Literature Review

Pathophysiology of Hemoptysis in Lung Disease

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Abstract

Hemoptysis is expectoration of blood with or without sputum originating from the lower airway. Even minor symptom of hemoptysis is a distressful for the patient. This condition is an alarming symptom that may lead to massive bleeding and life-threatening condition. When evaluating a patient presenting with expectoration of blood, one must determine the source of the bleeding and whether the patient is presenting with true hemoptysis or pseudo hemoptysis. Based on the underlying disease, hemoptysis can occur through several pathological mechanisms leading to bronchial artery rupture. Mostly, hemoptysis is caused by bronchiectasis, pulmonary tuberculosis, lung cancer, and pulmonary fungal infections. The incidence rate of the causative diseases may differ depending on geographical location. Pulmonary vascularization consists of two circulation pathways namely the pulmonary and bronchial circulation, each of which has its own role. Around 90% of hemoptysis cases are caused by the collapse of bronchial arteries due to increased pressure in its circuit. It is important to understand the pathophysiology and pathomechanism of hemoptysis for further management of diseases and clinical manifestation.

Keywords: bronchial circulation, hemoptysis, pathophysiology hemoptysis, pulmonary hemorrhage

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INTRODUCTION

Hemoptysis is derived from ancient Greek words *haema* means blood, and *ptysis* means spitting. Hemoptysis could be found in daily practice as a symptom of lower respiratory problems.[1,2] Hemoptysis occurs in 10% of patients with chronic lung disease. Although 90% of hemoptysis cases are self-limiting diseases, hemoptysis is a life-threatening condition that requires prompt diagnosis and treatment.[3]

Asphyxia is the leading cause of death in hemoptysis. In addition, in hemoptysis, cardiovascular collapse is often among the cause of death. The mortality rate from untreated massive hemoptysis is more than 50%.[4] Passage of relatively small amounts of blood is a symptom that should still be watched out for. Regardless of the quantity, the cause of hemoptysis must be identified immediately. It is important to initiate adequate treatment and to avoid fatal complications.[4,5]

Hemoptysis is often caused by bleeding from the bronchial circulation due to inflammatory process in the airway. Infection is the leading cause of hemoptysis in 60-70% cases. Inflammation and edema of airway can lead to rupture of surface blood vessels. Common causes of hemoptysis are classified into: infectious diseases, neoplastic, vascular, autoimmune and drug-related. The etiology of hemoptysis can affect treatment strategies. Detailed history-taking and careful physical examination are necessary to provide certain underlying diagnosis. This article aims to provide an in-depth literature review on hemoptysis, assessing its causes and pathophysiologic mechanisms. Also this article provided with details about anatomy of bronchial arteries which are responsible for hemoptysis.[4,6]

HEMOPTYSIS

Hemoptysis is defined as expectoration of blood from the lower respiratory tract or expectoration of sputum accompanied by bloody spots. In diagnosing hemoptysis, it is important to distinguish lower respiratory tract bleeding from

nasopharyngeal bleeding and gastrointestinal tract (pseudohemoptysis).[4,5]

Table 1. List of diseases causing hemoptysis[4]

Diseases Causing Hemoptysis	
Causes of hemoptysis from small vessel diseases	
Immunologic and vasculitis disease	1. Acute lung allograft rejection
	2. Antiphospholipid antibody syndrome
	3. Behçet disease
	4. Goodpasture's Syndrome
	5. Henoch-Schönlein Purpura
	6. Isolated Pulmonary Capillaritis
	7. Microscopic polyarteritis
	8. Mixed cryoglobulinemia Wegener granulomatosis
Cardiovascular diseases	Mitral stenosis
Coagulation Diseases	1. Latrogenic (anticoagulant/thrombolytic agents)
	2. Coagulopathies
Others	1. Diffuse alveolar damage
	2. Lymphangioleiomyomatosis
	3. Pulmonary capillary hemangiomatosis
	4. Pulmonary hemosiderosis
	5. Tuberous sclerosis
	6. Veno-occlusive diseases
Causes of hemoptysis from large vessel diseases	
Infectious diseases	1. Abscess
	2. Bronchitis (acute or chronic)
	3. Bronchiectasis
	4. Fungal infection
	5. Parasitic infection
	6. Pneumonia
	7. Tuberculosis or nontuberculous mycobacteria
Cardiovascular diseases	1. Arteriovenous malformation
	2. Bronchial artery aneurysm
	3. Bronchovascular fistula
	4. Congestive heart failure
	5. Pulmonary embolism or infarction
	6. Pulmonary hypertension
	7. Right-sided endocarditis
	8. Thoracic aortic aneurysm rupture or dissection
	9. Septic pulmonary embolism
Congenital diseases	1. Cystic fibrosis
	2. Pseudosequestration
	3. Pulmonary artery atresia or stenosis
Neoplastic diseases	1. Bronchial adenoma
	2. Lung metastasis
	3. Primary lung cancer
Vasculitic diseases	1. Behçet disease/Hughes-Stovin syndrome
	2. Lupus pneumonitis
	3. Takayasu arteritis
	4. Wegener's granulomatosis

