ catecholamines, sleep deprivation may be associated with insulin resistance.

Treatment

- Studies inconsistent in response to CPAP

Mechanisms contributing to CVD risk

Thrombosis

- ↑ platelet activation,
↑ fibrinogen
- Further studies are needed to confirm

Mechanisms contributing to CVD risk

Intrathoracic Pressure Changes

- ↑ negative pressure in chest cavity to levels approaching -65 mmHg.
- ↑ transmural gradients across the atria, ventricles, and aorta, and disrupts ventricular function and autonomic and hemodynamic stability.
- ↑ wall stress
- ↑ afterload
- ↑ atrial size
- Impaired diastolic function
- Thoracic aortic dilation (propensity toward dissection)

OSA

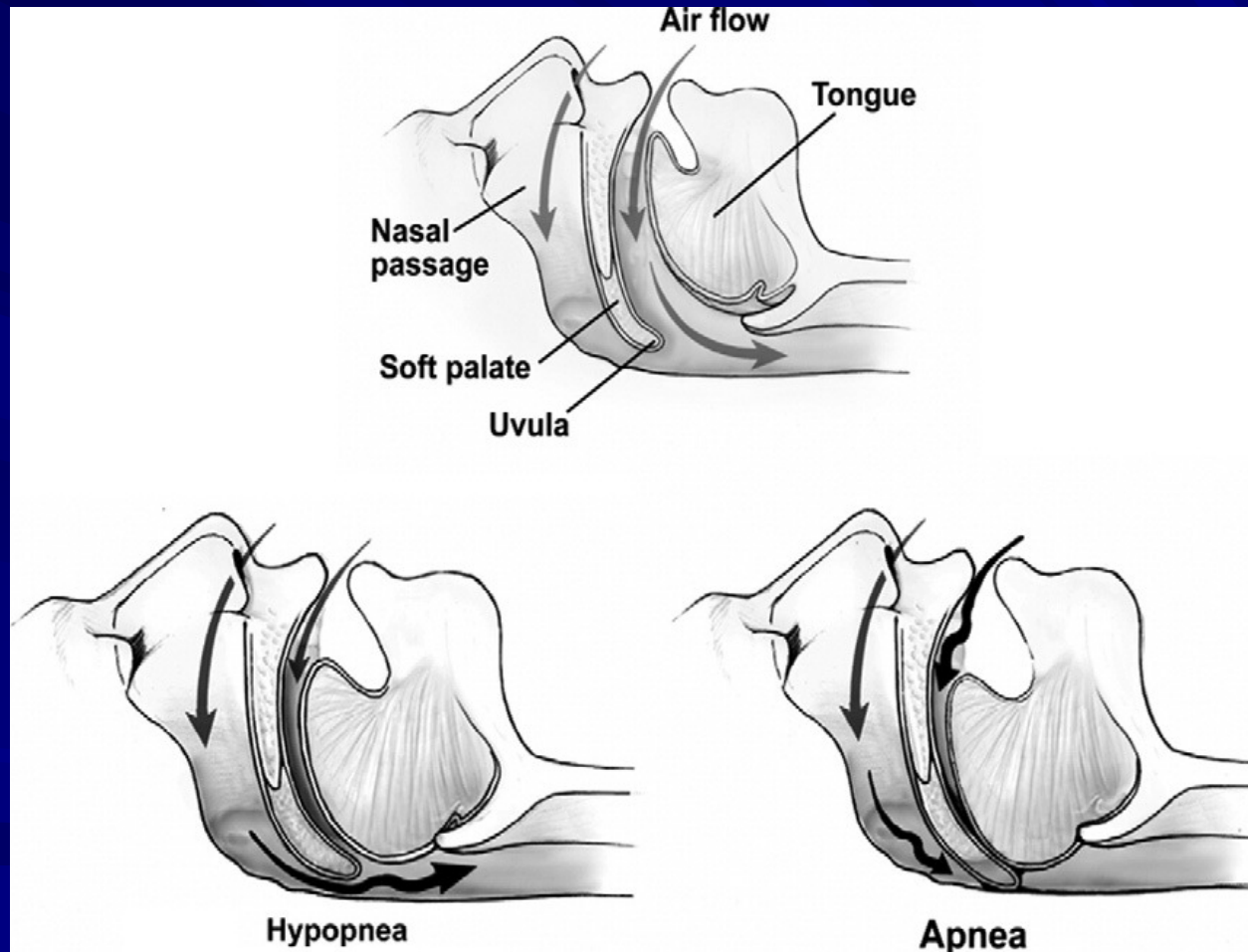
Clinical presentation

- Disruptive snoring
- Witnessed apnea or gasping
- Obesity and/or enlarged neck size
- Hypersomnolence
- Male gender
- Crowded appearing pharyngeal airway
- Increased blood pressure
- Morning headache
- Sexual dysfunction

