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CRYOTECHNOLOGY IN LUNG AND HEART-LUNG TRANSPLANTATION

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Bronchial complications, along with development and progression of chronic dysfunction on the background of chronic rejection, are factors that reduce the quality and life of lung and heart-lung recipients. They also increase the frequency of hospitalizations. Application of cryotechnology is based on the contact effect of extremely low temperatures on organs and tissues using a cryoprobe. This article demonstrates the experience of using cryotechnology in the diagnosis and treatment of complications in lung and heart-lung recipients.

Keywords: lung transplantation, heart-lung transplantation, bronchial complications, cryotechnology, cryoablation, cryobiopsy, cryoadhesion, extraction of airway foreign bodies.

INTRODUCTION

According to the World Health Organisation (WHO) 2019 report, chronic lung diseases, including chronic obstructive pulmonary disease (COPD), are the third leading cause of death worldwide [1]. It is important to note that this report does not take into account COVID-19-associated mortality, whose consequences increased mortality rates significantly due to the complicated course of the disease. Lung transplantation (LT) is currently the only curative treatment for severe chronic respiratory failure [2]. Sixty years have passed since the first LT was performed by J. Hardy et al. Since then, LT has come a long way from single transplantations with a high incidence of adverse outcomes to an almost routine treatment method [3].

Despite improvements in immunosuppressive therapy protocols, surgical techniques, donor organ preservation methods, as well as approaches to early rehabilitation of recipients, the average life expectancy of lung recipients remains at a relatively low level in comparison with recipients of other solid organs, for which there are a number of objective reasons. Based on evaluation of 16,156 consecutive adult LT recipients, Hayanga et al. found that survival rates were reduced in recipients with airway complications (54.6% vs 84.4%, at 1 year, and 33.2% vs 54.2% at five years) [4]. Several authors have reported the incidence of airway complications to be between 2% and 18% [5, 6], and most cases occur in the first year after transplantation. Among them, the greatest number comes from bronchial stenosis (BS), whose incidence varies from 1.4% to 32%. This undoubtedly demonstrates the high interest in methods aimed at early diagnosis and treatment.

At the same time, the main factor limiting the life expectancy of lung recipients is the development and progression of chronic graft dysfunction on the background of chronic rejection [7]. Differential diagnosis of some complications is sometimes difficult due to the similarity of symptoms and lack of pathognomonic signs.

Bronchial stenosis leads to impaired airway patency and decreased respiratory volumes, which, based on the totality of clinical manifestations, can also be interpreted as dysfunction of transplanted lungs. In this case, one of the main methods of differential diagnosis is endoscopic examination.

This article presents the main techniques of endoscopic diagnosis and treatment of airway complications in lung recipients using cryotechnology.

PHYSICAL PRINCIPLES OF CRYOTECHNOLOGY APPLICATION

Cryosurgical techniques used in endoscopic practice are based on local exposure of organs and tissues to low temperatures in the area of contact with the working surface of the cryoprobe. This technique allows for cryobiopsy, cryoablation, cryorecanalization, as well as removal of foreign bodies [8].

The cryoprobe works on the Joule–Thomson physical principle, which consists in changing the temperature of a liquefied gas as a result of a pressure drop from high to atmospheric pressure [9]. Nitrogen oxide (N_2O), carbon dioxide (CO_2), and liquid nitrogen (N_2) are used as liquefied gas. Transition of nitrogen from liquid to gaseous state when it enters from the cryoprobe nozzle is accompanied by a decrease in the temperature of the working part of the tool to –89 °C. Carbon dioxide has

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long been considered unsuitable for use in endoscopy because its expansion forms ice crystals that damage the endoscope. However, modern cryoprobes do not form such crystals, and CO_2 is a good alternative to N_2O, given its lower cost. Liquid nitrogen creates a temperature of –196 °C at the distal end during expansion [8]. That is why this gas has not been widely used due to its greater penetration depth and high risk of perforation.

CRYOBIOPSY IN THE DIFFERENTIAL DIAGNOSIS OF GRAFT REJECTION

Transbronchial lung biopsy (TBB) has become the gold standard for diagnosis of rejection in LT recipients. One of the modern methods is transbronchial lung cryobiopsy (TBLC). As a result of low temperatures, tissues are fixed to the distal edge of the cryoprobe.

Unlike traditional forceps biopsy, the quality of the diagnostic material obtained is much higher when performing TBLC, which is down to the absence of the effect of crushing by the brushes of biopsy forceps [10]. See Fig. 1.

