

Case Report

Chronic thromboembolic pulmonary hypertension in young woman with history of caesarian section

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Abstrak

Hipertensi pulmonal tromboemboli kronik merupakan salah satu subgrup dari hipertensi pulmonal. Penyakit ini merupakan kondisi medis yang sangat serius dan seringkali tidak terdiagnosis. Hipertensi pulmonal tromboemboli kronik umumnya tidak terdiagnosis karena gejala yang tidak spesifik dan kurangnya alat diagnostik. Tujuan presentasi ini adalah untuk menjelaskan mengenai etiologi, faktor resiko, diagnosis dan manajemen hipertensi pulmonal tromboemboli kronik. Wanita berusia 36 tahun datang dengan keluhan utama mudah lelah dan sesak bila beraktifitas sejak dua tahun yang lalu. Gejala ini timbul sekitar tiga bulan setelah melahirkan dengan seksio caesaria atas indikasi preeklampsia. Anamnesa lebih lanjut, pemeriksaan fisik, EKG dan ekokardiografi sangat mendukung ke arah diagnosis hipertensi pulmonal. Dari pemeriksaan sonografi vaskuler femoral tidak didapatkan adanya trombosis vena dalam (DVT). Scan perfusi paru menunjukkan bahwa pasien ini mengalami hipertensi pulmonal tromboemboli kronik. CT pulmonary angiography (CTPA) tidak mendapatkan adanya trombus sehingga pasien ini tidak layak dioperasi endarterektomi pulmonal. Pasien ini kemudian diterapi dengan vasodilator pulmonal, ACE inhibitor, diuretik dan mendapat antikoagulan oral untuk seumur hidup.

Abstract

Chronic thromboembolic pulmonary hypertension (CTEPH) is one of subgroups of pulmonary hypertension. This is a serious medical condition that severely under diagnosed. CTEPH is commonly underdiagnosed due to non specific symptoms and lack of diagnostic tools. The aim of this presentation is to discuss the etiology, risk factors, diagnosis and management of CTEPH. A 36-year-old woman presented with easily fatigue and dyspneu on effort since two years ago. The symptom occured about three months after she gave birth with caesarian section due to preeclampsia. Further history taking, physical examination, electrocardiography (ECG) and echocardiography were highly suggestive of pulmonary hypertension. No deep vein thrombosis (DVT) was found on vascular femoral sonography. It was found after the lung perfusion scintigraphy performed that she actually had CTEPH. This patient was categorized as inoperable because CT pulmonary angiography showed no thrombus. The patient got pulmonary vasodilator and oral anticoagulant for lifelong.

Keywords: CTEPH, CTPA, lung perfusion scan, oral anticoagulant, pulmonary hypertension

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Chronic thromboembolic pulmonary hypertension (CTEPH) is one of subset of pulmonary hypertension (PH). It develops when thromboembolic material obstructs pulmonary artery branches and mean pulmonary arterial pressure (mPAP) rises to ≥ 25 mmHg. CTEPH is responsible for significant levels of morbidity and mortality, especially when left untreated. Historically, 3-year mortality is reported as high as 90% in patients with a mean pulmonary artery pressure (mPAP) of > 50 mmHg.^{1,2}

The exact prevalence of CTEPH is still unknown. In the United States, registry data suggest that the incidence of CTEPH is between 3 and 30 per 1 million in the general population. It is estimated that an acute PE occurs in 0.5 to 0.6 million individuals each year, and CTEPH occurs in 3.8% of patients with a history of acute pulmonary embolism (PE).^{3,4} This figure may underestimate the true frequency of CTEPH, as the disease is often misdiagnosed because of nonspecific symptoms and a variable disease course. This is hindered by the observation that up to 40-60% of the patients have no known history or clinically apparent of acute pulmonary embolism episodes.^{3,5} In this case report, we present CTEPH case with no history of acute pulmonary embolism episode. The aim of this presentation is to discuss the etiology, risk factors, diagnosis and management of CTEPH.

