Recent Progress in the Management of Pulmonary Hypertension

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Pulmonary hypertension (PH) is a fatal disease caused by small pulmonary artery obstruction from vascular proliferation and remodeling. PH is characterized by elevated pulmonary arterial pressure and increased pulmonary vascular resistance, frequently leading to right-sided heart failure and death. The classification of PH has been recently updated to include 5 major categories of the disorder, are as: Group 1, pulmonary arterial hypertension (PAH); Group 2, PH due to left heart disease; Group 3, PH due to lung diseases and/or hypoxia; Group 4, chronic thromboembolic PH (CTEPH); and Group 5, others. Recently, significant progress has been made in the understanding of the pathophysiology, diagnosis and treatment of PH. Regarding the pathophysiology of the disorder, direct evidence for Rho-kinase activation in the pulmonary artery from PAH patients has been provided. Regarding diagnosis, optical coherence tomography is useful as a new differential diagnostic tool for distal type CTEPH vs. PAH. Regarding treatment, in addition to the conventional therapy, several new drugs are under clinical trial, including fasudil (a Rho-kinase inhibitor), riosiguat (a soluble guanylate cyclase activator), and imatinib (a tyrosine kinase inhibitor). In addition, pulmonary angioplasty and intensive immunosuppressive therapy may be effective for CTEPH and connective tissue disease-associated PAH, respectively. We briefly review the recent progress in the management of PH.   (*Circ J* 2011; **75:** 1801–1810)

Key Words: Pulmonary artery; Pulmonary circulation; Pulmonary hypertension; Heart failure

Pulmonary hypertension (PH), defined as a mean pulmonary arterial pressure (PAP) ≥25 mmHg at rest as assessed by right heart catheterization,[1–3] is a fatal disease caused by small pulmonary artery obstruction by vascular proliferation and remodeling.[4] PH is characterized by elevated PAP and increased pulmonary vascular resistance (PVR), frequently leading to right-sided heart failure (HF) and death.[4–6]

The classification of PH has been recently updated[2] to include 5 major categories of the disorder (**Figure 1**, **Table 1**). Group 1, pulmonary arterial hypertension (PAH), is a clinical condition defined as mean PAP ≥25 mmHg and pulmonary capillary wedge pressure (PCWP) ≤15 mmHg, which is characterized by the presence of pre-capillary PH in the absence of other causes of pre-capillary PH, such as PH because of lung diseases, chronic thromboembolic PH (CTEPH) or other rare diseases (**Figure 1**, **Table 1**).[2,3] Pulmonary veno-occlusive diseases (PVOD) and/or pulmonary capillary hemangiomatosis (Group 1') should be a distinct category but are not completely separated from PAH because they share similar characteristics with idiopathic PAH (IPAH) but also demonstrate some differences.[2,3] Group 2, PH caused by left heart disease, is characterized by the passive backward transmission of the pressure elevation (post-capillary PH).[3] There are 2 types of post-capillary PH: the normal transpulmonary

pressure gradient (TPG, determined as mean PAP minus mean PCWP) and PVR, which is defined as the passive post-capillary PH; the other is elevated TPG and PVR, the reactive post-capillary PH ("out of proportion" PH) (**Figure 1**, **Table 2**).[3] Group 3, PH due to lung diseases and/or hypoxia, is caused by hypoxic vasoconstriction as a result of lung diseases, in which PH is generally modest (mean PAP 25–35 mmHg).[2,3] Group 4, CTEPH is caused by chronic and mechanical obstruction of central and/or distal pulmonary arteries by thromboembolic masses (**Figure 1**, **Table 1**).[2,3,7] Group 5 consists of several remaining forms of PH, for which the etiology is unclear and may be multifactorial (**Figure 1**, **Table 1**).[2,3]

We briefly review the recent progress in the management of PH, in terms of pathophysiology, diagnosis and treatment.

New Insights Into the Pathophysiology of PH

The pathological changes of the pulmonary arteries in PH include endothelial injury, proliferation and hypercontraction of vascular smooth muscle cells (VSMC) and migration of inflammatory cells (**Figure 2**).[4,5,8]

PAH and Rho-Kinase Pathway
In the 1990s, Rho-kinase/ROK/ROCK was identified as an

Table 1. Clinical Classification of Pulmonary Hypertension (Dana Point, 2008)*

Group 1: PAH (Idiopathic PAH, Heritable PAH, Drug and toxin-induced)

    Associated with connective tissue disease, HIV, portopulmonary hypertension, schistosomiasis, and chronic hemolytic anemia, etc.

Group 1': PVOD and/or PCH

Group 2: Pulmonary hypertension due to left heart disease

    Including systolic and diastolic dysfunction, mitral or aortic valvular disease.

Group 3: Pulmonary hypertension secondary to lung diseases and/or hypoxia

Group 4: CTEPH

Group 5: Other

    Including hematologic disorders, sarcoidosis, pulmonary Langerhans cell histiocytosis, metabolic disorders, etc.

