

## The benefit of using a low dose calcium channel blocker in a patient with idiopathic pulmonary hypertension

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### Abstract

**Introduction:** Pulmonary arterial hypertension is defined by hemodynamic and pathophysiological changes of increased resting mean pulmonary arterial pressure  $\geq 25$  mmHg estimated by right heart catheterisation.

**Case report:** We describe a 44-year-old woman who presented for evaluation 13 years after being diagnosed with primary pulmonary hypertension. Over that extended period of time, she did not develop any changes in her coronary or pulmonary vascular measurements as documented by repeat catheterization. She did not have signs of systemic connective tissue disease. Throughout this time, she was managed with continuous medical treatment of low-doses of a Ca-channel antagonist (nifedipine 10mg twice per day) along with oral anticoagulant therapy. Her ongoing complaints were of fatigue when engaged in heavy physical activity, but there was no progression of symptoms. She also occasionally felt symptoms of increased heart rate and syncope. Auscultation revealed a systolic murmur along the left parasternal edge and an accented second sound of the pulmonary artery. Electrocardiography showed sinus rhythm and incomplete right bundle branch block. Echocardiography was consistent with signs of pulmonary hypertension.

**Conclusion:** A small number of patients with pulmonary hypertension have a good prognosis with treatment with modest doses of calcium blockers as seen in our patient who has had a stable course of disease for many years.

### Key Words

Primary pulmonary hypertension, calcium channel blockers, cardiac catheterization, echocardiography

### Introduction

**P**ulmonary arterial hypertension (PAH) is a chronic, progressive disease of the pulmonary vasculature resulting in right ventricular failure and death, if untreated<sup>1</sup>. PAH is defined as a hemodynamic and pathophysiological condition of increased resting mean pulmonary arterial pressure (mPAP)  $\geq 25$  mmHg; pulmonary capillary wedge pressure or left ventricular end diastolic pressure  $\leq 15$  mmHg; and pulmonary vascular resistance (PVR)  $\geq 3$  Wood units estimated by right heart catheterisation<sup>2</sup>. A registry of patients with PAH in France found a prevalence of about 15 cases per million population<sup>3</sup>.

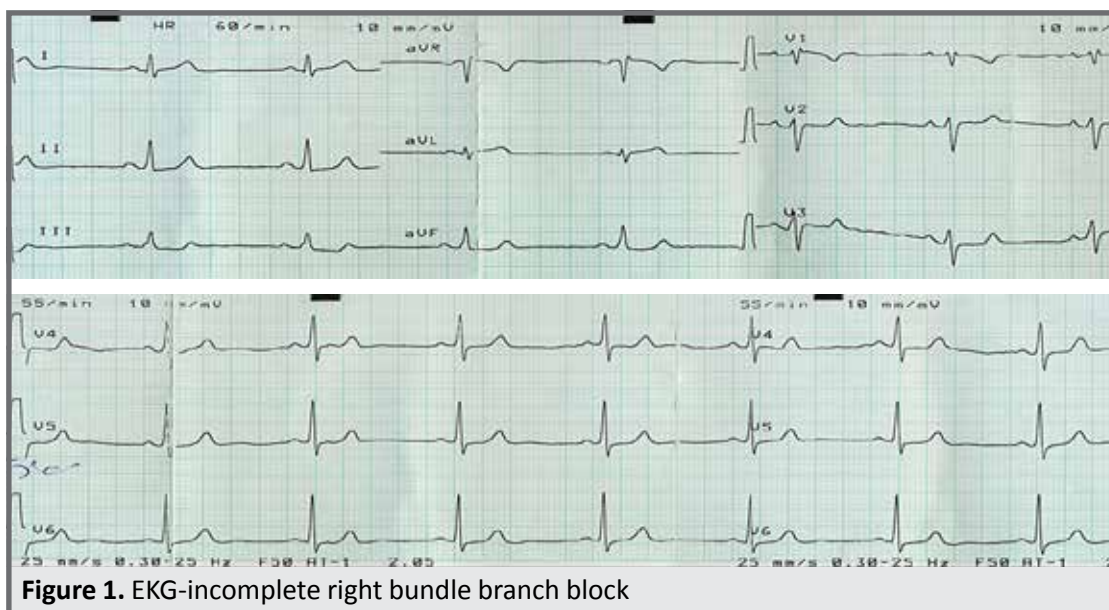
Idiopathic pulmonary arterial hypertension (IPAH) or primary pulmonary hypertension (PPH) is rare and difficult progressive disease with a prevalence of about 6 per million<sup>4</sup> characterized by elevated pulmonary artery pressure with no apparent cause<sup>5</sup>. IPAH occurs at a female-to-male ratio ranging from 2-9:1, depending on the treatment center sampled. The reasons for this female predilection remain unknown. Typically, younger

