Cryotherapy and Cryospray

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Introduction

Endobronchial cryotherapy refers to the use of freezing temperatures inside the airway, with the help of flexible cryoprobe or cryospray. While using cryoprobe, the cryogen is recirculated in the probe catheter and never released endobronchially. Spray cryotherapy (SCT), however, involves direct application of cryogen and hence its release inside the tracheobronchial tree. There are several uses for cryoprobes such as diagnostic biopsies and therapeutic interventions that work on two primary principles, that is, cryoadhesion and cryoablation.

Cryoadhesion refers to adherence of target tissue to the tip of cryoprobe due to rapid freezing of fluid in the interface and inside the tissue. This principle is used for retrieving endobronchial tissue including tumor and granulation tissue for diagnostic purposes as well as for intent of mechanical debulking. Some foreign bodies are also retrieved by using cryoadhesion and can lead to avoidance of rigid bronchoscopy. Finally, pulmonary parenchyma can also be adhered to tip of cryoprobe for a transbronchial cryobiopsy and has diagnostic applications for diffuse parenchymal lung disease and peripheral lung nodules.

Cryoablation refers to the tissue destruction induced by crystallization of intracellular water content and disruption of cell membrane upon freezing. A chain of events ensue, eventually leading to cell death and necrosis with resultant "slow" debulking of endobronchial tumors [1]. This effect of cryotherapy is also referred to as "Cold ablation" or cryodevitalization.

Historical Perspective

The word "Cryo" originates from the Greek word "kruos" and when translated to English means "ice cold" or "frost." The cryoprobe was initially devised for neurosurgical application [2]. The first use of cryotherapy in an endobronchial application was described in 1968 by Gage in the form of a rigid cryoprobe applicator on an endobronchial tumor [3]. It worked on the principle of using extreme cold in a rapid "freeze and thaw cycle" to incite cell death and cause tumor destruction [3, 4]. The advent of flexible cryotherapy probes in 1994 (ERBE Elektromedizin GmbH, Tübingen, Germany) led to widespread utilization of this technology, which now constitutes as the most common method of endobron-

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chial application [5]. This is in part due to the ease of application via either the flexible or rigid bronchoscope.

Spray cryotherapy was first described for endoscopic use in the esophagus in 1999 [6]. Several endobronchial applications have been explored since then for cryoablation for airway stenosis and an investigational utility in chronic bronchitis.

Equipment

The two essential components of cryotherapy include the cryogen and the delivery device.

The cryogen or the cooling agent is a liquified gas stored in a tank under pressure. The cryogen when applied in the form of cryoprobe or cryospray incites the freezing of tissue for the desired effect. The gases used for probe cryotherapy include nitrous oxide (N_2O), carbon dioxide (CO_2) and for spray cryotherapy include liquid nitrogen (N_2) [1, 7].

The delivery device includes three things:

1. The tank in which the cryogen is saved.
2. The console and the foot paddle for a controlled release of the cryogen by the proceduralist.
3. The probe or catheter delivers the cryogen to the desired target.

There are two vastly used ERBE probe cryotherapy systems. The previous generation console ERBOKRYO® CA (ERBE Elektromedizin GmbH, Tübingen, Germany) has an analogue

Fig. 12.1 Title: Cryotherapy Equipment. Description: (**a**) shows the old generation ERBOKRYO® CA unit. (**b**) Shows the Erbe pulmonology workstation that includes the newer generation ERBECRYO® 2 console. (Image© Erbe Elektromedizin GmbH)

switch and basic controls. It uses a foot paddle with a light indicator for when the device is activated. It also has an analog manometer that shows the pressure of gas, usually 45–50 bar (Fig. 12.1a). This machine uses N_2O or CO_2 with reusable cryoprobes and is not in production anymore.

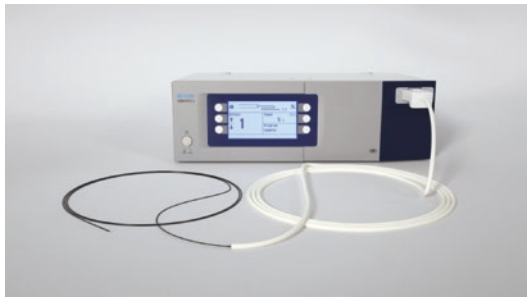

Fig. 12.2 Title: ERBECRYO® 2 console. Description: The newer generation cryotherapy console has a digital display. It has a broader functionality and the ability to select effect level and presets for application. (Image© Erbe Elektromedizin GmbH)

The newer generation ERBECRYO® 2 (ERBE Elektromedizin GmbH, Tübingen, Germany) uses CO_2 gas and has a digital display with a broader functionality (Fig. 12.2). Although it has similar clinical functionality, it has different presets for the user, including cryoablation, cryobiopsy, and free freeze option. It also shows the timer, effect level, and information on cryoprobe which is automatically detected by the console. This equipment is available as a standalone device or as a part of the Erbe pulmonology workstation (Erbe Elektromedizin GmbH, Tübingen, Germany) which combines units for electrosurgery, Argon plasma coagulation, and cryosurgery (Fig. 12.1b).

Flexible cryoprobes consist of a long-insulated catheter with a blunt metal tip and can be passed through a flexible bronchoscope for endobronchial utilization. The reusable cryoprobes are not in production anymore but still in use at some centers with the previous generation ERBOKRYO® CA console. They are 78–90 cm in length and

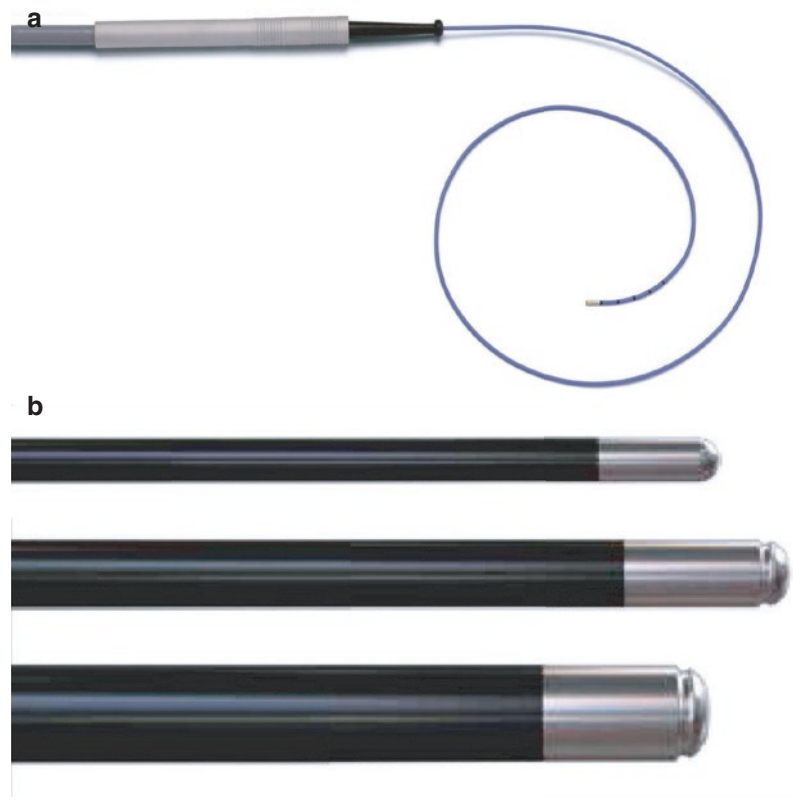

Fig. 12.3 Title: Cryoprobes. Description: (**a**) shows the reusable cryoprobe that is compatible with ERBOKRYO® CA console and is available in 1.9 mm and 2.4 mm size. (**b**) Shows the single use cryoprobes that are compatible with ERBECRYO® 2 and available in 1.1 mm, 1.7 mm and 2.4 mm size. (Image© Erbe Elektromedizin GmbH)

are available in 1.9 and 2.4 mm size (Fig. 12.3a), for use with a minimum working channel of 2.0 and 2.8 mm, respectively [1]. The tip of the reusable cryoprobe is approximately 6 mm in length [7, 8]. The single use cryoprobes are exclusively used with ERBECRYO® 2 console and are developed to overcome technical limitations with miniaturization as well as to better ensure reproducibility. These disposable cryoprobes also overcome the risk of cross-contamination that can be an area of concern with reusable probes [9]. They are 115 cm in length and available in 1.1 mm, 1.7 mm and 2.4 mm (Fig. 12.3b), for use with a minimum working channel of 1.2, 2.0, and 2.8 mm, respectively [7].

Rigid cryoprobes are also available as straight or right-angled tip and may have a reheating system to allow rapid thawing. They are 60 cm in length with a 3 mm diameter and 9.2 mm cooling tip [1]. The equipment for spray cryotherapy is described in a separate section in the later part of this chapter.

