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CHARACTERISTICS OF PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION IN RSUP DR. M. DJAMIL PADANG

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Abstrck*:*Background: *Pulmonary arterial hypertension (PAH) requires a series of physical and supporting examinations to reach diagnosis, recognizing basic characteristics, cardiac structure, and hemodynamic is expected to speed up diagnosis and prevent delays in therapy.* ***Methods:*** *This study is a descriptive observational study with retrospective approach conducted in 45 patients with high probability of PAH through echocardiographic examination.* ***Results:*** *Most people with PAH are women (73.3%) aged 55-64 years (22.2%). The most common chief complaint was shortness of breath (66.7%) with WHO-FC II (47.6%). A total of 68.9% of PAH patients had congenital heart disease. On ECG, most patients did not experience arrythmia (71.7%), with 22.2% patients had right atrial enlargement, 48.9% patients had right axis deviation, 39.2% patients had right ventricular hypertrophy, and 44.4 % experienced right bundle branch block. Chest radiography found cardiomegaly in 64.4% patients. Echocardiographic examination found 45.2% right atrial dilatation and 45.2% right ventricular dilatation, with mean MPAP 52.2±39.4 mmHg, and mean SPAP 79.3±27.6 mmHg. The most frequently used type of therapy was PDE-5 inhibitor (59.5%).* ***Conclusion:*** *Patients enrolled were mostly adult women who had shortness of breath and a history of congenital heart disease. Sinus rhythm was common, but right heart enlargement and RBBB were still found in ECG. Cardiomegaly is also commonly found in PAH patients, and there is an increased mean of MPAP and SPAP on echocardiographic examination. The most commonly used therapy is PDE-5 inhibitor.*

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INTRODUCTION

Pulmonary hypertension (PH) is a condition of increasing average pulmonary vascular pressure that can be caused by various things and with various mechanisms. This condition of increased blood pressure and pulmonary vascular resistance can cause disruption to the lung parenchyma and airway which ultimately reduces the patient's

ventilation function. In addition to impairing respiratory function, pulmonary hypertension can also cause right heart hypertrophy and can end in death due to right heart failure.[1]

The estimated prevalence of pulmonary hypertension is currently 1% of the global population, and 10% in the population over 65 years of age.[2] The life expectancy of patients with pulmonary hypertension at one, three, and five years was 68%, 48%, and 34%, with a median of 2.8 years.[3] Based on clinical pathophysiology and therapeutic considerations, pulmonary hypertension is classified into five groups: pulmonary arterial hypertension, pulmonary hypertension due to left heart failure, pulmonary hypertension due to lung disease or hypoxia, pulmonary hypertension due to chronic thromboembolism and other pulmonary artery obstruction, and pulmonary hypertension with multifactorial mechanisms.[4]

Pulmonary arterial hypertension (PAH) is a disease characterized by progressive connective tissue formation and proliferative changes in the pulmonary arteries leading to increased pulmonary artery pressure and pulmonary vascular resistance that can cause right ventricular heart failure and death.[5] Estimates of the incidence of PAH in the world range from 2.0 to 7.6 cases per million adults annually, while prevalence rates range from 11 to 26 cases per million adults. The prevalence and incidence of PAH in Indonesia is still unknown, but it is thought that lower-middle income countries have higher incidence rates than developed countries. The mortality rate of PAH is still quite high, although there have been many developments in treatment, the survival rate within three years is still recorded at 55-73%. Pulmonary arterial hypertension is subclassified into idiopathic, inherited, drug or toxin-induced, and associated with other diseases (connective tissue disease, HIV infection, portal hypertension, congenital heart disease, and schistosomiasis).[4,6,7]

Pulmonary arterial hypertension report data indicates a greater incidence in females who account for 70-80% of all PAH patients. Based on data from the US National Institutes of Health (NIH) and the US Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL), there is an increasing proportion of women with PAH compared to men. Although the incidence of PAH in women is four times higher than in men, the mortality rate is higher in men. report data indicates a greater incidence in females who account for 70-80% of all PAH patients. Based on data from the US National Institutes of Health (NIH) and the US Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL), there is an increasing proportion of women with PAH compared to men. Although the incidence of PAH in women is four times higher than in men, the mortality rate is higher in men.[8] In addition to an increase in the proportion of females in the PAH patient population, there is also a shift in the age of PAH patients from young adults to older age. Based on NIH data obtained in the 1980s, PAH was most commonly found in young adults, but more recent REVEAL data illustrates an increase in the average age of PAH patients from 36.4 to 47 years of age.[5]

