

Research Progress on Diagnosis and Treatment of Bronchiectasis with Massive Hemoptysis

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Abstract: Hemoptysis is a common clinical manifestation in patients with bronchiectasis and one of the main causes for hospitalization, and massive hemoptysis is the most dangerous clinical manifestation in patients with bronchiectasis with high mortality. The pathogenesis of hemoptysis due to bronchiectasis is that long-term chronic inflammation and hypoxia induce bronchiectasis and stimulate bronchial angiogenesis, and finally rupture to lead to different degrees of hemoptysis. At present, there is no unified standard for the definition of massive hemoptysis due to bronchiectasis. Medical history and physical examination, laboratory tests and impact studies contribute to the diagnosis of massive hemoptysis due to bronchiectasis and to the determination of the bleeding point. Maintenance of airway balance and hemostasis are the focuses of treatment for massive hemoptysis due to upper bronchiectasis, among which hemostasis includes medical conservative treatment, bronchial artery embolization and surgical treatment.

1. Introduction

Hemoptysis is a common clinical manifestation of bronchiectasis and one of the main causes of hospitalization of bronchiectasis patients [1,2], a cohort study of bronchiectasis in France, one in five patients with a history of hemoptysis [3]. Hemoptysis is a symptom of 23% of patients according to a US bronchiectasis research registry. A multicenter study showed massive hemoptysis in 2.22% of patients with bronchiectasis [4]. Among them, the condition of patients with massive hemoptysis due to bronchiectasis is extremely dangerous. If no timely intervention is carried out, it will cause airway obstruction and suffocation, leading to a sharp decline in oxygen delivery function and endangering the life safety of patients. A study has shown that the mortality rate of patients with massive hemoptysis is 4%-12% [5]. Among them, asphyxia is one of the main causes of death in patients with massive hemoptysis due to bronchiectasis in the acute phase, so we need clinical medical staff to pay attention to it and take corresponding prevention and intervention measures. However, there are few studies related to massive hemoptysis due to bronchiectasis. This paper mainly summarizes the research progress on massive hemoptysis due to bronchiectasis, which will help clinicians to better understand and treat the disease.

2. Pathogenesis of bronchiectasis with massive hemoptysis

Accord to "vicious circle" study of Cole et al. [6], bronchiectasis is due to mucociliary clearance damaged by the initial invasion of airway, make bacteria and epithelial cells in contact for a long time, thus triggering a chronic inflammatory reaction, the release of protease produce epithelial damage and further changes of mucociliary system, so that the pathogenic vicious circle and eventually lead to irreversible expansion and deformation of bronchial lumen. Due to the influence of anatomical factors, the bronchial lumen of patients with bronchiectasis is more prone to pathogen colonization. Long-term chronic inflammation and hypoxia induce the hypertrophy and tortuosity of bronchial arteries in accompanying regional bronchial tree, and at the same time, the body secretes angiogenic factors to stimulate the proliferation of bronchial vessels. The bronchial arteries then form enlarged abnormal collateral vessels and systemic circulation—pulmonary vascular anastomosis or arterial fistula. If small vessels on the surface of bronchial mucosa or bronchial aneurysm rupture, they will cause different degrees of hemoptysis [7,8].

Comprehensive literature report [9,10], the pathogenesis of hemoptysis is mainly divided into the following three categories: (1) early lesions involving the capillaries, under the stimulation of inflammation and other factors, increased permeability of capillaries caused blood exudation, clinical manifestations of phlegm with blood and other symptoms. (2) The invasion of small vessels by medium-term lesions results in the destruction of the anatomical structure of the small vessel wall, and moderate and equal hemoptysis may occur. (3) The scope of advanced lesions is enlarged. Under the long-term stimulation of chronic inflammation, the normal anatomical functions of lung tissue and its blood supply vessels are damaged. Under the action of pulmonary artery pressure, these vessels rupture and enter the air cavity to cause massive hemoptysis.

3. Definition of massive hemoptysis due to bronchiectasis

Bronchiectasis can be diagnosed with high-resolution computed tomography, and the ratio of the cross-sectional diameter of the internal airway to that of its accompanying artery (the ratio of arteries within the airway) is >1.0 [11]. Massive hemoptysis is one of the most serious complications of bronchiectasis. The definition of massive hemoptysis is still unclear at present. The definitions of massive hemoptysis in different literature are different, which often depends on the quantitative estimation of hemoptysis. For example, the hemoptysis occurs within 100-600 mL in 24 hours, or three times or more in one week. The hemoptysis occurs more than 100 mL every time. However, the hemoptysis is difficult to estimate accurately, and it is difficult to quantify hemoptysis clinically. There are significant subjective factors and errors. Therefore, it has been proposed in the literature that massive hemoptysis can be defined as any life-threatening hemoptysis, such as hemoptysis caused by unstable circulation or airway obstruction and asphyxia [12-14]. Therefore, there is still no unified standard for the evaluation of massive hemoptysis.

