The Challenge in Diagnosis and Current Treatment of Chronic Thromboembolic Pulmonary Hypertension

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ABSTRAK

Chronic thromboembolic pulmonary hypertension (CTEPH) saat ini masih mengalami underdiagnosis dan sebagai konsekuensinya juga undertreatment dalam praktik klinis. Kurangnya modalitas diagnosis dan ketersediaan modalitas tata laksana terutama di negara berkembang membuat diagnosis CTEPH sulit ditegakkan. Namun dengan indeks kecurigaan klinis terhadap CTEPH yang tinggi akan menuju ke diagnosis yang tepat dan terapi yang benar sehingga dapat menurunkan angka kesakitan dan kematian. Bila tidak diterapi, angka kesintasan rerata 6,8 tahun dan angka kematian dalam tiga tahun dapat mencapai 90%. Patofisiologi, diagnosis dan tatalaksana CTEPH perlu untuk diperkenalkan kepada para internis dan dokter pelayanan primer, sehingga outcome pasien dapat lebih baik.

Kata kunci: *chronic thromboembolic pulmonary hypertension, diagnosis, hipertensi pulmoner.*

ABSTRACT

Chronic thromboembolic pulmonary hypertension (CTEPH) is currently underdiagnosis and consequently undertreatment in the clinical practice. A deficient in diagnostic modality and treatment availability especially in developing countries makes the CTEPH diagnosis unlikely to confirm. However, high index of clinical suspicion of CTEPH will lead to proper diagnosis and correct treatment with significant reduction in morbidity and mortality. Left untreated, the mean survival time is 6.8 years and the three year mortality rate may be as high as 90 %. The pathophysiology, diagnosis and treatment of CTEPH are necessary to be shared among internists and primary care physicians, in order to improve the overall outcome of the patients.

Keywords: *chronic thromboembolic pulmonary hypertension, diagnosis, pulmonary hypertension.*

INTRODUCTION

Pulmonary hypertension is defined as an elevated mean pulmonary arterial pressure (mPAP) ≥25 mmHg in resting condition measured by invasive right heart catheterisation.[1] Current grouping of pulmonary hypertension have classified five groups of this disease, as follows: (1) Group 1 is pulmonary arterial hypertension, (2) Group 2 is pulmonary hypertension due to left heart disease, (3) Group 3 is pulmonary

hypertension due to lung disease and/or hypoxia, (4) Group 4 is chronic thromboembolic pulmonary hypertension (CTEPH) and other pulmonary artery obstruction, and (5) Group 5 is pulmonary hypertension with unclear mechanism and/or multifactorial origin.[1] As a clinical entity, however, CTEPH is currently underdiagnosis and consequently undertreatment. This fact may be due to lack of diagnosis modality and treatment availability especially in developing countries.

The prevalence of CTEPH is 3.2 cases per million person and the incidence is 0.9 cases per million person. Most CTEPH cases are preceded by episode of acute pulmonary embolism (75%) and deep veins thrombosis (56%), indicating that CTEPH is persistent thromboembolic state.[2] The incidence of CTEPH after an episode of acute pulmonary embolism varies between 0.1% and 9.2%.[2] This large range of reported CTEPH incidence following acute pulmonary embolism reflects the referral bias, difficulty in early diagnosis from several hospitals and variation of standardised diagnostic method.[2] However, a quarter of CTEPH patients does not experience previous acute pulmonary embolism and there is no direct association between acute pulmonary embolism with CTEPH.[2] Left untreated, the mean survival time is 6.8 years and in CTEPH patients with mean pulmonary artery pressure (mPAP) >50 mmHg the three year mortality rate is 90%.[3]

To lead the diagnosis of CTEPH, the high index of clinical suspicion is required and followed by several diagnostic modalities. The risk factors of CTEPH have been identified to aid the direction of diagnosis. The risk factors are splenectomy, indwelling catheters, indwelling pacemaker leads, infected ventriculoatrial shunts, levothyroxin treatment, malignancy, chronic inflammation condition such as osteomyelitis, inflammatory bowel diseases, systemic lupus erithematosus and antiphospolipid syndrome, and staphylococcal infection.[2] Since several treatment options are currently available and evolving significantly, internists and primary care physicians need to be familiarised with CTEPH in order to improve the overall outcome of the patients. This review intends to introduce the pathophysiology, the challenge in diagnostic modality and the current treatment strategy for CTEPH.