The main complications arising after cryobiopsy include bleeding [11, 12], as well as development of pneumothorax [13, 14].

From September 2019 to April 2022, 13 cryobiopsies were performed in 9 lung transplant recipients at Shumakov National Medical Research Center of Transplantology and Artificial Organs.

Biopsies were performed in the operating room under general anesthesia with the use of high-frequency ventilation and rigid bronchoscope. The video bronchoscope was sequentially inserted through the tube of the rigid bronchoscope into the subsegmental bronchi. A cryoprobe was inserted through the instrument channel of the endoscope. Then, liquefied gas was supplied through the cryoprobe for 3 seconds, which resulted in freezing of the nearby tissues in contact with it. The endoscope with cryoprobe and biopsy specimen was removed from the bronchial tree. The final stage was control bronchoscopy to assess the degree of bleeding and, if necessary, to achieve hemostasis. After the procedure, control chest x-ray was performed to exclude pneumothorax. Biopsy material was fixed in neutral formalin and sent for routine histopathological examination.

The average number of biopsies was 4–5 fragments. The average biopsy size was 12.4 mm^2, which is significantly larger than the average size of the material obtained by forceps biopsy (4.2 mm^2) ($p < 0.05$). The quality of histological preparations of lung biopsy specimens was significantly higher than that obtained by conventional forceps biopsy.

Seven recipients had post-TBLC complications: pneumothorax (3 cases, 2 of which required pleural cavity drainage, 1 was resolved conservatively (Fig. 2)); pulmonary hemorrhage that stopped conservatively (4 cases, 26%). No other complications were recorded.

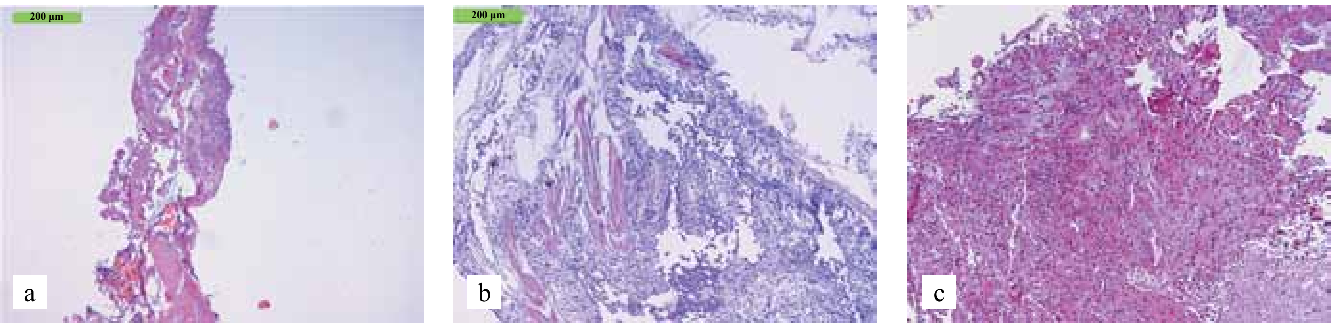

Fig. 1. Dimensions of cryobiopsy specimens: a, standard transbronchial biopsy; b, c, transbronchial lung cryobiopsy

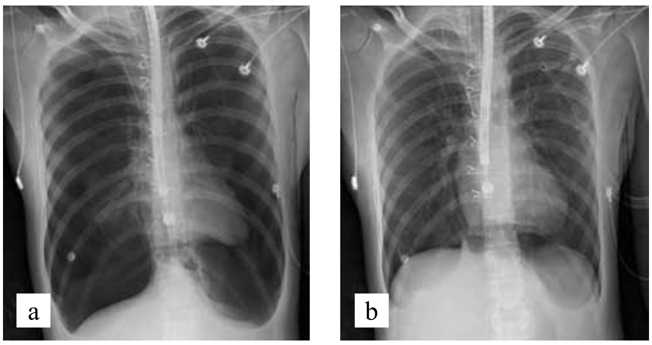

Fig. 2. Chest radiograph: a, bilateral spontaneous pneumothorax in a heart-lung recipient after transbronchial lung cryobiopsy; b, condition after drainage of the thoracic cavity

CRYOABLATION IN THE TREATMENT OF BRONCHIAL STENOSIS

Post-transplant BS is a persistent, breathing-independent narrowing of the lumen due to scar or granulation tissue. The most frequent periods of stenosis occurrence are the first 2–9 months after transplantation [15–19]. Recurrent stenosis of the intermediate bronchus, called vanishing bronchus intermedius syndrome (VBIS) (see Fig. 3), belongs to a separate group. The incidence of this complication is up to 2% [19]. The average life expectancy after diagnosis is up to 25 months [20].

