The Pathophysiology of Pulmonary Hypertension: From Biology to Current Clinical Classification

Anggoro Budi Hartopo
Department of Cardiology and Vascular Medicine
Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada - Dr. Sardjito Hospital, Yogyakarta, Indonesia

ABSTRACT

Pulmonary hypertension is an increased of pulmonary artery pressure exceeding 25 mmHg at rest. Endothelial dysfunction and imbalance between vasoconstriction and vasodilatation are the initial disturbance. Ensuing cellular changes are developing apoptosis-resistant endothelial cells, proliferative-prone smooth muscle cells, activated fibroblasts and inflammatory cells which occupy vascular microenvironment. The remodeling in the pulmonary vascular microenvironment affects its microcirculation result in progressively raised pulmonary artery pressure. The vascular obliteration due to plexiform lesion is the severe form of remodeling in pulmonary hypertension. Currently, combining the underlying biology and clinical characteristics, pulmonary hypertension is divided into five clinical classification. Each classification depicts the distinct pathobiology, clinical picture and, consequently, response to treatment. The investigation of deeper knowledge on biology mechanism in pulmonary hypertension is currently underway to explore the new treatment strategy to overcome the increased pressure in pulmonary artery.

The Diagnosis of Pulmonary Hypertension: Multimodality from Non-Invasive to Invasive Diagnostic

Hasanah Mumpuni
Department of Cardiology and Vascular Medicine
Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada - Dr. Sardjito Hospital, Yogyakarta, Indonesia

ABSTRACT

Pulmonary hypertension is adisease marked with increased of pulmonary artery pressure which is happened because of several diseases or other clinical conditions. This haemodynamic and pathophysiological condition is defined as increased of mean artery pulmonary pressure (MPAP) ≥ 25 mmHg at rest.

Hallmarks of pulmonary hypertension were observed from the history of disease, physical examination, chest x-ray and electrocardiography (ECG). Furthermore, right heart failure is also known due to pulmonary hypertension. Two-dimensional Transthoracal Echocardiography (TTE) examination with Doppler analysis is used as initial screening to estimate artery pulmonary pressure and to evaluate ventricle function. European Society of Cardiology (ESC) recommends first evaluation in significant group 2 and 3 of pulmonary hypertension are TTE examination, pulmonary function test, blood gas analysis, and chest imaging.

Definitive diagnosis of pulmonary hypertension is increase of mean pulmonary artery pressure ≥ 25 mmHg by right heart catheterization. From this method, other parameters can be assessed such as Pulmonary Vasculary Resistance (PVR) ≥ 3 mmHg/L/minute to diagnose pulmonary artery hypertension and Pulmonary Capillary Wedge Pressure (PCWP) to estimate left atrium pressure or left ventricle end diastolic pressure ≤ 15 mmHg (McGoon *et al.*, 2004, McLaughlin *et al.*, 2009, Galie *et al.*, 2009a). By right heart catheterization, vasoreactivity test also can be done to evaluate acute response of vasodilator, especially in hereditery PAH patient.

Doppler echocardiography has brought significant impact in medicine to determine intracardiac haemodynamic by non-invasive, so it contribute to diagnose suspicious of pulmonary hypertension and haemodynamic change related to increase of pulmonary pressure. Several echocardiography parameters and formulas have been studied to measure pulmonary artery pressure directly and indirectly, such as TVG (tricuspid valve gradient), PV AccT (Pulmonary Vein Accelerating Time), RAP (Right Arterial Pressure), TVI-RVOT (Time-Velocity Integral of Right Ventricle Outflow Tract).

The registry of congenital heart disease in Dr. Sardjito Hospital named as Congenital Heart Disease and Pulmonary Hypertension (COHARD-PH) which is being started from 2014 and has more than 1000 cases with majority of atrial septal defect has been used for several diagnostic studies to compare some variables like ECG, biomarker, echocardiography parameter with pulmonary artery pressure from right heart catheterization as the gold standar.