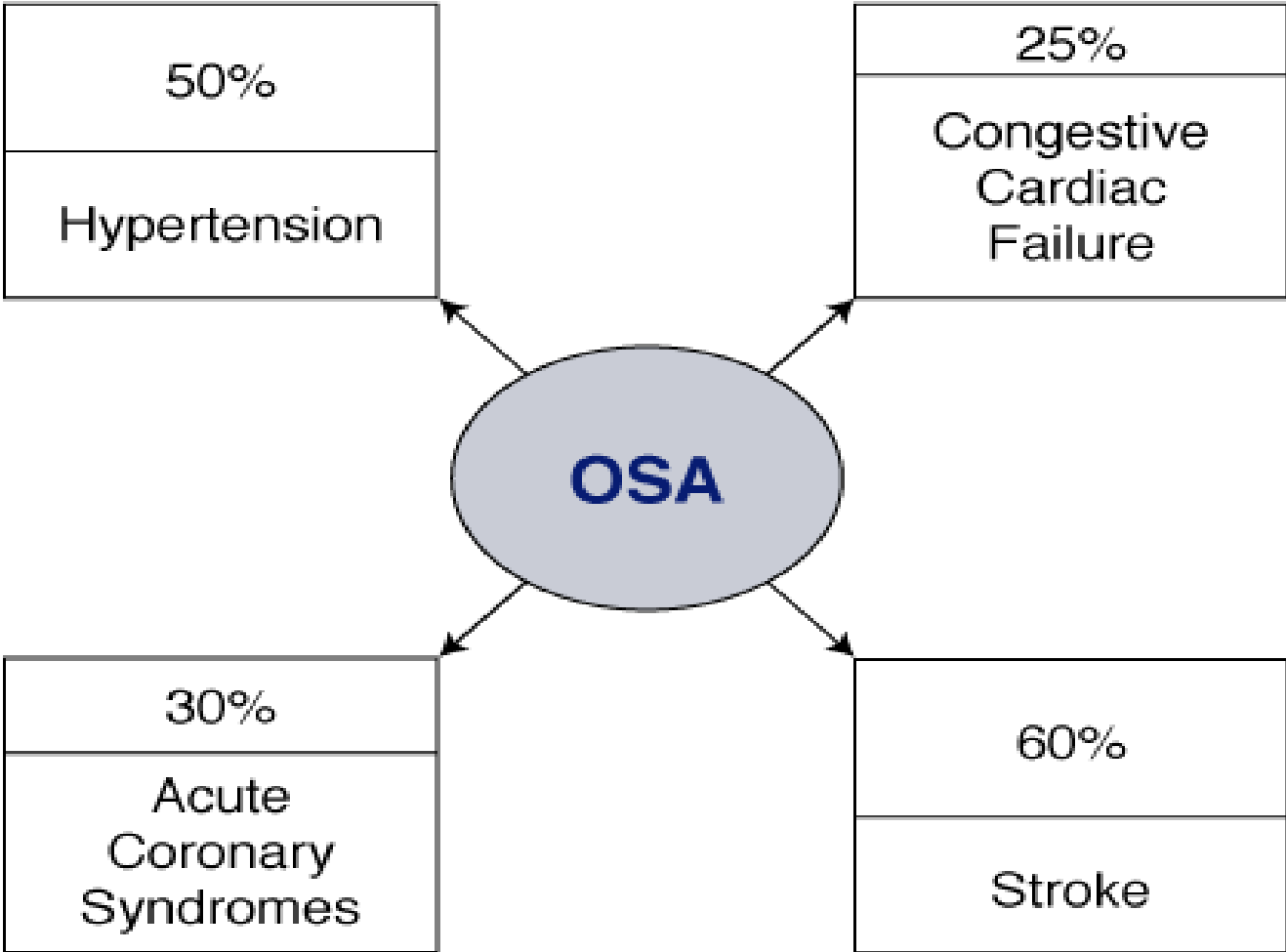
CVD and OSA Hypertension

- 50% of OSA patients have HTN
- 30% of HTN patients have OSA
- Non-dippers more likely to have OSA

Sleep Apnea



Prevalence of Obstructive Sleep Apnea



ARS Question

Which one of the following is false ?

