INDONESIAN HEALTH JOURNAL
https://ihj.rivierapublishing.id/index.php/rp
Volume 5 Number 2, June 2026
P-ISSN: 2963-3044
E-ISSN: 2963-3036

The Effects of Hypoxia in Patients with Atrial Septal Defect (ASD) and Eisenmenger Syndrome: A Case Report

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ABSTRACK

Background: Atrial septal defect (ASD) is a congenital heart disease characterized by an opening in the interatrial septum, allowing abnormal blood flow between the atria. In untreated cases, long-standing left-to-right shunting may progress to pulmonary arterial hypertension and eventually Eisenmenger syndrome, a severe condition associated with chronic hypoxemia, cyanosis, secondary erythrocytosis, and multiorgan complications. Case Presentation: A 46-year-old female patient was referred to Kudungga Regional Hospital with intermittent shortness of breath that worsened over four days, bluish discoloration of the fingers and toes, chest pain, palpitations, tremors, edema, and productive cough. Physical examination revealed cyanosis, clubbing fingers, periorbital edema, oxygen saturation of 74%, cardiomegaly, systolic murmur, and pulmonary rales. Supporting examinations showed biatrial enlargement and right ventricular dilation on electrocardiography, cardiomegaly and pulmonary hypertension on chest X-ray, elevated hemoglobin and hematocrit levels, thrombocytopenia, and severe pulmonary arterial hypertension on echocardiography. Echocardiography also revealed a secundum ASD with bidirectional shunt, right atrial and ventricular dilatation, right ventricular hypertrophy, severe tricuspid regurgitation, and preserved ejection fraction. The patient was diagnosed with secundum ASD bidirectional shunt, severe pulmonary arterial hypertension, Eisenmenger syndrome, bronchopneumonia, and hypoxia-induced tremor. Management included oxygen therapy, fluid restriction, diuretics, antibiotics, mucolytics, sildenafil, digoxin, antiplatelet therapy, and symptomatic treatment. After eight days of hospitalization, the patient showed clinical improvement and was discharged for outpatient follow-up. Conclusion: This case highlights the significant impact of hypoxia in ASD patients with Eisenmenger syndrome, particularly in causing cyanosis, secondary erythrocytosis, hyperviscosity symptoms, and neurological manifestations such as tremor.

Keywords: atrial septal defect; Eisenmenger syndrome; hypoxia; pulmonary arterial hypertension; case report.

INTRODUCTION

Defects in the interatrial septum, or atrial septal defect (ASD), are congenital heart diseases (CHD) in which there is a hole in the interatrial septum, allowing blood flow from the left atrium to the right atrium (Kumar et al., 2018). ASD has a prevalence of 1.6 per 1,000 live births and accounts for 8–10% of all congenital heart diseases (Jain & Dalvi, 2018). One of the unique characteristics of ASD is its slow clinical development, with most children and young adults showing no symptoms. This contributes to late diagnosis, so ASD is generally diagnosed in adulthood, accounting for 25–30% of new diagnoses (Brida et al., 2022).

Patients with congenital heart disease can survive and live into adolescence and adulthood, a condition known as Grown-Up Congenital Heart Disease (GUCH) or Adult Congenital Heart Disease (ACHD). GUCH and ACHD consist of two major groups, namely CHD with natural survival and CHD with a history of interventional therapy, either surgery or percutaneous procedures, during childhood. Research on CHD patterns with natural survival over 20 years in developing countries concluded that ASD is the most common defect, with a relative frequency of 53%, followed by ventricular septal defect/VSD (11%), Tetralogy of

Fallot/TOF (11%), aortic anomaly (7%), pulmonary stenosis (6%), and Ebstein's anomaly (4%). The survival rate of ACHD patients is influenced by various factors, such as birth history, age at diagnosis, complexity of pathology, whether surgery was performed, and, if surgery was performed, whether it was palliative or corrective (Gurvitz et al., 2025).

Atrial septal defects commonly do not cause symptoms. However, some patients with ASD are more likely to experience complications such as atrial arrhythmia, right heart failure, transient ischemic attack, mitral regurgitation, paradoxical embolism, pulmonary arterial hypertension, or Eisenmenger syndrome (Nashat et al., 2018; Puteri et al., 2022).