Modified from Simonneau et al[2] with permission.
PAH, pulmonary arterial hypertension; PVOD, pulmonary veno-occlusive disease; PCH, pulmonary capillary hemangiomatosis; CTEPH, chronic thromboembolic pulmonary hypertension.
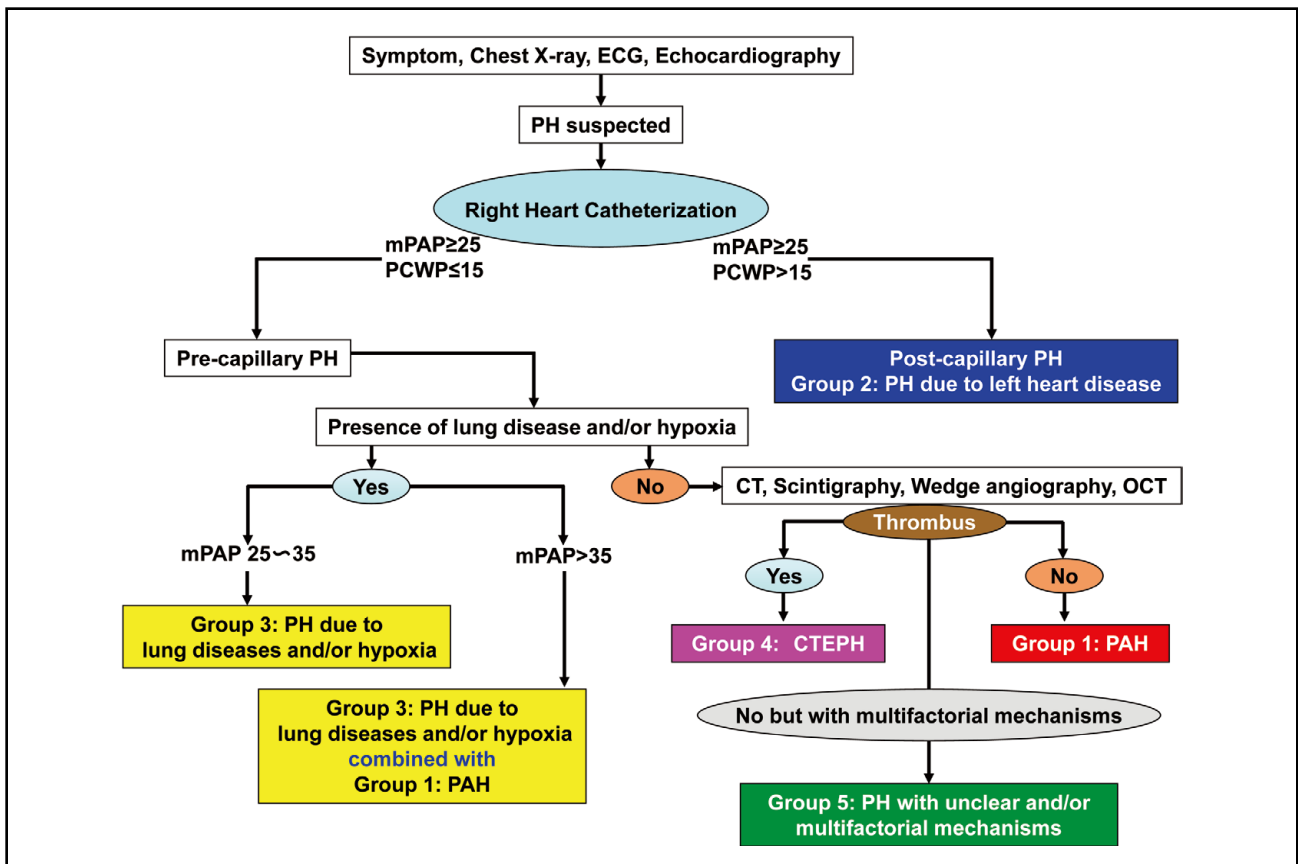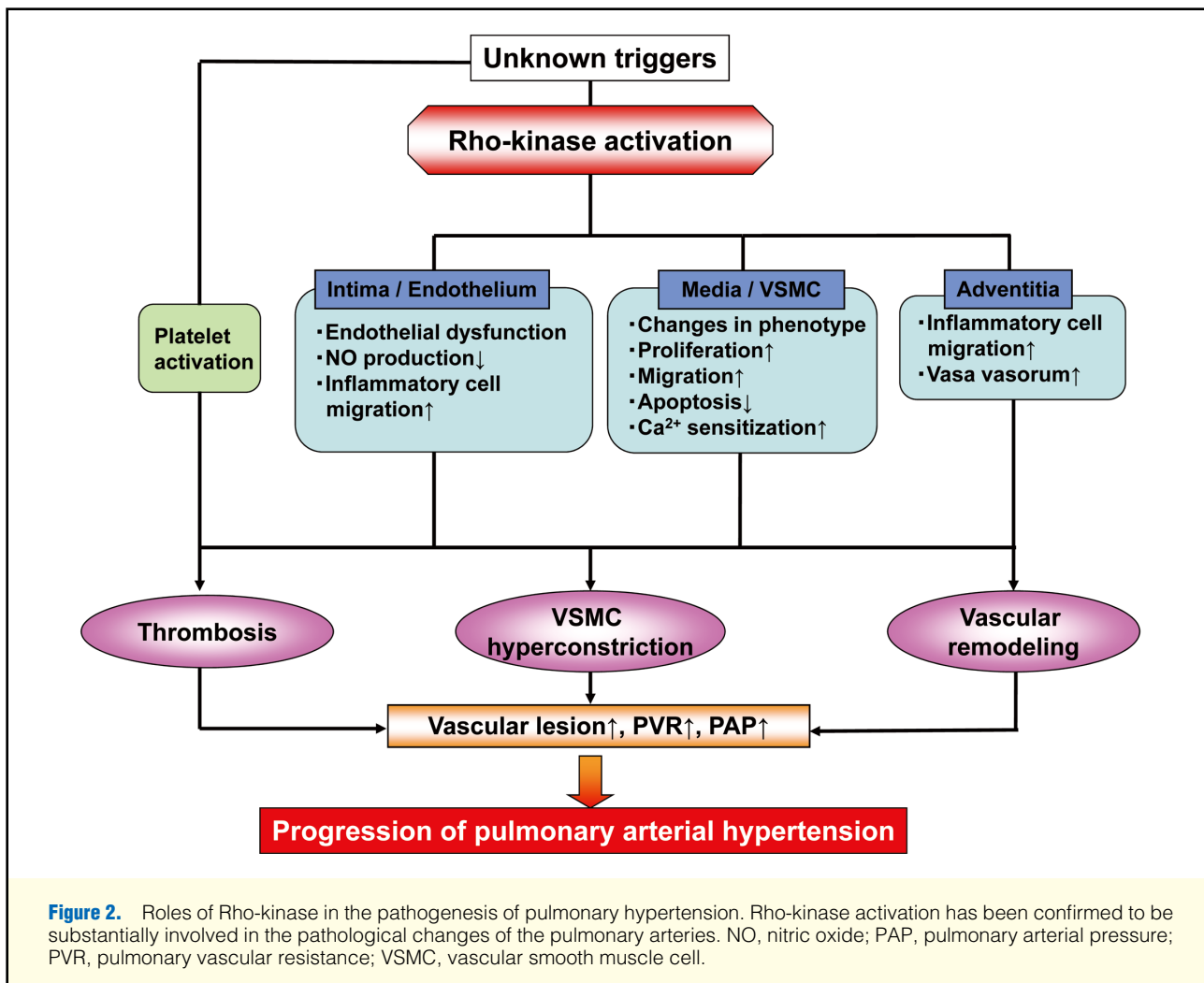