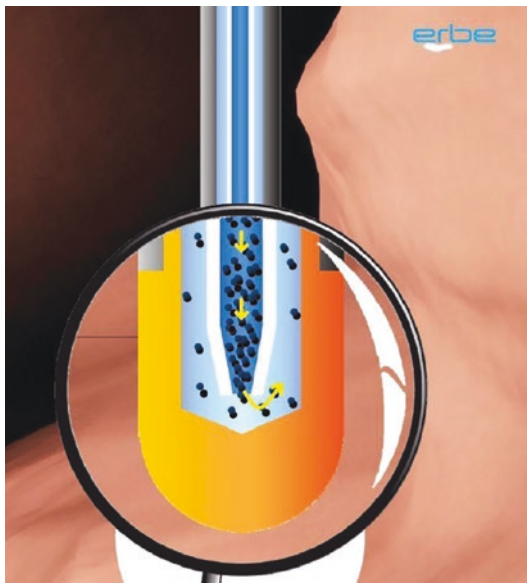

Fig. 12.4 Title: Joule-Thompson Effect. Description: Cryogen is released from the tank in a controlled fashion. It travels through the inner channel and is forced to pass through the nozzle at tip of the cryoprobe. The relaxation gather energy and cools down the surrounding region leading to a freezing effect. (Image© Erbe Elektromedizin GmbH)

Mechanism of Action

The freezing effect of probe cryotherapy is based on the Joule-Thompson effect (Fig. 12.4). The pressurized cryogen gas from the cylinder (either carbon dioxide or nitrous oxide) is forced through the narrow inner channel of the flexible cryoprobe to the tip of the probe. After passing the internal nozzle, the pressurized gas suddenly decompresses and cools. The relaxation of cryogen gathers energy from the surrounding area and cools down to the freezing temperature of the gas (−78.5 °C for CO_2 and –89 °C for N_2O) to incite freezing of tissue in contact with the tip of the probe [4]. Since it is a closed system, the cryogen does not come in direct contact with the tissue. The decompressed gas is then returned to the console via the external channel of cryoprobe which then dissipates into the surrounding atmosphere. In contrast, spray cryotherapy directly applies the liquid nitrogen to endobronchial tissue leading to a flash freeze. While the freezing temperature of CO_2 is −78.5 °C [4], the value can be reduced via the cryotherapy system to achieve temperatures between −35 °C and −50 °C at the tip of the probe which is required for an effective cell death in neoplastic tissue [7, 10].

Techniques and Application

The tissue effects of cryotherapy can be broadly classified into two categories based upon the underlying principle.

1. Cryoadhesion uses the strong adherence of cryoprobe and target tissue.
2. Cryoablation uses intracellular cell death from rapid freezing.

Cryoadhesion

Cryoadhesion works on the principle of freezing the fluid between the tip of the cryoprobe and the target as well as the fluid within the target. This leads to the formation of ice crystals and adheres

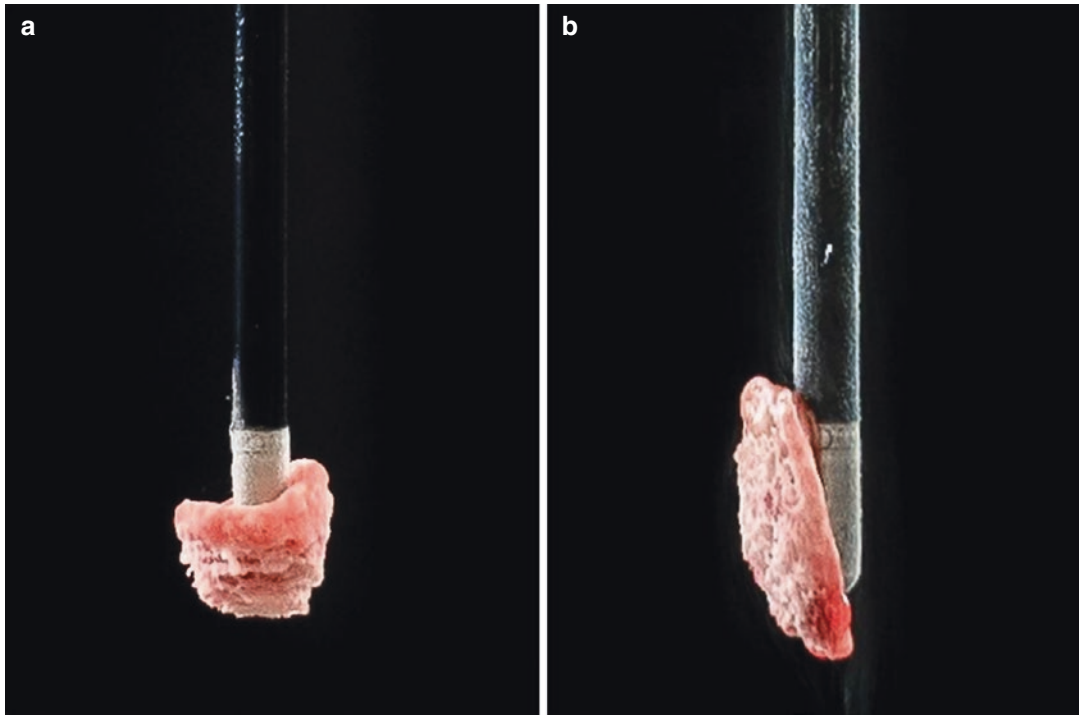

Fig. 12.5 Title: Cryoadhesion. Description: The target tissue can be adhered to the cryoprobe with either a "frontal" approach that leads to circumferential application (**a**) or the "lateral" approach that can adhere a longer segment (**b**). (Image© Erbe Elektromedizin GmbH)

the two surfaces together. This effect can be used with either a frontal or tangential approach (Fig. 12.5) to remove blood clots, extract foreign bodies, obtain endobronchial or transbronchial tissue biopsies, and recanalize the airway by extracting endobronchial tumors [7].

This cryoadhesive effect is dependent on the size of the frozen area which is in turn affected by the freeze time, contact area, moisture level, tissue/foreign body properties, the cylinder pressure, and ambient temperature of the environment [7]. Freeze time is the easiest to control by the operator. There is rapid freezing in the first 5 seconds following which the effect is gradually weaned due to freezing around the probe tip and thermal equilibrium which dissipates the surrounding heat to the frozen probe tip [7]. The freeze time can be controlled by allocating a preset or by pressing the pedal for longer period in the "free freeze" preset. The contact area is determined by the diameter of the probe tip with larger freezing effect exerted by the larger probe. The 1.7, 1.9, and 2.4 mm probes are adequate for both endobronchial and transbronchial use.

Moisture between the tip and target as well within the target plays a vital role for cryoadhesion. An organic material with good water content such as lung tissue, tumor, or a porous foreign body is more likely to freeze on contact with cryoprobe in comparison to an inorganic object such as metallic or plastic foreign body. Different body tissues respond differently to cryotherapy with some tissues being sensitive due to their water content (e.g., tumor, granulation tissue, mucus membrane). On the other hand, some tissues are resistant to effect of cryotherapy (e.g., cartilage, fat, connective tissue and fat). Therefore, the tracheobronchial wall which is mainly composed of fibrocartilaginous structure is less likely to be damaged from the effects of repeated application of cryotherapy, while a tumor attached to this wall will be affected significantly [1]. The ambient temperature of the working environment has a direct effect on the

pressure in the cryogen cylinder which can affect the performance of the machine. High environmental temperature can lead to high cylinder pressure which affects the evaporation pressure of liquid CO2. While a high pressure can be compensated by the machine, the low pressure can lead to poor freezing. Newer devices can alert the user of such issues [7].

Indications

The flexible cryotherapy probes are widely used upon the principle of cryoadhesion. The effect is useful for recanalization of central airway obstruction (whether malignant or benign); a tangential biopsy of infiltrating tumors, devitalizing tissue; removal of blood clots or foreign body; and for transbronchial biopsy in interstitial lung disease or peripheral lung nodules [9, 11]. The use of cryotherapy for these purposes of tumor debulking, endobronchial cryobiopsy, and cryorecanalization is endorsed by British thoracic society [12] and American College of Chest Physicians [13].

Cryotherapy is often used in conjunction with thermal therapies such as electrocautery, laser, argon plasma coagulation, balloon dilation, and airway stenting to restore and maintain airway patency. Unlike thermal therapy, it is safe to use with higher oxygen concentration and the preferred therapy when low fraction of inspired oxygen (FiO_2) cannot be tolerated by the patient. It is also safer to use around combustible substances such as stents and endotracheal tubes. Moreover, it does not interfere with cardiac pacemakers or implanted defibrillators unlike electrical therapy [1].