Keywords: Pulmonary hypertension; echocardiography; ECG; biomarker; right heart catheterization

The Management of Pulmonary Artery Hypertension: Multimodality from Medication to Intervention

Lucia Kris Dinarti
Department of Cardiology and Vascular Medicine
Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada - Dr. Sardjito Hospital, Yogyakarta, Indonesia

ABSTRACT

Pulmonary arterial hypertension is a group I of Pulmonary Hypertension according to ESC/ERS guidelines of Pulmonary Hypertension 2015 that is defineas an increase of mean PA pressure > 25 mmHg , PCWP < 15 mmHg and PVR >3 WU. The disease characterized by excessive pulmonary vasoconstriction and abnormal vascular remodeling that result in loss of vascular cross sectional area and increased in right ventricular afterload. Pathobiologic mechanisms of the disease include pulmonary endothelial dysfunction, which leads to impaired production of vasodilators, such as nitric oxide and prostacyclin, and over expression of vasoconstrictors, such as endothelin-1. Changes in nitric oxide pathways have been detected in patients with PAH.

Treatment includes conventional agents (anticoagulants, diuretics, digoxin, and supplemental oxygen, as well as calcium-channel blockers in selected patients), and target therapy based on 3 pathways. Recently, there are 12 agents from 3 groups that interfering 3 pathway (Endothelin Receptor Antagonist, Prostacyclin analoque and PDE5 I and soluble guanylate cyclase stimulators) are approved for the treatment of pulmonary arterial hypertension.

The pulmonary vasodilating effects of nitric oxide are mediated through its second messenger, cyclic guanosine monophosphate (cGMP), which is rapidly degraded by phosphodiesterases. Phosphodiesterase type 5 is the predominant phosphodiesterase isoform in the lung that metabolizes cGMP, and it has been shown to be up-regulated in conditions associated with pulmonary hypertension. By selectively inhibiting phosphodiesterase type 5, sildenafil citrate promotes the accumulation of intracellular cGMP and thereby enhances nitric oxide–mediated vasodilatation; it may also have anti proliferative effects on pulmonary vascular smooth-muscle cells. Many studies data from open label, uncontrolled trials involving patients with pulmonary arterial hypertension suggest that sildenafil citrate is beneficial in the treatment of pulmonary arterial hypertension.

Keywords : Pulmonary Arterial Hypertension; PDE5 Inhibitor; Sildenafil citrate

Current Treatment of NSTE-Acute Coronary Syndrome: The Role of Anticoagulant

Hariadi Hariawan
Department of Cardiology and Vascular Medicine
Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada - Dr. Sardjito Hospital,
Yogyakarta, Indonesia

ABSTRACT

Acute coronary syndrome is an amount of continual diagnosis which is consist of unstable angina, non-ST elevation myocard infarct, and ST elevation myocard infarct. Unstable angina and non-ST elevation myocard infarct are classified into non-ST elevation artery coronary syndrome.

Anticoagulant is an important pharmacologically strategy of non- ST elevation acute coronary syndrome management. Mechanism of anticoagulant can be achieved through some pathways from inhibition of formation and fibrin activity. Anticoagulant can efectively reduce coagulation cascade which aggravates myocard cell in acute phase (Eikelboom *et al*., 2000).

Anticipation of thrombosis and stabilization of plaque inside coronary vessel is the main purpose of antithrombosis therapy for non- ST elevation acute coronary syndrome patient. This treatment will reduce the ischemic complication, myocard cell infarction, and death (Theroux *et al*., 1998).

Anticoagulant which is mostly used is unfractionated heparin, low molecular weight heparin, and fondaparinux. Some studies show that low molecular weight heparin (LMWH) has profile, safety, and efficacy of progressivity inhibition of ischemic better than that of unfractionated hepatin (UFH). Besides, LMWH does not need diastases monitoring which is able to increase the hospital cost (Martin *et al*., 2004). The other studies show that fondaparinux gives crucial role of acute coronary syndrome management (Song *et al*., 2010).