Figure 1. Diagnosis and classification of pulmonary hypertension. CT, computed tomography; CTEPH, chronic thromboembolic pulmonary hypertension; ECG, electrocardiogram; mPAP, mean pulmonary arterial pressure; OCT, optical coherence tomography; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension.

Table 2. Definition and Classification of Post-Capillary Pulmonary Hypertension

Mean PAP ≥25mmHg

PCWP >15mmHg

   -Passive TPG ≤12mmHg

   -Reactive ("out of proportion") TPG >12mmHg

(Modified from Galie et al[3] with permission.)
PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; TPG, transpulmonary pressure gradient defined as mean PAP minus mean PCWP.

effector of the small GTP-binding protein Rho,[9,10] which plays an important role in various cellular functions, including smooth muscle contraction, actin cytoskeleton organization, cell adhesion and motility, cytokinesis, and gene expressions.[11–13] The Rho/Rho-kinase pathway has recently attracted much attention in the cardiovascular research field for several reasons (**Figure 2**). First, the Rho/Rho-kinase pathway plays an important role in various cellular functions that are involved in the pathogenesis of a variety of cardiovascular diseases.[12,14] Second, this intracellular signaling pathway is substantially involved in the effects of many vasoactive sub-

Figure 2. Roles of Rho-kinase in the pathogenesis of pulmonary hypertension. Rho-kinase activation has been confirmed to be substantially involved in the pathological changes of the pulmonary arteries. NO, nitric oxide; PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance; VSMC, vascular smooth muscle cell.

stances that are implicated in the pathogenesis of cardiovascular diseases.[12,14] Third, the so-called pleiotropic effects of statins, especially those of high doses of statins, may be mediated, at least in part, by their inhibitory effects on Rho, with a resultant inhibition of Rho-kinase.[12,14] Fourth, the important roles of the Rho-kinase pathway have been recently demonstrated in the pathogenesis of PAH (**Figure 2**).[5,15–19]
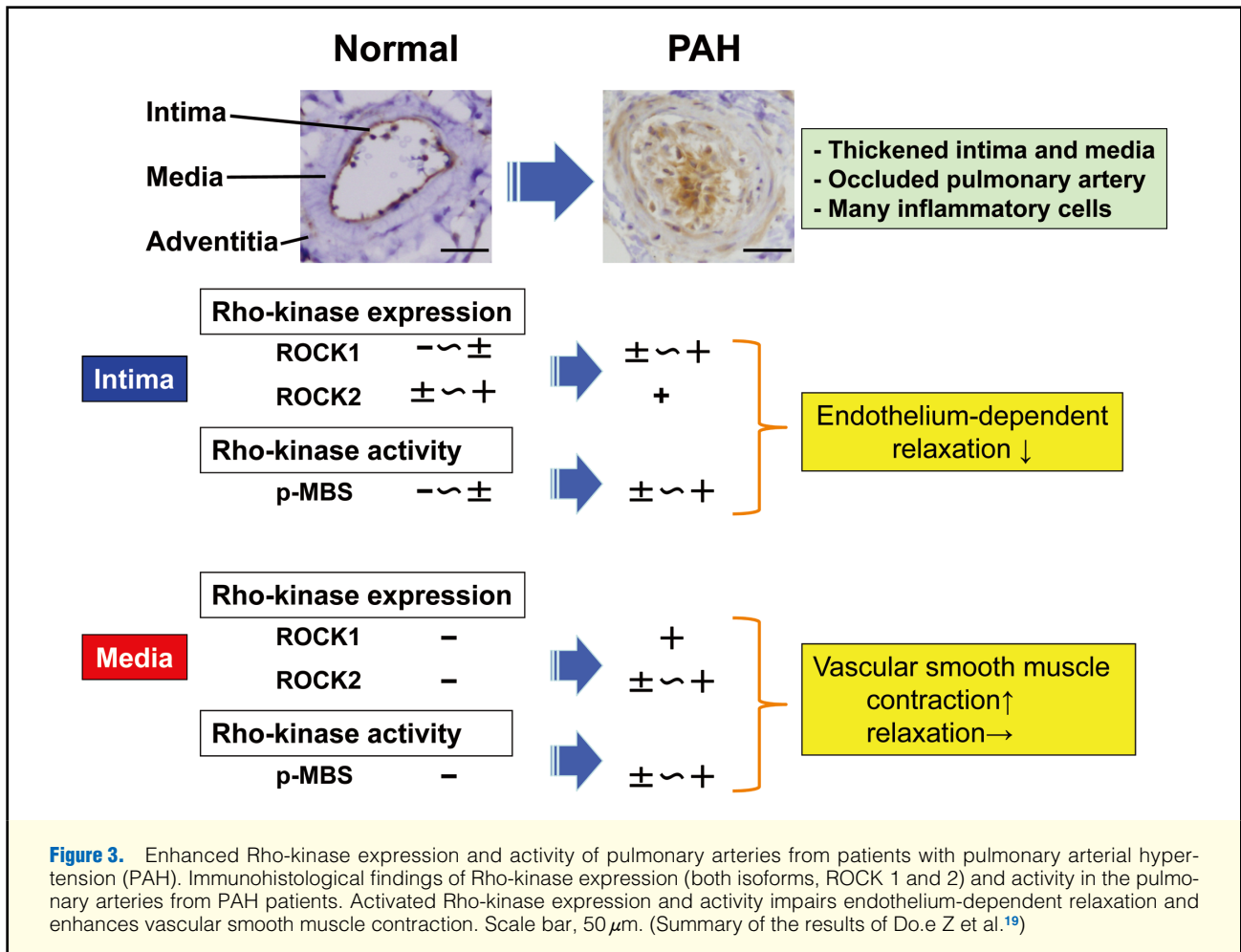
Rho-kinase suppresses myosin phosphatase activity by phosphorylating the myosin-binding subunit of the enzyme, thus augmenting VSMC contraction at a given intracellular calcium concentration.[20,21] VSMC hypercontraction mediated by activated Rho-kinase plays a key role not only in coronary artery spasm but also in PAH.[5,15,17,22–24] Rho-kinase inhibition may be preferable to calcium-channel blockers because of its selective spasmolytic effect on vascular hyperconstrictive segments.[5,15,22]

