

CLINICAL VIGNETTE

Pulmonary Hypertension

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Case Report

The patient is a 70-year-old woman with history of morbid obesity, hypertension and hyperlipidemia. She has shortness of breath for many years, and feels short of breath after walking one block. The patient was previously evaluated with a nuclear stress test with an EF of 55% and no stress induced ischemia. An echo showed an ejection fraction of 65-70% with moderate LVH, abnormal diastolic function, and mild aortic stenosis. She also had an angiogram that was negative. She has no history of cough, wheezing or asthma. She was told that she snores and is a lifelong nonsmoker.

A sleep study in 2011 revealed severe obstructive sleep apnea and she was started on CPAP. Pulmonary function tests showed decreased total lung capacity and expiratory reserve volume. The FVC was 2.28L 62% of predicted, and FEV1 was 1.7 L, 51% of predicted. The PFT findings were attributed to morbid obesity. ABG with ph 7.41, PCO2 36, PO2 81 without evidence of obesity hypoventilation syndrome. VQ scan was negative for pulmonary embolism.

In August 2012, she was admitted for worsening dyspnea on exertion and was found to have fluid overload. CT angiogram of the chest showed no pulmonary embolism and no consolidation. During her hospitalization the patient had junctional and sinus bradycardia on monitor and underwent pacemaker placement. Echo prior to diuresis showed EF 60-65%, moderately dilated left atrium, abnormal LV diastolic function, moderate to severe septal LV hypertrophy, moderately dilated right atrium, severe pulmonary hypertension with PA pressure 69-74 mmHg. She had a follow-up echocardiogram after diuresis and the EF was 60-65%, moderate septal wall hypertrophy, moderate dilated left atrium, mild pulmonary hypertension. PA pressure was estimated to be 40-45 mmhg. She had some improvement of her dyspnea on exertion after pacemaker placement and diuresis, but still experienced dyspnea on exertion. She started physical rehabilitation for possible deconditioning contributing to her symptoms.

In May 2013 she noted worsening shortness of breath and was able to walk only up to 50 feet before developing severe shortness of breath compared to her prior ability to walk to a block. She was aggressively diuresed with echocardiogram after diuresis of 15 liters showing that she had normal LV size, EF 60-65%, severe septal LVH, severely dilated RA, depressed RV function and enlargement of RV. PA pressures were 98-103, markedly increased from prior echo. Evaluation for pulmonary hypertension included HIV, ANA RF ANCA, and LFTs were normal, as well as VQ scan showing low probability of pulmonary embolism and CT chest showed airway disease. Heart catheterization revealed no obstructive CAD, but PA pressures of 83/69/75 mm Hg prior to nitrous oxide administration and PA pressure of 79/31/48 after 10 minutes of NO at 40 ppm. PW 12 mmhg prior to NO, cardiac output 3.9 L/min, cardiac index 1.56 L/min/m² by thermodilution prior to NO, cardiac index 1.60 L/min/m² post NO. These findings are consistent with pre-capillary pulmonary hypertension, felt to be idiopathic pulmonary artery hypertension. She started on tadalafil and declined treprostinil. She experienced some improvement of her dyspnea on exertion after starting tadalafil along with diuresis and treatment of OSA.

Pulmonary hypertension (PH) is characterized by elevated pulmonary arterial pressure (normal is less than or equal to 20 and PH is defined as mean pulmonary artery pressure greater or equal to 25 mm Hg at rest) and secondary right ventricular failure.

The WHO classifies pulmonary hypertension into five groups based on mechanism¹.