CTEPH – THE PATHOPHYSIOLOGY

The main pathology finding in CTEPH is an occlusive pulmonary arterial remodeling as a consequence of persistent thromboembolism in major pulmonary arteries.[1] In the affected artery, usually the elastic type pulmonary arteries such as major artery, lobar artery, segmental artery and subsegmental artery, organized chronic thrombi or emboli obstruct the blood flow which cause reduced distal perfusion.[1] The term chronic means that the obstruction takes place more than three months even after effective anticoagulation strategy.

The exact mechanism of the genesis of CTEPH is currently not fully understood. The reproduction of CTEPH in experimental cellular and animal model has been proven difficult, therefore hindering the elucidation of basic molecular mechanism behind CTEPH. In human study, the fibrotic transformation from pulmonary artery thrombus is a hallmark of CTEPH.[2,3] The intraluminal fibrotic tissue obstructs pulmonary artery blood flow. Abnormal trombus resolution and subsequent vascular remodeling with occlusive fibrotic transformation is currently suggested as an explained pathogenesis of CTEPH.[4] The schematic represantation of the pathophysiology of CTEPH is depicted in **Figure 1**.

In most cases, thrombi will disappear from blood circulation through haemostatic processess which includes thrombus degradation and organisation. During resolution of thrombi, leucocyte recruitment and angiogenesis have an important role.[4] In early phase, neutrophils and monocytes were recruited in the ongoing organised thrombi, in which monocytes express and secret chemoattractant mediator.[4] Several inflammatory markers are increased in plasma and thrombotic tissue in CTEPH, such as C-reactive protein (CRP), tumour necrosis factor-alpha and MCP-1.[4,5] The receptor of CRP, i.e. LOX-1 is highly expressed in the cells isolated from CTEPH specimens indicating the inflammatory thrombosis is prevailing in the

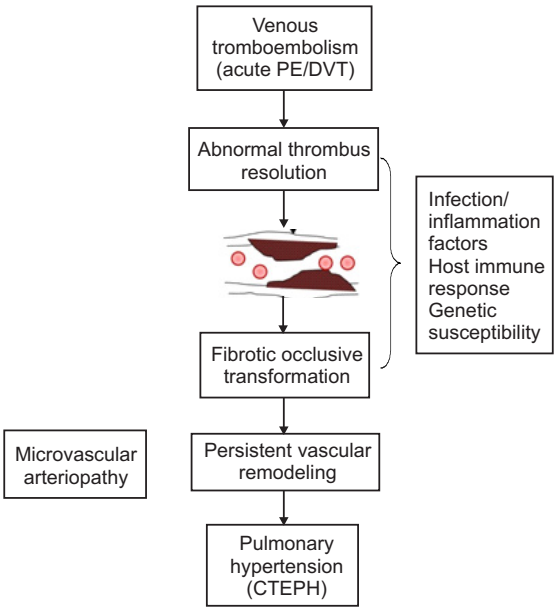

Figure 1. Schematic representation of pathogenesis of CTEPH[4]

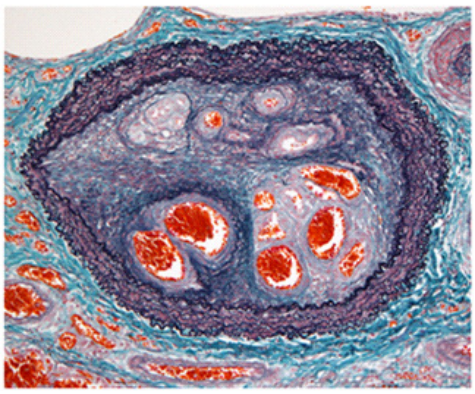

Figure 2. The pathologic appearance of organized thrombi in CTEPH of the pulmonary artery, showing the luminal narrowing alongside with organized thrombi. The thrombi contained fibrous intimal hyperplasia scattered by recanalized channels (Taken from: Ogawa and Matsubara, 201523 with permission)

pathogenesis of CTEPH.[4,5] Host immunology and genetic susceptibility are thought to be the predisposing factor to develop persistent occlusive thrombus.[4]