As mentioned above, bronchial stenosis can be divided by mechanisms of occurrence into the following groups: stenosis caused by the growth of scar tissue [21]; stenosis caused by the growth of granulation tissue.

Cryoablation, also referred to as cryotherapy, involves cycles of rapid freezing (–20 to –100 °C) and slow thawing of tissues, which leads to the formation of intracellular ice crystals and cell death [22–24]. The main mechanisms of intracellular effects are damage to mitochondria and other organelles, cellular dehydration, increased concentration of intracellular electrolytes, and denaturation of membrane lipoproteins. Vascular changes include initial vasoconstriction of arterioles and venules, vascular endothelial damage, decreased intracapillary hydrostatic pressure, and decreased blood flow. It is worth noting that the occurrence of thrombosis of the microvasculature of tissues exposed to low temperatures is the cause of minimal bleeding associated with this method.

It is customary to divide tissues into those that are more sensitive to freeze-induced devitalization, such as skin, mucous membrane, granulation tissue, and tumor cells, and those that are less sensitive, such as fat, cartilage, and connective tissue [25].

The depth of cryotherapy exposure in the bronchial tree is approximately 3 mm, but this depends on the exposure and the gas used [26]. This feature, together with the cartilage's resistance to cryotherapy, reduces the risk of airway perforation. It is important to note that the destructive effects of cryotherapy do not manifest themselves immediately, but are delayed. It takes several days to weeks for tissue necrosis to manifest, during which tissue rejection continues, sometimes requiring removal of necrotic scab during therapeutic bronchoscopy.

M.O. Maiwand et al. used cryoablation as a therapy for granulation stenosis in 21 recipients [27]. Each patient required an average of about 3 cryotherapy sessions. The endoscopic cryotherapy results were rated as excellent or good in 15 patients, and as satisfactory in 6 patients. Eight recipients required endobronchial stenting as part of comprehensive treatment, whereas cryotherapy and balloon dilatation alone were effective in 13 recipients.

Cryoablation complications include bleeding occurring both during the procedure and several days later, mucosal necrosis and bronchial wall perforation, edema, and lumen obstruction by necrotic tissues.

In our practice, cryotherapy was performed in 16 patients with cicatricial granulation stenosis of the intermediate bronchus; a total of 52 cryotherapy sessions were performed. In 30 cases, balloon dilatation was performed as an initial step in order to ensure adequate lumen and preserve ventilation of the distal parts of the lung. Then, three freeze-thaw sessions of 30–45 seconds each were performed using a cryoprobe with a diameter of 2.4 mm. Tissue-freezing time was controlled visually until ice formation on the cryoprobe surface stopped. Tissue thawing was stopped until the cryoprobe moved away from the mucosa. Then, the cryoprobe was moved 5–6 mm away from the affected area, and cryotherapy sessions were repeated until the stenosis area was completely treated (Fig. 4).

Control endoscopic examinations were performed on days 7, 14, and 21 after cryoablation. Twelve patients required repeated cryotherapy sessions. In 7 patients, stenting was performed to preserve the bronchial lumen. No cryotherapy-associated complications were observed.

FOREIGN BODY EXTRACTION

The cryoprobe can be used to extract foreign bodies, mucous and blood clots located in the lumen of the bronchial tree [28, 29].

Some types of foreign bodies, such as staples, metal prostheses, are more difficult to remove from the bronchial tree using a cryoprobe. However, the use of a small amount of sterile sodium chloride solution can improve the effectiveness of this procedure [30].

In our practice, blood clot extraction was performed after pulmonary hemorrhage. Two patients after lung transplantation had pulmonary hemorrhage, for which emergency bronchoscopy was performed. After effective hemostasis, there was still a picture of bronchial obstruction with hemorrhagic clots, cryoextraction was performed using a flexible bronchoscope and cryoprobe (see Fig. 5).

It is worth noting that the removed fragments were less subjected to fragmentation than when classical clot extraction methods were used.

Fig. 3. Variants of intermediate bronchial stenosis

CONCLUSIONS

According to the International Society for Heart and Lung Transplantation (ISHLT), there is a steady trend towards an increase in the total number of lung transplants [7]. However, complications occurring at different times after surgical intervention contribute to the decrease in the quality and duration of life in this patient cohort.