DISCUSSION

Nowadays, especially in national health insurance era, anticoaglant choice which combines the effectivities and management costs of non-ST elevation acute coronary syndrome is crucial.

Unfractionated Heparin (UFH)

The effect of UFH anticoagulant comes from acceleration of antithromblin III (AT-III) action which is circulated in blood stream. AT-III activates factor IIa, IXa, and Xa. It must be known that UFH anticoagulant effect is UFH-AT-III complex which does not break the formed thrombus, but this effect only prevent the thrombus propagation. A big benefit of UFH usages is UFH effect can be thightly monitored by activated partial thromboplastin time (Aptt) and activated clotting time (ACT). As the first invented drug, the disadvantage of UFH usage is bad bioavailability, probability event of heparin induce thrombocytopenia (HIT), and paradox thrombosis (Telford, 1981).

The new data of UFH for non-ST elevation acute coronary syndrome management is only for control agent as compared with newer anticoagulant. European Society of Cardiology (ESC) 2015 gives clue of UFH application in NSTE-ACS patient by 60-70 unit/kg bolus of UFH (maximally 5000 unit), followed by UFH infussion 12-15 unit/kg/hour (maximally 1000 unit/hour). UFH monitoring references use aPTT and ACT with the value 1,5 – 2,5 from normal limit (aPTT) and 250-300 seconds (ACT). UFH is better applicated for NSTE-ACS which has indication for coronary angiography. After percutaneus coronary intervention (PCI), UFH application should be stopped consider that high risk of bleeding (Roffi, 2015).

Nadroparin

Nadroparin is one of low molecular weight heparin (LMWH) first generation with average molecular weight 4.500 Dalton. This drug has anti-factor Xa ratio, better bioavailability, and longer half-time compared to UFH. Therefore, Nadroparin can be given subcutaneously (Davis R *et al*., 1997). FRAXIS trial (1999) shows that the clinical outcome of Nadroparin treatment for NSTE-ACS which is compared to UFH is not significantly different. However, the major bleeding risk of Nadroparin is much far higher than UFH. Nadroparin usage (patent brand : Fraxiparin) is not as popular as newer LMWH, the enoxaparin. Comparation between Nadroparin and Enoxaparin which was performed by Ostradal in 2008 shows that Enoxaparin is more effective in target achievement of anticoagulant effectin the first 3 hours after drug administration. Today, Nadroparin is not specifically recommended by AHA/ACC and ESC.

Enoxaparin

Enoxaparin is the only one LMWH which is recommended by AHA/ACC and ESC. This drug is the most used for NSTE-ACS management. ESSENCE (1997) and TIMI-11 B (1999) trial shows that the use of Enoxaparin 1 mg/kg/12 hours reduces the risk of death, myocardial infarction, and recurrent angina, and coronary angiography and revascularisation performance compared to UFH. Enoxaparin is eliminated through kidney, so that the dosage must be reduced into 1 mg/kg/24 hours if the glomerular filtration rate (GFR) below the 30 mL/minute and can not be administered if the GFR < 15 mL/minute. In NSTE-ACS patient which is treated by Enoxaparin and the last injection is less than 8 hour before PCI, there is no dosage addition which needs to be given. If the enoxaparin injection is more than 8 hours, additional enoxaparin injection can be administered by the dosage of 0,3 mg/kg IV (Roffi, 2015).

Fondaparinux

Fondaparinux is synthetic pentasacaride which is effectively linked to AT-III and causes predictable and faster inhibition activity of factor Xa. Fondaparinux also binds lower PF4 activation. Therefore, HIT is rarely produced by fondaparinux. OASIS-5 study (2006) is a study which search Fondaparinux role of NSTE-ACS management. OASIS-5 as non-inferior trial compared subcutan Enoxaparin 1 mg/kg/12 hours with Fondaparinux 2,5 mg/24 hours. Fondaparinux administration in patient which is going to perform PCI is associated to catheter-associated thrombus higher than Enoxaparin (0,9% vs 0,3%). It shows that Fondaparinux application requires UDH additional to reduce thrombus formation before coronary angiography and PCI. Fondaparinux is not more inferior for ischemic outcome (death, myocardial infarction, and refracter ischemia) than that of Enoxaparin when short, intermediate, and long follow-up (Yusuf *et al*., 2006). On the other hand, fondaparinux insidence for major bleeding is lower than enoxaparin. ESC recommends Fondaparinux is administered subcutaneously with the dosage of 2,5 mg/24 hours. NSTE-ACS patient with high risk of bleeding should be given therapy by fondaparinux administration as anticoagulant. Fondaparinux is not recommended for patient which is planned fpr revascularisation due to high thrombosis stent insidence.