Rho-Kinase and Inflammation A number of studies have suggested that inflammation may be involved in the pathogenesis of PAH.[5,25] Some patients with idiopathic PAH have immunological disturbances (eg, circulating auto-antibodies, such as antinuclear antibodies) and elevated circulating levels of pro-inflammatory cytokines (eg, interleukin-1 and -6).[25] It has been demonstrated that Rho-kinase is upregulated by inflammatory stimuli[12,26,27] and that Rho-kinase inhibition increases endothelial nitric oxide synthase (eNOS) expression

and inhibits inflammatory cell migration and angiotensin II-induced up-regulation of monocyte chemoattractant protein-1 and plasminogen activator inhibitor-1 in vivo or in vitro,[15] in which the Rho-kinase pathway may play an important role in the development of PAH.

Rho-Kinase and PAH Indeed, it has been demonstrated that long-term inhibition of Rho-kinase ameliorates monocrotaline (MCT)-induced PAH and hypoxia-induced PAH in animal models.[5,16,18,28] In those studies, Rho-kinase activity in the pulmonary arteries was enhanced, irrespective of the different etiologies, and long-term treatment with Rho-kinase inhibitors ameliorated endothelial dysfunction and suppressed hypercontraction and proliferation of VSMC and migration of inflammatory cells.[16,18,28] In clinical studies, it also has been demonstrated that a Rho-kinase inhibitor, fasudil, acutely improves pulmonary hemodynamics in patients with PAH.[17,24,29]

Enhanced Rho-Kinase Expression and Activity in Patients With PAH Recently, direct evidence for Rho-kinase activation has been demonstrated in patients with PAH,[19] where Rho-kinase activity is enhanced in circulating neutrophils and the pulmonary arteries from patients with PAH, resulting in hypercontraction of the artery (**Figure 3**). These findings support the previous findings in animal models of PAH and during right-heart cardiac catheterization in patients with

Figure 3. Enhanced Rho-kinase expression and activity of pulmonary arteries from patients with pulmonary arterial hypertension (PAH). Immunohistological findings of Rho-kinase expression (both isoforms, ROCK 1 and 2) and activity in the pulmonary arteries from PAH patients. Activated Rho-kinase expression and activity impairs endothelium-dependent relaxation and enhances vascular smooth muscle contraction. Scale bar, 50 μm. (Summary of the results of Do.e Z et al.[19])

PAH.[12,16–18,24,28,29] Thus, increased PVR may be caused, at least in part, by the activated Rho-kinase pathway.[19] In addition, in patients with PAH, eNOS expression is reduced and pulmonary VSMC are hyper-reactive.[19,30,31] Indeed, activated Rho-kinase causes several important abnormalities, including eNOS downregulation in endothelial cells, VSMC hyper-contraction through inhibition of myosin phosphatase, VSMC proliferation and migration, and inhibition of VSMC apoptosis (**Figure 2**).[12,15,27,32,33] Also, there is direct evidence that endothelial vasodilator function is impaired and VSMC contraction enhanced in pulmonary arteries from patients with PAH (**Figure 3**).[19] These findings are consistent with previous studies using MCT-induced PH in rats and hypoxia-induced PH in mice, and previous clinical studies of PAH patients.[16–18,24,29] Furthermore, the inhibition of Rho-kinase abolishes VSMC hypercontraction of pulmonary arteries from IPAH patients,[19] which is also consistent with a previous clinical study that showed acute inhibition of Rho-kinase improved pulmonary hemodynamics in PAH patients.[17,24,29] However, it still remains to be examined whether these functional abnormalities of the pulmonary arteries in patients with PAH can be ameliorated by long-term treatment with a Rho-kinase inhibitor. For this purpose, the effects of a long-acting oral form of fasudil in PAH patients are being examined in a clinical trial.

Post-Capillary PH (Left Heart Disease)
Left heart disease, including systolic and/or diastolic left ventricular (LV) dysfunction, is one of the most common causes of PH.[34] There are 2 types of post-capillary PH, passive and reactive types, which are defined as transpulmonary pressure gradient (defined as mean PAP minus mean PCWP) less than or greater than 12 mmHg, respectively (**Table 2**). Reactive post-capillary PH is considered to be caused by increased vasomotor tone of the pulmonary arteries and/or structural obstructive remodeling of the pulmonary resistance vessels.[3,35] Patients with post-capillary reactive PH are usually female, have valvular heart disease and elevated PAP with left heart disease.[36] It has been reported that patients with this disorder have an increased risk of postoperative right ventricular HF after heart transplantation.[37] However, the detailed mechanisms of the condition remain to be elucidated.