CASE ILLUSTRATION

A 36-year old woman presented to the outpatient clinic of National Cardiovascular Center Harapan Kita (NCCHK) with chief complaint of dyspnea on effort which occurred since almost two years ago. The symptoms started at around three months after she had caesarian section due to preeclampsia. The limitation of daily activity progressed slowly and even asymptomatic in some period, but was worsening in two months before she came to the clinic. Since the symptoms occurred at the degree of her ordinary activities, she was in functional class III of New York Heart Association (NYHA) classification. There was no orthopnea, nor paroxysmal nocturnal dyspnea. She had recurrent history of edema in lower feet, and non productive cough since two months ago. There was no history of syncope, chest pain or hemoptysis. She denied any routine drugs usage or history of contraceptive pill consumption. She had no history of asthma, allergy or history of previous lung infection. No history of congenital heart disease in the family.

She had history of hypertension grade I which occurred since she was pregnant two years ago. No dyslipidemia, diabetes mellitus, or family history were found in this patient.

On physical examination, she was *compos mentis*, blood pressure was 104/79 mmHg, heart rate 100/min and peripheral oxygen saturation was 100%. Her conjunctiva were not anemic and the sclera were not icteric. Jugular venous pressure was 5 + 3 CmH₂O. Heart auscultation revealed normal first heart sound and accentuated pulmonary component of second heart sound. No murmur nor gallop were heard. The breath sound was vesicular in both lungs, without rales nor wheezing. Her abdomen was soft with palpable liver approximately 2 cm below costal border, and peristaltic sound was normal. Extremities were warm and there were minimal pretibial edema in both feet. No peripheral cyanosis were noted.

Electrocardiography (ECG) showed sinus rhythm with QRS rate of 94 beats/minute, QRS axis was 105°, with pulmonal P wave morphology. PR interval was 0.16s, QRS duration 0.08s, R wave was dominant over S wave with R/S > 1 in right precordial lead V1, and T wave inversion on the V1 – V6, I, II, III, avF, suggesting right ventricular strain (Figure 1). The conclusion of the ECG recording was sinus rhythm with right axis deviation with right ventricular hypertrophy and right atrial enlargement. Chest X-ray showed 60% of cardiothoracic ratio with normal aortic segment. The pulmonic segment was prominent with the cardiac apex pointing upward. Cardiac waist was normal, without sign of infiltration nor congestion (Figure 2).

Laboratory examination of routine hematology, renal function, electrolyte, liver function and thyroid function are within normal limit. ANA test was positive, but with low titer (1:20). Echocardiography showed severe PH with mean pulmonary arterial pressure of 45 mmHg. Right atrium and right ventricle were dilated with interventricular septum (IVS) paradox and left ventricular (LV) D-shaped. Left systolic function was decreased with ejection fraction (EF) 43%. Right ventricle contractility was already reduced with tricuspid annular plane systolic excursion (TAPSE) 1.6 cm. There was also moderate tricuspid regurgitation with tricuspid valvular gradient (TVG) 84 mmHg. There was no any sign of left ventricular dysfunction, left atrium was within normal limit and no other abnormality found in valves beside tricuspid valve.