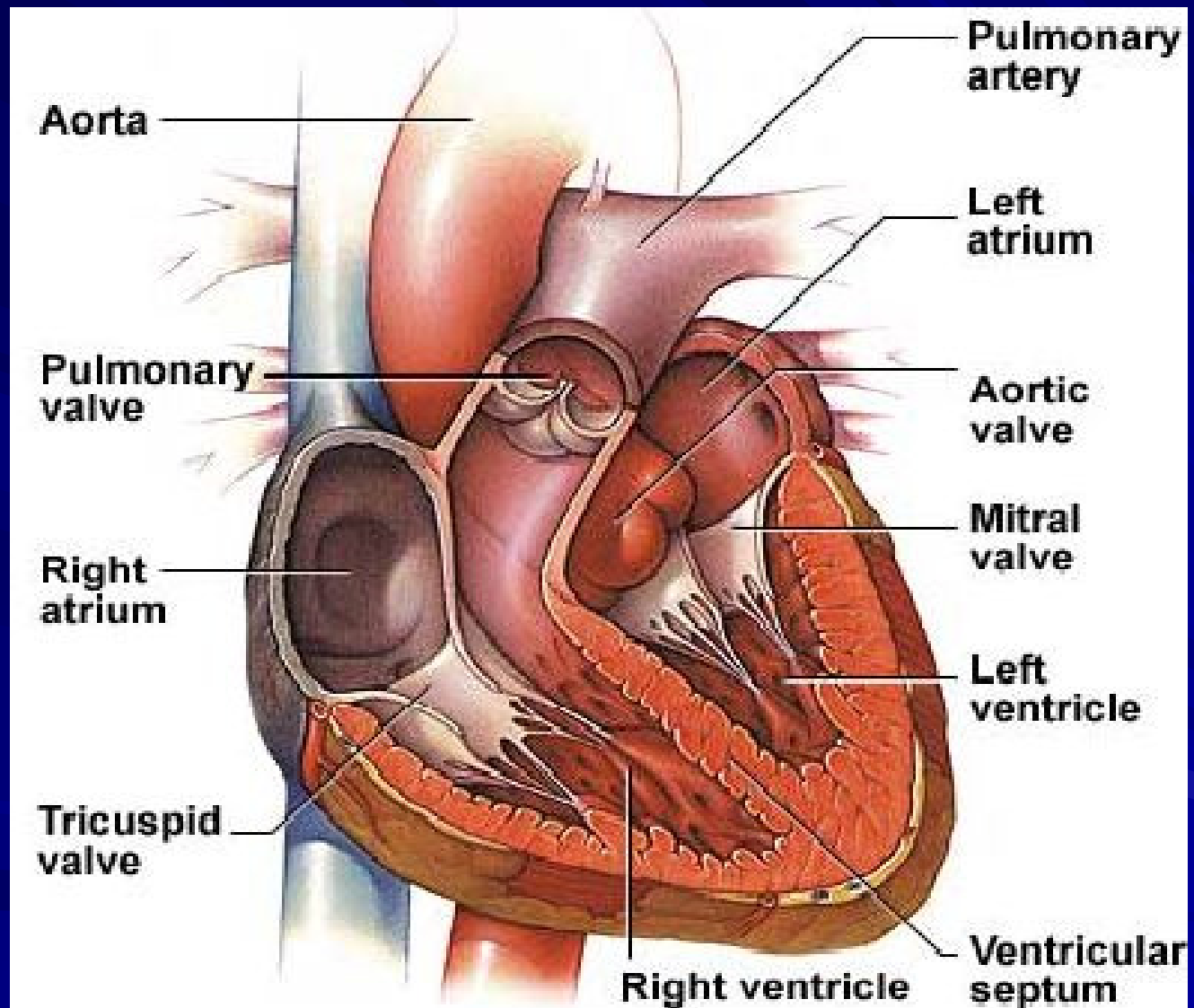
Obstructive sleep apnea (OSA)

1. ↑ wall stress
2. ↓ afterload
3. ↑ atrial size
4. Impairs diastolic function

Pulmonary Hypertension

Normal Pulmonary Vascular Bed

- Normal pulmonary vascular bed
 - Low pressure
 - Low resistance
 - Highly compliant system
- Acute and chronic injury leads to abnormal pressure and resistance.