4. Diagnosis and treatment of massive hemoptysis due to bronchiectasis

4.1. Medical history and physical examination

A detailed understanding of the patient's medical history and physical examination is helpful for the diagnosis of the patient's disease. Comprehensive physical examination helps us to identify the source of bleeding and the cause of hemoptysis. The first step in receiving the patient is to understand the current history of hemoptysis, the precipitating factors, relevant past history of hemoptysis, and the concomitant disease history. The initial age of hemoptysis, specific volume of hemoptysis, the nature of hemoptysis and accompanying symptoms are important for the initial diagnosis. A study

has shown that [15], not quit smoking, course of disease more than 5 years are the high risk factors of massive hemoptysis bronchiectasis. Post-tuberculosis is a common cause of bronchiectasis, and patients with post-tuberculosis bronchiectasis have a significantly lower BMI and a significantly higher frequency of hemoptysis compared to other causes [16]. In addition, the history of diabetes mellitus is also one of the high risk factors for massive hemoptysis [15]. Therefore, it's necessary to understand the patient's related medical history, which can help us to improve our vigilance and prevention of massive hemoptysis in patients with bronchiectasis. Meanwhile, bronchiectasis with massive hemoptysis needs to exclude the possibility of hemoptysis caused by other causes. A detailed understanding will help us to distinguish massive hemoptysis caused by other causes, such as pulmonary tuberculosis, lung cancer, lung abscess, and heart disease. It also helps us to differentiate the bleeding from hemoptysis or hematemesis.

4.2. Laboratory examination

Initial evaluation should include complete laboratory tests such as sputum culture, routine blood tests, coagulation functions, arterial blood gas analysis, and liver and kidney functions. A complete laboratory examination can help us to identify possible hemoptysis caused by other causes, such as abnormal coagulation, and evaluate complications caused by hemoptysis. Sputum culture is a very important examination, and invasive bacteria such as *Pseudomonas aeruginosa* or fungi (such as *Aspergillus*) have been shown to be a common cause of hemoptysis [17]. And *Pseudomonas aeruginosa* is a common co-infection flora in bronchi, so perfecting sputum culture can help to give corresponding anti-infection treatment. In addition, the improvement of coagulation function and liver and kidney function can help us to exclude the possibility of hemoptysis caused by other causes, such as autoimmune lung-kidney syndrome.

4.3. Imaging examination

Imaging is essential for the diagnosis of massive hemoptysis, allowing the etiology to be clarified and the site of bleeding to be identified. Chest X-ray photography (chest radiography) is one of the most convenient and economic radiological examinations, which can identify which side of the lung is bleeding and to some extent identify such as lumps, pneumonia, chronic lung disease, bronchiectasis, and cavitory lesions, providing effective clues for identifying the causes of hemoptysis. However, chest radiography only shows the positive and negative sides, and thus has the disadvantages of less important information and low diagnostic sensitivity [18]. With the development of imaging, especially the emergence of chest CT, as CT can detect distal bronchial lesions, the collected imaging data in more detail greatly improve the diagnosis rate of hemoptysis. among them, the MDCT section is a continuous 1 mm slice, which can significantly improve the diagnosis rate and confidence of bronchiectasis compared with the HRCT section with 1 mm for every 10 mm [19]. In addition, CTA can non-invasively reconstruct the pulmonary vessels, which can help us to identify the vessels causing hemoptysis due to bronchiectasis. Studies have reported that MDCTA can effectively reconstruct the bronchial artery and non-bronchial system artery related to hemoptysis [20]. And it can evaluate the source of abnormal blood vessels (from bronchial artery or non-bronchial system), the number, diameter and morphology of bronchial artery, to provide conditions for guiding further interventional embolization treatment. At the same time, the identification of abnormal arteries before endovascular intervention will help to select the embolic approach to the blood vessels, select the appropriate embolic agent, and avoid the occurrence of bolt leakage and ectopic embolism [21,22].