Bivalirudin

Bivalirudin is the newest anticoagulant generation which inhibits thrombin (factor Iia) directly without AT-III association. The main bivalirudin application is for anticoagulant which is utilised to heart catheterization. ACUITY study (2008) shows bivalirudin is linked to small risk of bleeding

compared to indirect anticoagulant. Bivalirudin is now recommended by AHA/ACC for the management of NSTE-ACS which is planned to PCI with the class recommendation 1B. Meanwhile, ESC in 2018 decrease the recommendation class of bivalirudin from 1A to 2B because VALIDATE-SWEDEHEART (2017) announces that UFH is the anticoagulant which is recommened for PCI on NSTE-ACS. UFH has thrombosis stent risk lower than Bivalirudin (Neumann *et al*., 2018).

CONCLUSION

Anticoagulant therapy is the main therapy for NSTE-ACS. This therapy inhibits thrombin propagation to improve clinical outcome. Choice for anticoagulant is related to patient's clinical profile and the next action to the patient. Enoxaparin and fondaparinux are recommended for NSTE-ACS patient because of better bioavailability and higher ratio of anti-factor Xa:IIa. The anticoagulant effect of enoxaparin and fondaparinux is more predictable than UFH. Another that, the cost for therapy is lesser since daily monitoring for bleeding effect is not required. UFH is recommended for NSTE-ACS patient which is going to do revascularisation because stent thrombosis level is better than bivalirudin. The use of anticoagulant for NSTE-ACS which has benn conducted PCI must be stopped due to the high risk of bleeding.

The Multimodality Diagnosis of Venous Thromboembolism

M. Taufik Ismail
Department of Cardiology and Vascular Medicine
Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada - Dr. Sardjito Hospital,
Yogyakarta, Indonesia

ABSTRACT

Venous thromboembolism (VTE) is a blood clot in a vein, which comprises Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE). VTE is the third leading vascular diagnosis after myocardial infarct and stroke. Diagnosis of VTE is important to reveal the disease not only in the tip of an iceberg phenomenon. Clinicians diagnose the disease firstly by clinical manifestation, but clinical diagnosis of DVT and PE are unreliable. Laboratory tests such as D dimer tend to have high sensitivity but a very low specificity. Thus, there is a need for more accurate and noninvasive diagnostic tests, not only to diagnose but also for proper localization and monitoring during and after treatment. Many guidelines suggest incorporating clinical assessment, imaging, and D-dimer testing into the diagnostic algorithms of patients with suspected deep venous thrombosis (DVT) and pulmonary embolism (PE).

The imaging modality of DVT has evolved over the past few decades, from conventional contrast venography (first described in 1963) and duplex sonography (in 1980s) to computed tomography (CT)/magnetic resonance venography and scintigraphy. Contrast venography was the first imaging procedure available for diagnosing DVT and is still considered as the gold standard. Clot being identified as a filling defect or non-opacification of the vein. The primary diagnostic Ultrasound criteria for acute DVT remains non-compressibility of the vein with secondary diagnostic criteria being echogenic thrombus within the vein lumen, venous distention, complete absence of spectral or color Doppler signal within the vein lumen, loss of flow phasicity, and loss of response to valsalva or augmentation.