Cryorecanalization

Patient with endobronchial tumor and airway obstruction can benefit from endoscopic debulking if the airway and parenchyma distal to this obstruction are salvageable. The principle of cryoadhesion can be used to remove exophytic endoluminal tumor or granulation tissue for an immediate effect on airway patency. The cryoprobe is activated on contact with target tissue for 3–15 seconds to incite cryoadhesion followed by a rapid pull with the intent of removing large pieces of tissue (Fig. 12.6). Since the debulked tissue is too large for working channel of bronchoscope, the probe is removed en-bloc and thawed in saline [14]. The bronchoscope should be quickly reinserted to assess any bleeding from the site. For a central tumor, any size cryoprobe can be used depending on the intended size of tissue fragments. Typically, the larger probes (1.7, 1.9, and 2.4 mm) are utilized for central cryodebulking due to larger size effects which lead to more efficient tumor removal and recanalization and yield larger tissue fragments for pathological testing [7]. This method is safe and effective for rapid debulking of endobronchial tumor and restores airway patency more rapidly than its counterpart cryodevitalization.

The goal of cryorecanalization (also referred to as cryodebulking) is to improve the patient's performance status and survival even if they are not eligible for surgical treatment [12]. The overall efficacy of cryorecanalization in symptom palliation is reported in 70–90% patients [14]. The largest analysis on cryorecanalization by Maiwand et al. ($n = 476$) reported a mean of 2.4 cryosurgical treatments in malignant endobronchial tumors. The study reported that 86% had improvement in ≥ 1 symptoms (hemoptysis, cough, dyspnea, and chest pain). The mean Karnofsky score improved from 59.6 to 75.2 and the average increase in Forced expiratory volume in the first second (FEV1) and Forced Vital Capacity (FVC) was 90 and 130 mL, respectively [14, 15].

In addition, Schumann et al. ($n = 225$) described the use of cryorecanalization in symptomatic airway stenosis and noted a 91.1% success rate. In this retrospective analysis, length of lesion more than 2 cm was associated with unsuccessful intervention. Adjunctive modalities such as stent (4.9%) or APC (16.4%) were used infrequently [16]. Another retrospective analysis by Inaty et al. ($n = 156$) reported restoration of airway patency in 95% patients with improvement in respiratory symptoms noted in 82% of symptomatic patients. Adjunctive modalities such as mechanical debridement (51%) and thermal therapy (EC 30%, APC 17%) were used much more frequently in this study. They noted cryotherapy

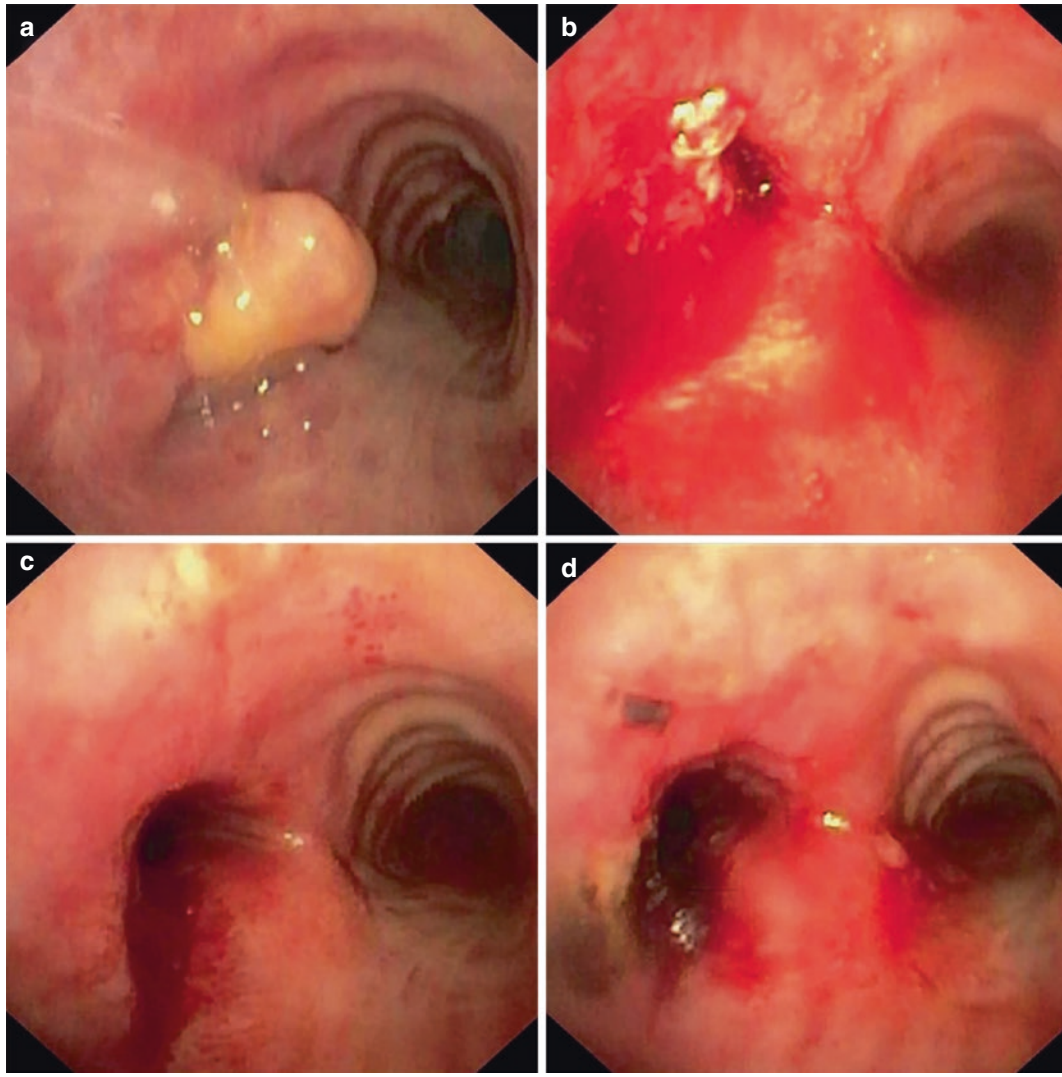

Fig. 12.6 Title: Cryorecanalization. Description: (**a**) shows a necrotic tumor in left mainstem orifice resulting in complete obstruction. (**b**) Shows the effect of partial removal of this tumor using cryodebulking technique. (**c**) Shows the result of complete cryorecanalization with restoration of patency of left mainstem bronchus. (**d**) Shows a follow up bronchoscopy at 4 weeks. (Images courtesy of Dr. Nicholas Pastis, The Ohio State University Hospital, Columbus, Ohio)

was most efficacious in treating central airway lesion [17]. A smaller prospective study by Hetzel et al. (n = 60) reported successful recanalization in 83% out of which 61% had complete and 22% had partial improvement in patency [5]. Another small study by Yilmaz et al. (n = 40) reported successful cryorecanalization in 72.5% patients. They also reported that the success rate was related to the presence of the distal involvement and the older age of obstruction [18].

Cryoadhesion and Foreign Body Removal

Foreign body aspiration is common in children younger than 3 years old and in adults after sixth decade of life. Flexible bronchoscopy has gained significant experience with various apparatuses available for endobronchial use. It has therefore replaced rigid bronchoscopy as a less invasive alternative [19]. When flexible bronchoscopy

fails to perform, a cryoprobe can be used by adhering the aspirated object to the tip of the cryoprobe [1]. There are several case reports that describe the use of cryotherapy for this particular application for removal of chewing gums, mucus plugs, aspirated food material, etc. [1].

In a small in vitro study, it was noted that most organic objects (such as aspirated food, clots, and mucus plugs) are retrievable, while some nonporous objects (such as teeth or bones) and inorganic objects (such as metallic paper clips) are not easily adherent to the cryoprobe. The study highlights the ease of use as well as the variability in the application of cryotherapy for foreign body removal and recommends an external test to confirm the target object will be adherent to the tip of the probe [20]. The use, however, can be limited by lack of equipment and absence of experience in using the technology [21]. The use of cryotherapy for retrieval of foreign bodies can therefore be reserved as a second-line interventions or to avoid rigid bronchoscopy depending upon the nature of the foreign body.

Cryoadhesion and Mucus Plugs/Blood Clot Retrieval

Massive airway bleeding and subsequent blood clot formation can lead to life-threatening airway obstruction. The ensuing loss of ventilation and oxygenation calls for immediate recanalization. Several conditions can predispose a critically ill patient to massive hemoptysis, e.g., bronchiectasis, cystic fibrosis, tuberculosis, malignancy, post-biopsy, and pathologic or iatrogenic coagulopathy (e.g., during extracorporeal membrane oxygenation). Traditionally rigid bronchoscopy has been recommended as it permits use of larger instruments for suction. However, it requires technical equipment and adequate training. Flexible bronchoscopy has emerged as a less complicated alternative and has almost replaced rigid bronchoscope for this indication. A large bore "therapeutic" bronchoscope can effectively remove large blood clots by using powerful suctioning. In addition, flexible forceps can be used for large adherent clots.