Pulmonary arterial hypertension (PAH) is the most frequent complication found in patients with CHD, especially those who have a large left-to-right intracardiac shunt (LR shunt), which can eventually cause Eisenmenger syndrome (Rochmat et al., 2024). PAH is defined by a mean pulmonary artery pressure of more than 25 mmHg at rest or 30 mmHg during exercise/activity.

Eisenmenger syndrome (ES) is defined as a process in which a long-standing left-to-right cardiac shunt due to a congenital heart defect eventually reverses into a cyanotic right-to-left shunt (Pradhan et al., 2021). Central cyanosis is the primary clinical manifestation that leads to secondary erythrocytosis and various multiorgan complications, which increase morbidity and affect quality of life. Appropriate follow-up and early diagnosis are necessary to prevent complications promptly (Arvanitaki et al., 2022).

This case report aims to determine the effect of hypoxia on ASD patients with Eisenmenger syndrome so that appropriate management can be provided without causing conditions that worsen the patient's prognosis.

METHOD

Anamnesis and Physical Examination

A 46-year-old female patient was referred to Kudungga Regional Hospital, East Kutai, with complaints of intermittent shortness of breath for 1 month, worsening in the last 4 days, accompanied by bluish discoloration of the fingers and toes, which had been experienced for the past 6 years. Complaints were accompanied by left chest pain radiating to the left arm like stabbing and palpitations that were affected by activity with short attacks and improved with rest. The patient also complained of frequent tingling and shaking in both hands during activity, swelling in the face, abdomen and both feet that came and went, and a cough with phlegm for 4 days. There was no fever, nausea, or vomiting. The patient had a history of complete treatment for pulmonary tuberculosis for 12 months during elementary school and a history of scoliosis. At the age of 30, the patient had been examined by a cardiologist and was diagnosed with a leaky heart, but never continued the examination or treatment.

On physical examination, the patient was found to be weak and appeared cyanotic. Blood pressure was 128/88 mmHg, pulse rate was 89 beats/minute, respiratory rate was 28 breaths/minute, temperature was 36.5 $^{\circ}$ C, and oxygen saturation in all four extremities was 74%. In addition, periorbital edema was found in both eyes and cyanosis in the lip mucosa, which improved with oxygen administration. On lung examination, *rhonchi* and *rales were heard* in both lung fields. On cardiac examination, cardiomegaly was found, the iktus cordis shifted laterally in the sixth intercostal space in the left anterior axillary line, and a systolic murmur in the third intercostal space in the left parasternal line. On abdominal examination,

there was tenderness in the epigastric area and no enlargement of intra-abdominal organs. On extremity examination, there were signs of cyanosis in the fingers and toes, which improved with oxygen administration, clubbing of the fingers, tremors in both hands, and minimal leg edema (Figure 1).

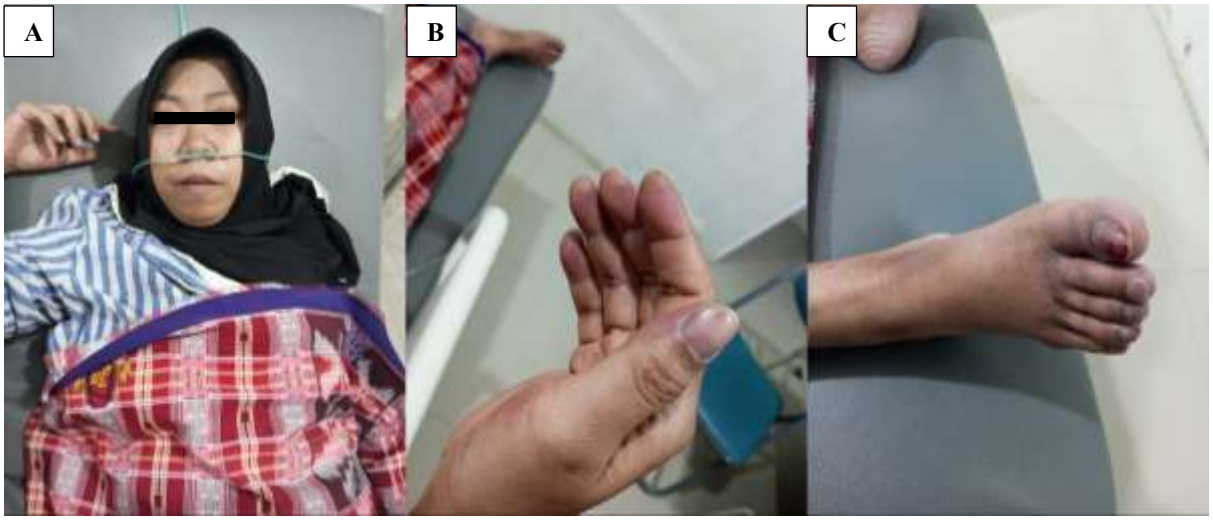

Figure 1. Clinical picture patient. (A) Periorbital edema and cyanosis central. (B) Clubbing or *clubbing finger* accompanied by cyanosis. (C) Edema legs below minimum.