women of childbearing age between ages 21 and 40 develop IPAH<sup>6,7</sup>. However, IPAH can also affect individuals in their fifth and sixth decades of life or older<sup>6</sup>.

Based on data from an American Registry, idiopathic hypertension represent 40% of PAH, while pulmonary hypertension (PH) associated with other diseases is found in about 50% of cases<sup>8</sup>. In developing countries, schistosomiasis is a common cause of PAH, and the estimated number of registered cases worldwide is about 200 million<sup>9</sup>.

According to the most recent classification of pulmonary hypertension based on clinical and pathophysiological characteristics, PAH is divided into 5 groups: 1) idiopathic PAH, 2) PAH due to left heart disease, 3) PAH due to lung diseases and hypoxia, 4) PAH due to chronic thromboembolism, 5) PAH associated with multifactorial diseases (systemic connective tissue diseases, hematological, and metabolic disorders)<sup>10</sup>.

PPH usually develop slowly. Patients remain minimally symptomatic for many years. Most patients with PAH present with exertional dyspnea that progresses



**Figure 1.** EKG-incomplete right bundle branch block

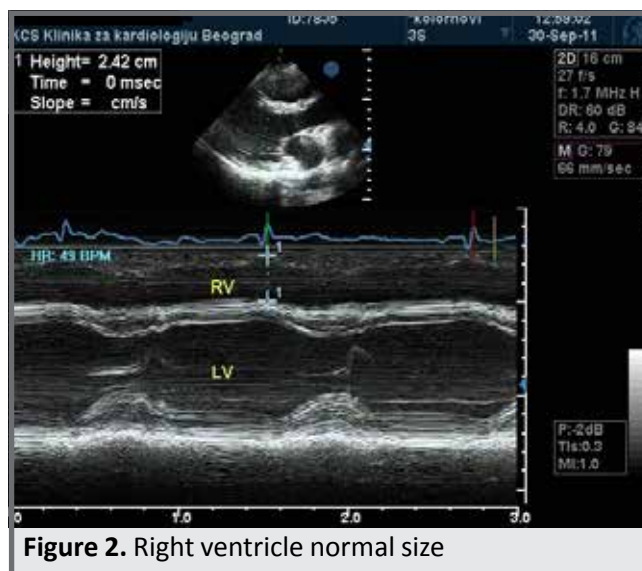
over months or even years. Exertional chest pain, syncope, and lower extremity edema are indicative of more severe pulmonary hypertension with impaired right heart function. Diagnosis is often delayed due to the subtle findings on physical examination and the nonspecific symptoms experienced by most patients<sup>3,11,12</sup>.

Establishing the diagnosis and etiology of PAH requires a comprehensive evaluation that includes pulmonary function testing, connective tissue disease serology, echocardiography, cardiac catheterization, and tests to exclude chronic thromboembolic disease. Echocardiography is often the first diagnostic test to evaluate for the possibility of pulmonary hypertension<sup>13</sup>. Once the diagnostic evaluation has suggested PAH, right heart catheterization is required to confirm the presence and to determine the severity of pulmonary hypertension, to exclude left-sided heart disease or potentially correctable intracardiac left-to-right shunting, and to perform acute vasodilator testing<sup>14,15,16</sup>.

