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IDIOPATHIC PULMONARY ARTERY HYPERTENSION

SUMMARY

Primary pulmonary artery hypertension is defined as a mean resting pulmonary artery pressure > 25 mmHg or a mean pulmonary artery pressure > 30 mmHg with exercise. The World Health Organizations definition is a pulmonary artery systolic pressure > 40 mmHg during echocardiography. Symptoms of pulmonary hypertension include shortness of breath on minimal exertion, fatigue, chest pain, dizzy spells and fainting.

All patients with pulmonary artery hypertension must undergo diagnostic procedure, which means the right heart catheterization with vasodilators tests, followed by therapeutic support in the sense of anticoagulant therapy (warfarin) and oxygen. The final therapeutic choice is administration of the following drugs (or their combination): Calcium channel blockers, prostacyclines (epoprostenol, iloprost), antagonist of endothelin-1 receptors (Bosentan), phosphodiesterase type 5 inhibitors (sildenafil). There is a strong sentiment that identifying and treatment of disease at an earlier stage may be even more beneficial.

Key words: **primary pulmonary artery hypertension**

Primary pulmonary hypertension is a rare lung blood vessel disorder in which the pressure in the pulmonary artery rises above normal levels. The definition of pulmonary hypertension has varied over the years. When pulmonary hypertension occurs in the absence of familial cause, it is referred to as primary pulmonary hypertension. A proposal of the Third World Symposium on pulmonary arterial hypertension held in Venice, Italy, in 2003, was that the term "primary pulmonary hypertension" should be replaced by the term "idiopathic pulmonary hypertension" (IPAH). Pulmonary artery hypertension is defined as a mean resting pulmonary artery pressure > 25 mmHg or a mean pulmonary artery pressure > 30 mmHg with exercise. The World Health Organizations definition is a pulmonary artery systolic pressure >40 mmHg during echocardiography. Symptoms of pulmonary hypertension include shortness of breath with minimal exertion, fatigue, chest pain, dizzy spells and fainting (1-5).

IPAH occurs predominantly in females in ratio 2:1. The average age of the onset is between 20 and 40, but it can occur at any age. Ten percentage of cases in the US are people over the age of 60 (6).

During the past ten years, understanding of pathogenesis of IPAH has changed, from focusing of vasoconstriction to focusing on impaired cellular proliferation and apoptosis. In our current understanding of IPAH, there is a complex interplay of imbalances in proliferative and apoptotic processes. The system involved includes endothelial

production of prostacyclins, nitric oxide, endothelin-1 and other substances mediating cell growth and cell death. In addition, dysfunction of vascular smooth muscle cells and adventitial cells seem to be involved. The characteristic pathological finding in IPAH is uncontrolled cellular (endothelial) proliferation (7-9).

In 2000, the bone morphogenetic receptor type 2 (BMPR-2) genes was identified in patients with family and sporadic IPAH. This receptor is a member of the transforming growth factor-β (TGF-β). What was interesting was the discovery of genetic background of IPAH (10).

The baseline therapy that should be administered to all the patients with IPAH is anticoagulation with warfare, since it has been shown in retrospective studies to prolong the survival of those patients (11).

• C*alcium channel blockers:* Calcium channel blockers are administered to a small group of patients who demonstrate acute vasorectivity in vasodilatator testing. The testing is conducted with nitric oxide, prostaciclyne or adenosin during the right heart catheterization. In order to find vasodilatative response, patients should be re-tested after 8 to 12 weeks of therapy, since not all the patients with an acute response will have a long-term response, as well. This procedure is very important because non-responders may have adverse clinical effects with calcium channel blockers (12, 13).

• *Prostacyclines:* Epoprostenolol represents the first major medicine in the treatment of IPAH. Prostacyclins have many effects, including vasodilatation, antiplatelet activity, antiproliferative activity and inhibition of endothelin-1. The studies of epoprostenol showed dramatic effects during the 12th week, including improvement in exercise capacity and decrease in mean pulmonary arterial pressure. However, epoprostenol is not an easy drug to administer. Its short half-life and instability require a continuous IV delivery system, with very serious complications. Iloprost, an inhalation form of prostacyclines, is in use in Europe as well as Beraprost which is in oral form (14, 15).

• *Endothelin-1 antagonists:* Bosentan is dual endothelin-1 receptors antagonist. It affects both the A and B endothelin-1 receptors. While the A receptors mediate vasoconstriction and proliferation and the B receptors mediate vasodilatation, nitric oxide and prostacycline production, the overall drug effect was positive. A major advantage of bosentan over epoprostenol is its oral administration. It requires monitoring since it affects liver function and warfarin metabolism and it cannot be used in pregnancy. Selective endothelin-A receptors antagonists, sitaxsentan and ambrisentan, have underwent clinical trials (16-18).

• *Nitric oxide enhancers:* Nitric oxide is a potent pulmonary vasodilator. It also has antiproliferative and antiplatelet effects. It acts through increase in intracellular cyclic guanosine monophosphate (cGMP). Today, more attention is being focused on inhibition of cGMP breakdown by phosphodiesterase type 5 inhibitors, primarily sildenafil (viagra). Currently available medicines from this family are sildenafil, tadalafil and vardenafil (19).

We can conclude that all patients with IPAH should receive warfarin and supportive care (diuretics and oxygen) when needed. Right heart catheterization with vasodilator testing should be conducted, both to define the disease and its hemodinamic severity and to test for an acute vasodilator response.

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IDIOPATSKA PLUĆNA ARTERIJSKA HIPERTENZIJA

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SUMMARY

Primarnu plućnu hipertenziju možemo definisati kao stanje u kome je vrijednost srednjeg arterijskog pritiska u plućnom koritu, tokom mirovanja, veća od 25 mmHg ili, ako se ovaj pritisak poveća na vrijednosti većoj od 30 mmHg tokom vježbe. Svjetska zdravstvena organizacija, pak, definiše primarnu plućnu arterijsku hipertenziju kao stanje gdje je povećana vrijednost sistolnog arterijskog pritiska u plućnoj cirkulaciji viša od 40 mmHg tokom ultrazvučnog ispitivanja. Glavni simptomi koji prate ovo oboljenje su: otežano disanje pri minimalnim naporima, lako zamaranje, bolovi u grudima, vrtoglavica, nesvjestica.

Svi bolesnici moraju da prođu dijagnostičku proceduru, koja u osnovi podrazumijeva kateterizaciju desnog srca sa vazodilatatornim testom, a nakon toga, terapijsku podršku u smislu primjene antikoagulantne terapije i kiseonika. Definitivan terapijski izbor je primjena nekih od sljedećih lijekova (ili njihova kombinacija): blokatora kalcijumskih kanala, prostaciklina (epoprostenol, ilioprost), antagonista endotelin - 1 receptora (Bosentan), i inhibitora fosfodiesteraze (Sildenafil).

Ključne riječi: **primarna plućna arterijska hipertenzija**