Surgery specimen shows that CTEPH lesion is similar to atherosclerotic lesion.[5] There are two types of intimal lesion from the surgery specimen, as follows: (1) fibrous plaque with angiogenesis and (2) atherosclerotic plaque composed of cholesterol, macrophage, T lymphocyte and calcium.[5] Pathologic examination reveals several grades of thrombi remodeling and organisation with degrees of inflammation and types of cells mixed with organised and thickened intima in which scattered by collagen, calcification and atherosclerosis.[5,6] **Figure 2** shows an example of CTEPH specimen of pulmonary artery.

Angiogenesis in CTEPH depends on vasa vasorum originates from systemic circulation of bronchial artery. The collateral of bronchial artery is opened in response to occlusion in pulmonary artery. Positive angiogenesis regulator is increased during thrombus organisation processess. Activated endothelial cells migrate and penetrate occlusive thrombus starting recanalisation and remodeling.[4] In addition to major pulmonary artery, small distal pulmonary vessel may undergo similar remodeling which contribute to the pathogenesis of CTEPH. Clinical facts support the suggestive pathogenesis, as follows: (1) lack of association between increased pulmonary artery pressure and obstruction of pulmonary vascular examined by angiography, (2) progression of pulmonary hypertension despite absence of recurrent emboli, (3) persistent high pulmonary vascular resistance in CTEPH if compared with acute pulmonary embolism with similar degree of vascular obstruction.[5]

Vascular lesion in CTEPH involves two vascular components, i.e. major artery or macrovascular and small artery or microvascular.[4] Organised thrombus which strongly attach to the medial layer of elastic type pulmonary artery is the main pathology in macrovascular lesion. These thrombus are scattered, replace normal intimal layer and express excessive plasminogen activator inhibitor type 1 (PAI-1) which hinder fibrinolysis activity of adjacent normal endothelial cells.[4] Collateral vessels from broncial artery vascularise the area originally nurture by obstructed vessel and therefore, maintain the organised thrombus.[2] Microvascular lesion includes distal muscularisation, concentric fibroelastosis in intimal layer, eccentric intimal fibrosis, medial hyperthrophy and plexyform lesion.[2,4] These arteriopathies are due to sequelae of endothelial dysfunction, abnormal proliferation of vascular smooth muscle cells

and endothels, fibroblastic migration, smooth muscle cell migration, reduced smooth muscle cells apoptosis and in situ thrombosis.[4]

There are four type of CTEPH pathologies according to Jamieson classification, i.e. type I is thrombus in major vessels and clearly seen in the major pulmonary artery, it constitute 12% of cases, type II is no thrombus in major vessels, there is intimal thickening with webs in bifurcations of lobar arteries, it constitute 38% cases, type III is thrombus and vascular lesion in distal vessels and localised in segmental and subsegmental branches, it constitutes 39.3% cases and type IV is no proven thromboembolic material despite surgery exploration and intimectomy.[2]

CTEPH – THE DIAGNOSIS

Guideline in Diagnostic Flow

In the early stage of disease, the signs and symptoms are not specific or even undetected. In the later stage, the signs of right heart failure are clearly seen. The clinical picture of CTEPH is in somedegree similar to acute pulmonary embolism or idiophatic pulmonary artery hypertension.[1] High index of suspicion is necessary to lead for working up the diagnosis of CTEPH. To diagnose CTEPH, the signs and symptoms should be existed after 3 months following the effective anticoagulants in order to differentiate with subacute pulmonary embolism.[1] Around 75% CTEPH patients have previous history of acute pulmonary embolism and 56% have previous deep vein thrombosis.[7]

The guideline of European Society of Cardiology (ESC) published in 2015 provides an algorithm to diagnose CTEPH. The presence of pulmonary hypertension is detected firstly by non invasive transthoracal echocardiography. Moderate to high probability of pulmonary hypertension from echocardiogram prompts further diagnostic follow up. The ventilation/perfusion lung scan (V/Q scan) is the firstline imaging modality to diagnose CTEPH. It gives 96-97% sensitivity and 90-97% specificity.[1] Multidetector CT pulmonary angiography (MDCTPA) is next imaging modality to confirm the diagnosis of CTEPH after V/Q scan. Both V/Q scan and MDCT pulmonary angiography have high sensitivity, specificity and accuracy to detect and diagnose CTEPH. Invasive procedure, such as right heart catheterisation and/or selective pulmonary artery angiography, is recommended for the final diagnostic step (**Figure 3**).[1]