Inspection Support

On examination electrocardiography obtained impression sinus rhythm with *biatrial enlargement* and dilation ventricles right (Figure 2). On the AP Thorax X-ray examination, it was found impression bronchopneumonia, cardiomegaly, pulmonary hypertension, and scoliosis *dextroconvex thoracic vertebra* (Figure 3). On examination laboratory blood obtained Hb 21.6 g/dL, Ht 67.3%, erythrocytes 7,490,000/µL with morphology normochromic normocytic, leukocytes 7,070/µL, thrombocytopenia 84,000/µL, GDS 88 mg/dL, urea 24 mg/dL, creatinine 0.59 mg/dL, SGOT 26 U/L, SGPT 24 U/L, and rate sediment blood 1 mm/hour. On examination of the morphology of the peripheral blood smear of erythrocytes, the impression of normochromic normocytic, spherocytes, fragmentation, stomatocytes, polychromacy was found. On the morphology of the peripheral blood smear of leukocytes, the impression of sufficient numbers was found with a ratio of *polymorphonuclear* (PMN) more than *mononuclear* (MN), severe toxic granulation, severe hypersegmentation, vacuolization, atypical lymphocytes, and *Dohle bodies.* On the morphology of the peripheral blood smear of platelets, the impression of a decreased number was found, the form of *giant cell thrombocytes, mega thrombocytes,* and *micro thrombocytes was found.* Echocardiography revealed severe pulmonary arterial hypertension, a secundum *bidirectional shunt ASD* with a defect diameter of 1.7 cm and an IAS of 4.0 cm, right atrial and ventricular dilatation, right ventricular hypertrophy, *concentric remodeling* of the left ventricle, diastolic left ventricular dysfunction, severe tricuspid regurgitation, and an EF of 79% (Figure 4). Sputum gram stain examination revealed gram- positive coccus bacteria.

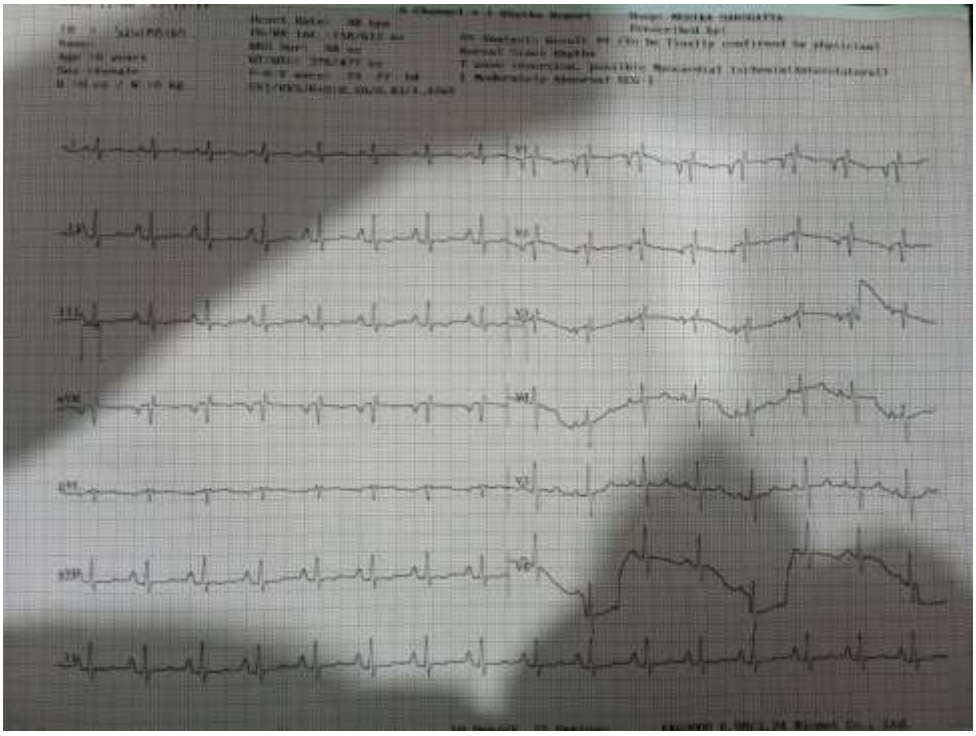

Figure 2. Patient's ECG results obtained impression sinus rhythm with rhythm regular, HR 98 times/ minute, normoaxis, *biatrial enlargement*, and obtained *RV strain* in leads II, III, aVF, V1-V5 which indicates existence dilation ventricles right.