Pulmonary Hypertension (PH) (PAH) Definition

- PH – the presence of abnormally high pulmonary vascular pressure.
- PAH – pulmonary artery hypertension is a category of PH.
 - mPAP of >25 mm Hg
 - PCWP normal
 - LAP normal
 - LVEDP ≤ 15 mm Hg
 - PVR > 3 Wood units

Pulmonary Hypertension World Health Organization Classification

**Group 1
“PAH”**

**Group 3 PH with Lung Ds and/or
Chronic Hypoxia**

**Group 2
PH with Left Heart Ds.**

**Group 4
Chronic Thrombosis
(clot) PH**

**Group 5
Miscellaneous**

Pulmonary Hypertension WHO Classification

Group 1 “PAH”

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graph TD; A([Group 1 "PAH"]) --> B([Idiopathic PAH (formerly primary) Familial (genetic) PAH Bone morphogenic protein Receptor 2 BMPR2 gene]); A --> C([PAH related to: (formerly secondary) Connective tissue ds. HIV Portopulmonary Congenital heart ds Toxins/Diet pills]);
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Idiopathic PAH
(formerly primary)
Familial (genetic) PAH
Bone morphogenic protein
Receptor 2
BMPR2 gene

PAH related to:
(formerly secondary)
Connective tissue ds.
HIV
Portopulmonary
Congenital heart ds
Toxins/Diet pills

2009 WHO Classification of PH

1. Pulmonary arterial hypertension (PAH)
 1. Idiopathic (IPAH)
 2. Familial (FPAH)
 3. Associated with (APAH)
 1. Connective tissue disorder
 2. Congenital systemic to pulmonary shunts
 3. Portal hypertension
 4. HIV infection
 5. Drugs and toxins
 6. Other (thyroid disorders, glycogen storage ds, Gaucher's ds, hereditary hemorrhagic telangiectasia, hemoglobinopathies, chronic myeloproliferative disorders, splenectomy)
 4. Associated with significant venous or capillary involvement
 - 1.4.1 Pulmonary veno-occlusive disease (PVOD)
 - 1.4.2. Pulmonary capillary hemangiomatosis (PCH)
 5. Persistent pulmonary hypertension of the newborn

Pulmonary Hypertension (PH)

2. Pulmonary Hypertension with Left Heart Disease

- includes left heart diseases atrial or ventricular
- left sided valvular heart disease

Pulmonary Hypertension (PH)

3. Pulmonary Hypertension Associated with Lung Diseases and or Hypoxemia.
 - Chronic obstructive lung diseases
 - Interstitial lung disease
 - Obstructive sleep apnea (OSA)
 - Alveolar hypoventilation
 - Chronic exposure to high altitude
 - Developmental abnormalities

Pulmonary Hypertension (PH)

4. Pulmonary Hypertension due to Chronic Thrombotic and/or Embolic Disease CTEPH

- Thromboembolic obstruction of proximal pulmonary arteries
- Thromboembolic obstruction of distal pulmonary arteries
- Nonthrombotic pulmonary embolism (tumor, parasites, foreign material)

1-4% of patients who sustain a venous thromboembolism are at risk of developing chronic thromboembolic pulmonary hypertension (CTEPH) up to two years after the episode.. Crucial to r/o presence of CTEPH

Pulmonary Hypertension (PH)

5. Miscellaneous

This category involves PH related to inflammatory or neoplastic processes in the pulmonary microcirculation.

- Sarcoidosis is the main etiology in this group.
- Adenopathy, tumor, fibrosing mediastinitis

Pulmonary Hypertension

■ Symptoms

- Dyspnea on exertion
- Fatigue
- palpitations
- chest pain
- Syncope
- Lower extremity edema

indications
of more
severe PH
impaired RH
function

Diagnosis

- Women affected more commonly than men
- All ages
- Mean age 36 to 50 years

Diagnostic Evaluation

- Establish etiology
 - PFT
 - Connective tissue ds. Serology
 - Echocardiography
 - Cardiac catheterization
 - Tests to exclude chronic thromboembolic ds.