Chronic Thromboembolic PH
CTEPH is caused by mechanical obstruction of pulmonary arteries by residual pulmonary thromboembolism (PTE) or in situ thrombosis,[3] which may be initiated or aggravated by abnormalities in the clotting cascade, endothelial cells or platelets.[3,38] Although inflammatory infiltrates are commonly detected in pulmonary endarterectomy specimens, it remains unknown whether thrombosis or platelet dysfunction is the cause or consequence of the disorder.[3] It has been reported that the plasma levels of factor VIII are elevated in patients with CTEPH.[39] Although Rho-kinase is activated in patients
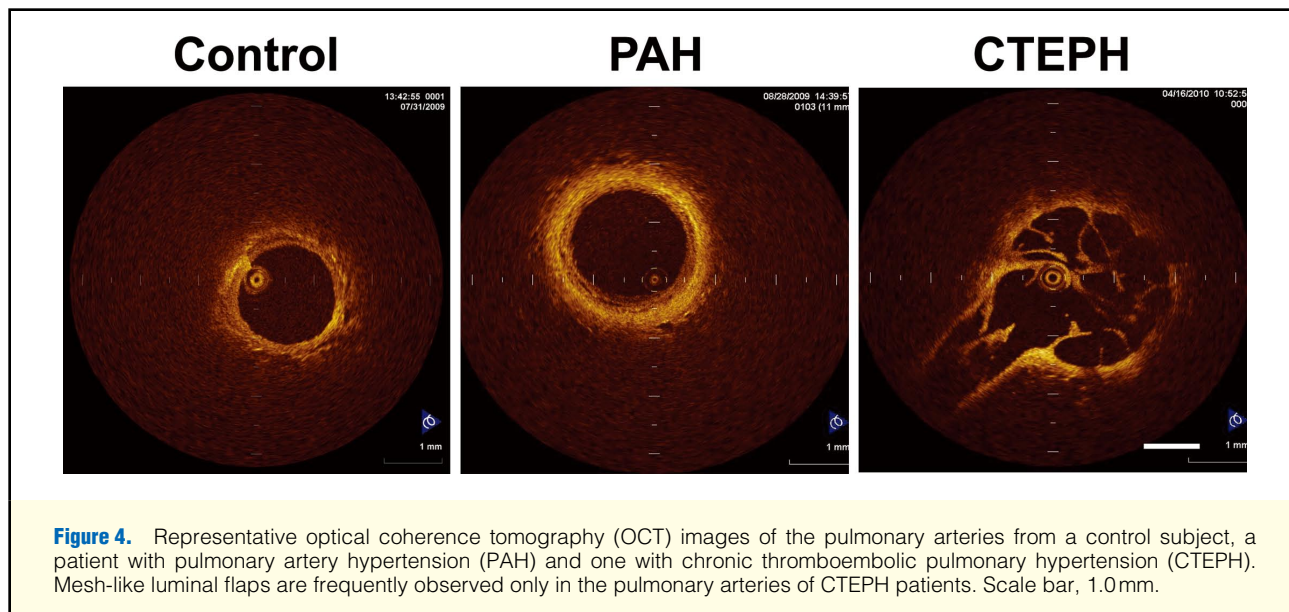
Figure 4. Representative optical coherence tomography (OCT) images of the pulmonary arteries from a control subject, a patient with pulmonary artery hypertension (PAH) and one with chronic thromboembolic pulmonary hypertension (CTEPH). Mesh-like luminal flaps are frequently observed only in the pulmonary arteries of CTEPH patients. Scale bar, 1.0mm.

with PAH, it may not be the case with CTEPH.[19] CTEPH is regarded as a consequence of PTE caused by venous thromboembolism; however, the occurrence of CTEPH in patients with acute PTE or deep venous thrombosis is rare.[3] Thus, it is highly possible that the pathophysiology PAH and CTEPH is different.

Recent Progress in the Diagnosis of PH

Right-Heart Catheterization
Cardiac catheterization is important not only for diagnosing PH and excluding other causes but also to evaluate disease severity and prognosis assessment. Patients with PAH should have a normal PCWP, high PAP, high PVR, and normal or high right atrial pressure. When a wedge pressure cannot be obtained, direct measurement of LV end-diastolic pressure is advised (**Figure 1**).[3]

Optical Coherence Tomography (OCT)
OCT is an interferometer-based optical imaging modality that produces a 2-dimensional image of optical scattering from internal tissue microstructure with a high resolution of approximately 10–20μm, which is 10-fold higher than that of intravascular ultrasound.[40–42] A recent report has demonstrated the usefulness of OCT as a novel diagnostic tool for differential diagnosis of distal type CTEPH from PAH.[7] Pulmonary arteries larger than 1mm had no obstruction in controls and PAH patients, although the media of the arteries appeared to be thickened in PAH patients compared with controls.[7] In contrast, half of the CTEPH patients had occlusion of the pulmonary arteries, probably by thrombus, and more than half of them showed flaps in the lumen of the pulmonary arteries (**Figure 4**).[7]

Pathohistological studies have demonstrated that idiopathic PAH (IPAH) is associated with abnormal vascular structures, including medial and/or intimal hypertrophy, concentric and/or eccentric intimal fibrosis, obstruction in the arterial lumen, and aneurysmal dilatation in vessels smaller than 300μm.[19] In contrast, CTEPH results from the obstruction of pulmonary arteries by thrombus, mainly observed in large vessels.[43]