5. Treatment

5.1. Maintain airway patency

The first step in the treatment of acute massive hemoptysis due to bronchiectasis is to keep the airway patency and vital signs stable as far as possible: (1) The first point of keeping the airway open is to protect the non-bleeding lung, which can be achieved by turning the patient to the bleeding side so that blood is isolated by gravity into the bleeding lung and the non-bleeding side remains intact and completely ventilated [23]. (2) Cough reflex is a protective mechanism in human body, which can clear the blood and secretions in the airway through cough to reduce the possibility of suffocation. Patients should be encouraged to clear the airway hematopoiesis through cough. (3) Bronchoscopy is an important tool for the diagnosis and treatment of massive hemoptysis. Bronchoscopy can be divided into rigid bronchoscopy and flexible bronchoscopy. Rigid bronchoscopy can quickly attract blood while keeping the airway clear. Emergency intervention of endoscopic surgery is usually the only way to overcome the asphyxia or pre-asphyxia condition at present [24], but the rigid bronchoscopy needs to be performed under general anesthesia. And the operation is complex, and the airway cannot be reached except for the trachea, bulge and main bronchus. Flexible bronchial tube diameter is relatively small, easy to use, can reach the trachea subsection, help quickly find the source of bleeding. FOB can identify 73% to 93% of the bleeding sites of massive hemorrhage attack. A study showed that in patients with bronchiectasis hemoptysis, 9.2% of the CT scan found bleeding source is uncertain on both sides. Only through bronchoscopy localization bleeding source, and the last hemoptysis attack within 48 hours after bronchoscopy can better detect bleeding source [25]. At the same time, endoscopic treatment such as local spraying of normal saline with ice blocks, dilution of adrenaline, thrombin or fibrin complex to constrict blood vessels for hemostasis is feasible. Or when petechia is directly observed under a bronchoscope, hemostasis can be performed through laser, electric knife, argon knife or freezing technology to play a role in isolating the bleeding source.

5.2. Hemostasis

5.2.1. Conservative treatment in internal medicine

At present, the common drugs for conservative treatment of massive hemoptysis include vasoactive drugs, drugs for correcting coagulation disorders, and traditional Chinese medicines, including pituitrin, hemagglutininase, ethambutol, vitamin K, aminotoluic acid, Yunnan Baiyao Capsule, and phentolamine. Its vasoactive drug pituitrin is known as "internal medicine hemostatic forceps", and intravenous injection can cause pulmonary vasoconstriction, pulmonary circulation blood pressure drop, and blood clot formation at vascular damage, so as to achieve the purpose of hemostasis. Phentolamine is an alpha receptor blocker, which has the effect of relaxing blood vessels, and reflex excitation of cardiac beta receptor at the same time, to enhance myocardial contractility, and significantly increase cardiac output. Pulmonary artery pressure, pulmonary capillary wedge pressure, pulmonary vascular resistance, and systemic vascular resistance are decreased, so that pulmonary arterial and venous pressure and bronchial arterial pressure are decreased simultaneously to exert the hemostatic effect. Studies have shown [26], pituitrin combined with phentolamine for massive hemoptysis patients have better hemostatic effect, at the same time can significantly reduce the risk of adverse reactions. If the patients with massive hemoptysis suffer from thrombocytopenia or abnormal coagulation function inside and outside the blood vessel, the hemostasis should be treated by transfusion of blood products such as platelets, fresh frozen plasma, and cryoprecipitate while using hemostatic drugs. Li Fajiu et al. studied [27] 72 patients with massive hemoptysis. Among them, 35 patients were treated with hemostatic drugs only, and 37 patients were treated with hemostatic

drugs combined with cold precipitation. The results showed that the coagulation function of patients treated with cold precipitation was significantly improved, and the use of cold precipitation could shorten the time of hemoptysis and reduce the occurrence of adverse reactions. A prospective cohort study showed that 70% of patients could immediately stop bleeding by using plasma exchange and autologous platelet-rich plasma isolation to extract autologous platelet-rich plasma, positioning the bleeding site with the assistance of bronchoscopy and simultaneously instilling autologous platelet-rich plasma, but the sample size of this study was small, and a large sample size RCT was required to identify its effect on the in-hospital management of massive hemoptysis.