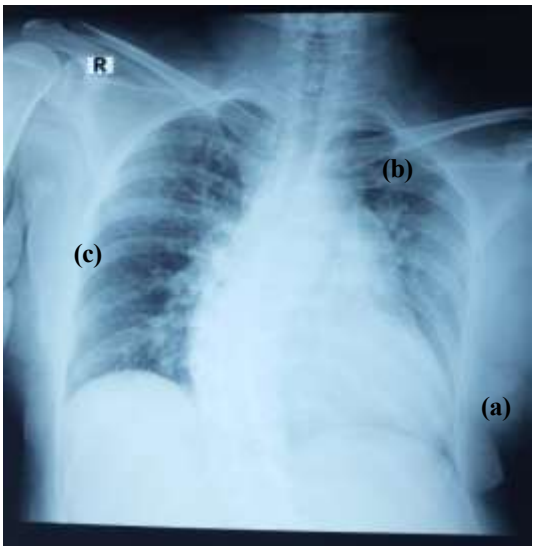

Figure 3. AP Thorax X-ray results obtained description in the form of (a) *rounded apex; (b)* prominent pulmonary cone; (c) *pruning* vessels peripheral pulmonary blood.

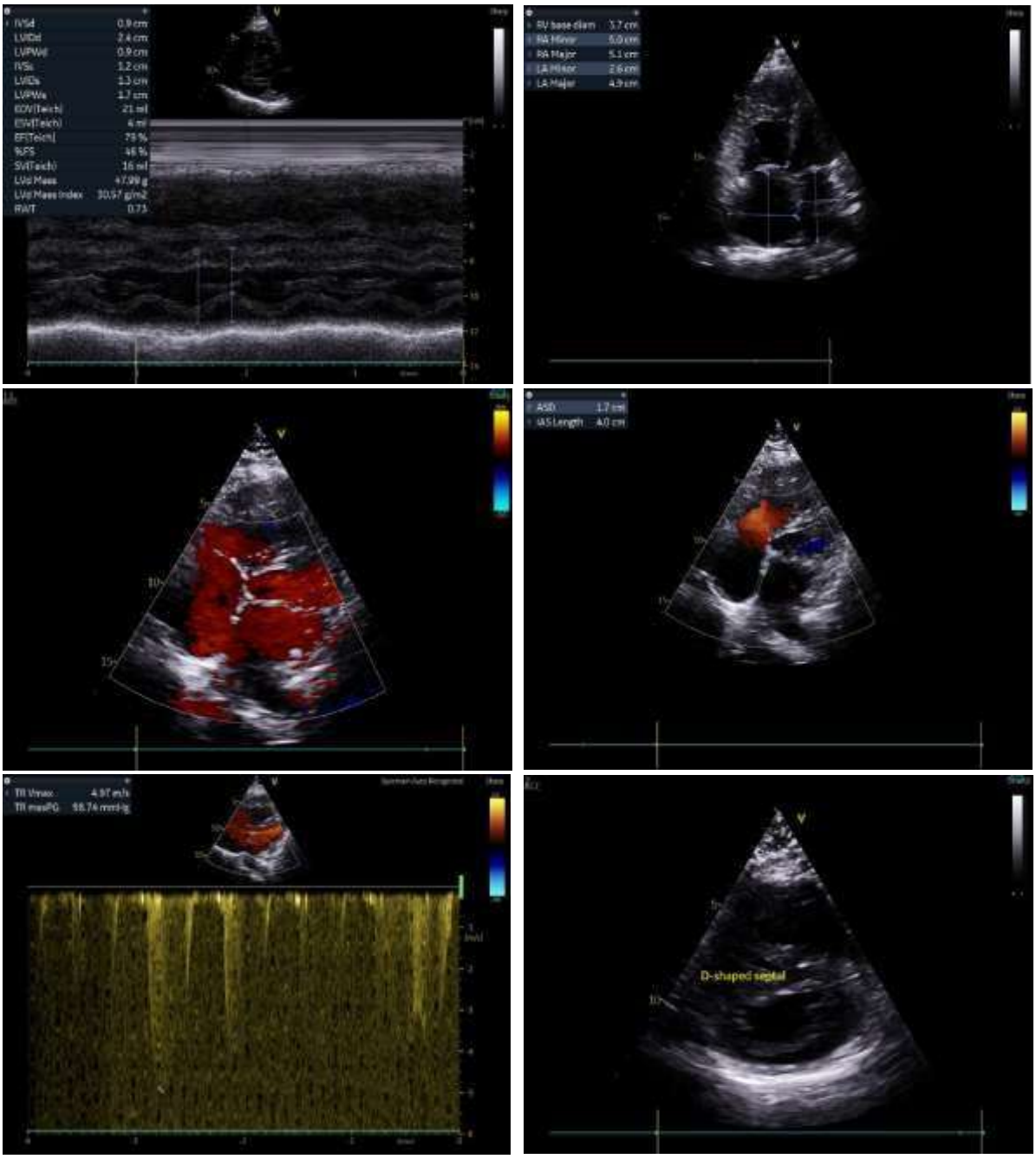

Figure 4. *Doppler echocardiography* results obtained image of 1.7 cm secundum ASD *bidirectional shunt,* regurgitation tricuspid, dilated ventricles right, right atrial dilation, left ventricle *D-shaped,* hypertrophy ventricles right. Impression of severe pulmonary hypertension in a way qualitative with EF 79% and TAPSE 1.6 cm.

Diagnosis and Management

Diagnosis Work in the form of secundum ASD *bidirectional shunt* with severe pulmonary arterial hypertension, Eisenmenger syndrome, bronchopneumonia, and *hypoxic-induced tremor.* Patients treated in the HCU room with governance beginning giving oxygen *simple mask* 6 liters / minute for maintain level saturation above 75%, for overcome hypoxemia. Administration fluid infusion Nacl 0.9% 14 drops/ minute and restriction drink maximum 1.2

liters / day for optimize ventricular *preload* right without cause excess fluid body. Furosemide 1x20 mg orally is given for manage excess fluids and reduce burden ventricles right.

Giving Ceftriaxone injection 1 gram every 12 hours initiated for overcome infection bacteria from results Gram staining of sputum. Mucolytic agents namely N-acetylcysteine 2x200 mg orally and nebulized Lasalcom 1 respul given every 8 hours for increase effort