Table 2. List of diseases causing hemoptysis (Cont.)

Diseases Causing Hemoptysis	
Causes of hemoptysis from large vessel diseases	
Others	1. Chronic obstructive airway disease
	2. Drug
	3. Foreign body
	4. Iatrogenic (Swan-Ganz catheter)
	5. Interstitial fibrosis
	6. Lung contusion
	7. Pulmonary endometriosis
	8. Trauma
	9. Dieulafoy's disease or the bronchus
	10. Cryptogenic hemoptysis

Based on the underlying disease, hemoptysis is the result of several pathological mechanisms. The causes of hemoptysis are divided into parenchymal disease, airway disease, and vascular disease. Hemoptysis originates from both great and small blood vessel.[4,5] Bleeding from small vessels is caused by immunologic, cardiovascular vasculitis, and coagulation disorders. Bleeding from large vessels is often caused by tuberculosis (TB), bronchiectasis, fungal infections, and malignancy (Table 1).[4]

Massive hemoptysis may increase risk of mortality up to 80% in untreated patients.[7] Various studies have defined the range of massive hemoptysis differently from 100 mL to more than 1000 mL in 24 hours.[3,4,8] Initial estimation of blood loss is frequently incorrect; therefore, hospitalized patients' blood loss should be monitored daily. There is a lack of universal consensus on the quantification and severity of hemoptysis. National Respiratory Referral Hospital, Persahabatan, using Busroh Criteria for massive hemoptysis:

a) Coughing up blood ≥600 mL per 24 hours and persisting under observation
b) Coughing up blood ≥250 mL but <600 mL per 24 hours and hemoglobin (Hb) level <10 g/dL, with ongoing bleeding
c) Coughing up blood >250 mL but <600 mL per 24 hours, Hb level >10 g/dL and within 48 hours conservative treatment the bleeding has not stopped.[9]

Each case of massive hemoptysis does not only depend on the quantity of blood loss but also on the mechanism of the blood expulsion and the pre-

existing pulmonary dysfunction. Death from asphyxia occurs long before massive blood loss or before hemorrhagic shock develops. This is mainly due to low tracheobronchial volume (150-200 mL) so even a small amount of blood loss can alter the balance of gas exchange in the lungs.[3] In addition, the anatomic dead space in the main airway is around 100-200 mL, so the volume-based definition of massive hemoptysis is more relevant and can be life-threatening.[10]

LUNG VASCULARIZATION

Lung organs have two pathways to supply blood. Approximately 90-99% of gas exchange and tissue perfusion is carried out by the pulmonary arteries, and the remaining 1-5% is derived from the bronchial arteries.[3,4,11] The pulmonary arteries originate from the right ventricle and branch into billions of pulmonary capillaries, and enclose the alveoli to allow gas exchange. Meanwhile, the bronchial arteries originate from the descending aorta and are arranged parallel to the bronchi and supply blood through its branches. The bronchial arteries arise from the aorta or intercostal arteries. Bronchial arteries are part of the systemic circulation with high resistance and low capacitance system. The bronchial arteries receive approximately 2% of cardiac output (Figure 1).[2,4,5,11]

