Cryotherapy: Application in the Airways

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Introduction and Definition of Procedure

Cryotherapy is a technique that uses very low temperatures, below the freezing point, for a suitable period of time in pathological tissues in order to obtain irreversible damages [1, 2]. The use of low temperature in the treatment of pathological tissues found place originally in neoplastic lesions [1] in several medical fields like neurosurgery, urology, ophthalmology, and dermatology, leading to the use of cryotherapy, also called "cryosurgery." Different body tissues have different "cryosensitivities," mainly depending on their water content and microcirculation: most of neoplastic tissues, granulation tissue, the skin, endothelium, mucous membrane, and nerves are cryosensitive, while connective tissue, nerve sheath, cartilage, fat, and fibrosis are cryo-resistant. For this reason, cryotherapy is effective on highly cellular and well-vascularized tumors such as bronchial carcinomas, carcinoids, or granulomas, while it is not effective for management of paucicellular lesions, such as fibrotic stenosis, cartilaginous, and bony lesions.

The application of cryotherapy in the airways found its main indication in restoring airway patency from endobronchial tumor; other indications are treatment of early stage lung cancer, endobronchial biopsy, and foreign body removal. The main advantage of using cryotherapy over other debulking techniques is its high safety: in fact, the tracheobronchial wall, due to its fibrocartilaginous structure, could not be damaged by low temperatures, even when used for a prolonged period or when used repeated times in the same setting. Therefore, cryotherapy could be used safely to treat small lesions or lesions in small caliber bronchi.

The procedure can be done via rigid or flexible bronchoscope. The most commonly used cooling agent is nitrous oxide (N_2O), which is stored under high pressure in a liquid state. The passage of high-pressured N_2O to atmospheric pressure forces the agent to expand resulting in a temperature of -89°C at the distal probe tip; this thermodynamic effect is called "Joule-Thomson" effect: when a highly compressed gas expands rapidly, a low temperature occurs and rapid control of variations in flow and, therefore, in temperature allows the tip to be cooled. The endobronchial tumor is subjected to repeated freeze-thaw cycles determining a cytotoxic effect: the tissue necrosis

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takes place after few days from the procedure, and a cleanup bronchoscopy can be needed to remove the necrotic tissue several days after; this application of the technique is not suitable for patients with acute symptoms due to airway stenosis. Another application of cryotherapy is called "cryoextraction" or "cryo-recanalization" [3] and consists of freezing the tumor and removing it away: in this case, the removal of the tissue is immediately effective and does not require cleanup bronchoscopy; this application can also be used in patients with acute symptoms.

The maximum yield in endobronchial debulking is reached when cryotherapy is used along with other techniques like photodynamic therapy, neodymium-doped yttrium-aluminum-garnet (Nd:YAG) laser, stents, and electrocautery. However, compared with other techniques (mostly laser procedures), the main advantage of cryotherapy is its better safety profile, with no or few risk of airway perforation; moreover, it is also less expensive, probes are resistant, staff does not require personal protective devices, procedures could be performed using high oxygen flow and in patients with airways stent, and there is no need of special training [4]. In contrast, the most important limitation is the delayed effect of the cryogenic damage and the different response in different tissues; for this reason, cryotherapy could not be useful alone in the management of life-threatening airway obstructions. Therefore, cryotherapy in some cases needs to be integrated with all the other techniques cited above in order to achieve a better therapeutic result and to manage complications. It has to be underlined that cryotherapy alone plays no role when the obstruction is due to external compression.

Samples obtained with cryoextraction are also suitable for molecular analyses [5]: the good quality of specimens obtained and the absence of crush artifacts have led to its use for endobronchial and trans-bronchial lung biopsy in lung diseases [6].

Cryotherapy Damage: Molecular Bases

The destroying of pathological tissue takes place via two mechanisms, an immediate effect that occurs within 1 h from the application of cryotherapy and a delayed effect that occurs later (from several hours to days). Due to the temperature drop at freezing range, crystal ice formation occurs both in intracellular and in extracellular compartments. This leads to (a) intracellular organelles damage, especially mitochondria [5]; (b) intracellular hyperosmolarity followed by cell shrinkage and dehydration; and (c) water that gets into the cells, swelling them and breaking the nuclear and cytoplasmic membranes. Moreover, there is a direct damage of the cellular membrane by the crystal ices. To have a maximum lethal effect, it is necessary to have large ice crystals, especially intracellular: this is achieved with a rapid cooling followed by slow thawing.