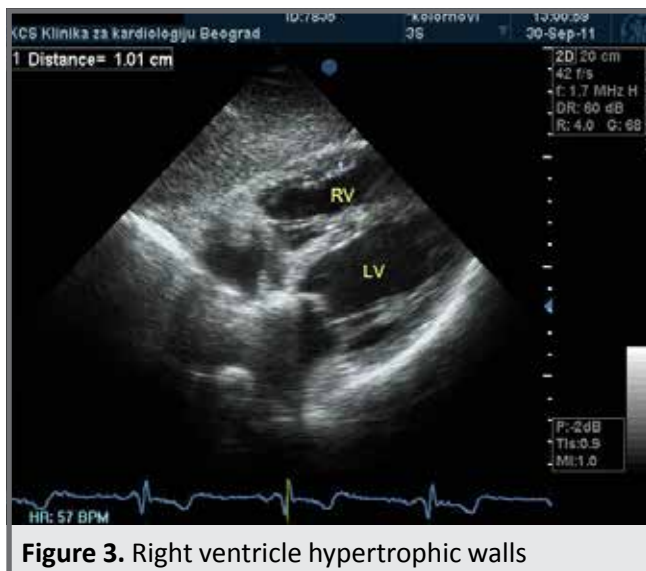
## Case report

We present a clinical case of 44 year-old woman, former smoker, obese, with two children who came for cardiac examination 13 years after she had primary pulmonary hypertension initially diagnosed. Her initial evaluation then included right heart catheterization, selective pulmonary angiography and selective coronary angiography. There were no significant changes found at that time in her coronary arteries nor disorders in the pulmonary vascular network. However, high pressures in right heart pulmonary artery (PA) were registered (100/40-65mmHg), along with hypertention of the right ventricle (RV) (95/0-10mmHg) and elevated capillary wedge pressures (20/6-12mmHg). She was evaluated for the presence of systemic connective tissue disease, which was excluded. On echocardiography, she was found to have an enlarged PA (4.2cm diameter) and its branches (left PA 2.1 cm and right PA 2.0 cm). From then until now, the patient has been on the same medical treatment of low-doses of a Ca channel antagonist (nifedipine 2x10mg) along with oral anticoagulant therapy,

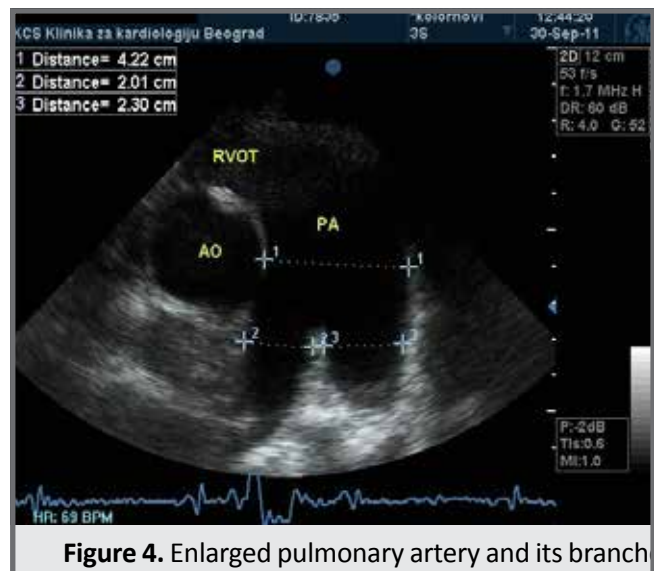
steady state, with no progression of symptoms. She has felt tired only during times of higher physical activity, and has sometimes felt symptoms of increased heart rate and syncope. Auscultation revealed systolic murmur along the left parasternal edge and accented second tone of the pulmonary artery. Electrocardiography (ECG) showed sinus rhythm, with a normal electrical axis and incomplete right bundle branch block (**Figure 1**). Echocardiography pointed out that the right ventricle was of normal diameter, with hypertrophic walls, good contractility, and an enlarged pulmonary artery with its branches (**Figures 2,3,4**). Systolic pressure in the right ventricle could not be estimated by Doppler due to a small amount of tricuspid regurgitation, but all other echocardiographic signs of pulmonary hypertension were noted (**Figure 5**). Catheterization was redone and registered pressures were unchanged from the examination done 13 years earlier (PA pressure 60/40-58 mmHg, RV pressure 70/0-10 mmHg, capillary wedge pressure 17/12-14 mmHg).