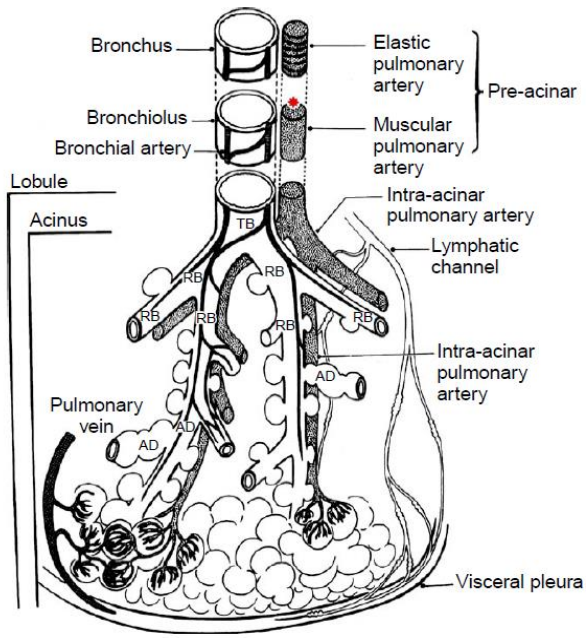

Figure 1. Schematic of blood supply in the lung[12]

Bronchopulmonary anastomoses connect the bronchial and pulmonary arteries at the level of alveoli and respiratory bronchioles. Blood drainage in bronchial arteries occurs due to the passage of blood from the bronchial veins to the right atrium and from the pulmonary veins to the left atrium (Figure 1).[4,11,13] Several disorders may damage this mechanism, including:[3]

a) Hypoxic vasoconstriction.
b) Pulmonary artery thrombosis or thromboembolism.
c) Vasculitis.
d) Chronic inflammatory or malignant disease.
e) Pulmonary vascular malformations.

In this condition, compensation occurs in the pulmonary arteries resulting in dilatation of the bronchial arteries and their anastomoses. Thus, the percentage of cardiac output flowing through the bronchial arteries increases.[11] In pulmonary disease conditions such as systemic hypoxemia, alveolar hypoxia, pulmonary infarction, and various chronic inflammations in the chest cavity, the bronchial arteries dilate to supply oxygenated blood to the ischemic area. The walls of the bronchial arteries are thinner and more fragile, as well as the burden of systemic arterial pressure and disturbances due to chronic disease may lead to tearing or bleeding from the airways, manifesting as hemoptysis.[2–4,11]

The intensity of coughing and the amount of expelled blood in each patient vary depending on the degree of pulmonary impairment or the impact of the underlying disease and the type of blood circulation involved.[1]

Study showed that about 90% of hemoptysis originates from the bronchial arteries, about 5% from the pulmonary arteries, and the other 5% from non-bronchial systemic arteries.[2–4] When bleeding occurs between the three locations, sensory receptors can be irritated via afferent nerves from the cough reflex, namely cranial nerves V, X, XII, and superior laryngeal nerves. Then through the efferent nerves, including spinal nerves and recurrent laryngeal larynx, the blood is expelled with or without other secretions.[5]

PATHOPHYSIOLOGY OF HEMOPTYSIS IN TUBERCULOSIS

In lung tuberculosis (TB), several mechanisms can induce hemoptysis. Hemoptysis occurs in both active and inactive lesions and depends on the size.[1] Proliferation and enlargement of bronchial arteries can be found in pulmonary infections such as bronchiectasis, pneumonia, and tuberculosis. So it can be concluded that bronchial arteries have an important role in lung infection.[11]

Infection by *Mycobacterium tuberculosis* is one of the most common causes of hemoptysis worldwide. Hemoptysis in the presence of TB is primarily caused by several etiopathologies, including bronchiectasis, aspergillomas, broncholiths, reactivation of TB, scar carcinoma, chronic bronchitis, pulmonary cavity's colonization, and vascular abnormalities such as pseudoaneurysms.[11,14] In active infection, cavitary lesion with inflammation may cause bronchial and alveolar ulceration that leads to necrotizing and erosion surrounding bronchial and alveolar blood vessels.[1,11]