The described mechanisms are coupled with vascular injury. Vascular injury happens in the thawing phase: with cooling there is vasoconstriction and a progressive loss of circulation that is restored when the temperature rises above zero. The restoration of circulation is accompanied by a hyperemic response with consequent edema, increasing capillary permeability, platelet aggregation, and micro-thrombi formation. This leads to loss of circulation in 30–40 min. Some cells die by apoptosis some hours later after the application of cryotherapy due to an immunological mechanism. Apoptosis is promoted by DNA fragmentation, cytokine release, inflammation, and ischemic injury. The damaged tissue by cryoprobe corresponds to the frozen tissue: the central part becomes necrotic for the direct damage of the low temperatures and for the ischemic and apoptotic phenomena; the peripheral zone, where the temperature ranged between 0 and -40 °C, is partially destroyed containing a mixture of dead and alive cells [1].

Low-temperature damages depend on several factors, like the cooling rate (faster is more destructive), the minimum temperature reached, the thawing rate (slower is more destructive), and the number of freeze-thaw cycles performed. Moreover, the tissue water content is related to the tissue cryosensitivity: the higher the water content, the more cryosensitive the tissue. Malignant tissue is hypervascularized, and even if this feature could render the tissue more resistant to low temperatures

due to a large warm blood flow that dissipates the thermal effect, the microcirculation is particularly sensitive to cryotherapy, leading to vasoconstriction, endothelial injury, and increased blood viscosity due to the formation of platelet plug and consequent thrombosis with ischemia.

History and Historical Perspectives

The effects of low temperatures on living tissues have been well known for many years [7]. Egyptians and Greeks were aware of the analgesic and anti-inflammatory properties of cold, but only in the nineteenth century, the extreme cold was used for the first time for the local destruction of living tissue: James Arnott used a mixture of salt and crushed ice for tumor palliation with a consequent reduction of pain and local hemorrhage; he then proposed its potential use for cancer, acne, breast and uterine cancer, headaches, and anesthetic purposes. With salt/ice mixture, a temperature of -24°C was reached and this was not enough to treat tumors efficiently: it was only with the introduction of refrigerants that lower temperatures could be reached.

In the late 1800s, there was an increasing interest in liquefying gases: Cailletet first demonstrated that oxygen and carbon monoxide could be liquefied under high pressure; in 1895 there was the first commercial production of liquid air by von Linde, and rapidly there was a large spread of liquefied gases on trade [8].

Exploiting the "Joule-Thomson" effect, liquid gases were proposed as refrigerants in the 1900s, chiefly in dermatologic diseases. Campbell White used for the first time liquid air as refrigerant to treat several kinds of skin conditions, including lupus erythematosus, herpes zoster, nevi, varicose leg ulcers, and cancer like epitheliomas. The use of liquid oxygen was limited at the beginning of the twentieth century, and it was mainly used to treat acne. In the same period, carbon dioxide snow was popularized because it was easily compressed and suitable for local treatments.

In 1950, liquid nitrogen took the place of oxygen due to its similar properties compared to liquid air and to oxygen but with less explosive potential [8]: it was used firstly for skin lesions and then has been used in the following years for cancer therapy in many anatomic areas. In 1913 Cooper, a neurosurgeon, invented a liquid nitrogen probe that reached a temperature of -196°C: he treated Parkinson's disease by freezing the thalamus and also inoperable brain tumors. Amoils introduced the "cryoextraction" technique: it was used in ophthalmology to remove cataract and subsequently was used in neurosurgery and in gynecology. By this time, there were more and more applications of cryotherapy in different diseases, and almost all researches were about liquid nitrogen, which is actually the most common used. Compared to carbon dioxide, liquid nitrogen reaches lower temperature, so it is suitable for both benign and malignant lesions.