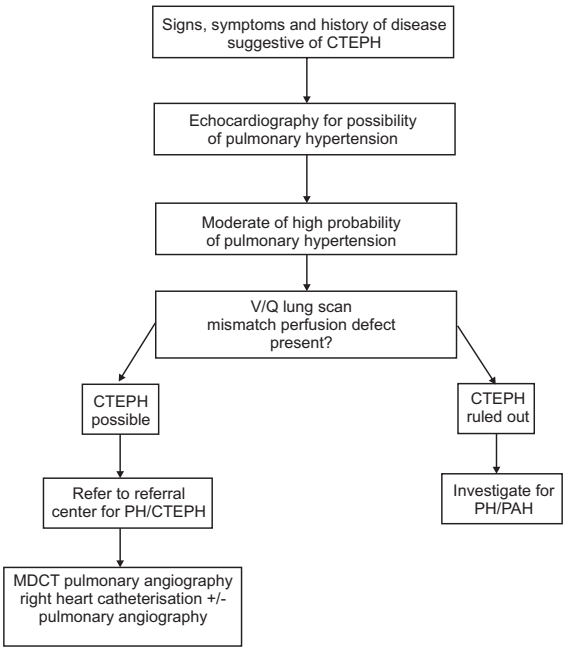

Figure 3. Diagnosis flow of CTEPH based on European Society of Cardiology guideline 2015[1]

Routine Examination

Routine examination such as chest X-ray in the early disease is normal. In the progressing disease, the signs of pulmonary hypertension can be detected in chest X-ray, i.e. major pulmonary artery dilatation, cardiomegaly and oligemia. Lung function test may be useful to exclude primary lung disease which may be an underlying cause of pulmonary hypertension. Laboratory examination does not have value to diagnosis CTEPH. Electrocardiogram supports the presence of pulmonary hypertension although its sensitivity and specificity is not adequate (55% and 70%, respectively). Most CTEPH patients have electrocardiogram patterns of right axis deviation (50%) and negative T wave in V1-V4 precordial leads (62%).[8]

Echocardiography

Transthoracal echocardiography examination is the first step to diagnose pulmonary hypertension.

It estimates the pulmonary artery pressure with continuous wave Doppler examination. The effect of pulmonary hypertension on the heart can be detected such as right atrial and right ventricle dilatation, right ventricle systolic function and left ventricle function.[1,8] The presence of pulmonary hypertension signs in echocardiogram should be sought by experience echocardiographers, such as the alteration of LV geometry (LV-D shape), RV geometry (RV and RA dilatation with tricuspid valve regurgitation) and the Doppler measurement of pulmonary artery pressure (mean or systolic pressure).

Ventilation Perfusion Lung Scan (V/Q Lung Scan)

V/Q lung scan has negative predictive value of >98%, sensitivity of 96% and specificity of >90% to detect CTEPH.[8] This value gives superiority of V/Q lung scan to rule-out CTEPH if the V/Q lung scan examination is normal. V/Q lung scan is an initial screening to diagnose CTEPH before proceeding to MDCTPA which have less sensitivity to detect CTEPH.8 Positive finding in V/Q scan suggestive CTEPH indicates the working diagnosis of CTEPH, however other condition may cause similar finding such as pulmonary venoocclusive disease.[9] Easier interpretation and highly objectivity of V/Q lung scan makes it useful to screen CTEPH in the early phase of disease. V/Q lung scan has higher sensitivity to detect CTEPH in the more distal vessels.8 Furthermore, it only needs small amount of radiation, no intravenous contrast agent required and cost effective.[10]

The characteristic of CTEPH in V/Q lung scan is wedge-shaped perfusion deficit with normal ventilation pattern. Similar pattern is found in mediastinis fibrosa dan pulmonary venoocclusive disease.[9] Other patterns may indicate other diseases, such as total loss of regional perfusion in lung carcinoma or vasculitis and small peripheral non-segmental perfusion defect in pulmonary arterial hypertension. The distinguished pattern of CTEPH in V/Q lung scan prompts the confirmatory imaging modality with MDCTPA.[8,11]