Meanwhile, among the many imaging modality for PE, V/Q lung scans and CT pulmonary angiography (CTPA) are the best-validated and most widely used. Others include lower-extremity compression ultrasonography, thoracic ultrasonography, and magnetic resonance imaging (MRI). CT pulmonary angiography (CTPA) is the initial modality of choice in evaluating patients with suspected PE. CT showing emboly at the segmental or more proximal pulmonary level is adequate proof of PE in patients with a non-low clinical probability. Pulmonary angiography has remained the gold standard for the diagnosis or exclusion of PE, but is rarely performed now as less-invasive CT angiography offers similar diagnostic accuracy. CUS or TOE could be done in the case of unstable condition to undergo CT angiography.

An Update on Management of Venous Thromboembolism and Chronic Venous Diseases

Suci Indriyani
Department of Cardiology and Vascular Medicine
Faculty of Medicine, Universitas Indonesia / National Cardiovascular Center Harapan Kita,
Jakarta, Indonesia

ABSTRACT

Venous thromboembolism (VTE) encompassing both deep vein thrombosis (DVT) and pulmonary embolism (PE) incidence increases sharply with age and appears steady over the last 25 years, despite preventive strategies. Almost two-thirds of VTE cases are isolated deep vein thromboses (DVTs), and 80% are proximal.

Three phases of care have been described for the management of VTE. First, an acute phase (day 0 to as long as day 21) encompasses the initial occurrence/diagnosis of the clot, where clot propagation is likely to occur without therapy. Therapy in this phase is often with higher doses of oral agents or parenteral therapy (±warfarin) to treat the initial clot. Second, a long-term active treatment phase (3 months to as long as 6 months) ensures the appropriate treatment of the initial clot with (typically) an oral anticoagulant agent. Third, an extended phase (also known as secondary prevention) may follow for those having a high risk of clot recurrence, balancing this risk with that of major bleeding. This later extended phase must be informed by patients' values and preferences.

Anticoagulation therapy is a cornerstone of VTE treatment. Its options include unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), fondaparinux, vitamin K antagonists (VKAs), and direct oral anticoagulants (DOACs). Deciding on which anticoagulant to use depends on the indication, the patient's underlying condition, the patient's preference, and the patient's risk of bleeding.

Recurrence risk is high, especially within first 6 months. Early- and mid-term complications include thrombosis extension, and PE and DVT recurrence. Long-term complications include post-thrombotic syndrome (PTS), defined as chronic venous symptoms and/or signs secondary to DVT. It represents the most frequent chronic DVT complication, occurring in 30–50% of patients within 2 years after proximal DVT. Previous ipsilateral DVT, proximal location (ilio-femoral>popliteal), and residual veins obstruction are most significant PTS risk factors. Obesity and poor INR control during the first 3-months treatment are additional independent risk factors.

Chronic venous disease (CVD) is a debilitating condition that result in varicose veins, or advance to severe skin changes and venous ulceration. Both reflux and obstruction account for the pathophysiology of CVD; however, reflux has a much higher prevalence in patients presenting with the different stages of CVD including venous leg ulcers (VLU), but obstruction has a higher rate of patients developing venous ulceration and has much more rapid progression of disease. Whether reflux or obstruction as the cause of symptomatology and clinical presentation of patients, both condition lead to increased of venous pressure. The severity of CVD is usually evaluated by means of the CEAP (Clinical, Etiologic, Anatomic, Pathophysiologic) classification system.

The goal of CVD treatment is to decompress sources of increased venous pressure. Initial therapy with graduated compression stockings (GCS) is recommended for most patients. More aggressive initial treatment may be considered in patients who present with complications such as recurrent superficial vein thrombosis, bleeding varicose veins, or ulceration. Advanced treatments include surgery (vein stripping and high ligation) and endovascular methods (Radiofrequency, laser ablation and mechano-chemical methods can lead to damage and contract the venous wall, have been used successfully to treat GSV reflux).