In 1968, Gage reported the first endoscopic treatment on a bronchial tumor in the USA. Subsequently, other authors reported their first experience of the application of cryotherapy in the airways for endobronchial tumor debulking: in 1986 Maiwand [9] reported 75 cases of advanced tracheal and bronchial carcinoma (mainly squamocellular carcinoma), in which cryotherapy was used to relieve symptoms. A rigid Storz bronchoscope was used with a rigid cryoprobe, in general anesthesia, using Venturi positive pressure ventilation during the procedure. Endobronchial tissues were frozen with nitrous oxide, at a temperature of -70 °C for 150 s, and afterward thawing was allowed separating the cryoprobe from the tissue. The tumor was then frozen again at the same site for a further 150 s. A second treatment was done after 2, 4, and 8 weeks, depending on the patient's response and on the clinical findings. Symptoms like stridor, dyspnea, and hemoptysis improved in the majority of patients. In 12 cases, the condition of patients did not improve, in 6 patients there was a progressive worsening, and 1 patient died from nonsurgical cause. No cardiovascular complications occurred. Homasson et al. [10] reported the application of cryotherapy for tracheobronchial obstructions with a semirigid cryoprobe through a rigid bronchoscope: out of 21 patients with malignancy, mainly with

squamocellular carcinoma, a good response was achieved in 13 cases. Since then, several studies have investigated the role of cryotherapy in patients with lung cancer, so that cryotherapy was included in international guidelines [1] as one of the available treatments of endobronchial exophytic malignancy and early stage lung cancer.

Despite those promising results, the delayed effect of cryotherapy and the need of further procedures to remove the necrotic tissue led to an increase in the use of other more "immediate" techniques, like Nd:YAG laser, and to a provision of cryosurgery. The advent of flexible cryoprobes, suitable for the flexible bronchoscope, made cryotherapy more widespread than in the past [7]. Moreover, the possibility to extract immediately the tumor with cryoextraction [3] overcame the problem of a delayed effect. The combination of cryotherapy with other therapeutic modalities for lung cancer (chemotherapy, radiation therapy, and other debulking techniques like stent or laser) produced encouraging results [5]. Homasson et al. [11] demonstrated that chemotherapy might be more effective after cryotherapy: the authors explained this effect with the trapping of the anticancer drug in the tumor and immediately the surrounding area due to vascular stasis. Fang et al. analyzed 59 patients with malignant endobronchial masses removed with cryotherapy before chemotherapy [12]: cryotherapy was found to be effective especially for those who can receive chemotherapy due to improvement of performance status after cryotherapy. The combination of cryotherapy and molecular target therapy (gefitinib) resulted in a better stabilization and progression of disease and a better survival in patients with NSCLC (non-small cell lung cancer) when compared with molecular target therapy alone [13].

Cryotherapy would also increase the radiosensitivity of a tumor [14]: initial cryotherapy followed by irradiation was administrated in 38 patients with NSCLC. A better survival was associated both with the efficiency of the initial debulking by cryotherapy and with the local control induced by the irradiation, suggesting a potentiation of irradiation by cryotherapy.

Finally, a new method of delivering cryotherapy was proposed: the so-called spray cryotherapy, a noncontact system to deliver liquid nitrogen through an endoscopic catheter. Rapid freezing and thawing of the targeted tissues causes cellular death and hemostasis. However, intraoperative complications could be higher compared with the standard application of cryotherapy due to nitrogen retention: it should be avoided with adequate venting of the gas with a rigid bronchoscope or an endotracheal tube, to prevent blood oxygen falls and barotraumas.

Indications and Contraindications

The main indications of cryotherapy are listed below [2]:

- Endobronchial lung cancer
- Early stage lung cancer
- Metastatic disease
- Benign and rare tumor
- Foreign body removal

Endobronchial Lung Cancer

Patients with lung cancer present, in approximately 30% of cases, with obstruction of the central airways; with symptoms like cough, dyspnea, hemoptysis, and recurrent infections [15]; with a consequent decrease in quality of life and survival. According to international guidelines [16], patients with endobronchial tumor are not eligible for surgical treatment alone and should be treated with a debulking endoscopic technique in order to improve symptoms related to airway obstruction, to improve performance status, and to improve survival (grade D): the debulking technique should be chosen between electrocautery/diathermy, argon plasma coagulation, laser, cryotherapy and cryoextraction, photodynamic therapy, brachytherapy, and stent placement [17].