Computed Tomography Pulmonary Angiography

Multidetector CT pulmonary angiography (MDCTPA) is an imaging modality to confirm CTEPH after positive or non conclusive result of V/Q lung scan. The 3D multiplanar reconstruction can be accomplished to visualize the branches of pulmonary arteries. Resolution of imaging is precise (0.5 mm) in whole field therefore allowing quick acquisition and short breathholding time (5-10 seconds). MDCTPA with 64-detector has 97% sensitivity and 95% specificity to detect lobar CTEPH and 86% sensitivity and 93% specificity to detect segmental CTEPH. Higher 320-detector have greater sensitivity of 98% and specificity of 97% in lobar CTEPH and sensitivity of 94% and spesificity of 95% in segmental CTEPH.[12,13]

The characteristic of CTEPH in MDCTPA is mosaic perfusion defect in lung parenchym, organised eccentric thrombus surrounding proximal pulmonary vessels, broncial arteries opened collateral, various size of lobar and segmental arteries, total or partial obstruction of pulmonary artery, dilatation of main pulmonary artery, right ventricular enlargement, filling defect, irregular vessel thickening, stenosis of pulmonary vessel and intraluminar webs and bands appearances.[14] Furthermore, other examination can be performed with MDCTPA such as assessment of pulmonary and bronchial vessel anatomy to determine the operative procedure, evaluate perioperative risk, evaluate the mediastinum, lung and aorta and examine right ventricle structure.[8]

Right Heart Catheterisation and Pulmonary Angiography

Right heart catheterisation is performed to confirm the positive or inconclusive result on V/Q lung scan. The haemodynamic data can be evaluated with right heart catheterisation. The haemodynamic parameter is predictor of prognosis and risk for patients candidate to be performed pulmonary endarterectomy (PEA).14 The definitive diagnosis of CTEPH by right heart catheterisation is the finding of precapillary pulmonary hypertension (mPAP $\geq$25 mmHg, PCWP $\leq$15 mmHg and PVR >2 Wood units) in patients with chronic thromboembolic obstruction or organised thrombus.[8]

Right heart catheterisation is accomplished concomitantly while performing selective pulmonary angiography. Right heart

catheterisation and selective pulmonary angiography is the gold standard to confirm CTEPH. Selective pulmonary angiography is performed to determine the extent and distribution of CTEPH, such that the eligibility of PEA can be selected. Typical angiographic defect in CTEPH is the evidence of organisation and recanalisation over thromboembolic material. These evidence are webs or bands appearance, intimal irregularity, sudden narrowing, proximal obstruction and pouch defect.[5,15]

CTEPH-THE TREATMENT

Guideline in Treatment

The guideline of CTEPH treatment from European Society of Cardiology (2015) confirms three modalities, i.e. (1) surgery, (2) drugs and (3) intervention.1 The surgery is performed by pulmonary endarterectomy which has become main modality to cure CTEPH. The drugs used in CTEPH are the combination of oxygenation, diuretics and anticoagulant. Patients, whether treated by drugs or by surgery or intervention, must take lifelong anticoagulant to prevent the recurrence thromboembolism and the progression of thombus in pulmonary arteries. Warfarin is the anticoagulant most commonly prescribed in CTEPH and the international normalized ratio (INR) value is the indicator of acceptable anticoagulation state in the target range of 2 to 3.1 Riociguat is novel drug with proven efficacy to treat CTEPH. The intervention procedure is recommended for patients whom PEA can not be done or the risk of operation is high. Balloon pulmonary angioplasty is the intervention procedure currently develop in selected patients (**Figure 4**).[1]

Pulmonary Endarterectomy

Pulmonary endarterectomy (PEA) is procedure of choice to remove pulmonary artery obstruction in CTEPH. PEA procedure is delicate and complicated. A strict post operative management is mandatory. PEA procedure is curative for most patients. It is effective and has high success rate if performed with adequate patient selection, smooth operation technique and good post operative management. The mortality rate in the center with experience team is less than 5% (2.2%-4.7%).[3]