**Figure 2.** Right ventricle normal size



**Figure 3.** Right ventricle hypertrophic walls



**Figure 4.** Enlarged pulmonary artery and its branches

## Discussion

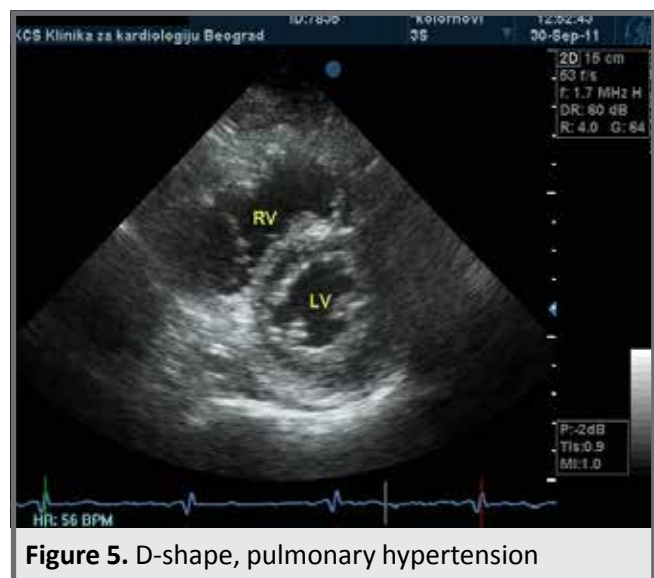
Modern drug therapy can lead to a significant improvement in patients with pulmonary hypertension with little change symptomatic status and a slower rate of clinical deterioration<sup>17</sup>. Pharmacologic agents used in the treatment of PAH include calcium-channel blockers (CaCB), prostanoids, endothelin antagonists, and phosphodiesterase type 5 inhibitors. These agents all have pulmonary vasodilatory effects and all except CaCBs also have antiproliferative properties<sup>13</sup>. Only 10–15% of patients with all types of pulmonary hypertension seem to respond favourably to high-dose vasodilators such as CaCBs and these drugs are used as standard therapy in PPH. Retrospective studies have shown improved survival in patients with PPH who are anticoagulated but there are no randomized controlled trials (RCT) published with data available to support this therapy. Consensus based on clinical experience, however, suggests that anticoagulation is a useful treatment, supporting the idea that there is a thrombotic component to the illness<sup>5,18</sup>.

Supplemental oxygen can help symptomatically with exercise tolerance. Diuretics are used to treat right heart failure and remove peripheral edema, along with digoxin as a positive inotrope. There are no convincing trial data to support their use but clinical experience suggests that these treatments are beneficial<sup>5</sup>.

In the past few years, treatment of PAH has undergone an extraordinary evolution. A meta-analysis performed assessing 23 RCTs in PAH patients reports a 43% decrease in mortality and a 61% reduction in hospitalizations in patients treated with specific drug therapies vs. patients randomized to placebo<sup>19</sup>.

The enthusiasm for the use of CaCBs in IPAH dates back to 1992, with the publication of a study that demonstrated 95% 5-year survival in a very select group of patients with IPAH who exhibited an acute vasodilator response to CaCBs<sup>20</sup>.