In the 1980s, the introduction of the laser technique implied a temporary provision of cryotherapy, but its utility was later revalued either for endobronchial tumor debulking or for

enhancing the effects of chemotherapy and radiotherapy. Several studies described the yield of cryotherapy in endobronchial tumor debulking: rigid and flexible probes have been used, via a rigid or a flexible bronchoscope; the airway recanalization was obtained subjecting the endobronchial tumor to various freeze-thaw cycles and repeating bronchoscopy a second time if necessary to clean up the airways, or using recanalization with the immediate removal of the frozen tissue.

Different outcomes have been reported for cryotherapy depending on the pattern of tumor growth in the airways: polypoid lesions and small tumors with a depth of penetration <10 mm are particularly suitable for cryotherapy; conversely in cases with deeper penetration in the submucosa or extrinsic diseases, cryotherapy alone is not indicated for restoring the airway patency and other techniques are suggested [9].

Interestingly, in the report of Maiwand [12], a better survival was reported in patients with squamous cell carcinoma and in patients with undifferentiated large cell carcinoma, while a worse survival was reported in patients with undifferentiated small cell carcinoma and in those with adenocarcinoma. Those results are consistent with others reported in the following years, confirming that patients with squamous cell carcinoma benefit from cryotherapy much more than other types of tumor.

Finally, in patients with lung cancer, the application of cryotherapy optimizes the effects of chemo- and radiotherapy, by improving patients' performance status and survival.

Early Stage Lung Cancer

The disease-free survival in patients with early stage lung cancer treated with surgical therapy is around 90%. Endoscopic procedures could be of value instead of surgical procedures because they offer similar disease-free survival with less perioperative mortality, morbidity, and costs [18]. International guidelines [19] suggest that cryotherapy, photodynamic therapy, electrocautery, or brachytherapy should be used as a treatment option in patient with early stage lung cancer (squamocellular type) not eligible for surgical therapy (recommendation 1C). The use of Nd:YAG laser is not recommended in those patients due to the risk of airway perforation. Compared with other methods, cryotherapy achieves tumor destruction without inducing collagen damage or bronchial wall perforation [19].

Metastatic Disease

Endobronchial metastases from extrapulmonary tumors are rare findings, and as primary lung cancer, patients suffer from symptoms related to tracheobronchial tree obstruction [20].

Benign and Rare Tumors

The key role of endoscopic techniques in the management of patients with benign airway obstruction is well known. As each endoscopic technique has its advantages and disadvantages, combining more than one method to treat benign tracheobronchial tumor is advised, in order to remove the tumor completely and reduce the incidence of recurrence as far as possible [21]. Only few case series or case reports investigated the role of cryotherapy in benign tracheobronchial tumor like hamartoma [22] and schwannoma [23], lipoma [24], and tracheobronchial carcinoid tumors [25].

Foreign Body Removal

Beyond its conventional use in patients with lung cancer, cryotherapy was found to be effective in foreign body removal. Its effectiveness depends on the cryo-adherence of the aspirated body. Porous structures, like pills, food, blood clots, or peanuts, are more adherent compared with bones, metal, or teeth [1]. It can be performed at the bedside, also in intensive care unit [26], and in many cases eliminates the need for rigid bronchoscopy. Several reports described various foreign bodies that were successfully

removed with cryotherapy, including chewing gum [27], blood clots [26, 28], mucus plug [28], granulation tissue [29], aspirated food material [1], and also aspergilloma [30].

Contraindications

Contraindications of cryotherapy are mainly extra-luminal airway obstruction and cryo-resistant tissues like collagen tissue, poorly cellular tumors, and fibrous scars: in those cases, cryotherapy alone is not indicated. Cryotherapy is not indicated in benign tracheal or bronchial stenosis caused by fibromas, lipomas, or post-intubation stenosis [3, 22].