Cryotherapy has been well described for the removal of extensive clot burden in tracheobronchial tree. It is especially helpful to remove fragile clots that would otherwise break into smaller fragments while using forceps. In addition, large clots that are adherent to the bronchial wall can be difficult to remove with the suction force of the bronchoscope alone. Cryoextraction is very successful in these cases as either an en-bloc or piecemeal removal (Fig. 12.7). A single-center retrospective review by Narin et al. (n = 38) reviewed efficacy of cryoprobe extraction and reported 92% overall success in the subgroup of blood clots [22]. Another review by Schmidt et al. (n = 16) evaluated the efficacy of cryoextraction in critically ill patients with 68.8% patients on ECMO (extracorporeal membrane oxygenation). They noted successful application in 56.2%; however, repeat cryoextraction was needed in 56% [23].

Endobronchial Cryobiopsy

A frozen tissue sample from a central or peripheral tumor and even the pathological lung parenchyma can be removed with the intent for further histopathological sampling. The underlying principle uses cryoadhesion to extract the targeted specimen, wherein the removed fragment is frozen in contact with the tip of the cryoprobe [7].

To obtain a cryobiopsy, the probe is advanced through the working channel of flexible bronchoscope into the bronchus. A short freezing cycle of 3–5 seconds is activated to freeze the target tissue surrounding the probe tip. The duration of freeze is variable and depends on the cryosurgical unit, the cryogen, and the probe size. A pre-biopsy freeze ball test is helpful to determine the freeze duration. It is performed by dipping the tip of cryoprobe in water and observing the time needed to form the desired ice ball which correlates with the size of harvested specimen. After the desired time of freezing, both the flexible bronchoscope and cryoprobe are swiftly removed as a unit since the harvested specimens are too large for working channel of the bronchoscope (Fig. 12.8). This maneuver also prevents any damage to the working channel from the frozen tip of the cryoprobe [24]. After removal, the biopsy specimen at tip of

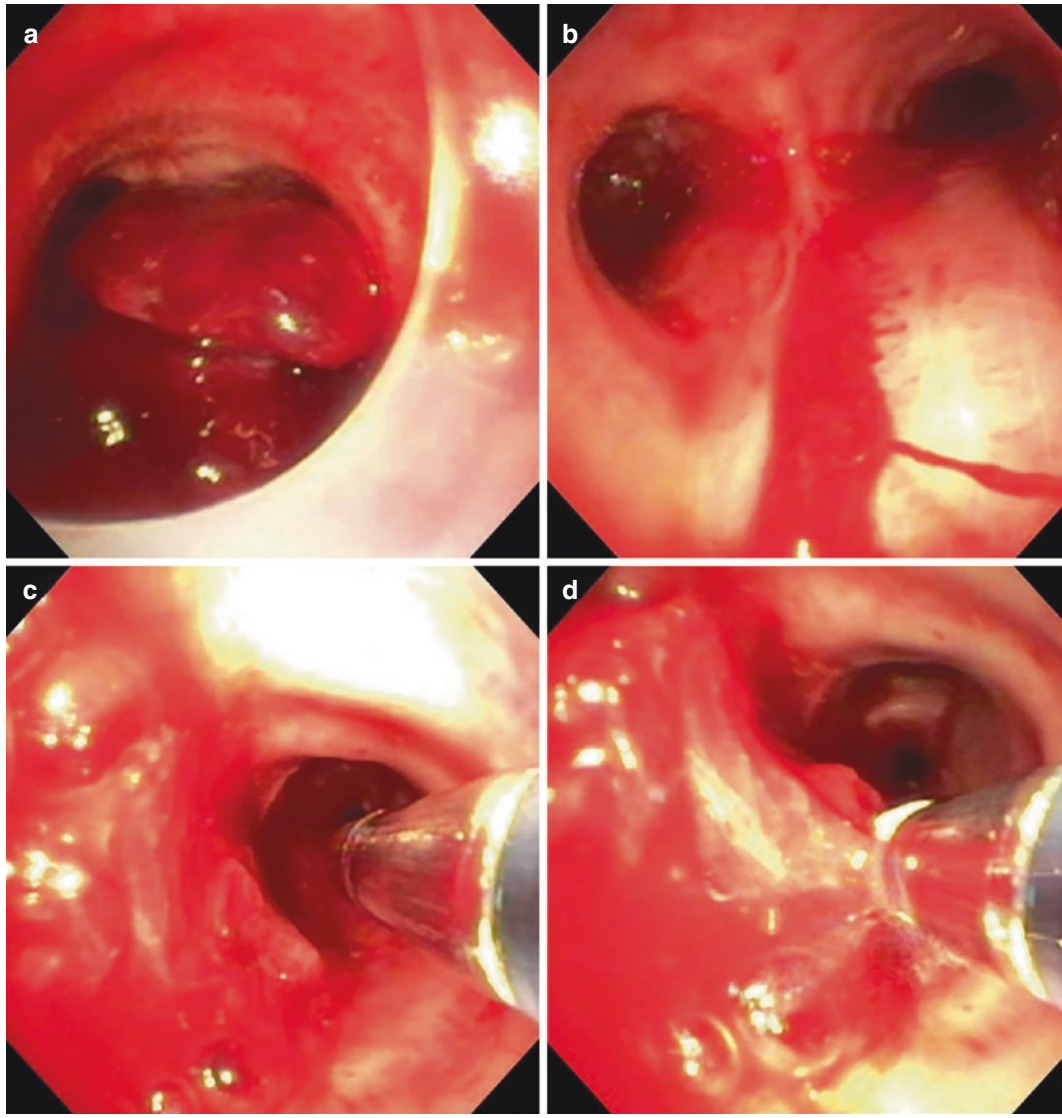

Fig. 12.7 Title: Cryotherapy for blood clot removal. Description: Fig. A shows a large saddle clot in distal trachea extending into bilateral mainstem. Fig. B shows the restoration of central airway patency after removal of this clot with cryotherapy. Fig. C and D shows the technique with application of cryoprobe tip to large clot in left mainstem and subsequent adherence on freezing that facilitates its removal. (Images courtesy of Dr. Christian Ghattas, The Ohio State University Hospital, Columbus, Ohio)

cryoprobe is thawed in normal saline and collected in an appropriate medium such as neutral 10% buffered formalin. The bronchoscope is quickly reinserted to the site of biopsy to monitor for any post-biopsy bleeding.

Endobronchial cryobiopsy can be deemed superior to traditional forceps biopsy due to larger sample size and low biopsy-related tissue alterations including crush artifact [24]. Conventional forceps-mediated endobronchial biopsy has a diagnostic yield of 72–88% [9]. A cryoprobe also allows wider angle of positioning including an almost tangential approach which can otherwise be a limiting factor with forceps. In addition, the size can be regulated by duration of freeze in contrast to using a different size for