Diagnosis of pulmonary hypertension requires clinical suspicion based on symptoms, physical examination, and investigation of hemodynamic criteria by echocardiographic examination and right heart catheterization. The examinations performed can also determine the prognosis and therapy to be given to patients with pulmonary hypertension.[9] Symptoms of pulmonary hypertension are nonspecific, therefore inappropriate, incomplete, and delayed examination in diagnosing pulmonary hypertension is very common, this delay in diagnosis is reported to occur in 85% of patients at risk for pulmonary hypertension.[10] The incidence of pulmonary arterial hypertension can be said to be rare, but will become a huge burden for the patients.

METHODS

This is a descriptive observational study with a retrospective approach using data sources from medical records of patients with PAH at Dr. M. Djamil Padang Hospital in 2017-2021. The population of this study is all patients registered in cardiovascular department at Dr. M. Djamil Padang Hospital who had been diagnosed with PAH between 2017-2021. The research sample is the entire population that have a high probability level of PAH through echocardiographic examination, and patients with incomplete echocardiographic examination data are excluded. The instruments used in this study are secondary data in the form of patient medical records in the medical records section and registry data of the cardiology and vascular medicine department at Dr. M. Djamil Padang Hospital. The data obtained will be processed through univariate analysis. This study has passed the ethical clearance by Komite Etik Penelitian Kesehatan of Dr. M. Djamil Hospital Padang.

RESULTS AND DISCUSSIONS

Results

This research was conducted in the medical records and registry section of the Department of Cardiology and Vascular Medicine, RSUP Dr. M. Djamil Padang regarding the characteristics of pulmonary arterial hypertension patients in 2017-2021. The research was conducted from January to March using the total sampling method. A total of 58 patients had a high probability of PAH, there were 13 patients' echocardiography data (22.4%) that were incomplete so there were 45 patients who were determined to be research subjects who met the sample criteria.

Table 1. Description of basic characteristics of PAH patients.

Characteristics		Frequency (n)	Percentage (%)
Age	<18 years old	3	6,7
	18 – 24 years old	9	20
	25 – 34 years old	5	11,1
	35 – 44 years old	9	20
	45 – 54 years old	6	13,3
	55 – 64 years old	10	22,2
	65 – 74 years old	3	6,7
Gender	Male	12	26,7
	Female	33	73,3
Main complaint	Breathing difficulties	30	66,7
	Chest pain	10	22,2
	Heart palpitations	2	4,4
	Others	3	6,7
WHO *Functional Class*	WHO-FC I	4	8,9
	WHO-FC II	27	60
	WHO-FC III	9	20
	WHO-FC IV	5	11,1
Blood Pressure	Systolic, mmHg (average±SD)	111,6±22	
	Diastolic, mmHg (average±SD)	70,6±13	
Heart Rate		94,4±18,6	
BMI, kg/m^2 (average±SD)		25,3±3,9	
Type of PAH	Congenital	31	68,9
	Non-congenital	14	31,1

Table 1 shows the most frequently diagnosed cases of PAH patients are in the 55-64 year age group (22.2%). Female has a greater proportion (73.3%) than male (26.7%). The chief complaint most often fell into the breathing difficulties category (66.7%). The WHO-FC level of PAH severity with the highest proportion was WHO-FC II (60%), the average systolic blood pressure of the 45 patients was 111.6 ± 22 mmHg, and diastolic blood pressure of 70.6 ± 13 mmHg. The average BMI for the entire sample was 25.3 ± 3.9 kg/m2. The type of PAH with congenital heart disease accounts for more than half of the total cases of PAH (68.9%).