The Importance of Multimodality on Atrial Fibrillation Screening and Diagnosis

Sunu Budhi Rahardjo
Departement of Cardoilogy and Vascular Medicine
Faculty of Medicine, Universitas Indonesia / National Cardiovascular Center Harapan Kita
Jakarta, Indonesia

ABSTRACT

Atrial fibrillation is the most common cardiac arrythmia. It impairs cardiac function and increases the risk of stroke. The incidence of atrial fibrillation increases with age. Early diagnosis of atrial fibrillation, ideally before the first complication occurs, remains challenge, as shown by patients who are only diagnosed with the condition when admitted to hospital for acute cardiac decompensation or stroke. The diagnosis of AF requires rhythm documentation using an electrocardiogram (ECG) showing the typical pattern of AF; absolutely irregular RR intervals and no discernible, distinct P waves. By accepted convention, an episode lasting at least 30 seconds is diagnostic. Individuals with AF may be symptomatic or asymptomatic ('silent AF'). Many AF patients have both symptomatic and asymptomatic episodes of AF. Silent, undetected AF is common, with severe consequences such as stroke and death. Prompt recording of an ECG is an effective and cost-effective method to document chronic forms of AF. The technology to detect paroxysmal, self-terminating AF episodes is rapidly evolving. There is good evidence that prolonged ECG monitoring enhances the detection of undiagnosed AF, e.g. monitoring for 72 h after a stroke, or even longer periods. Pulse palpation and daily or repeated short-term ECG recordings increase AF detection in populations over 75 years of age. The presence of atrial lead in patients with implanted pacemakers of defibrillators allow continuous monitoring of atrial rhythm. Using this technology, patients with atrial high rate episodes (AHRE) can be identified. Ongoing studies will determine whether such early detection alters management (e.g. initiation of anticoagulation) and improves outcomes.

The Management of Stroke Prevention in Atrial Fibrillation Patient with Multimorbid: Focus on Elderly and Renal Impaired Patient

Erika Maharani
Department of Cardiology and Vascular Medicine
Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada - Dr. Sardjito Hospital, Yogyakarta, Indonesia

ABSTRACT

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. The prevalence is constantly rising, even after adjusting for age and presence of structural heart disease. The most common underlie diseases of persistent and permanent AF are hypertension, valvar, ischaemic, and other types of structural heart. Lone AF accounts for approximately 15% of AF cases. The pathomechanism of AF is now thought to involve an interaction between initiating triggers, often in the form of rapidly firing ectopic foci located inside one or more pulmonary veins, and an abnormal atrial tissue substrate capable of maintaining the arrhythmia. AF increases the risk of stroke sixfold and is associated with a twofold increase in mortality, which remains above 1.5-fold after adjusting for co-morbidity, predominantly caused by cerebrovascular events, progressive ventricular dysfunction, and increased coronary mortality. This risk for thromboembolism can be substantially reduced with anticoagulation treatment. The decisions for using anticoagulation should be predominantly based on the presence or absence of well established risk factors for thromboembolism (CHADS2VAS score), including previous stroke or transient ischaemic attack, valvar or other structural heart disease, hypertension, diabetes, age more than 65 years, vascular disease, and sex.

While most patients with non-valvular atrial fibrillation (AF) benefit from anticoagulation to prevent ischaemic stroke and systemic embolism, multi-morbid patient – the elderly and renal insufficiency patients face high risks of both thromboembolism and bleeding during antithrombotic therapy. The use of warfarin reduces the rate of ischemic stroke in patients with atrial fibrillation but requires frequent monitoring and dose adjustment. Novel oral anticoagulant (NOAC) now has been extensively used as a first line therapy for thromboembolic prevention in atrial fibrillation patients. Rivaroxaban, one of NOAC is an oral factor Xa inhibitor. It may provide more consistent and predictable anticoagulation than warfarin especially in multi-morbid patient with high risk of bleeding. The Rivaroxaban Once-daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) compared the oral factor Xa inhibitor rivaroxaban with warfarin for prevention of all stroke and systemic embolism in 14.264 patients with AF. In patients with atrial fibrillation, rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism. There was no significant between-group difference in the risk of major bleeding, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group.

Keywords: atrial fibrillation; rivaroxaban; multi-morbid patients