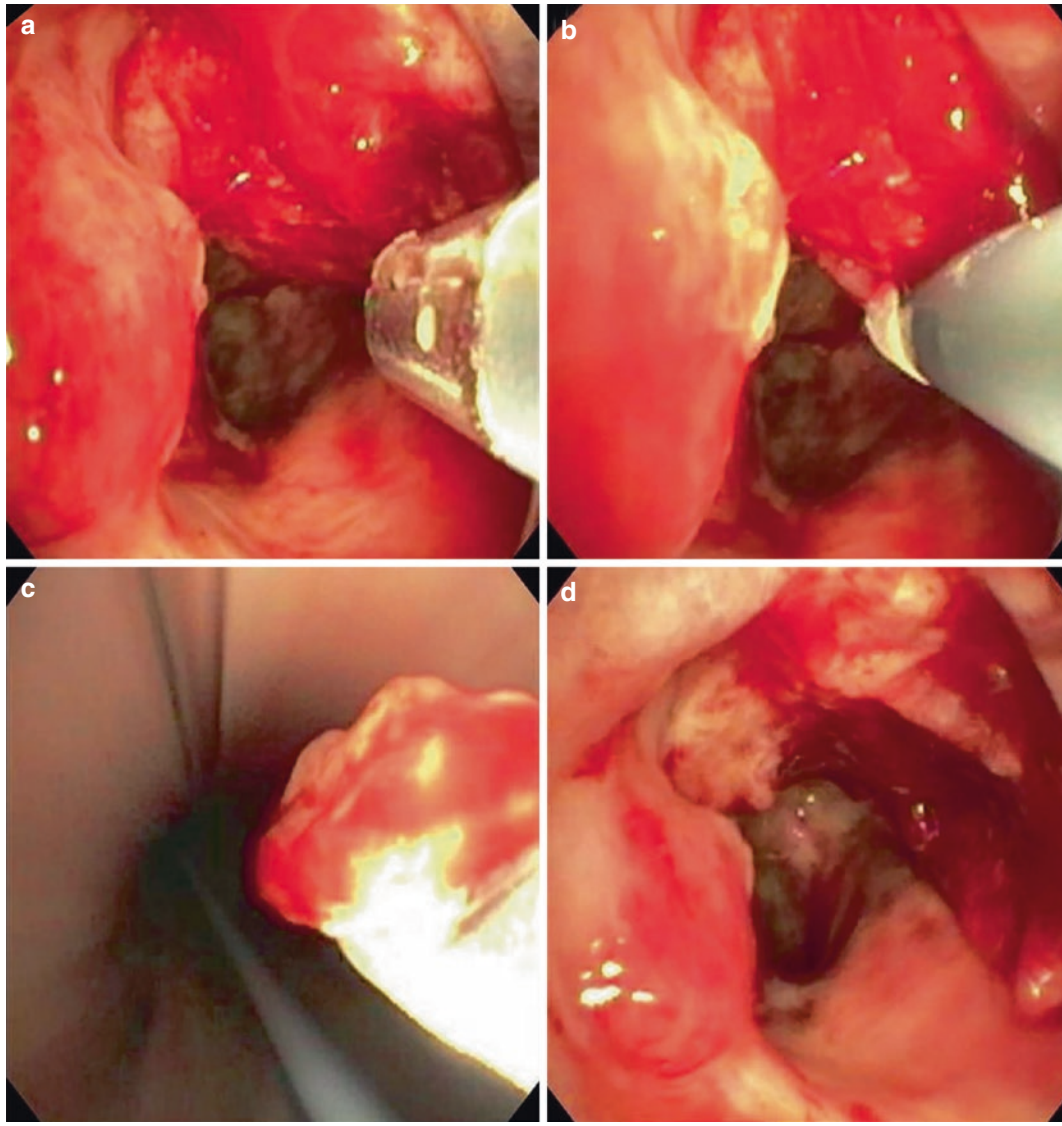

Fig. 12.8 Title: Endobronchial cryobiopsy. Description: Fig. A show an exophytic tumor in distal trachea. Fig. B shows the cryoprobe with lateral application to the tumor followed by rapid freeze. Fig. C shows the en-bloc removal and the retrieved tissue in endotracheal tube. Fig. D shows the target site without signs of major bleeding and the defect in the tumor at the site of cryobiopsy. (Images courtesy of Dr. Alberto Revelo, The Ohio State University Hospital, Columbus, Ohio)

forceps [24]. Endobronchial cryobiopsy can be obtained in a wide array of lung cancers (either primary bronchogenic or metastatic), sarcoma, lymphoma, leiomyoma, chondroma, and carcinoid. Moreover, higher quality detection of both cytoplasmic and nuclear antigens has been noted in cryobiopsy specimens [4, 25]. It can also be used for benign indications such as granuloma and endobronchial tuberculosis.

Hetzel et al. (n = 600) coordinated a prospective randomized multicenter trial at 8 centers. Endobronchial cryobiopsy was noted to have 95% rate of diagnosis in comparison to 85.1% in conventional forceps biopsy ($p < 0.001$) whilst having no difference in the incidence of significant

bleeding [24]. Schumann et al. (n = 296) compared endobronchial cryobiopsy and forceps biopsy in the same patient in the first 55 patients and reported a higher diagnostic yield (89.1% vs. 65.5%, $p < 0.05$) as well has significantly larger sized biopsies and artifact-free tissue sections for cryobiopsy compared with forceps biopsy ($p < 0.0001$) [26]. In another study, El-Dahdouh et al. compared cryobiopsy to traditional forceps biopsy in the same patient; the former was noted to have lesser crushing and loss of architecture ($p < 0.001$), larger diameter of sample (1.4 cm vs. 0.5 cm, $p < 0.001$), and better diagnosis rate (100% vs. 80%). The rate of hemorrhage was not significant different by either technique [27]. Similar results were noted in other studies comparing these two interventions [28]. The utility for obtaining a biopsy of flat mucosal lesions has been explored with improvement in mean volume and diagnostic yield [29]. The optimal number of endobronchial cryobiopsy has also been evaluated by Segmen et al. (n = 50) with a significant difference noted till the second biopsy (p = 0.031) and no additional value noted with third or fourth biopsy specimen [30]. Finally, Jabari et al. (n = 60) reported that a 5 second freeze times yields a larger specimen in comparison to a 3 second freeze or forceps biopsy ($p < 0.001$) [31].

The safety and efficacy of endobronchial cryobiopsy have been described in multiple studies. In the Schumann paper, the overall bleeding has been reported to 5.1% with mild bleeding in 11 cases (3.7%), moderate bleeding in 3 cases (1.0%), and severe bleeding in only 1 case (0.3%) [26]. The risk of bleeding doesn't appear to differ significantly between cryotherapy and mechanical forceps [24]. Although a longer freeze time is noted to procure larger specimens, it doesn't appear to have an impact on the bleeding frequency either [31].

Transbronchial Cryobiopsy for Lung Cancer

Transbronchial lung cryobiopsy (TBLC) is commonly utilized for diagnosis of diffuse parenchymal lung disease. It may also offer a viable option for diagnosis of peripheral lung nodule where a complete characterization of tumor is required (including molecular alterations). Forceps biopsy have a similar drawback with small sample size, crush artifact, and hemorrhage that can lower the quality of specimen and influence the histopathological analysis [9]. TBLC for diagnosis of lung cancer is at an early investigational phase and additional evidence is required to assess safety and efficacy.

A pilot study described the use of thin cryoprobe for peripheral ground glass opacities and noted diagnostic yield of 82.6–91.6% [9, 32]. In comparison, the radial endobronchial ultrasound (EBUS)-guided transbronchial needle aspiration (TBNA) has a yield between 46 and 86.7% [9]. The advantage of cryobiopsy arises from the large sample size and preserved lung architecture with surrounding areas of healthy tissue. This could lead to improved molecular targeted therapy and have a potential impact on management of non-small cell lung cancer.

The use of thin cryoprobe has also been described for sampling mediastinal lesions under the guidance of EBUS. A dual-center clinical trial compared transbronchial needle aspiration and mediastinal cryobiopsy guided by EBUS in the same patient. Prior to the mediastinal cryobiopsy, the airway wall was opened with an electrocautery needle knife. The study noted a significantly higher diagnostic yield with cryobiopsy (91.8 vs. 79.9%), although it was nonsignificant for common malignancies. A higher percentage of samples were noted to be adequate for molecular testing in cryobiopsy group (93.3% vs. 73.5%; $p < 0.001$) [33].

Safety Concerns and Contraindications

The contraindications of cryotherapy include general contraindication for bronchoscopy such as the inability to tolerate general anesthesia. A basic rule of safety while using cryoprobe for any endobronchial intervention is to monitor the site of application visually and control the movement of the cryoprobe tip whilst using the freeze function. It is not uncommon for a bystander airway wall to get accidently adhered at the frozen tip leading to an inadvertent fixation. The best course of action here is to stop further freezing and let the tip thaw passively until the wall is released

from the tip. If a release is attempted at normal mucosal site before the tip is thawed, airway mucosal or wall injury and tear can happen with consequent bleeding or ulceration.

The risk of bleeding should be kept in consideration while pursuing cryorecanalization for it can lead to moderate bleeding with a risk as high as 4–25% [14]. Although the application of cryotherapy leads to vasoconstriction, its hemostatic effect is limited to the immediately adjacent area. The tumor-tissue interface is farther away from the cryoprobe tip and is more prone to bleeding due to neovascularization. Finally, cryotherapy has limited efficacy for removal of inorganic or metallic foreign bodies [20].

Cryoablation

Cryoablation (also referred to as cryodevitalization) works by using the freezing temperatures to induce intracellular and extracellular ice crystal formation with repeated freeze-thaw cycles. This leads to cell death and enables tissue devitalization and necrosis [1]. This method of devitalization is also referred to as slow ablation and is not suitable for patients with critical airway stenosis and acute symptoms. Tissue destruction using cryoadhesion, mechanical measures (using rigid bronchoscope), or thermal therapy (laser, electrocautery, argon plasma coagulation, etc.) is more suited in those situations and can be combined with cryoablation for a tailored approach to central airway obstruction.