Table 2. EKG, chest radiography and echocardiography of PAH patients

Characteristics		Frequency (n)	Percentage (%)
EKG image			
Rhythm	Normal	33	71,7
	Atrial flutter	1	2,2
	Atrial fibrillation	6	13
Right atrial enlargement		10	22,2
Right axis deviation		22	48,9
Ventricular Hypertrophy	No ventricular hypertrophy	22	43,1
	Right ventricular	20	39,2
	hypertrophy	9	17,7
	Left ventricular hypertrophy		
RBBB		20	44,4
Chest Radiograph			
	Normal	16	35,5
	Cardiomegaly	29	64,4
	Pulmonary segment dilatation	13	28,8
Echocardiography Image			
Right heart dilatation	No dilatation	8	9,6
	Right atrial dilatation	37	45,2
	Right ventricular dilatation	37	45,2
MPAP (average±SD mmHg)		52,2±39,4	
TRV (average±SD m/s)		4,2±1	
SPAP (average±SD mmHg)		79,3±27,6	

Most patients with PAH did not experience any forms of arrythmia (71.7%), right atrial enlargement was found in 22.2.7% of the sample, right axis deviation was found in almost half of the total sample (48.9%), right ventricular hypertrophy was found in as many as 39.2%, left ventricular hypertrophy 17.7%, and right bundle branch block 44.4% of the total patients. On chest radiography examination, some PAH patients had experienced cardiomegaly which included 64.4% of patients, pulmonary segment dilatation was found in 28.8% of patients. In echocardiography examination, atrial and ventricular dilatation were found in 45.2% patients. The average mean pulmonary arterial pressure (MPAP) of all samples was 52.2 ± 39.4 mmHg, the average tricuspid regurgitation velocity (TRV) 4.2 ± 1 m/s, and the average systolic pulmonary arterial pressure (SPAP) was 79.3 ± 27.6 mmHg.

Table 3. Description of PAH patient therapy

Characteristic		Frequency (n)	Percentage (%)
Therapy	Calcium channel blocker	1	2,4
	PDE-5i	15	33,3
	Prostacyclin analogs	6	13,3
	Prostacyclin analogs + PDE-5	10	22,2
	Others	13	28,8

Administration of PDE-% inhibitor type drugs is the most commonly used drug. PDE-5 inhibitors as monotherapy covers 33.3% of patients, followed by combination of prostacyclin analog therapy with PDE-5 inhibitors in 22.2% of patients, prostacyclin analog monotherapy in 13.3% of patients, and non-specific therapy drugs in 28.8% of patients.

Discussion

The largest age group that experienced PAH was women and the age group 55-64 years. The large number of women who experience PAH can be associated with mutations in the BMPR2 gene, a receptor that functions in cell growth, which occurs more often in women than men. BMPR2 mutations can cause a remodeling process in small pulmonary arteries with the proliferation of myofibroblasts and arterial smooth muscle, thus narrowing the diameter of the vascular lumen and causing high pressure on the blood vessel walls. [11] The high numbers of PAH patients aged between 55-64 years can be associated with cellular aging caused by the buildup of reactive oxygen species (ROS) which in the long term can cause dysfunction. endothelium, causing remodeling and imbalance of vasoactive agents in the pulmonary arteries, causing vasoconstriction and increased intravascular pressure in old age.[12,13]

The types of PAH determined in this research patient data are divided into PAH related to congenital heart disease (CHD) and PAH not related to CHD. The results found were 68.9% were PAH with CHD, and 31.1% were PAH without CHD. The high rate of PAH associated with CHD in this study is supported by the COHARD-PH Indonesia study which found that 77% of CHD patients were suspected of having PH through echocardiography, and 66.9% were found to have PAH through right heart catheterization. [14] Causes of PAH related with CHD depending on the type of abnormality that occurs in the patient, PAH in CHD patients can occur due to a left to right shunt, which causes increased pressure on the right side of the heart. Increased pressure on the right side of the heart will also have an impact on the pulmonary arteries which, if it occurs over a long period, causes endothelial dysfunction, and increased vascular resistance in the pulmonary blood vessels which ultimately causes pulmonary arterial hypertension. The types of abnormalities that are often found are ventricular septal defect (VSD), atrial septal defect (ASD), and persistent ductus arteriosus (PDA).[15]

Most of the PAH patients in this study sample did not experience arrythmia, but there were several cases of atrial fibrillation in 13% of cases. Atrial fibrillation might occur due to increased pulmonary vascular resistance (PVR) which can cause chronic right ventricular pressure overload. This excess pressure in the right ventricle results in tricuspid regurgitation which is followed by an increase in right atrial pressure. Increased pressure in the right atrium that persists over a long time induces atrial dilatation and electrophysiological remodeling which can predispose to atrial arrhythmias. [16]