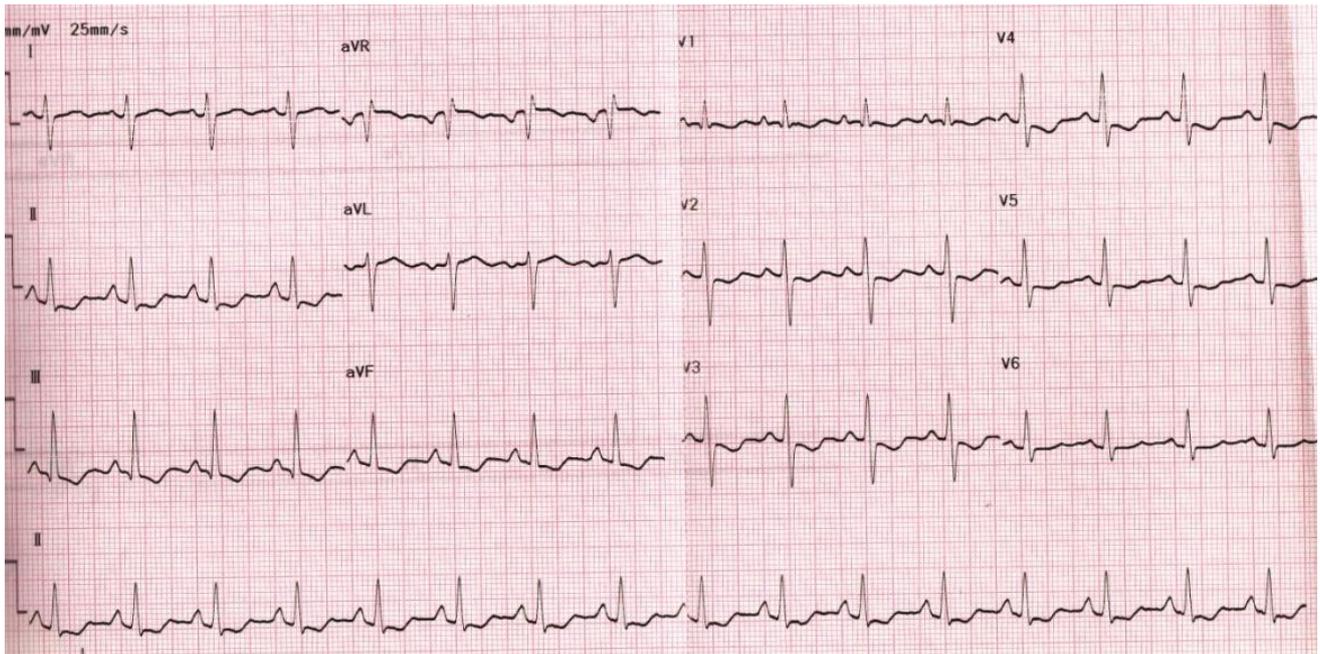


Figure 1. The ECG show sinus rhythm with right axis deviation, Pulmonal P wave, with R/S > 1 in lead V1 suggesting right ventricular hypertrophy, and T wave inversion on the V1 – V6, I, II, III, aVF leads, suggesting right ventricular strain

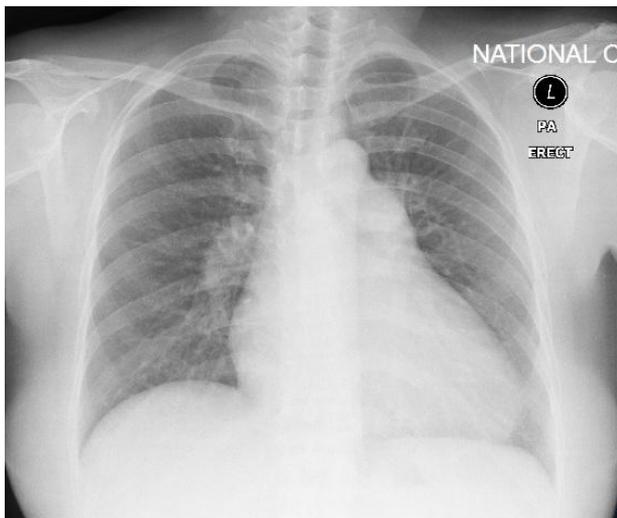


Figure 2. Chest X-ray showed 60% of cardiothoracic ratio with normal aortic segment. The pulmonic segment was prominent with the cardiac apex pointing upward. Cardiac waist was normal, without sign of infiltration nor congestion

Vascular femoral sonography examination revealed normal flow on arteries and veins. There were no sign of chronic venous insufficiency nor deep vein thrombosis at both lower extremities.

Lung perfusion scan was then performed. On the right lung radioisotope uptake activity on the upper and lower lobus was homogen, no segmental perfusion was detected. On the left lung, segmental perfusion defects were detected in anteromedio basal

and superior segment of lower lobus (Figure 3). It was concluded from the lung perfusion scan that there were chronic pulmonary embolism at the left lung. Chest CT scan and pulmonary angiography showed a cardiomegaly with dilated right atrial and right ventricle with enlargement of main pulmonary artery. But no thrombus on pulmonary arteries were found.

To confirm the diagnosis of pulmonary hypertension, she underwent right heart catheterization (RHC), which showed mean pulmonary arterial pressure of 54 mmHg and there was no structural abnormality or defect of the heart.

This patient was then given sildenafil 25 mg (t.i.d), furosemide 40 mg (as needed) and Warfarin 2 mg (o.d). Two months after the treatment, her functional capacity were improved. The result of 6 minute walk test was 360 metres with aerobic capacity of 6.9 METS.