The technique for cryoablation is simple. The tip of cryoprobe is applied on the tumor for 10–30 seconds followed by a period of passive thawing (Fig. 12.9). Adjacent zones that are three to 5 mm apart are treated with slight overlap. A freeze-thaw cycle is usually repeated at least two–three times for effective tissue devitalization [14]. Although the freeze time is usually 10–30 seconds, longer times (up to 3 minutes) have been described in literature. However, some studies suggest that a shorter freeze time is just as effective for devitalization and a freeze time over 2 minutes is not necessary [7, 34].

The effect of cryotherapy on tissue can be subdivided into immediate (within an hour) and delayed (over hours to days). The immediate effect is due to the formation of ice crystals in both intracellular and extracellular compartments. This leads to direct cell injury from cell membrane damage and indirect cell death from intracellular organelle damage which further leads to intracellular hyperosmolarity, influx of water, and swelling of nucleus and cell itself leading to rupture [1, 10]. In addition, rapid cooling leads to vasoconstriction and loss of circulation. This is coupled with a vascular injury in thawing phase when the temperature rises back to baseline and restores circulation. This leads to an initial hyperemic response with increased capillary permeability, endothelial injury, and tissue edema. Subsequently, it leads to platelet and micro-thrombi formation and hyper-viscosity leading to loss of circulation in about an hour [1, 14]. The delayed effect of cryotherapy stems from further cell apoptosis promoted by ischemic injury and resultant cytokine release and immune-mediated mechanisms. This effect continues for oncoming hours to days and corresponds to the extent of frozen tissue. The most significant effect is at center of the freezing point and it blunts towards the periphery which contains a mixture of live and dead tissue. It is therefore important to pursue cryoablation at multiple sites on the target tissue for a more homogenous effect.

Cryoablation is affected by the tissue water content, coldest temperature, freeze time, the rate of cooling and thawing as well as the number of times the cycle is repeated. While a temperature of −10 °C initiates tissue death, a target lower than −35–50 °C is often required for effective devitalization [7, 10]. A fast rate of cooling and slow thawing is the prime destructive factor and leads to the most effective cell death [10]. The cooling rate of flexible cryoprobes is often over −1500 °C/min which is far more than the −10 to −50 °C/min cooling rate necessary for ice crystallization in tissue. While thawing cannot be controlled directly, a slower (passive) thawing contributes to osmotic cell lysis by intracellular concentration of water [7].

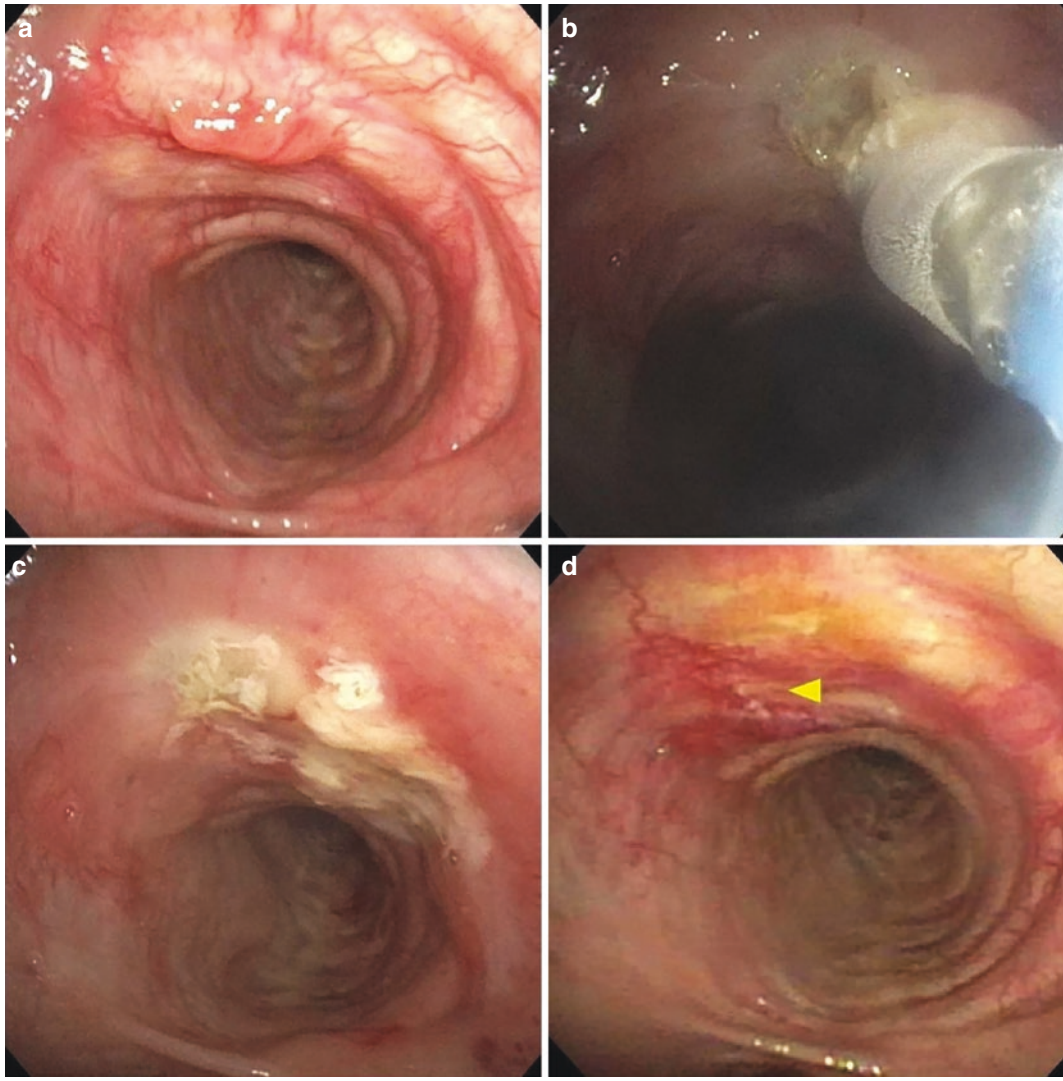

Fig. 12.9 Title: Cryoablation. Description: Fig. **a** shows a left mainstem endobronchial carcinoid tumor. Figure **b** shows the application of cryoablation therapy in repeated freeze-thaw cycles. Figure **c** shows the mucosal changes at the site of lesion after cryoablation. Figure **d** shows the follow up bronchoscopy with resultant necrosis of lesion site

Indications

Cryoablation can be used as an adjunctive therapy for endobronchial disease and is commonly used for both benign and malignant conditions. As mentioned earlier, it is a form of slow ablation and induces delayed tumor necrosis of endoluminal tissue into sloughed necrotic debris that may require a follow-up bronchoscopy for removal in 1–2 weeks [14]. Therefore, it is more suited for subacute airway stenosis where additional time can be afforded. Cryoablation is less commonly used for non-malignant conditions or for inoperable microinvasive lung carcinoma. There is potentially a positive effect on bleeding due to vasoconstriction and hemostatic effect following cryoablation [23]. Application prior to mechanical debulking may benefit in minimizing the risk of bleeding.

Evidence

The efficacy of contact probe cryotherapy with the intent of cryoablation has been evaluated in

multiple studies that have reported a successful restoration of airway patency and performance status in 60–90% cases with a synergistic effect from radiation and chemotherapy [14]. The early work from 1993 by Marasso et al. ($n = 234$) using a 3.2 mm probe for a freeze time of 1–2 min repeated 2–3 times via a rigid bronchoscopy reported outcomes in 170 patients with malignant lesions. The use of cryotherapy led to improvement in dyspnea in 81% and reduction or resolution of hemoptysis in 93% in patients with malignant tumors [34]. Maiwand et al. ($n = 153$) in a prospective study used temperatures of −70 °C to tumor site using a 2.2 or 5 mm cryoprobe via a rigid bronchoscope for two sessions of 3-min periods followed by a cleanup bronchoscopy (usually at 2 weeks). He reported a subjective symptomatic improvement for cough (68.3%), dyspnea (63.9%), hemoptysis (92.7%), and chest pain (55.5%). He also reported a mean increase in FEV1 by 110 cc, FVC by 90 cc, and Karnofsky performance status by 54.6% [35]. Another smaller study by Walsh et al. ($n = 33$) reported improvement in overall symptoms, stridor, dyspnea, and hemoptysis. They also reported relief of obstruction in 77% by bronchoscopic assessment [36]. Mathur et al. ($n = 20$) also reported complete removal of endobronchial component in 90% patients [37].

For benign disease, Mu et al. ($n = 76$) reported the efficacy and safety of endobronchial cryotherapy as freeze-thaw cycles every 2 weeks for granular endobronchial tuberculosis. This retrospective study noted a complete removal of endobronchial lesions in 100% patient when endobronchial cryotherapy was used alongside anti-tuberculosis therapy in comparison to 78.9% in patients with anti-tuberculosis therapy alone. The study also noted a faster rate of disappearance in combined therapy [38].