Group 1 PAH includes sporadic idiopathic pulmonary arterial hypertension (IPAH), heritable IPAH and PAH due to diseases that involve the small pulmonary muscular arterioles including connective tissue disease, HIV infection, portal hypertension, congenital heart disease, schistosomiasis, chronic hemolytic anemia, pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis. Drug and toxin-induced PAH are also in group 1 PAH. Group 2 PH are due to left heart systolic dysfunction,

diastolic dysfunction or valvular heart disease. Group 3 PH are due to severe COPD, interstitial lung disease, mixed restrictive and obstructive lung disease, sleep-disordered breathing, alveolar hypoventilation disorders. Lung disease with mildly abnormal pulmonary function should not be looked as the cause of PH. Group 4 PH are due to thromboembolic occlusion of the proximal or distal pulmonary vasculature. Group 5 PH include patients with myeloproliferative disorders, systemic disorders, metabolic disorders and sickle cell disease. The mechanism is unclear.

Epidemiology

It is estimated that there are 5-15 cases per 1,000,000 adults for group 1 PAH². The prevalence for other groups of pulmonary hypertension varies amongst different conditions: there is a 15-20% prevalence of mild PH in patients with OSA³. A study of 794 patients with systemic sclerosis reported PAH in 12 percent of patients⁴. Pulmonary hypertension is progressive and fatal if untreated. The rate of progression varies depending on the type of PH⁵. Patients with pulmonary hypertension, especially those with pulmonary arterial hypertension, are at higher risk when undergoing anesthesia and major surgery and have higher postoperative complications⁶⁻⁸.

Diagnostic Evaluation

An echocardiogram can be used to estimate the pulmonary artery systolic pressure, assess right ventricular size, thickness, function, right atrial size, left systolic, diastolic function and valve function. In severe pulmonary hypertension, RV enlargement, RV hypertrophy, right atrial enlargement and tricuspid regurgitation can be seen on echo⁹.

Pulmonary function testing is performed to evaluate lung disease that may contribute to pulmonary hypertension. Usually severe interstitial lung disease or obstructive lung disease produces pulmonary hypertension. Mildly abnormal PFT does not lead to pulmonary hypertension¹⁰. Patients with pulmonary hypertension also commonly have nocturnal desaturations and overnight oximetry can be used to determine if supplemental oxygen is needed¹¹. V/Q scan is used to assess for thromboembolic disease and CT angiogram of the chest can then be performed to confirm a positive V/Q scan¹².

Laboratory testing in the evaluation of pulmonary hypertension includes HIV testing to screen for HIV associated pulmonary hypertension, liver tests to screen for portopulmonary hypertension, ANA, rheumatoid factor and ANCA to screen for connective tissue disease.

Exercise testing with a six-minute walk test is used to establish a baseline to assess response to therapy and gives prognostic information. Patient who can walk a longer distance during the 6MWT have a longer survival. The test can also detect exercise-induced pulmonary hypertension¹³⁻¹⁵.

Right heart catheterization is used to differentiate pulmonary arterial hypertension from pulmonary hypertension due to left heart disease. Pulmonary arterial hypertension is confirmed when the mean pulmonary artery pressure is >25 mm hg at rest and the mean pulmonary capillary wedge pressure is < 15 to exclude PH due to left heart disease (group 2 PH)¹.

Treatment

Treatment is guided by disease severity and type of pulmonary hypertension. The primary therapy depends on the underlying cause of pulmonary hypertension. For group 1 PAH, there is no effective primary therapy and advanced therapy is needed.

Advanced therapy includes prostanoids, endothelin receptor antagonists, phosphodiesterase 5 inhibitors, and calcium channel blockers for group 1 PAH. For most patients in group 2 PH, they should be avoided and for Group 3, they are not approved in the US. For patients in Group 4, these drugs can be considered for patients who have symptoms despite anticoagulation or thromboendarterectomy. Group 5 PH, studies have looked at advanced therapy only in sarcoidosis.

In group 2 PH, the pulmonary hypertension is due to left heart disease and therapies include management of systolic dysfunction, diastolic dysfunction and valvular heart disease.

For patients with group 3 PH, the pulmonary hypertension is due to hypoxemia from COPD, interstitial lung disease, sleep apnea, mixed restrictive and obstructive pattern. Oxygen supplementation has been shown to improve mortality.

Patients in group 4 PH have pulmonary hypertension due to thromboembolic disease. Anticoagulation is the primary medical therapy.