The CaCBs that have been predominantly used in reported studies are nifedipine, diltiazem, and amlodipine, with particular emphasis on the first two<sup>(21)</sup>. The daily doses of these drugs that have shown efficacy in IPAH are relatively high, 120–240 mg for nifedipine,



**Figure 5.** D-shape, pulmonary hypertension

240–720 mg for diltiazem, and up to 20 mg for amlodipine. It is advisable to start with a low dose, e.g. 30 mg of slow release nifedipine twice a day, 60 mg of diltiazem three times a day, or 2.5 mg of amlodipine once a day and increase cautiously and progressively to the maximum tolerated dose<sup>13,22</sup>.

In contrast, our patient has a stable course of disease for many years at a low dose of Ca blockers (2x10mg nifedipine).

CaCBs remain a treatment option only for patients with a positive vasodilator challenge. In a retrospective study, 12.6% of patients with idiopathic PAH had evidence of acute pulmonary vasoreactivity and received CaCB therapy. Of the entire cohort of patients, only 6.8% had long-term response<sup>21</sup>. Similarly, in a previous report of the French registry, only 10.3% of patients with idiopathic PAH had a positive vasoreactivity test<sup>3</sup>.

## Conclusion

The treatment approach for PAH patients should be based after a compound strategy of evaluation of severity, assessment of vasoreactivity, estimation of efficacy, and based on treatment outcomes from a combination

of different drugs plus interventions<sup>17</sup>.

Treatment goals in PAH patients are numerous. Improving the patients symptoms, which commonly include dyspnea and fatigue, are principal. Also, a very important aim of therapy is to reverse or prevent progression of the disease, decrease the number of hospitalizations, normalize cardiac output and prevent the need for lung transplantation<sup>2</sup>.

A variety of pharmaceutical substances may play roles as mediators through a final common pathway of pulmonary angiogenesis and may therefore be appealing therapeutic targets. These include vasoactive intestinal polypeptide<sup>23</sup>, platelet-derived growth factor<sup>24</sup>, serotonin and its receptors and transporter<sup>25</sup>, and Rho kinase inhibitors<sup>26</sup>. Clinical trials for many of these substances are underway<sup>13</sup>.

Despite the existence of a new generation of expensive drugs and the multiplex pathophysiology of the disease, our patient has thus far had an excellent response to classical therapy of very low doses of Ca-blockers (Nifedipine 2x10mg). She represents one of the rare cases of patients (6.8% according to the current literature), who has a good response to vasodilator therapy without worsening either of symptoms or pulmonary hypertension parameters over a prolonged period of time (over 13 years).

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## Sažetak

### **Dobar efekat niskih doza blokatora kalcijumskih kanala kod bolesnice sa idiopatskom plućnom hipertenzijom**

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**Uvod:** Plućna hipertenzija je hemodinamsko i patofiziološko stanje povećanog srednjeg arterijskog pritiska u plućnoj arteriji, preko 25mmHg u miru, procenjenog kateterizacijom desnog srca.

**Prikaz bolesnika:** Pacijentkinja starosti 44 godine dolazi na kardiološki pregled 13 godina nakon što joj je postavljena dijagnoza primarne plućne hipertenzije. Na koronarnim arterijama nisu viđene promene. Isključeno je postojanje sistemske bolesti vezivnog tkiva. Od tada do danas je na istoj terapiji - niskim dozama antagonista Ca (Nifelat 2x10mg) uz oralnu antikoagulantnu terapiju, stabilnog stanja, bez progresije tegoba. Zamara se isključivo pri većem fizičkom naporu, ponekad oseća ubrzani srčani rad i nesvesticu. Objektivno čujan sistolni šum uz naglašen drugi ton nad plućnom arterijom, elektrokardiogram sinusni ritam, inkompletni blok desne grane. Ehokardiografski pregled pokazuje znake plućne hipertenzije. Zaključak: Mali broj bolesnika sa plućnom hipertenzijom koja se odlikuje vazokonstriktornim svojstvima imaju dobru prognozu na terapiji visokim dozama kalcijumskih blokatora dok naša pacijentkinja ima dugogodišnji stabilan tok bolesti na niskoj dozi Ca blokatora.

**Ključne reči:** primarna plućna hipertenzija, blokatori Ca kanala, kateterizacija, ehokardiografija.