cleaning secretion respiratory tract during patient experience Bronchopneumonia. Additionally, mucolytic agents can suppress coughing and prevent the risk of respiratory tract bleeding. Ranitidine injection 50 mg every 12 hours and antacid syrup 3 times a day orally are given to manage the patient's symptoms.

aim of administering Digoxin 1x0.125 mg orally is for increase contractility ventricles right and control beat heart. On the day third treatment, the dose of oral Sildenafil is increased from 50 mg every 12 hours to 8 hours as response to signs persistent pulmonary arterial hypertension. Nospirinal 1x40 mg orally is given for hinder platelet aggregation in the pulmonary artery with method hinder Work substance vasoactive thromboxane A2, which is considered with notice incident polycythemia and thrombocytopenia in patients.

Trihexyphenidyl 2x2 mg orally is given for manage tremor symptoms in patients, and Mecobalamin 2x500 mcg orally for guard regeneration cell suspected nerve disturbed consequence hypoxia.

After treated for 8 days, the patient show repair clinical and permitted for care road with drug Discharge: Cefixime 2x200 mg orally, N-acetylcysteine 2x200 mg orally, Antacid syrup 3x1 cth orally, Aminophylline 3x100 mg orally, Digoxin 1x0.125 mg orally, Sildenafil 3x50 mg orally, Trihexyphenidyl 2x2 mg orally, and Mecobalamin 2x500 mcg orally. At the time of the first check-up, the patient did not complain of shortness of breath even though the oxygen saturation was 76%.