DISCUSSION

Etiology and risk factors of CTEPH

CTEPH occurs in about 0.5% to 4% of patients with a history of PE.¹ International registry of CTEPH reported a history of acute PE in 74.8% of CTEPH patients and 56.1% with previous deep

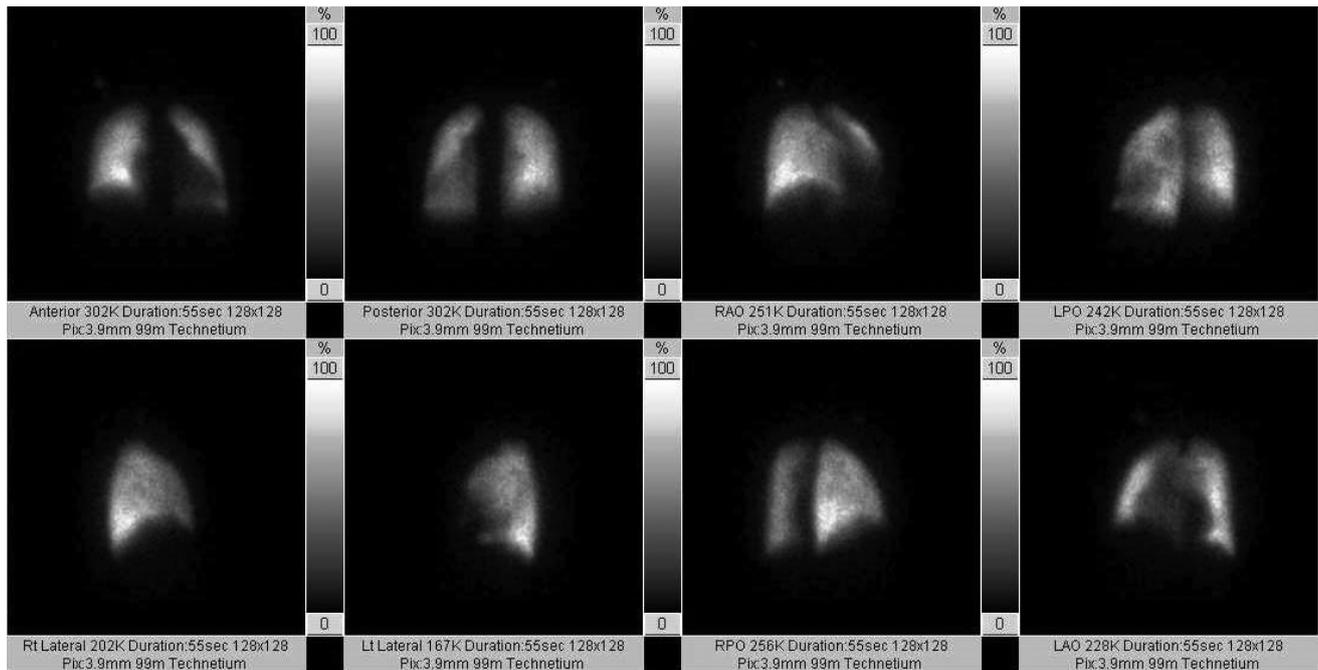


Figure 3. Lung perfusion scan showed segmental perfusion defects were detected in anteromedio-basal and superior segment of lower lobe on the left lung

vein thrombosis.⁶ This is in contrast with previous retrospective reports indicating no history of venous thromboembolism in 40% to 60% of the patients.⁵ It is possible that PE is simply undiagnosed in some patients. In the majority of patients, months or even years (the so-called “honeymoon period”) may pass after PE before clinically significant pulmonary hypertension manifests. This presumed gradual progression of pulmonary hypertension occurs in the absence of documented recurrent pulmonary embolic events and is thought to reflect progressive remodeling of the unobstructed pulmonary vasculature, stimulated by increased blood flow through these vessels. When there is no history of PE, the etiology is uncertain.⁷

In our patient, no documented event of acute PE episode. But the symptoms started three months after she had caesarian section due to preeclampsia. Hypercoagulability during pregnancy is associated with a 5-fold increased risk in venous thromboembolism. Pulmonary embolism complicating pregnancy has incidence rates ranging from 0.11 to 0.73 per 1000 deliveries.⁸ Furthermore, women with pre-eclampsia have a small but significantly higher risk of subsequent thromboembolic disease.⁹ It is very likely that this patient actually had ‘silent pulmonary embolism’ after her caesarian section and had ‘honeymoon period’ before the first symptom developed.