Several criteria to select patients candidate for PEA is important to increase success rate and reduce mortality rate. The criteria generally accepted are patients with WHO functional class II-IV, reachability of thrombus by surgery

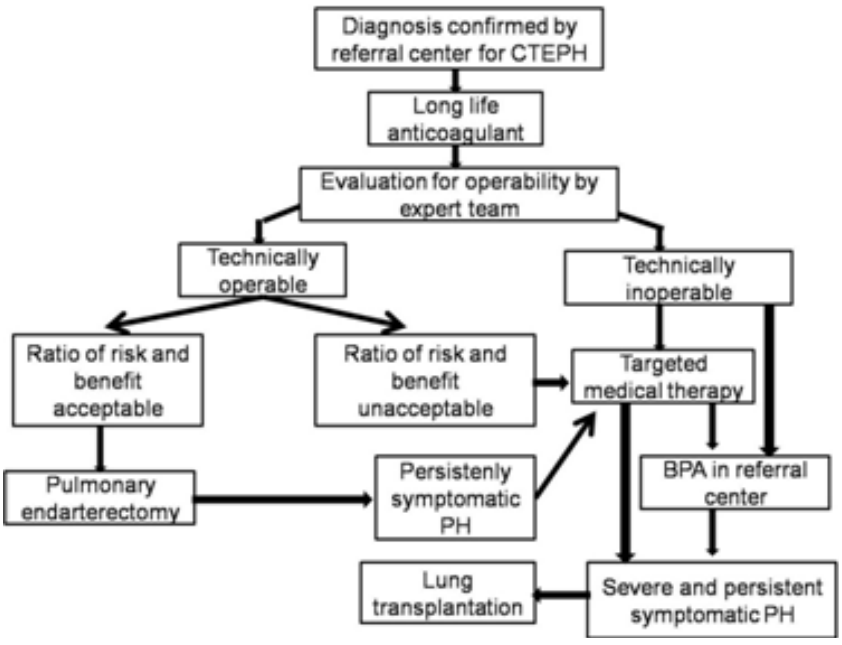

Figure 4. Treatment flow for CTEPH based on European Society Cardiology Guideline 2015[1]

in main, lobar and segmental pulmonary artery, proportional PVR value and right ventricle function.[1,3] Other consideration is comorbity which may affect peri operative and post operative risk.

The PEA procedure involves the removal of all obstructive thromboembolic material from pulmonary artery including intimal and superficial medial layers. The goal is to reduce PVR, improve right ventricle function and increase ventilation/perfusion matching.16 Based on Jamieson classification, PEA is more effective in lesion type 1 and 2. In lesion type 3, an experience center can perform the PEA with satisfactory result although persistent pulmonary hypertension may ensue.[3]

Table 1. Operability with PEA in CTEPH based on Jamieson criteria[3]

Type	Explanation	Operability
1	Clot in main vessel Clearly identified while opening pulmonary artery (20 % cases)	Operable
2	Only intimal thickening is seen Endarterectomy field seen early in main, lobar or segmental vessels (70 % cases)	Operable
3	Distal disease PEA limited in the branches of segmental and subsegmental vessels (10 % cases)	Operable
4	Intrinsic small vessel disease Secondary thrombus may occur due to stasis	Inoperable

Drugs Treatment

All patients with CTEPH must be given lifelong anticoagulant treatment with vitamin K antagonist, warfarin, in order to prevent in situ pulmonary artery thrombosis and recurrent venous thromboemboli.[1] The target range for effective anticoagulant state is the INR value of 2 to 3.1 However, currently no randomised controlled trial for anticoagulant in CTEPH patients. Although PEA is curative treatment for CTEPH, around 35% patients still experience persisten or recurrent CTEPH after surgery. In these such population, targeted therapy with drugs is strongly indicated. Several non randomised small studies indicate the improvement of clinical and functional class of CTEPH patients after being treated with prostanoid (intravenous epoprostenol, inhaled iloprost or subcutaneous treprostinil).[17] BENEFit trial compared bosentan, a dual endothelin receptor antagonist, and placebo in 157 patients with in-operable or persistent/recurrent CTEPH for more than 16 weeks. It showed that bosentan can not improve 6 minute walking distance, WHO functional class and time to clinical worsening.18 Based on this trial, bosentan is not recommended to treat CTEPH although for idiopathic pulmonary artery hypertension it is proven beneficial. The trial with other endothelin receptor antagonist, macitentan, for CTEPH is on going.[19]