Computed Tomography (CT) Scan
The role of chest CT scan has been established for both determining the presence and severity of PAH based on the diameter of the main pulmonary arteries and for diagnosing CTEPH. High-resolution CT scan can be reconstructed specifically to look at the lungs in detail (eg, the presence of PVOD) in each patient without the need for additional radiation.[3,44] Typical CT scan images from PVOD patients show diffuse, poorly-defined centrilobular nodular opacities with associated septal line thickning.[44]
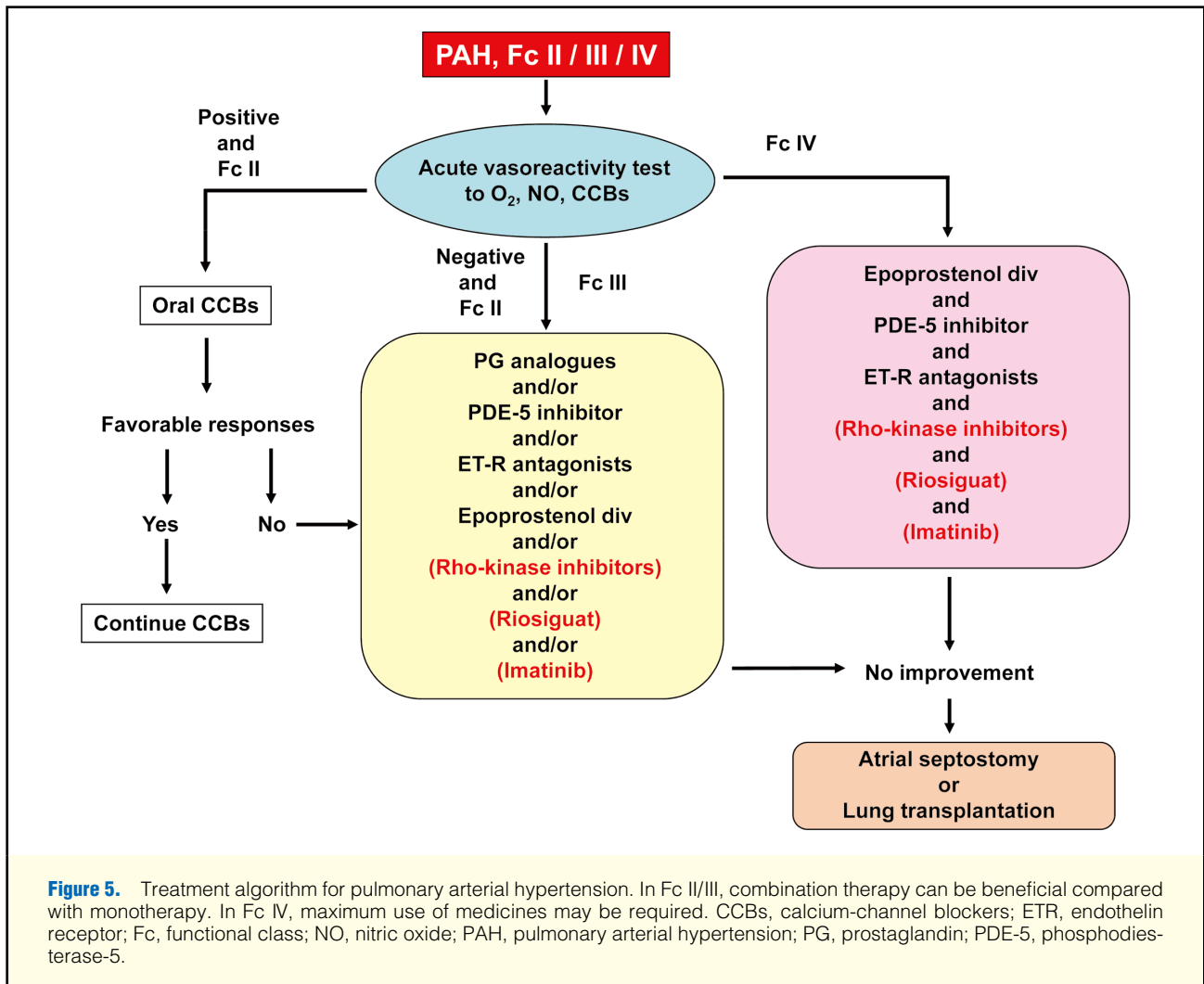
New Treatment Algorithm of Pre-Capillary PAH

The new treatment algorithm of PAH and connective tissue disease-associated PAH (CPAH) are shown in **Figures 5** and **6**, respectively.

Lifestyle Modification
Heavy physical activity or isotonic exercise often causes right ventricular failure in patients with PAH/CTEPH.[5,45] Thus, low-level exercise in their daily life is recommended for those with PAH/CTEPH, because low-level physical training improves endothelial function, exercise capacity and quality of life, not only in those with coronary artery disease but also in those with PAH.[5,45] High altitude and infections should also be avoided because the former may produce hypoxic pulmonary vasoconstriction and the latter are fatal in some patients.[5] In general, pregnancy is also not recommended in young women with PAH, because of the high mortality.[3,5]

Prostacyclins
Intravenous epoprostenol improves symptoms, 6-min-walk distance, hemodynamics and survival in patients with IPAH.[46] It has been reported that intravenous epoprostenol improves survival rate in comparison with historical controls, with 1-, 2-, 3-, and 5-year survival rates of 85%, 70%, 63%, and 55%, respectively,[47] although this prostacyclin analog needs to be delivered by continuous intravenous infusion. Thus, it is important for patients with PAH/CTEPH to learn the techniques of sterile preparation of the drug, operation of an

Figure 5. Treatment algorithm for pulmonary arterial hypertension. In Fc II/III, combination therapy can be beneficial compared with monotherapy. In Fc IV, maximum use of medicines may be required. CCBs, calcium-channel blockers; ETR, endothelin receptor; Fc, functional class; NO, nitric oxide; PAH, pulmonary arterial hypertension; PG, prostaglandin; PDE-5, phosphodiesterase-5.

ambulatory infusion pump and sterile handling of a central venous catheter. Epoprostenol therapy should be started during hospitalization and the starting dose of epoprostenol ranges between 0.5 and 1 ng·kg^{-1}·min^{-1}.[47] Its dose should be carefully increased in a step-wise manner on the basis of symptoms and side effects of the drug, because chronic overdose administration can cause high cardiac output failure. The side effects of intravenous epoprostenol include headache, jaw pain, flushing, nausea, diarrhea, skin rash, and musculoskeletal pain.[8] In addition, infections and infusion interruptions can be life-threatening. Because of its considerable complexity, epoprostenol therapy should only be performed in centers with experience. Currently, 4 prostacyclin analogs are licensed for the treatment of PAH: epoprostenol, treprostinil, iloprost (in the USA and some European countries) and beraprost (in Japan and Korea).[48] Prostacyclins are the treatment of choice in patients with severe PAH, and their earlier use may also benefit PAH patients with mild-to-moderate severity.[48] The advantages of prostacyclins are also noted in their integral role in combination therapy when a patient's condition has deteriorated following monotherapy with other agent (**Figures 5,6**).[6,48]