Safety Concerns and Contraindications

Contact probe cryotherapy is a relatively safe modality with minimal risks. It doesn't impose the fire risk of thermal therapy and is relatively easier to learn. In addition, it has almost no risk of airway perforation [39]. Still, the proceduralist must exercise care while activating cryoprobe inside the airway. Any inadvertent contact to the tracheobronchial wall with an accidental tug can lead to significant mural injury. This requires caution, especially in pediatric patients due to smaller cross-section of the airways and softer cartilage.

Cryoablation is a slow form of ablation and not ideal for the management of acute airway obstruction. Cryodebulking if applicable can be pursued for a more rapid effect. Moreover, it is not helpful for extrinsic airway compression and is less effective for management of pauci-cellular lesions such as lipomas, fibrotic stenosis, postintubation strictures, and cartilaginous or bony lesion [1]. Airway edema is common after the application of cryotherapy due to resultant immune response from cell death [14]. Application to critical airway stenosis can initially lead to worsening symptoms due to narrowing from edema. In addition, necrotic sloughed up tissue can also cause airway obstruction.

Cryospray

Spray cryotherapy (SCT) pertains to endobronchial application of medical-grade liquid nitrogen (N_2) via a radial head catheter in a small, accurately directed, uniform spray in multiple locations inside the tracheobronchial tree. This allows for treating a relatively large area of irregular surface encountered in endobronchial disease. This direct application can yield temperatures as low as −196 °C by phase transformation of nitrogen from liquid to gas [1, 40]. It was initially developed for endoscopic use in esophagus and its utility in tracheobronchial tree was later explored in an animal study by Au et al. [40].

Indications

The TruFreeze® system (Steris Endoscopy, Dublin, Ireland) received FDA approval in 2012 and is available for a multitude of benign and malignant etiologies such as tracheal stenosis, tumor destruction, hemostasis, post-lung transplant anastomotic strictures, and stent management. It can generate adjustable flow rates (12.5 and 25 watts) from the console and is delivered

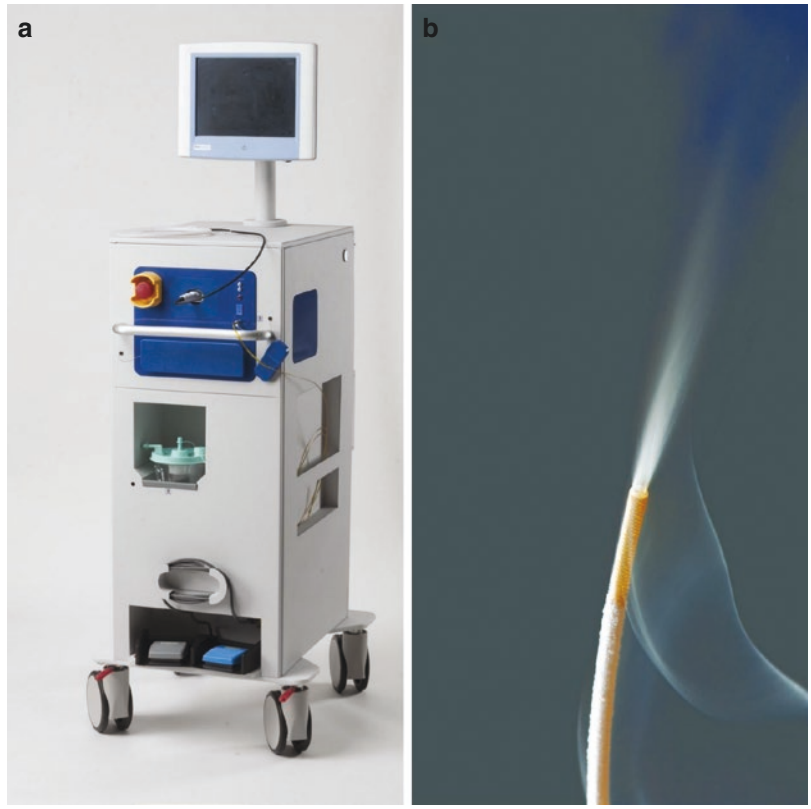

Fig. 12.10 Title: TruFreeze® system. Description: Fig. **a** shows the TruFreeze® system console. Figure **b** shows the Air PV™ catheter for endobronchial application of spray cryotherapy. (Images courtesy of STERIS Endoscopy. Unauthorized use not permitted)

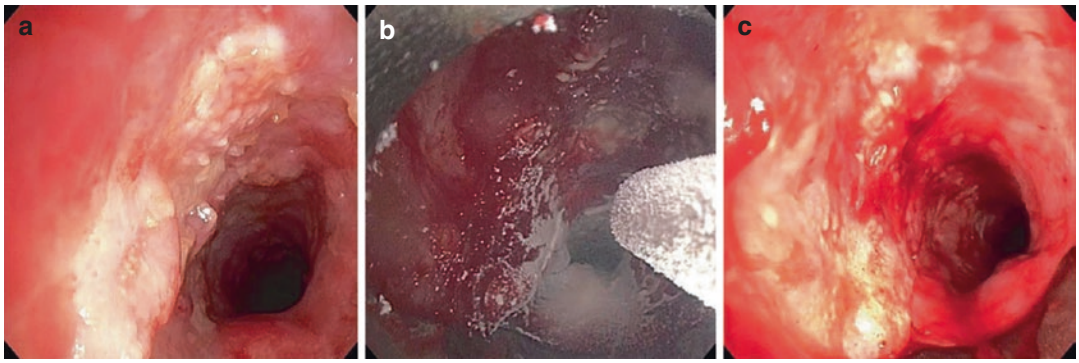

Fig. 12.11 Title: Spray cryotherapy for cryoablation. Description: Fig. **a** shows a mid-tracheal stenosis and endobronchial mucosal changes in setting of radiation therapy. Figure **b** shows direct application of liquid Nitrogen to target site with flash freeze effect. Figure **c** shows post treatment changes after passive thawing is allowed and blanching of mucosa. (Image: Courtesy of Dr. See Wei Low and Dr. Otis Rickman, Vanderbilt University Medical Center, Nashville, Tennessee)

to the site of application via the 7-French Air PV™ catheter for the passive venting method (Fig. 12.10). The direct endobronchial application of nitrogen for an approximately 5 s freeze cycle incites flash freeze with intracellular crystal formation while sparing the cryoresistant extracellular matrix (Fig. 12.11). The intact extracellular matrix is suggested to heal with reduced fibrosis. Therefore, the use of SCT alongside balloon bronchoplasty in benign bronchial lesions facilitates easier dilation by two mechanisms; a softer scar that prevents lac-

eration and reduced incidence of laceration which prevent further scarring and stricture formation [40]. In malignant lesions, after debulking the superficial tissue with faster thermal ablation, SCT can be preferentially used at the base of the lesion which is composed of normal and abnormal tissue. The underlying tissue matrix is preserved with SCT and regrows with minimal fibrosis in contrast to thermal ablation [41]. In addition, SCT leads to vascular stasis and can be used prior to mechanical debulking for hemostatic control. For bulky lesions and critical airway stenosis, complementary therapies such as balloon bronchoplasty, mechanical debridement, and endobronchial stenting are often necessary since SCT does not produce immediately visible effects.

In recent years, spray cryotherapy has been investigated for chronic bronchitis as well. RejuvenAir® System (CSA Medical, Inc., Lexington, MA) is currently under investigation for this application and uses a radial spray catheter and an algorithm to deliver a nominal metered cryospray in a protocolized dosing patter in two sessions (Fig. 12.12). The study hypothesizes that the cryospray application leads to destruction of abnormal surface epithelium and promotes regrowth with normal ciliated epithelium. Consequently, there is a reduction in chronic inflammation and mucosal swelling [42]. This application of spray cryotherapy is currently under investigation.

Evidence

Spray cryotherapy has been evaluated in multiple studies and has noted promising results. A large multi-institutional registry by Finley et al. ($n = 80$) reported restoration of airway patency in 98.8% of patients. In addition, the number of airway stenosis with grade >75% reduced from 74% pre-treatment to 10% post-treatment [43]. In another single-center, retrospective review by Janke et al. ($n = 22$), use of SCT was associated with a 86.4% of the patients experiencing an improvement in grade of stenosis [44]. The utility of SCT in benign strictures has also been demonstrated by Fernando et al. ($n = 35$) with 85% improvement in symptoms when it was used alongside balloon bronchoplasty and highlights the role of adjunctive modalities when using SCT [45]. Similarly, Browning et al. ($n = 27$) utilized additional modalities in 39% of their procedures [41].