RESULTS AND DISCUSSION

Eisenmenger syndrome represents the most advanced and severe form of pulmonary arterial hypertension associated with unrepaired congenital heart disease. This condition typically occurs in patients with long-standing left-to-right shunts (*LR shunt*) who have not undergone timely surgical closure or intervention. Initially, these lesions cause fluid *overload* in the pulmonary vasculature due to the lower pulmonary vascular resistance compared to the systemic circulation. Over time, persistently high pulmonary blood flow triggers remodeling of the pulmonary artery wall, characterized by vasoconstriction, media hypertrophy, fibrosis, and in situ thrombosis. This pathological remodeling increases pulmonary vascular resistance, ultimately reversing the shunt to a right-to-left (*LR shunt*). This reversal is driven by structural and functional changes in the pulmonary vasculature, influenced by the imbalanced production of vasoactive substances including endothelin-1, thromboxane A2, prostacyclin, and nitric oxide (Elsaka et al., 2021).

Pulmonary arterial hypertension (PAH) is a disease with a poor prognosis and high mortality rate, defined as a mean pulmonary artery pressure (mPAP) > 25 mmHg at rest and > 30 mmHg during activity. The main characteristic of PAH is progressive pulmonary artery occlusion resulting in a gradual increase in pulmonary vascular resistance (PVR) and pulmonary artery pressure, accompanied by irreversible pulmonary vascular remodeling and the development of right heart failure (RHF) (Yu et al., 2018).

The prevalence of PAH associated with *LR shunt* CHD in developing countries ranges from 1.6-12.5 cases per million adults, with 25-50% of patients having Eisenmenger syndrome. Registry of *Congenital HeART Disease in Adults and Pulmonary Hypertension* (COHARD-PH), a central hospital-based registry in Indonesia found that more than 70% of CHD patients had complications of pulmonary arterial hypertension, most of which were atrial septal defects (ASDs) · PAH in secundum ASDs was closely related to age, defect size, female gender, and the status of the defect not yet closed (Forlemu et al., 2022). Secundum ASDs were the most common defect, accounting for 80% of all ASD cases, where defects occurred in the fossa ovalis. Most ASD patients presented with symptoms in the third or fourth decade of life accompanied by pulmonary arterial hypertension with progression of Eisenmenger syndrome (Malik et al., 2020).

In addition, in a study conducted by Therrien et al., ASD patients with Eisenmenger syndrome had a significantly larger defect size than controls (3.7 ± 1.2 cm compared to 1.9 + 0.7 cm). Similarly, the patient in this case was 46 years old, female, and had a secundum ASD with a defect size of 1.7 cm, so it can be said that the size of the ASD plays a major role in hemodynamics that cause *shunt reversal* and Eisenmenger syndrome.

Typical clinical manifestations of Eisenmenger syndrome include chronic hypoxemia which physiologically increases erythrocyte production (secondary erythrocytosis/ polycythemia) as a compensatory mechanism for inadequate oxygen supply to tissues where low arterial oxygen levels will stimulate the bone marrow through the release of erythropoietin in the kidneys which will increase red blood cell production resulting in an increase in red blood cell mass, hematocrit, and blood viscosity (Alamin et al., 2024). However, this increase in serum viscosity will actually reduce the speed of blood flow and perfusion to tissues and disrupt oxygen delivery to tissues, so that hyperviscosity syndromes such as mucosal bleeding, myocardial ischemia, and neurological symptoms (ranging from headaches, visual disturbances, loss of concentration, paresthesia, muscle weakness, vertigo, seizures, to stroke) (Banerjee & Opotowski, 2024).

In this case, the patient exhibited classic symptoms of systemic hypoxia, including shortness of breath, especially during activity, central and peripheral cyanosis, clubbing of the fingers, and elevated hemoglobin and hematocrit levels on laboratory blood tests. The patient also exhibited symptoms of hyper viscosity syndrome, including ischemic chest pain and paresthesias, particularly in the fingers.

Clubbing of the fingers that occurs in patients is caused by the accumulation of megakaryocytes of platelet cells in the capillaries of the blood vessels of the fingers and periosteum that release *platelet-derived growth factors* and *transforming growth factors*, cytokines and mitogens. This is a manifestation of thrombocytopenia which is explained that there is a direct relationship between oxygen saturation and thrombocytopenia and an inverse relationship with hemoglobin especially after the age of 3 years. According to Edwin et al., it is said that the decrease in platelet production is caused by ineffective thrombopoiesis, short platelet lifespan, and decreased platelet function inversely proportional to the increase in hematocrit that occurs (Destriyana et al., 2019). Another hypothesis says that the right to left shunt that distributes intact megakaryocytes across the blood marrow barrier through the systemic circulation system through the lungs, where megakaryocyte cytoplasm is usually broken down into platelets, so that megakaryocytes are fragmented and limit platelet

production. In fact, the greater the right to left shunt, the lower the systemic arterial oxygen saturation, the higher the hemoglobin, and the lower the platelets (Garcia et al., 2018).