Pulmonary Hypertension Detection/Diagnosis

Echo with Doppler

- Best test to detect
- PAP
 - 35-40 borderline
 - 40-55 mild
 - 55-75 moderate
 - >75 mm Hg severe
- ESTIMATE only – confirm with RH Cath

Pulmonary Hypertension Detection/Diagnosis

■ Other findings

- Right heart chamber enlargement
- Paradoxical motion of the interventricular septum
- Tricuspid insufficiency
- Pericardial effusions

Pulmonary Hypertension Confirmation/Diagnosis

Right Heart Catheterization Gold Standard

- Oxygen saturations (SVC, IVC, RV, PA, SA)
- Right atrial pressure
- Right ventricular pressure
- PAP, systolic, diastolic, mean
- PCWP, left atrial pressure, or left ventricular end diastolic pressure
- Cardiac output/index
- Pulmonary vascular resistance
- Systemic blood pressure
- Heart rate
- Response to acute vasodilator

Pathology and Pathogenesis PAH

- Right Ventricle
- Major determinant of functional capacity and prognosis in PAH
- RV hypertrophy and dilatation by \uparrow afterload
- RV compensatory response variable
- Some compensate/other decompensate
 - Thinning and dilation of the wall and reduce the RV EF

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Pathology and Pathogenesis PAH

- Molecular Abnormalities in PAH
- Characterized by endothelial dysfunction
- ↓ ratio of apoptosis/proliferation in pulmonary artery smooth muscle cells
- Thickened, disordered adventitia – excessive activation of adventitial metalloproteases
- No single cause – “multi-hit model” likely

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Pathology and Pathogenesis PAH

Genetics

- Inherited in <10% of cases

Abnormalities in the blood and Endothelium

- Platelets depleted by serotonin
- Endothelial dysfunction is common
- PAH endothelium ↑ production vasoconstrictor/mitogenic compounds

Treatment

- Diet
- Exercise
- Appropriate vaccinations
- Avoidance of pregnancy
- Warfarin – all patients with IPAH
- Diuretics – RV volume overload
- Oxygen maintain O₂ sat >90%
- CCB – only for those with positive acute vasodilator response

PAH Treatment

Prostacyclins

- Epoprostenol – IV – very short $\frac{1}{2}$ life, improves exercise capacity, hemodynamics – only tx. shown to improve survival – critically ill
- Treprostinil – IV or sc – longer $\frac{1}{2}$ life – inhaled just approved by FDA, 4 times daily
- Iloprost – inhaled – needs 6 inhalations for up to 20 min.
- All \$100 K/yr or more (generic \$70 K)

PAH Treatment

Endothelin Receptor Antagonists

- Bosentan – oral – twice daily slows clinical decline, liver enzyme ↑ 10%
- Ambrisentan – oral – once daily – less liver enzyme ↑
- Fluid retention in both
- They improve exercise capacity in PAH
- Monitor LFT's monthly indefinitely
- \$50 K

PAH Treatment

Phosphodiesterase 5 inhibitors

- Sildenafil – oral – TID –
- Tadalafil – oral – once daily – newly approved by FDA, same efficacy, side effect profile as sildenafil,
- Both \$10 K /yr
- PDE-5 inhibitors improve exercise capacity and hemodynamics in PAH

PAH Treatment

Combination Therapy

- Widely used (almost 50% of pts)
- Sildenafil plus epoprostenil improves exercise better than mono therapy
- More expensive – but usually covered

PAH

Newer Therapeutic approaches

Investigational Therapies

- Vasoactive intestinal peptide and tyrosine kinase inhibitors
- Serotonin antagonists

ARS Question 2

What is the *BEST* test to detect PH?

1. PFT's
2. Stress Test
3. Echo
4. Cardiac cath

Pulmonary Hypertension Summary

- Important to suspect PH in pts with exertional symptoms
- Cardiac echo most important test for detection
- Right Heart cath needed to confirm
- New therapies are effective at improving symptoms, function, survival but only partially effective
- Newer therapies needed