Safety Concerns and Contraindications

The most common side effect reported with use of SCT is the risk of pneumothorax. The direct endobronchial application of nitrogen leads to phase transformation of liquid nitrogen to gas which expands the lung volume to higher threshold of capacity leading to barotrauma. In addition, it can displace oxygen leading to hypoxia. These effects were significantly highlighted by the early data including Finley registry noting a 19% rate of complication supposedly due to barotrauma [43]. The lack of experience in using SCT in airway

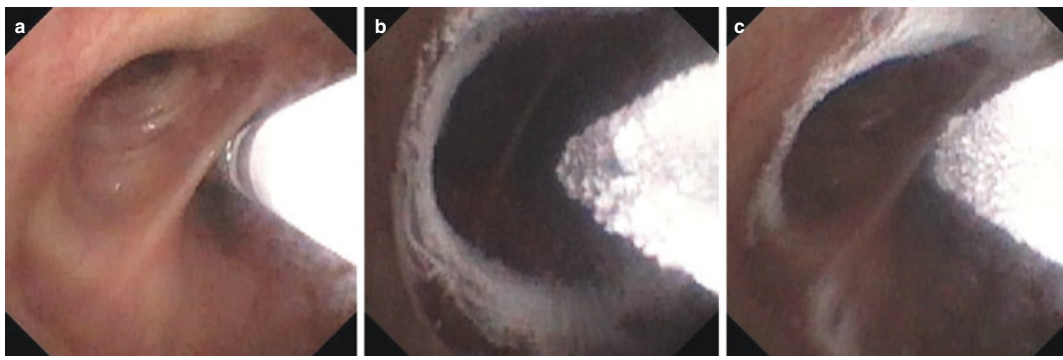

Fig. 12.12 Title: Spray cryotherapy in RejuvenAir® System. Description: Fig. **a** shows the tip of radial spray catheter positioned at the site of application. Figure **b** shows the direct endobronchial application of liquid nitrogen resulting in flash freezing. Figure **c** shows the passive thawing of the targeted region. (Images courtesy of Dr. Christian Ghattas, The Ohio State University Hospital, Columbus, Ohio)

likely led to high incidence rate during its early adoption. Subsequent studies reported routine egress of nitrogen during "passive venting" which relies on the principle that the nitrogen gas formed during SCT application will egress through path of least resistance, that is, via endotracheal tube to the atmosphere [40]. The protocol for passive venting was later developed and uses the following steps during SCT application (1) Deflate endotracheal tube cuff (2) Disconnect tube from ventilator circuit (3) Visualize passive egress (misting of gas through endotracheal tube or rigid bronchoscope, by a designated person (4) Confirm lack of chest wall rise during spray (5) Remove bronchoscope between treatments (6) Monitor hemodynamic data—Heart rate, blood pressure, oxygen saturation and telemetry (7) Treat proximal lesion first (8) Abort procedure if passive venting is compromised. In addition, the manufacturer recommends a minimum vent area of ≥20 mm^2 between the outer diameter of bronchoscope and inner diameter of endotracheal tube for the nitrogen gas to passively egress. It is important to avoid deploying SCT beyond anatomical obstructions such as severe airway stenosis (>90%) or while the bronchoscope is wedged within the lumen. While using rigid bronchoscope, jet ventilation should be halted during the spray to avoid pushing the gas downstream. While the development of passive venting protocol has reduced the risk of pneumothorax, the necessary apnea while holding ventilation can potentiate to risk of hypoxia, hypercarbia, respiratory acidosis, and bradycardia.

SCT is most often used with endotracheal tube or rigid bronchoscope. While use with laryngeal mask airway (LMA) is reported, there is concern of laryngospasm which can prevent the passive egress. In addition, accidental dislodgment can allow nitrogen to vent down into the stomach [41]. Overall, SCT is a relatively safe modality with low complicate rate of approximately 3% in both benign and malignant airway disease and is noted to be safe for application near a silicone, hybrid, or metal stent [41, 45]. A case series by Bhora et al. reported SCT as a safe adjunct modality for the management of benign tracheal stenosis suggesting value in patients who have failed conventional therapies [46].

Advantages of Cryotherapy

Cryotherapy offers many advantages over thermal therapies. It takes away the risk of airway fire, especially if the targeted area is near a combustible substance such as airway stent or endotracheal tube. It doesn't require lowering the inspired fraction of oxygen (FiO_2) to less than 40% in contrast to thermal therapies which pose a risk of airway fire at higher FiO_2. Finally, it avoids the risk of injury to extracellular matrix (e.g., cartilage) due to its low water content and allows regeneration with minimal fibrosis which can be an unintended side effect of thermal ablation.

The addition of endobronchial cryotherapy to chemoradiation therapy was compared in a prospective cohort study by Rashad et al. ($n = 60$) in malignant endobronchial obstruction. Combined therapy led to significant improvement in respiratory symptoms, respiratory function tests, mean Karnofsky score as well as medial survival [47]. Cryotherapy is also hypothesized to have a synergistic effect to immunotherapy that can potentiate the treatment response to anti-programmed death-ligand 1 (PDL-1) monotherapy, that is, PD-L1 ≥ 50% or tumor expressing EGFR (epidermal growth factor receptor) mutations (Clinicaltrials.gov Identifier: NCT04793815, NCT02759835). The mechanism of action involves the abscopal effect wherein local radiation therapy to primary tumor site releases the tumor antigens into circulation and triggers a systemic immune response to metastatic lesions. The cell necrosis from local cryoprobe application is hypothesized to mimic the effect of local radiation.

Limitations

Cryotherapy has an extensive array of clinical applications. However, its widespread use has been limited due to significant practice variations amongst institutions. It is considered a slow form of ablation that often requires a follow-up bronchoscopy and has a variable utility for acute or critical airway stenosis. It is relatively easier to

learn cryotherapy techniques in comparison to other more invasive interventions such as thermal therapies or mechanical debulking. However, most pulmonary and critical care training programs do not have the ability or protocols to train their fellows in cryosurgery with a goal for proficiency. In the United States, the use of cryotherapy is often limited to interventional pulmonology. These overall limitations are reflected in the reported use of cryotherapy in Acquire registry. Despite a low overall complication rate of 3.8%, cryotherapy was only used in 8% of the cases (out of 1115 therapeutic procedures in 15 institutions) [48].

Summary and Recommendations

Application of cryotherapy as a local ablative modality has demonstrated efficacy and safety in a wide array of trachea-bronchial pathologies. It can augment the efficacy of other systemic therapeutic agents such as chemotherapy, radiation therapy, and immunotherapy. It is also an effective tool for recanalization of critical airway stenosis and allows retrieval of tissue for diagnosis. Unlike thermal ablation therapies, cryotherapy leads to tumor destruction without heat-related denaturation and can have a similar effect by releasing intracellular contents into circulation.

Future Research Directions

The efficacy and safety of percutaneous cryoablation for management of non-operable stage 1 tumors have been evaluated for many years now. It has demonstrated local control and survival rate comparable to radiofrequency ablation and sublobar resection. Several studies have reported great success with an overall 3 and 5 year survival rate of approximately 80 and 68%, respectively [14, 49–51]. While efficacious, it is associated with significant adverse effects including a high risk of pneumothorax (12–62%), hemoptysis (0–62%), fever (3–42%), and pleural effusions (14–70%) [14]. Endobronchial approach for peripheral ablation has been suggested by some with the hope of reducing some of these adverse events. In addition, it can also lead to a "one-stop shop" tactic for diagnosis, staging, and treatment of early-stage lung cancer.

However, up until recently, there has been a lack of stable and accurate navigation platforms as well as cryoprobes that are thin enough to be advanced to the periphery. The advent of "Robot Assisted Navigation Bronchoscopy" (RANB) has demonstrated a stable navigation system that can provide a channel to peripheral lung regions. In addition, the targeted application can be confirmed with real time, in-suite cone-beam computed tomography imaging. This allows for delivery of ablative therapies such as microwave, radiofrequency, and photodynamic therapy with precision [52]. The widespread utilization of RANB and the development of thinner cryoprobes have paved the path for cryotherapy to be used for diagnostic modality in the targeted periphery. The utility for targeted cryobiopsy of peripheral lung nodules has been already be described [32]. However, the therapeutic applications for endobronchial cryoablation to peripheral lung nodule are currently lacking. The major limitation for this application is the limited depth of penetration of cold via thin cryoprobes. For a successful ablation using cryotherapy, the ideal zone of freezing would extend approximately 1 cm beyond the radiographically designated tumor region. Unfortunately, cryotherapy suffers from heat/cold sink effect. If the target tumor is closely related to a vessel >3 mm in diameter, the efficacy of cryotherapy to extract the heat and incite a strong freeze may be limited due to heat convection from adjacent circulation [53]. Regardless, it could be lucrative for application to centrally located parenchymal tumors due to relative preservation of surrounding collagenous architecture and minimal damage to the important structures.

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