5.2.2. Bronchial artery embolism

With that development of interventional medicine, bronchial artery embolization has become the first choice for the treatment of massive hemoptysis and repeat hemoptysis due to bronchiectasis. The research of Baorui Chen et al. showed that [28]: 63 cases of bronchiectasis with massive hemoptysis patients after bronchial artery embolization, hemostatic total effective rate was 97%, the cure rate was 83%, the main adverse reactions including low grade fever, intercostal pain, sternal burning sensation, dysphagia and other discomfort, after symptomatic treatment can be significantly relieved, but half a year in five patients with hemoptysis again symptoms, recurrence rate was 8%, within one year in seven patients with hemoptysis again symptoms, recurrence rate was 11%. Donghui Ma et al have shown that [29] after BAE surgery, the total effective rate and the cure rate of 46 patients with massive hemoptysis due to bronchiectasis were 91. 3% and 69. 6%, respectively. The total effective rate was significantly higher than that of the control group, and the incidence of adverse reactions was significantly lower than that of the control group. By observing 159 patients with massive hemoptysis due to bronchiectasis, Khalil et al. found that [30] the curative rate was 79% after BAE operation. In addition, BAE is characterized by high safety, rapid onset, less complications and repeatable treatment. At the same time, it can effectively prepare patients for elective surgery and reduce the risk of perioperative bleeding in patients. However, BAE has a high recurrence rate, which is related to the non-bronchial systemic collateral and the significantly increased recurrence rate of bronchopulmonary shunt.

5.2.3. Surgical treatment

With the wide application of bronchopulmonary embolism and the high risk, trauma and high mortality of emergency operation, emergency operation is currently rarely used as the preferred treatment for bronchiectasis with massive hemoptysis. Studies have shown that the incidence of postoperative complications in patients receiving emergency pneumonectomy due to bronchiectasis with massive hemoptysis is 25.8%-29.6%, and the in-hospital mortality is 5.1%-15% [31]. Surgery for bronchiectasis with massive hemoptysis is associated with a high risk and a high mortality rate for patients with a significant decrease in secondary pulmonary function [32], greatly limiting its clinical application. However, patients who have received BAE are still at risk for recurrent hemoptysis, requiring surgery as an emergency response if other approaches fail [33]. According to research conducted by Bing Wang et al. [34], surgical approaches include traditional thoracotomy and video-assisted thoracoscopic surgery. Compared with traditional thoracotomy, video-assisted thoracoscopic surgery has the advantages of less complications, short operation time, less intraoperative blood loss, less postoperative drainage. It can improve postoperative pain management, and shorten postoperative hospital stay, which is the first choice for surgical treatment. In addition, compared to elective pneumonectomy, emergency surgery mortality significantly increased. A study showed that [35] surgical resection was divided into three groups: emergency resection, planned resection (after hemorrhage control) and planned resection (after discharge). The mortality rates in

each group were 35%, 4% and 0%, respectively. Studies have demonstrated the importance of avoiding emergency resection where possible, using non-surgical methods to stop bleeding before any resection and optimizing the patient's condition to minimize morbidity and mortality. Tao Ge et al. [36] found no hemoptysis recurred during the follow-up period after operation among the 21 patients who adopted BAE combined with pneumonectomy for the treatment of bronchiectasis with hemoptysis. And only one patient had mild hemoptysis during the follow-up period, this indicated that the combined operation could improve the long-term efficacy of BAE alone.

6. Summary and outlook

Massive hemoptysis is one of the most fatal clinical manifestations of bronchiectasis and one of the causes of hospitalization for bronchiectasis patients. The diagnosis of massive hemoptysis due to bronchiectasis needs to be evaluated and distinguished from other etiologies by history, physical examination, laboratory and imaging studies, of which imaging studies are the most important. The treatment of massive hemoptysis due to bronchiectasis includes stabilization of airway and hemostasis. Among them, stabilization of airway and prevention of asphyxia are the most important rescue functions during acute hemorrhage period. Bronchoscopy plays an important role in stabilizing airway. It can not only clear the accumulated blood in airway, but also help to quickly find the source of hemorrhage and conduct endoscopic hemostasis treatment. Hemostatic treatment include conservative drug therapy, bronchial artery embolization, and surgical treatment. Among them, massive hemoptysis is treated with poor drug effect and can be used as a treatment before and after bronchial artery embolization. Bronchial artery embolization is that first choice for hemostatic treatment at present, with good hemostatic effect and high safety, but it has the characteristic of insufficient repeated rebleeding. Surgical treatment can be the final option for patients with recurrent bleeding and poor medical and BAE treatment, but emergency surgical treatment should be avoided as much as possible. At present, the research on massive hemoptysis due to bronchiectasis is relatively few, including the research on high risk factors and prognosis of massive hemoptysis due to bronchiectasis. The research is in the stage of research and exploration, and more scientific research and clinical practice are required to explore and promote.

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