Post TB sequelae with ectasis, hypervascularization, cavitary lesion, dilated bronchial blood vessel, and collateral anastomosis is usually found in inactive TB with hemoptysis.[1] In sequalae of TB infection, hemoptysis results from remodeling of lung parenchymal and vasculature. Recurrent or chronic infection and inflammation lead to permanent damage and dilatation not only on the bronchial lumen but also its arteries. Infection and/or inflammation presented in normal anastomoses between bronchial and pulmonary blood vessels become larger resulting in heavier blood flow through dilated bronchial arteries. Thus, the bronchial vessels become hypertrophied and ectatic. The new and collateral blood vessel made by angiogenic growth factors namely vascular endothelial growth factor (VEGF) is thin walled which is more prone to rupture. Hypervascularity, structural disturbances, and infection exposure in blood vessel make it more prominent to bleeding.[15]

Tuberculous cavities usually develop from caseous lesions that have liquefied and necrotic. Most of the cavities have collagen and spongy tissue on the inner and outer layers, and there is granulation tissue and capillaries between them. There is an incomplete thrombosis of the central vein, which can easily be affected by TB infection and cause hemoptysis. Pulmonary TB lesions can usually block blood vessels that carry blood at high pressure, causing damage and rupture of Rasmussen's aneurysm.[16]

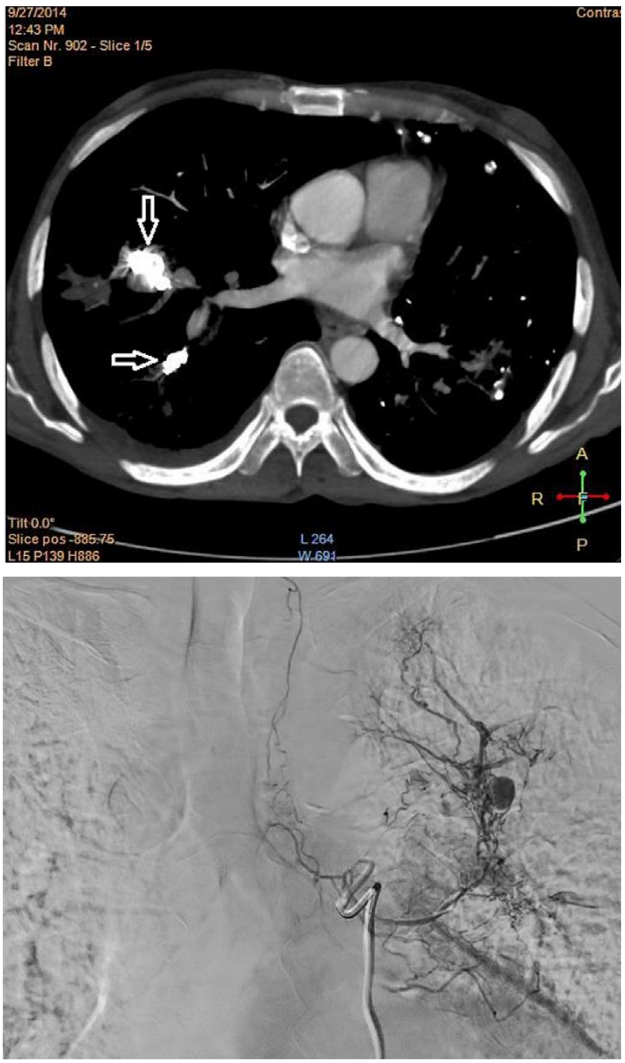

Figure 2. Rasmussen's Aneurysm[14,18]

Rasmussen's aneurysm was discovered by a Danish doctor named Fritz Valdemar Rasmussen. Rasmussen aneurysms have been described as pulmonary vessels penetrating the cavity wall of pulmonary TB, with aneurysmal enlargement occurring in 5% of patients with chronic cavitary tuberculosis (Figure 2). Cavities in pulmonary TB are formed due to the mechanism of TB immunopathogenesis which causes granulation tissue to form cavities. The inner walls of blood

vessels (adventitia and media) around the cavity are also coated with a layer of fibrinogen leading to thinning of the vessel wall and subsequent aneurysm formation and rupture leading to hemoptysis.[14,16–20]