Phosphodiesterase-5 (PDE-5) Inhibitors
Sildenafil, a potent and highly specific PDE-5 inhibitor, im-

proved exercise capacity, symptoms and hemodynamics in patients with PAH in the Sildenafil Use in Pulmonary Hypertension (SUPER) trial.[49] Side effects include headache, flushing, dyspepsia, and epistaxis. Tadalafil, which is also effective and well tolerated in patients with PAH, has already been in clinical use (**Figures 5,6**).[50]

Endothelin (ET) Receptor Antagonists
Bosentan is the first drug in this class of ET antagonists that block both ETA and ETB receptors. Clinical trials have shown that treatment with bosentan increases exercise capacity and improves symptoms and pulmonary hemodynamics, not only in patients with PAH but also in those with Eisenmenger syndrome.[51,52] The adverse effects of bosentan include headache, hypotension and liver dysfunction.[53] Ambrisentan is a selective ETA receptor antagonist and its long-term use is also effective in improving symptoms, exercise capacity, pulmonary hemodynamics and time to clinical worsening in patients with PAH (**Figures 5,6**).[3]

Immnosuppressive Therapy (Cyclophosphamide)
It is widely accepted that immunological and inflammatory mechanisms contribute to the initiation and progression of PAH associated with connective tissue disease (CPAH), such as systemic sclerosis (SSc), systemic lupus erythematosus
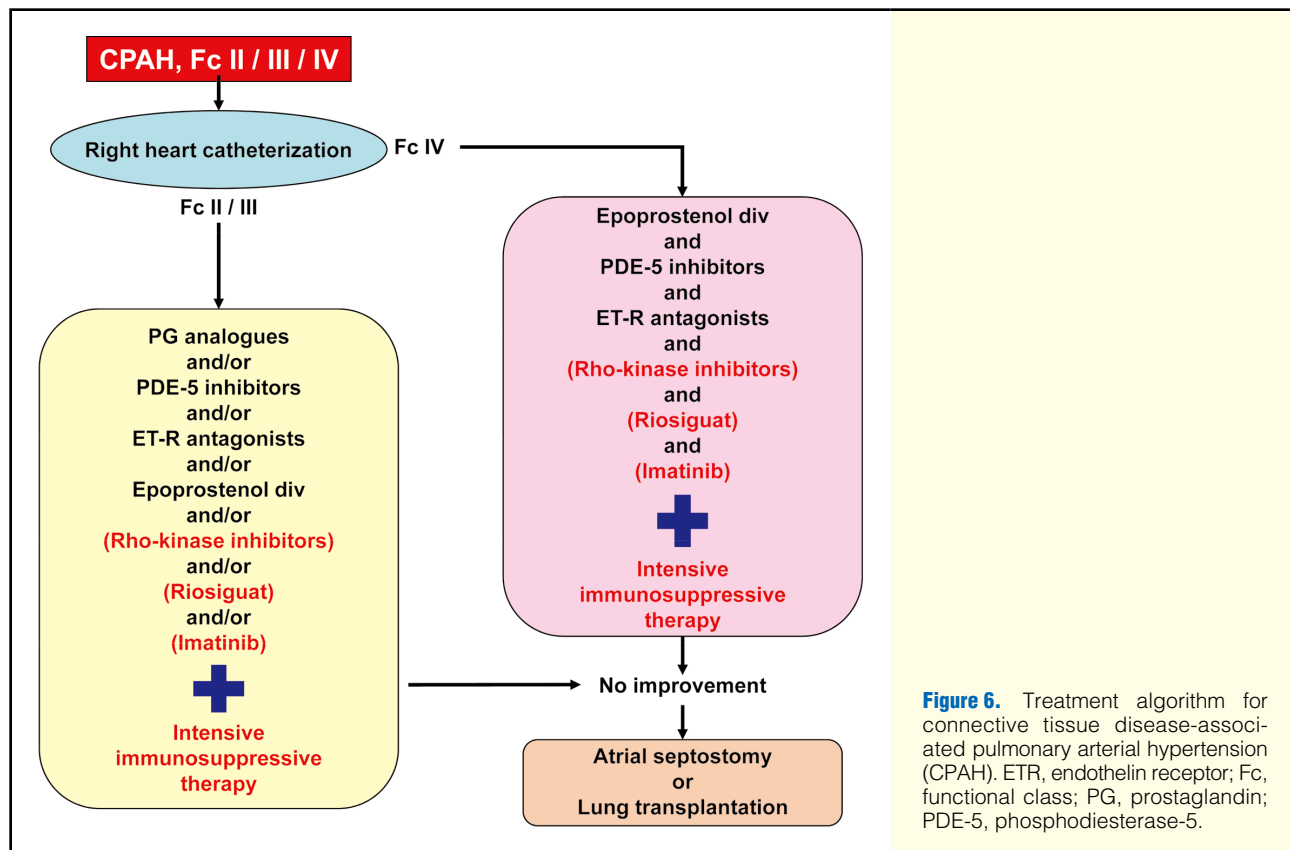
Figure 6. Treatment algorithm for connective tissue disease-associated pulmonary arterial hypertension (CPAH). ETR, endothelin receptor; Fc, functional class; PG, prostaglandin; PDE-5, phosphodiesterase-5.

(SLE) and mixed connective tissue disease (MCTD).[4,25] Indeed, inflammatory cells (eg, macrophages and lymphocytes) have been detected in the plexiform lesions of the lung from CPAH patients.[54,55] It has been recently reported that immunosuppressive therapy is effective in patients with SLE or MCTD, whereby half of those who responded to first-line immunosuppressive therapy alone showed improvement in symptoms, exercise tolerance and pulmonary hemodynamics.[56,57] A recent study has demonstrated that intensive immunosuppressive therapy combined with cyclophosphamide and glucocorticosteroid on the top of conventional vasodilator therapy markedly improves pulmonary hemodynamics and long-term prognosis of patients with CPAH other than SSc-associated PAH (**Figure 6**).[58] The effects of the intensive immunosuppressive therapy are evident when it is started immediately after the diagnosis of CPAH;[57,58] however, future studies are required to identify the effects in a larger number of patients.