Riociguat is novel drug from the soluble guanilat cyclase (sGC) stimulator class. It has dual action, i.e. to increase sGC sensitivity from endogenous nitric oxide and elevate sGC activity independently from nitric oxide.[20] The net effect of these properties are increased vasodilatation, antifibrotic activity, antiproliferative action and antiinflammation. The CHEST trial involving 261 patients in operable CTEPH or patients with persistent/recurrent CTEPH after PEA randomised for riociguat and placebo. It showed more efficacy in riociguat arm as compared to placebo.[20] In CHEST-2 trial the improvement is persisted in 1 year follow up and survival rate is 97.[21] Based on this trial, riociguat is recommended in symptomatic patients, persisten/recurrent CTEPH after surgery or inoperable CTEPH.[1,17]

Balloon Pulmonary Angioplasty

Balloon pulmonary angioplasty (BPA) is relatively new procedure indicated in CTEPH patients who are not suitable for PEA or patients with residual or recurrent PH after PEA. It offers advantages over PEA, such as: (1) BPA can resolve the distal small lesions which cannot be reached with PEA and (2) BPA is a less-invasive procedure which does not need general anes¬thesia.[22] Since BPA is originated from Japan, Japanese Circulation Society release the guideline for patients candidate for BPA, as follows: (1) patients unsuitable for PEA (lesion is not reachable, major comorbidities and persistent/residual/recurrent CTEPH after PEA), (2) patients with drugs treatment but fail to improve (WHO functional class ≥III after

treatment, mPAP ≥30 mmHg or PVR ≥300 persistent), (3) patients choice to have BPA after thorough informed consent about risk and benefit of BPA and PEA and (4) cases without serious complication, multiorgan failure or iodine allergy.[23]

Unlike PEA, BPA does not remove intraluminal thrombus or thrombotic material from pulmonary artery. BPA procedure makes medial layer dissection in the balloon inflation site and in situ thrombus partially disrupted from vessel walls.[23] In facts BPA procedure has similar technique as PEA, only in BPA the thrombi are not removed from the luminal blood vessel, but rather forced to one side so that luminal vessel become larger.[23] After the BPA, some parts of vessel walls becoming thin because of dissection, where the angioplasty than applied and produce expanded lumen diameter over time with little risk of restenosis (**Figure 5**).[23]

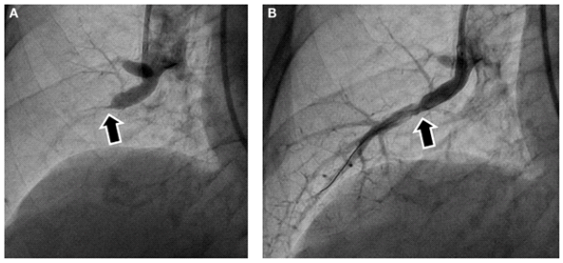

Figure 5. The procedure of BPA shows (A) the obstruction (arrow) in the pulmonary artery depicted in pulmonary angiography and (B) after BPA procedure the obstruction (arrow) is cleared and blood flow appears until peripheral artery. (Taken from: Ogawa and Matsubara, 2015[23] with permission).

The successful BPA is influenced by the extent and angiographic characteristics of the thromboembolic lesions, which can be classified as follows: ring-like stenosis lesion (type A), web lesion (type B), subtotal lesion (type C), total occlusion lesion (type D) and tortuous lesion (type E). The most favourable outcome is encountered in type A and B, whereas type D and E associate with lower success rate and high complication rate.[24]

CONCLUSION

The pathophysiology of CTEPH involves the derangement of pulmonary macrovascular and microvascular. The diagnosis of CTEPH requires high index of clinical suspicion, step-by-step proper imaging modalities and adequate expertise to interpret the imaging. The treatment of CTEPH comprises surgery with PEA, drugs with anticoagulant and riociguat and intervention with BPA. Better diagnosis and correct patient selection to treatment strategy will improve survival of patients with CTEPH.

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