Frailty of the bronchial and pulmonary artery walls is caused by granulation connective tissue replacing the tunica media and adventia. Then over time, it is replaced by a layer of fibrin, causing erosion of the arterial wall, resulting in a pseudoaneurysm. At this time, nutritional intake begins to be disturbed, resulting in hypoxic vasoconstriction mechanisms, intravascular thrombosis and edematous compression. This condition may lead to massive hemoptysis. Under normal conditions, an increase in intraarterial pressure can be compensated by the body. However, in chronic inflammatory conditions such as pulmonary TB there is an increase in pulmonary artery pressure.[14,17–19]

Hemoptysis may occur due to increased pulmonary artery pressure or compensation through the bronchial arteries. When the pulmonary artery pressure increases, the bronchial arteries dilate so that their thinner and more fragile surfaces are more susceptible to rupture or tear. Hemoptysis ranks second as one of the causes of death in patients with pulmonary tuberculosis. Death in hemoptysis is often caused by asphyxia, hemorrhagic shock, or both, so hemoptysis should not be underestimated. Pulmonary tuberculosis with hemoptysis can also increase the risk of TB transmission due to a greater bacterial load. In addition, hemoptysis can also cause complications, including pulmonary atelectasis. Rasmussen's aneurysm is a rare sequela of pulmonary tuberculosis but may result in life-threatening condition of hemoptysis.[14,16,17]

BRONCHIECTASIS

Bronchiectasis is an abnormal dilatation in bronchus and bronchioles caused by destruction of bronchial cartilage due to recurrent infection. Fibrosis of lung tissue also leads to bronchiectasis. Repeated bacterial infection leads to change in the surrounding bronchial arteries, hypertrophy, distortion, aneurysm formation, pulmonary vascular anastomosis, fistula formation or increased vascularization. Any of the above arterial rupture can cause massive, rapid, and fatal hemoptysis.[1,11,21]

In patients with bronchiectasis, hemoptysis is caused by hypertrophy of the bronchial arteries resulting in rupture of the bronchial arteries into the bronchial lumen. The bronchial arteries are branches of the thoracic aorta which possess higher systemic pressure than the pulmonary vessels. Normally, the bronchial arteries are present in the bronchi. In bronchiectasis, the pulmonary artery remains patent but as the disease progresses a thrombus form in the pulmonary artery. Then, recanalization occurs through bronchopulmonary anastomoses with dilated bronchial arteries. The modality for diagnosing bronchiectasis is high-resolution computed tomography (HRCT), showing ectasis in the bronchi and fusion of the bronchial arteries or the "signet-ring sign" (Figure 3).[2,11]

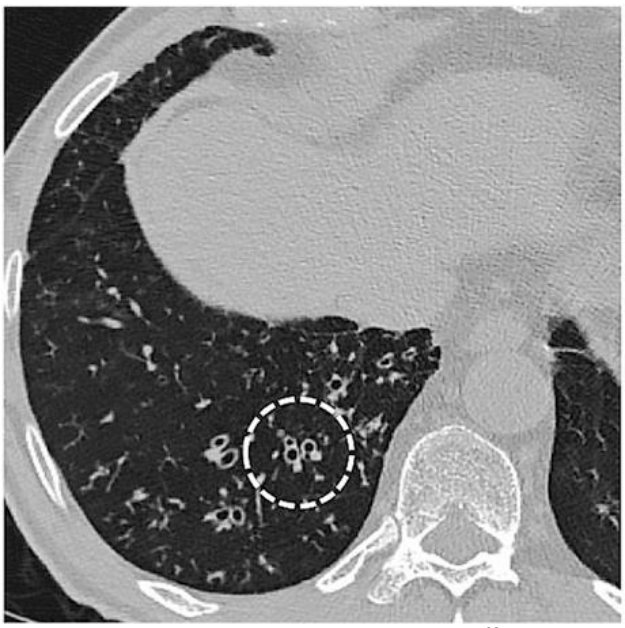

Figure 3. Signet ring signs from HRCT[22]