Phlebotomy therapy is not performed even though the patient has a Hb value > 20 g / dL (21.6 g / dL), Ht > 65% (67.3%), accompanied by symptoms of hyperviscosity syndrome considering patient morbidity. In one study, it was found that microcytosis caused by iron deficiency due to inappropriate phlebotomy was the strongest independent predictor for cerebrovascular events (Perhimpunan Dokter Spesialis Kardiovaskular Indonesia [PERKI], 2022). In some conditions such as refractory / severe hyperviscosity syndrome without iron deficiency or surgery will be performed, phlebotomy can be considered, by removing 250-500 ml of blood followed by administration of 250-500 ml of isotonic fluid intravenously.

Given that decreased oxygen saturation has clear implications for brain oxygenation, several studies have investigated motor activity at the motor cortex and spinal cord levels during hypoxia. The results of a study by McKeown et al. suggest that competing processes regulate motor pathway output during involuntary contractions, with neuromodulators, autonomic tone, and afferent feedback being differentially affected by hypoxia in each individual. Prolonged hypoxia can cause irreversible neuronal loss, thus exacerbating neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. Hypoxia significantly affects neuronal function, particularly dopaminergic neurons in the substantia nigra, which are crucial for motor control (Gao et al., 2024; McKeown et al., 2019).

Based on the above data, it can be assumed that the tremors in the patient were induced by systemic hypoxia. Trihexyphenidyl (THP) therapy is a muscarinic antagonist that acts centrally through dopaminergic neurons with a mechanism that may involve increasing dopamine release from presynaptic vesicles and is used to reduce involuntary movements and eliminate tremor (Tarigan, 2025).

The patient in this case had bronchopneumonia confirmed by sputum gram staining. Acute bronchopneumonia infection likely contributed to the worsening clinical condition by increasing oxygen requirements and triggering decompensated heart failure. Adequate treatment of bronchopneumonia improves survival in patients with Eisenmenger syndrome (Khan et al., 2018). According to the Indonesian Pulmonary Infectious Diseases Association (PERKI), patients with pulmonary arterial hypertension are at higher risk of respiratory tract infections, especially pneumonia, which accounts for approximately 7% of deaths in this population. Although there are no definitive studies proving its benefit, current recommendations suggest routine influenza and *Streptococcus pneumoniae vaccination* in patients with pulmonary arterial hypertension as a preventive measure (Perhimpunan Dokter Spesialis Kardiovaskular Indonesia [PERKI], 2021).

As a precursor of reductive glutathione, N-acetylcysteine (NAC) contains an active thiol group, is a commonly used expectorant drug and is able to dissolve mucus and reduce oxidation or inflammation. In addition, NAC can treat pulmonary fibrosis by inhibiting endothelial cell proliferation, reducing collagen formation induced by TGF- β, and regulating gene expression and signal transduction systems, thus playing an important role in improving PVR. Based on research conducted by Yu et al., after receiving NAC treatment, the pulmonary arteries of rats showed a decrease in mean right ventricular pressure (mRVP), mean pulmonary artery pressure

(mPAP), right ventricular hypertrophy index (RVHI), and pulmonary vascular resistance (PVR) compared to controls.

Phosphodiesterase type 5 inhibitors (PDGE5i) such as sildenafil and tadalafil have shown beneficial effects on both functional capacity and pulmonary hemodynamics in patients with pulmonary arterial hypertension associated with CHD, including those with Eisenmenger syndrome (class 1 recommendation). These agents inhibit the breakdown of cGMP, thereby enhancing vasodilatory effects and promoting pulmonary vascular smooth muscle relaxation.

Digoxin is administered from the time a patient is first hospitalized. Traditionally, digoxin has been used as a positive inotropic agent in the management of right ventricular heart failure (RHF), particularly in the setting of right ventricular dysfunction. Previous studies have reported a transient increase in right ventricular ejection fraction after digoxin administration. Furthermore, digoxin remains used in selected cases of chronic right ventricular failure, as adjunctive therapy when signs of low *output* persist or in the presence of atrial arrhythmias (Diller et al., 2021).