Findings of right ventricular hypertrophy in PAH patients at RSUP Dr. M. Djamil Padang in 2017-2021 reached 39.2%. Right ventricular hypertrophy is one tool that can

determine the prognosis of PAH patients, PAH patients with findings of right ventricular hypertrophy have a 4.3 times greater risk of death than patients without findings of right ventricular hypertrophy.[17] Right ventricular hypertrophy is a form of initial adaptation of the heart to increased load on the pulmonary arteries to reduce pressure on the heart wall by increasing muscle contractility and increasing heart wall thickness. This initial inotropic response is known as homeometric adaptation, where the ventricular response is an increase in myocardial inotropy to restore stroke volume without changing the geometry of the heart chambers.[18]

Right bundle branch block (RBBB) is often found on ECG examinations at the time of diagnosis of PAH patients (44.4%). Right bundle branch block may occur due to structural changes in the heart in PAH patients which cause changes in pressure, and infarction in the tissue which can damage or stretch the right bundle of the heart, this can disrupt electrical activity in the His-Purkinje system, especially in the right bundle so that RBBB occurs. [19]

Echocardiography examination of PAH patients found quite a lot of cases of enlargement of the right atrium and ventricle, namely 45.2%. Right ventricular dilatation is a further response to right ventricular hypertrophy due to increased load on the pulmonary artery. If homeometric adaptation fails and can no longer improve systolic function, right ventricular dilatation is the only effective response to increasing afterload. This form of adaptation is called hetero-metric adaptation, where an increase in end-diastolic volume will also increase in stroke volume, thereby reversing the stroke volume and maintain cardiac output.[18] Right atrial dilation can increase due to the progression of pulmonary hypertension which causes tricuspid regurgitation which causes blood to flow back into the atrial chamber and increases pressure in the right atrial chamber. An increase in right atrial pressure over a long period will cause dilatation of the right atrial chamber.[20]

The mean MPAP in this study was 52.2 ± 39.4 mmHg (normal: 4 – 12 mmHg), SPAP was 79.3 ± 27.6 mmHg (normal: 18-25 mmHg), and TRV was 4.2 ± 1 m/s (cut off value 2.55 m/s under normal condition). Systolic pulmonary arterial pressure is related to the pulsation components of the blood vessels, including the ejection characteristics of the right ventricle and the elasticity of the proximal pulmonary arteries, impaired pulmonary artery elasticity due to vasoconstriction or lesions on the walls of the pulmonary arteries in PAH patients will cause an increase in SPAP from the normal range of 18-25 mmHg.[21] Meanwhile, the cause of tricuspid regurgitation in PAH, without any organic disease of the tricuspid valve, is due to annular dilation of the tricuspid valve and dilatation of the right ventricle which causes changes in the position of the papillary muscles which are responsible for preventing leaks in the valves, resulting in tricuspid regurgitation.[2]

The type of drug most widely used as specific therapy for PAH patients is PDE-5 inhibitor as monotherapy which includes 33.3% of patients, followed by combination prostacyclin analog therapy with PDE-5 inhibitor in 22.2% of patients, prostacyclin analog monotherapy which includes 13.3%, and CCBs were only used by 1 patient (2.4%) as specific therapy for PAH. The high use of PDE5i, especially the sildenafil type, is more widely used because its use is considered a cost-effective option compared to beraprost which is a prostacyclin in functional classes II and III in Indonesia. Even though the price of sildenafil is higher than beraprost, generic sildenafil is more widely used because it is considered to have better value for money. Sildenafil also received approval from the Food and Regulatory Agency (BPOM) to be designated as a medication for patients with PAH indications in Indonesia and has become part of the national formulary which can receive reimbursement through the universal healthcare coverage program in Indonesia.[23]

This research is a retrospective observational study that only uses medical records as a source of research data, so the suitability of examination results at the time of diagnosis is not always correct. Some incomplete medical records also require researchers to complete data requirements through interviews, which can cause data accuracy to decrease, as well as causing several variables for special purposes not to be implemented.

CONCLUSSION

Patients with PAH are predominanty in the 55-64 year age group, with the majority of women. The main complaint that is most often found is breathing difficulties with WHO FC II. The average body mass index is categorized as overweight. The most common type of PAH is the type that is related to congenital heart. Based on electrocardiographic images, most patients did not experience any type of arrythmia, but right axis deviation and RBBB were commonly found in PAH patients. Cardiomegaly was frequently found in PAH patients through chest X-ray, with enlargement of the right atrium and ventricle through echocardiography. The drug most commonly used in PAH patients is the PDE-5 inhibitor group as monotherapy.

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