Complications

In contrast with other techniques, cryotherapy was proven to be more safe, especially when compared with laser therapy, due to the lack of perforation risk [22]. The most common complications reported [3] are hemoptysis (4–10%), bronchospasm (4.5%), cardiac arrhythmia (11%), and death (1.3%). In a large case series of 521 patients, Maiwand reported an overall postoperative complication rate of 9%, including 21 cases of hemoptysis (4%), 12 cases of postoperative atrial fibrillation (2%), and 16 cases of respiratory failure (3%). Seven patients (1.2%) died due to respiratory failure [14]. In another study by Maiwand et al. [31], out of 153 consecutive patients, complications were seen in 11 (3 bleeding, 1 pneumothorax, 5 respiratory failure, and 2 complications related to anesthesia), with no perioperative mortality. Transient fever was observed in the immediate postoperative period, maybe due to cell necrosis and the release of tumor necrosis factor [22, 32]. Finally, in the review of Lee et al. [18], out of more than 2000 patients, complications like hemorrhage, mediastinal emphysema, atrial fibrillation, and dyspnea occurred in 11.1% of patients. Most of those complications were treated with conservative methods, while mortality occurred in 7.1% of cases within 30 days from the operation, mainly due to respiratory failure following the disease progression. Thus, considering that cryotherapy is a palliative treatment in patients with poor clinical conditions or with reduced life expectancy, the complication rate could be considered acceptable and relatively low, especially when compared with other endobronchial debulking modalities.

Description of the Equipment Needed

The cryotherapy equipment has several advantages like reusable probes, compact design, setup simplicity, and no risk of airway fire. Cryotherapy procedures need to be performed in a bronchoscopy suite, through rigid or flexible scopes, with a special cryotherapy equipment that consists of a cryotherapy unit, a gas tank, and cryoprobes. Cryotherapy unit incorporates a console that regulates the flow of cooling agents, either nitrous oxide (N_2O), carbon dioxide (CO_2), or liquid nitrogen (N_2), via a foot pedal with a manometer showing gas pressure (usually 45–50 bar) and a gas tank (N_2O, CO_2, or N_2 gas tank). Mainly, two different kinds of probes are available for the application of cryotherapy in the airways, rigid and flexible cryoprobes: flexible probes are of 78–90 cm in length and are available in two sizes, 1.9 and 2.4 mm, for use with minimal working channel diameter of 2.0 and 2.8 mm. Rigid probes are larger, 60 cm long and 3 mm in diameter with a cooling tip of 9.2 mm. Rigid probes could be straight or right-angled and have a reheating system that allows the activation of the thawing phase immediately after cooling. In contrast, the thawing phase with flexible probes is passive meaning that each cycle of freezing and thawing lasts double of time compared with a rigid probe.

Different probes are designed for cryo-recanalization [3]: probes are 78 cm in length and 3.2 mm in diameter and have a stable attachment of the central gas channel in the probe tip, resulting in greater stability to traction. The freezing power is greater due to a

larger surface area. About cooling agent, CO_2 and N_2O are the cooling agents most commonly used. The achieved tissue temperature is a key factor to obtain tissue damage. Probes' tip is cooled by gas decompression (N_2O) and reaches a temperature of -89.5 °C, according to the "Joule-Thomson" effect: it dictates that a compressed gas passing from the pressure in which it is stored (in the tank) to the atmospheric pressure rapidly expands and undergoes cooling. Spray cryotherapy is another way to deliver a cooling agent: it uses a 7F catheter delivering in its tip gaseous liquid nitrogen (N_2) and generating a spray with an exit temperature of -196°C.

Application of the Technique

Like other endoscopic procedures, a thorough medical history, including information about current medications, should be collected. Blood tests and imaging studies need to be performed and checked. Informed consent is also needed. A flexible bronchoscopy should be performed before the cryotherapy in order to better visualize the lesion that need to be treated.

Endobronchial Tumors

After inserting the cryoprobe into the bronchoscope, the tip of the probe is placed tangentially or perpendicularly or within the lesion. Generally, three cycles of freezing and thawing are performed in each location, with a freezing time of around 2–3 min. At the end of each freezing cycle, the frozen area (the so-called ice ball) is well visible and becomes less viewable at the end of the thawing phase. After three cycles, the probe tip is moved into an adjacent part of the lesion. Tissue necrosis by cryogenic damage is complete about 8 days after application. Following this period, the necrotic tissue could be eliminated by expectoration or a second bronchoscopy, which is needed in order to mechanically remove the necrotic tissue, especially if cryotherapy is used alone as debulking technique, and to treat the adjacent parts if necessary (Fig. 9.1).