Group 5 PH patients have unclear multifactorial mechanisms. The therapy is to treat the underlying cause which include myeloproliferative disorders, sarcoidosis, neurofibromatosis, vasculitis, glycogen storage disease, chronic renal failure on dialysis and tumor obstruction.

In all groups, the following therapies should be considered: 1) diuretics can treat fluid retention due to pulmonary hypertension, 2) oxygen supplementation for those patients with resting, nocturnal and exercise-induced hypoxemia, 3) anticoagulation for patients with idiopathic pulmonary hypertension, hereditary pulmonary artery hypertension, drug-induced pulmonary artery hypertension, and group 4 PH, 4) digoxin for group 3PH and group 2 PH 5) exercise¹⁶.

Before starting therapy, patients undergo hemodynamic assessment and a vasoreactivity test with nitric oxide. The test is positive if the mean pulmonary artery pressure decreased at least 10 mmHg to value less than 40 mmHg, increased or unchanged cardiac output, minimally reduced or unchanged systemic blood pressure. If the test is positive, patient can start trial of long-acting oral calcium channel blocker with diltiazem or amlodipine. Patients with negative vasoreactivity test should start prostanoïd, endothelin receptor antagonist, or phosphodiesterase 5 inhibitor. For patients who are refractory to all therapy, lung transplant or creating right to left shunt by atrial septostomy can be considered¹⁶.

Prostanoids include intravenous epoprostenol, intravenous treprostinil, subcutaneous treprostinil, inhaled treprostinil and inhaled iloprost. Epoprostenol should be considered as the first line agent in patients with severe disease. Inhaled treprostinil can be offered as therapy for WHO functional class III patients. Inhaled iloprost has advantage of targeting lung vasculature and does not need IV administration.

Endothelin receptor antagonists: Endothelin-1 is a vasoconstrictor and smooth muscle mitogen. High levels been noted in the lungs of patients with PAH. Available agents are bosentan and ambrisentan. Adverse effects include hepatotoxicity and peripheral edema. They are also teratogens.

PDE5 inhibitors include sildenafil, tadalafil, and vardenafil and prolong the vasodilatory effect of nitric oxide. Guanylate cyclase stimulant stimulates the nitric oxide receptor and is not yet available.

Clinical studies are starting to look at combination therapy including combining epoprostenol to bosentan (BREATHE-2 trial), treprostinil and sildenafil or bosentan (TRIUMPH trial and oral treprostinil to phosphodiesterase-5 inhibitor or endothelin receptor antagonist (FREEDOM-C and FREEDOM C-2 trial¹⁷.

An algorithm developed during the 4th World Symposium on Pulmonary Hypertension recommends the following agents for use depending on the patient's WHO functional class¹⁶.

WHO functional class II: preferred agents include ambrisentan, bosentan, sildenafil and tadalafil. WHO class III: preferred agents include ambrisentan, bosentan, IV epoprostenol, IV or subcutaneous treprostinil, inhaled iloprost, sildenafil or tadalafil. WHO class IV: preferred agent is IV epoprostenol. IV treprostinil is a reasonable alternative and inhaled iloprost can be used for patients who refuse or cannot receive IV therapy.

With severe symptomatic PAH, patients have high mortality and morbidity due to progressive heart failure and may be considered for a right to left shunt either via atrial septostomy or transcatheter Potts shunt. The atrial septostomy connects the left and right atrial cavities and can increase cardiac output to help improve systemic oxygen delivery. The mortality can be as high as 15-20%. Transcatheter Potts shunt puts a right to left shunt between the left pulmonary artery and the descending aorta. Mortality is higher in adult patients than in children^{18,19}.

Bilateral lung or heart-lung transplantation is considered for patients who are class III or IV. The guidelines for referral for transplant include: Mean right atrial pressure >10 mmHg, mean pulmonary artery pressure > 50 mmHg, cardiac index < 2.5 l/min per m², failure to improve despite medical therapy or with rapidly progressive disease²⁰.

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