LUNG CANCER

Lung neoplastic lesions causing hemoptysis are divided into primary and metastatic lesions. Symptoms of hemoptysis in lung cancer patients are estimated to be 7-35%. Approximately 20-60% of primary lung cancer patients will eventually develop symptoms of hemoptysis, and 3% of them die due to massive hemoptysis. Hemoptysis in lung cancer metastases occurs only if the lesion is located in the

endobronchial lumen.[1,23]

Hemoptysis is generally divided into massive and sub-massive (non-life-threatening) hemoptysis. The incidence rates of massive and sub-massive hemoptysis are 3.3% and 16%, respectively. Massive hemoptysis usually depends on the type and location of the tumor. Massive hemoptysis is often caused by squamous cell tumors located in a central area or major airway. In sub-massive hemoptysis, there is no known cause yet. Sub-massive hemoptysis is more common in about 98% of cases. In contrast to squamous cell carcinoma (SCC), this type of adenocarcinoma cancer often originates in the peripheral areas. Hu et al (2013) showed that central lesions of lung tumors with symptoms of hemoptysis had the worst prognosis. It is because the tumor's location is easier to invade large blood vessels, although it is usually easier to detect with simpler investigations.[24]

Nichols et al (2012) stated that hemoptysis and SCC were significantly related. In terms of histological cell types, SCC is a type of tumor that often forms cavities and then invades blood vessels, cutting off blood supply and causing ischemic necrosis. However, SCC can fatally invade large blood vessels because of its central location.[24,25]

Therefore, SCC is contraindicated with bevacizumab therapy due to the inhibition of vascular endothelial growth factor (VEGF), which can lead to more frequent of hemoptysis. From the analysis results, VEGF expression, extra-tumor microvessel density (MVD), tumor necrosis, vascular invasion, and coagulation function described vascular invasion. All are important mechanisms of hemoptysis in lung adenocarcinoma. It can be concluded that the cancer cells in lung cancer patients with hemoptysis symptoms are more likely to invade other organs. In addition, hemoptysis can also be used as an independent prognostic factor with poor outcomes in lung cancer patients.[24,25]

PULMONARY MYCOSES

Pulmonary mycoses with hemoptysis symptoms include aspergillosis, coccidioidomycosis, and pulmonary histoplasmosis. Angioinvasion of fungal elements can cause structural damage to parenchymal and blood vessels, causing pulmonary infarction and bleeding. Aspergillosis is a type of pulmonary mycoses that often causes hemoptysis and it is estimated that 90% of people with aspergillosis have experienced at least one episode of hemoptysis in their lifetime. Hemoptysis is the most common symptom manifestation in patients with aspergilloma with an incidence rate of about 50-90%. The condition is rare but can be mild to life-threatening. The estimated mortality rate from massive hemoptysis is 38%. The dilated bronchial artery or intercostal artery is often surrounded by the cavity, which is highly susceptible to rupture and leads to massive bleeding.[1,11,21]

The pathogenesis of hemoptysis in pulmonary aspergillosis is local vascular invasion of the preexisting lung cavity and cystic spaces by *Aspergillus fumigatus*. Collateral vessels are formed between the bronchial and systemic arteries of the chest wall. The anastomosis causes an increase in blood supply to the infected tissue and mechanical friction between the fungus ball and the walls of the blood vessels around the cavity can be a predisposing factor for massive hemoptysis. The pathogenesis of hemoptysis in patients with pulmonary histoplasmosis and coccidiomycosis are through calcification of local lymph nodes. Calcification causes erosion of adjacent vascular vessels such as the bronchial arteries and surrounding tissues. Other several mechanisms of hemoptysis in fungal lung infections include 1) release of endotoxin by fungi accompanied by hemolytic material and 2) the length of the destructive process in the lungs due to infection in the pulmonary arteries causes prolonged inflammation so that the pulmonary arteries are always open.[1,26,27]

CONCLUSIONS

Hemoptysis must be distinguished from bleeding from organs other than the lungs (pseudohemoptysis). Mostly caused by a collapse of

the bronchial circulation due to the formation of bronchopulmonary anastomoses as a compensatory mechanism for increased pulmonary intraarterial pressure. Underlying lung disease may be the basis for the different mechanisms and pathophysiology of hemoptysis. Treatment strategies can change according to the etiology, and the primary types of treatments include medical management, embolization, and surgery.

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