Certain medical conditions are associated with an increased risk of CTEPH, including previous splenectomy, the presence of a ventriculo-atrial shunt, infected pacemaker, previous and recurrent VTE, chronic venous ulcers, thyroid hormone replacement therapy and malignancy.¹⁰ In this patient, vascular femoral sonography found no deep vein thrombosis (DVT) or other medical conditions associated with CTEPH. Thus, the diagnosis of CTEPH in this patient was nearly missed.

Clinical manifestations and initial non invasive assessment of CTEPH

Signs and symptoms

There are no specific signs or symptoms for CTEPH. The symptoms of CTEPH are indistinguishable from other subgroups of PH, making the diagnosis more challenging.¹ Patients generally present with progressive dyspnoea on exertion, oedema and/or signs of right heart dysfunction including fatigue, chest pain and syncope. Cardiac auscultation may reveal an accentuated pulmonic component to the second heart sound and delayed closure of the pulmonic valve (split P2). Other signs may include a palpable left parasternal heave, a right ventricular S3 or S4 gallop, prominence of the jugular A wave or V wave, hepatojugular reflux, and lower extremity edema.¹¹

In our patient, the symptoms started to occur two years ago and progressing in two months, with worsening functional capacity and recurrent pretibial edema. There was no episode of syncope or exertional angina. At physical examination, there was an accentuated pulmonic component of second heart sound. There were an increased of jugular venous pressure and hepatomegaly in the patient. The symptoms and signs of these patient were highly suggestive of pulmonary hypertension and right heart dysfunction.

Electrocardiography

Common electrocardiogram findings on PH include right atrial enlargement, right axis deviation, and right ventricular enlargement, often with a strain pattern.¹² T wave inversion, representing the repolarization abnormalities associated with right ventricular hypertrophy, is usually seen in the anterior precordial leads and may be mistaken for anteroseptal ischemia.^{11,13} ECG of our patient showed normal sinus rhythm, right axis deviation (RAD), right atrial enlargement (RAE), and right ventricular hypertrophy (RVH) which were compatible with ECG findings on PH. When ECG findings are present, they may be helpful prognostically because the presence of right atrial enlargement has been associated with a 2.8-fold greater risk of death over a 6-year period of observation, and RVH carried a 4.3-fold greater risk of death.¹¹ And in one study, increased P wave amplitude was found to correlate with worse survival.¹² In our case, the presences of RAE and RVH were associated with a worse prognosis for this patient.

Chest X-ray examination

The chest X-ray can help determine the presence and cause of pulmonary hypertension, but the findings are often nonspecific.¹² Findings on the chest radiograph in the early stages of CTEPH may be normal, but as disease progresses, signs that suggest the presence of PH include an enlarged main and hilar pulmonary artery shadows with “pruning” or attenuation of peripheral pulmonary vascular markings and right ventricle (RV) enlargement would be occurred. Central pulmonary artery enlargement often occurs with more advanced disease. The lung fields may be clear, have areas of hypoperfusion (Westermark sign), or have evidence of previous infarction (Hampton hump).¹⁴ The chest radiograph also allows to show findings consistent with underlying

disease processes, such as hyperinflation (COPD), kyphosis (restrictive lung disease), or pulmonary venous congestion (pulmonary venous hypertension, pulmonary veno-occlusive disease, or pulmonary capillary hemangiomatosis).¹² Our patient’s chest X-ray were supportive for the evidence of PH in advanced stage, which showed cardiomegaly with upright apex and prominence of the right heart border (sign of RV enlargement), and prominent pulmonal segment with “pruning” of pulmonary artery. Westermark sign and Hampton hump weren’t present. No sign of lung disease or pulmonary venous congestion from the X-ray make the diagnosis of PH group 3 (due to lung disease) and PH group 2 (due to left heart disease) could be excluded.