As described in *the 2025 ACC/AHA/HRS/ISACHD/SCAI Guideline for Management of Adults with Congenital Heart Disease,* closure of both intracardiac and vascular *shunts* is contraindicated in patients with Eisenmenger syndrome because it may increase perioperative risk as well as the risk of short- and long-term morbidity and mortality (grade 3 recommendation).

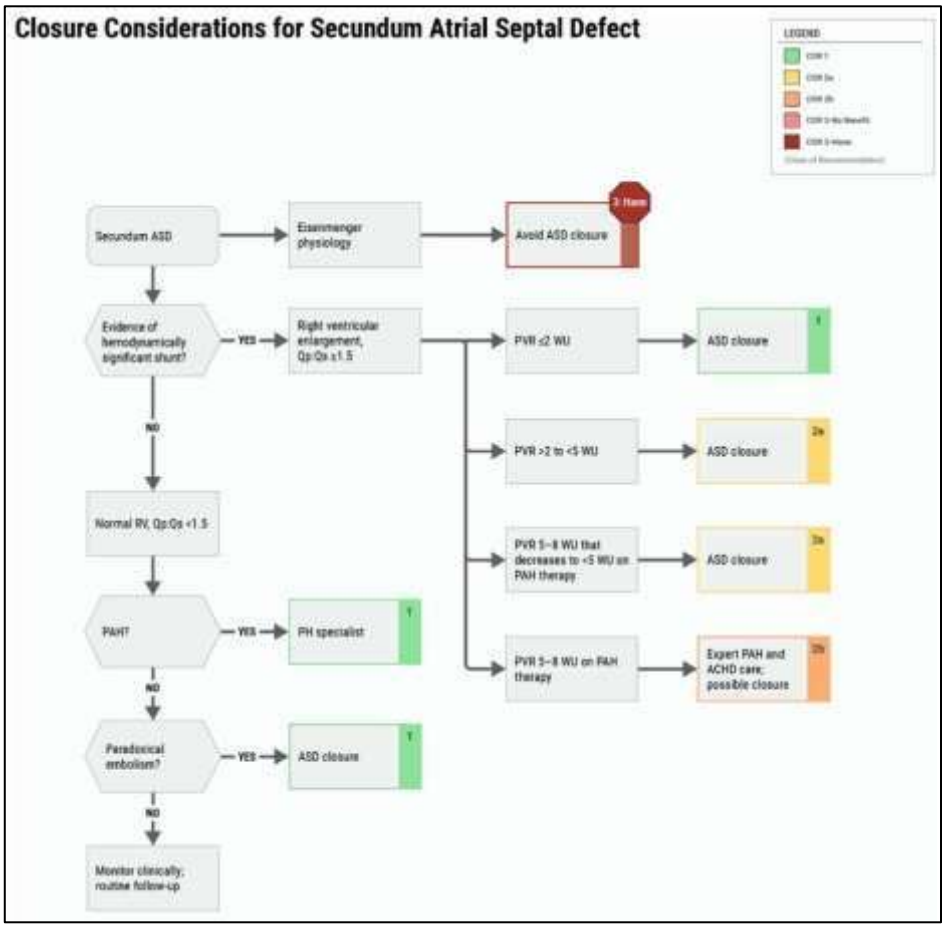

Figure 5. Closure Consideration Curve for ASD Secundum

Based on Figure 5, the patient in this case falls into the class 3 category (red box), which includes patients with Eisenmenger physiology. The presence of a right-to-left *shunt serves as a compensatory mechanism to reduce right ventricular afterload.* Surgical and percutaneous closure would eliminate this compensatory pathway, significantly increasing right ventricular *afterload* and increasing the risk of rapid clinical deterioration or death. Therefore, in accordance with international guidelines and based on the hemodynamic data obtained, closure of the atrial septal defect in this patient is considered contraindicated. Long-term management should focus on patient education, support, and empowerment in managing this complex disease and enabling each patient with Eisenmenger syndrome to achieve their full life potential.

CONCLUSION

This case report emphasizes the importance of early detection and proactive management of ASD to prevent the development of Eisenmenger syndrome, particularly in resource-constrained healthcare systems where delayed follow-up can lead to irreversible pulmonary vascular pathology. A collaborative, multidisciplinary approach is essential to optimize patient outcomes in similar cases.

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