New Agents

Rho-Kinase Inhibitor Fasudil is a potent and selective inhibitor of Rho-kinase,[20] with its inhibitory effect on Rho-kinase being 100- and 1,000-fold more potent than on protein kinase C and myosin light chain kinase, respectively.[15] Long-term oral treatment with fasudil markedly ameliorated PH and pulmonary vascular lesions in a MCT-induced model in rats[16] and a hypoxia-induced model in mice.[18] Intravenous administration of fasudil also effectively reduces PVR in patients with PAH.[17]

Recent studies in a rat model of MCT-induced PH demonstrated that prostacyclin and its oral analog, beraprost sodium (BPS), do not have an inhibitory effect on Rho-kinase and that combination therapy with fasudil and BPS is more effective than each monotherapy for ameliorating PH.[59,60] Indeed, it was demonstrated that IPAH patients with intravenous prostacyclin therapy showed favorable acute responses to fasudil.[17,29] Thus, it is highly anticipated that combination therapy with prostacyclin and fasudil will have more beneficial effects in the treatment of PAH.

Bosentan, a dual inhibitor of ETA and ETB receptors, is another effective drug for the treatment of PAH in the clinical setting.[53,61–63] However, not only ET but many other vasoactive substances (eg, serotonin, thrombin and platelet-derived growth factor) are involved in the pathogenesis of PAH, and importantly, all of them could activate the Rho-kinase pathway.[12,15,27,33] Because Rho-kinase inhibitors could inhibit signal transductions initiated by any of these vasoactive substances, it is possible that they exert more broadly beneficial effects than each single receptor antagonist.[12,15,27,33] Recently, a clinical trial has been started to examine the mid-term effect of the long-acting oral form of fasudil in patients with PAH in Japan (**Figures 5, 6**).

Riociguat Riociguat is a novel, first-in-class oral drug that directly stimulates soluble guanylate cyclase, both independently of the endogenous vasodilator NO and in synergy with NO.[64,65] Phase III clinical trials with riociguat are evaluating the long-term safety and clinical effectiveness of the agent in PAH and CTEPH patients (**Figures 5, 6**).[64–67]

Imatinib Platelet-derived growth factor (PDGF) plays a critical role in the VSMC mitogen-activating signal transduction pathways associated with VSMC hyperplasia in PAH.[68,69] Imatinib, a tyrosine kinase inhibitor of PDGF receptors, is expected to be a novel therapeutic agent for PAH, and is also under clinical trial (**Figures 5, 6**).[70]

New Treatment Algorithm of Post-Capillary PH

Medications for Chronic HF

No specific therapy has yet been developed for post-capillary PH,[3] which is thus currently treated by drugs for the underlying diseases, including diuretics, nitrates, angiotensin-converting enzyme inhibitors, β-blockers and angiotensin-receptor blockers.[71] Chronic trials with epoprostenol or bosentan in advanced HF have been terminated early because of an increased event rate in the investigational drug group compared with the conventional therapy group.[72–74] Thus, novel therapeutic options need to be developed for post-capillary PH.

New Agents

Rho-Kinase Inhibitor   In animal models of diastolic HF (DHF), it has been demonstrated that activation of cardiac Rho-kinase is associated with the development of DHF and that cardiac Rho-kinase activity is highly correlated with myocardial stiffness of the LV in DHF.[75] Furthermore, long-term inhibition of Rho-kinase with fasudil ameliorates DHF, independent of blood pressure-lowering effects, including the transition to decompensated HF, whereby amelioration of LV myocardial stiffness, but not that of LV relaxation properties, may be involved in the beneficial effects of fasudil.[75] Future studies are needed to examine the long-term effect of the oral form of fasudil in patients with PH caused by left heart disease.

Sildenafil   Oral treatment with sildenafil exerts protective effects at the myocardial level in HF, targeting cardiac remodeling and PH due to left heart disease in animal models.[76] The beneficial effects of sildenafil were also observed in patients with HF in a prospective, randomized, placebo-controlled study, where it improved functional capacity and clinical status, suggesting that LV diastolic function and cardiac geometry are additional targets of benefits with chronic PDE5 inhibition.[77,78]

Riociguat   Phase III clinical trials of riociguat are evaluating its long-term safety and clinical effectiveness in PH caused by left heart disease.[64–67]

New Treatment Algorithm of CTEPH

Pulmonary Artery Angioplasty

Pulmonary thromboendoarterectomy is an established treatment for CTEPH, resulting in significant improvement in right ventricular hemodynamics and function.[43] However, this surgical treatment is limited to central-type CTEPH and is not feasible for distal-type CTEPH.[43,79] Although percutaneous transluminal pulmonary angioplasty (PTPA) was reported to improve pulmonary hemodynamics, symptom, and 6-min walking distance,[80] the procedure is limited by complications (eg, pulmonary hemorrhage and pulmonary edema).[79,80] Indeed, distal-type CTEPH remains a serious condition with poor prognosis because of the lack of effective treatment.[43] Accordingly, safer PTPA procedures have been recently developed with smaller sized balloons for less lobes per procedure, which may facilitate PTPA with less complications.[81]

Future Perspectives

PH remains a fatal disease, leading to right ventricular failure and premature death. Although significant research progress has been made on the pathogenesis, especially with regard to Rho-kinase, the detailed mechanisms of the disorder remain to be elucidated. In clinical practice, significant progress has also been made for both diagnosis (eg, OCT) and treatment (eg, new ET blockers, Rho-kinase inhibitors, riociguat, and imatinib). The usefulness of these new drugs remains to be fully examined in future studies.

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