Echocardiography

Echocardiography has the advantage of detecting underlying causes or comorbidities, such as left-sided cardiac disease, valvular abnormality, chamber mass, or intracardiac shunt.¹⁵ Findings on echocardiogram that are suggestive of elevated pulmonary pressure include enlarged right atrium and ventricle, RV hypertrophy, globally reduced RV systolic function, pulmonary artery dilatation, interatrial septal bowing to the left, and LV to appear D-shaped. Value of pulmonary systolic pressure and tricuspid regurgitation velocity could be used to determine the possibility of PH diagnosis.^{2,12,16}

Echocardiography of the patient showed enlarged RA and RV, reduced RV contractility (TAPSE 1.6 cm), IVS paradox and LV D-shaped. PA systolic pressure > 50 mmHg (83 ± 5 mmHg) with features suggesting of elevated pulmonary pressure make the diagnosis of PH in these patients are likely (Class I, level of evidence (LOE) B). And in the patient, there was no any sign of left ventricular dysfunction or hypertrophy, left atrium was within normal limit and no other abnormality found in valves beside tricuspid valve make the cause of pulmonary hypertension due to left heart disease in this patient was excluded finely.

Diagnostic modalities of CTEPH

Diagnostic guideline of PH (Figure 9) consist of recommendations based on evidence and concepts that have evolved from formal research and observations that apply to general populations. There have been numerous and evolving versions of diagnostic algorithms for the evaluation of PH but all

algorithms have consistently recommended the use of a radionuclide ventilation/perfusion (V/Q) scan to screen for CTEPH.¹⁷ V/Q scans are particularly useful in determining CTEPH and differentiating CTEPH from other causes of PH. V/Q scanning demonstrated a sensitivity of 90%-100% and specificity of 94%-100% for differentiation between idiopathic pulmonary arterial hypertension (IPAH) and CTEPH.¹⁸ Normal V/Q scan rules out CTEPH and perfusion scans (rather than ventilation) are abnormal in virtually all CTEPH patients.² Recent data showed that 98.7% of patients had abnormal perfusion scans and 19.0% had abnormal ventilation scans.^{1,6} Underutilization of V/Q scans in screening PH invites potential misdiagnosis of PAH. In the recent report from the Pulmonary Arterial Hypertension Quality Enhancement Research Initiative registry in USA, 43% of PAH patients never had a V/Q scan leading up to their diagnosis.¹⁹

CT pulmonary angiography (CTPA) has the advantage of being a non-invasive, cross sectional technique with a spatial resolution close to conventional pulmonary angiography.²⁰ CTPA may reveal organised thrombi lining the proximal pulmonary vessels, abrupt tapering or amputation of vessels or subtle intraluminal fibrous webs may be seen in CTEPH operable patients. Other findings include dilatation of proximal pulmonary arteries and right heart chambers, scarring and a mosaic perfusion pattern.²¹ Contrast-enhanced CTPA may be used as a complementary tool in CTEPH but does not replace the ventilation/perfusion scan.² Eventhough multidetector CTPA had specificity of 99%, it only had sensitivity of 51% in detecting CTEPH.¹⁷ Screening PH with only CT angiogram potentially misses CTEPH.¹

Management of CTEPH

Surgical pulmonary endarterectomy (PEA) has become the gold standard for curative treatment of proximal CTEPH, resulting in a significant reduction of PA pressure and improvement in right ventricular function, quality of life and survival.⁵ For our patients, the PEA has not become a considerable option management since the location of their thrombus was not accessible from CTPA which means the thrombus are either microthrombus or located in the distal arteries.

For medical management of CTEPH, the patient should receive life-long anticoagulation (usually

with oral vitamin K antagonists adjusted to a target INR between 2.0 and 3.0) to prevent *in situ* pulmonary artery thrombosis and recurrent venous thromboembolism.^{1,2} Specific PAH drug therapy may still play a role in CTEPH patients, especially when the surgical therapy is not an option (Class IIB, LOE C). The reason is from the histopathological examination of distal arteries in CTEPH patients reveals vascular changes similar to those in patients with idiopathic PAH and as in PAH.¹⁷ There are several studies and small trials suggesting benefits of endothelin receptor antagonists, Phosphodiesterase type 5 (PDE-5) inhibitors and prostanoid to CTEPH patient, but the data is still limited and requires further studies. At present, no specific medical therapy has been widely approved for CTEPH.^{5,18} Our patients got Warfarin for the oral anticoagulant, diuretics and renin angiotensin aldosterone system (RAAS) blockers for the heart failure and PDE-5 inhibitors as a pulmonary vasodilator. Two months after she was given the medical therapy, her functional capacity was improved from NYHA functional class III to class II. Her congestive symptoms were still occurred infrequently, and they were could be managed by oral diuretic (Furosemide). She was planned to have re-evaluation by echocardiography six months after the medical therapy were started.

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