Early diagnosis of complications can improve long-term results after lung and heart-lung transplantation.

TBLC in lung recipients is a highly informative and relatively safe procedure [31, 32]. It can be used to obtain material with greater diagnostic value compared with conventional forceps biopsy. In our study, the incidence of complications is comparable to similar data described in the literature.

It is worth noting that there is no single approach in the treatment of bronchial stenosis [17, 33]. Cryoablation is one of the components of combined treatment in this group of patients [34]. In our practice, no cryotherapy-associated complications were encountered. This suggests that the technique is relatively safe. At the same time, recurrent stenosis after cryoablation makes it necessary to use combined techniques to restore airway patency.

Extraction of foreign bodies, in particular blood clots, using a cryoprobe, is an alternative highly effective method of restoring airway patency. This manipulation significantly reduces the duration of intervention compared to mechanical capture and extraction.

Thus, the use of cryotechnology in endoscopic interventions in lung recipients is a highly effective technique that allows solving a wide range of problems. This has a positive impact on the effectiveness of LT.

The authors declare no conflict of interest.

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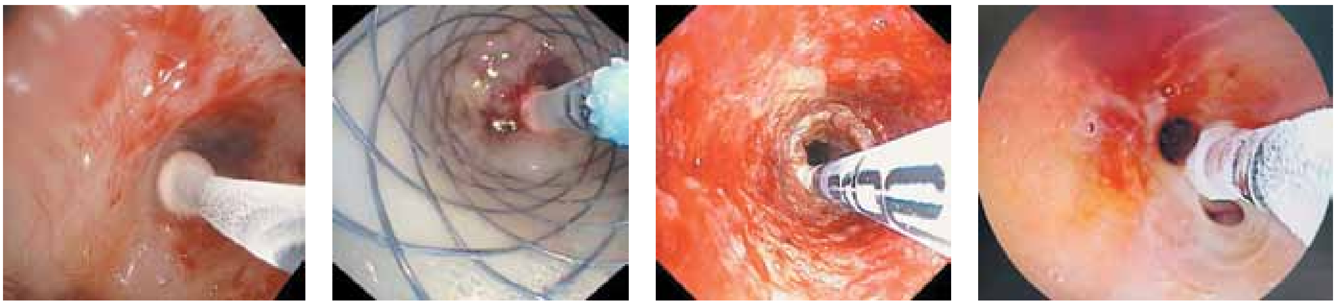

Fig. 4. Cryotherapy with a 1.9 mm and 2.4 mm probe

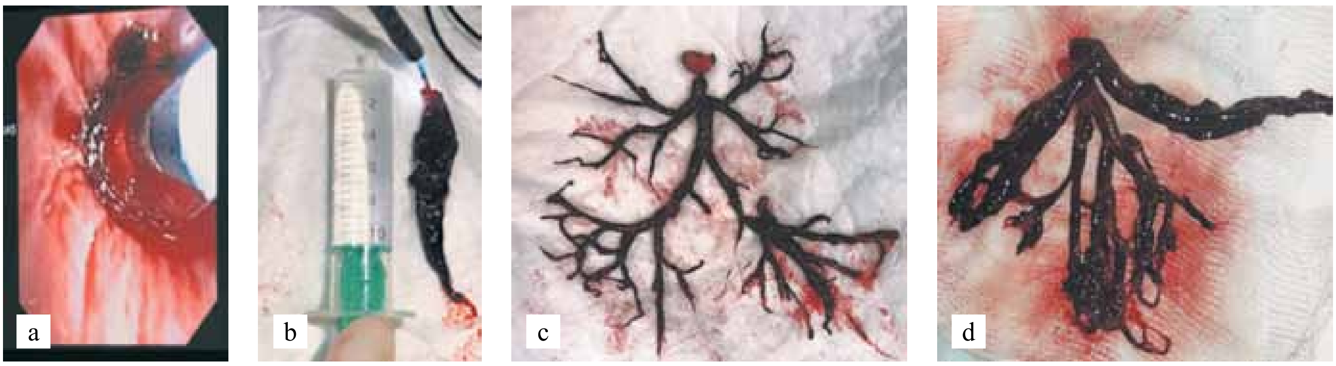

Fig. 5. Clot extraction using a cryoprobe: a, the moment of clots extraction; b–d, extracted clots

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