Early Stage Lung Cancer

If autofluorescence endoscopy is available, it could be used to define the lesion limits; other-

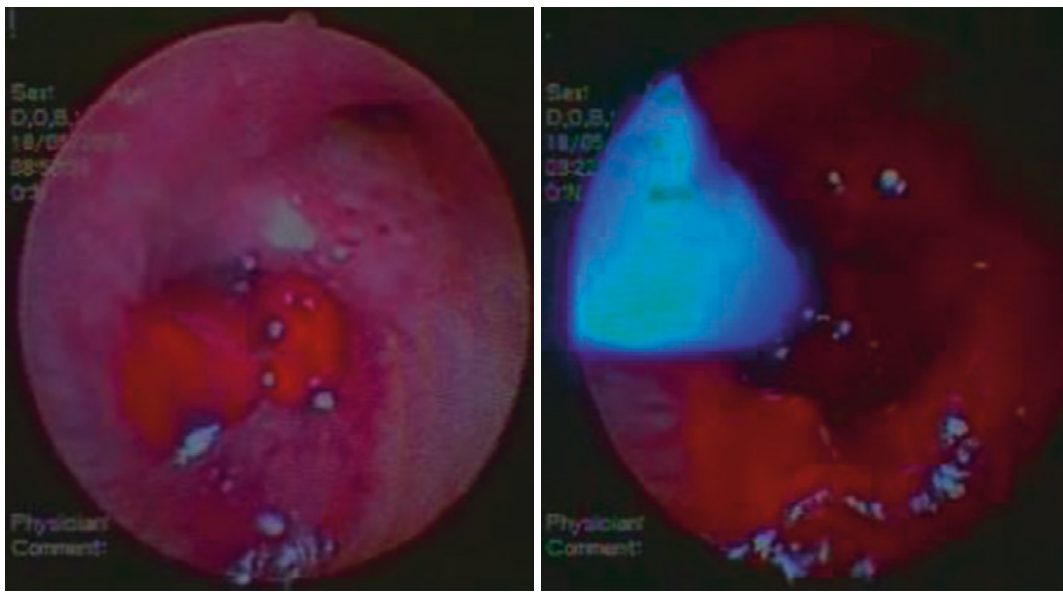

Fig. 9.1 Endobronchial obstruction caused by lung cancer

wise, a margin of 5–10 mm around the visible limits of the tumor should be treated.

Cryo-recanalization

Cryo-recanalization is used for the extraction of benign and malignant tissue. The probe is inserted into the working channel; its tip is placed inside the tumor and then cooled. The destruction due to cryotherapy is visible, allowing the assessment of the local extension of tissue freezing. Together with the bronchoscope, the cooled tissue incorporated at the tip of the probe is pulled out of the respiratory tract. The procedure could be repeated until no relevant stenosis is observed. A newly developed kind of cryoextraction is the lung cryobiopsy technique: with this procedure, trans-bronchial biopsy samples are up to eight times larger than samples taken with forceps, the quality for histological examinations is higher, and additionally no crush artifacts or bleeding is shown [7].

Foreign Body Removal

Foreign body could be cooled and removed with a mechanism similar to cryo-recanalization: a difference in the application of the technique could be the shorter cooling time, for example, clots that could be cooled in 10 s (Fig. 9.2).

Spray Cryotherapy

Spray cryotherapy does not use the "Joule-Thomson" effect, providing a uniform and planar distribution of the liquid nitrogen droplets to the target tissue at a temperature of -196 °C. This allows treating a relatively large area of the central airways despite the irregular surfaces often encountered in endobronchial disease. Understanding the mechanism and potential risks for this new therapy is essential for its safe application to patients. When the liquid nitrogen is delivered to the airway, it undergoes phase transformation and becomes nitrogen gas: it has the potential to displace oxygen and expand

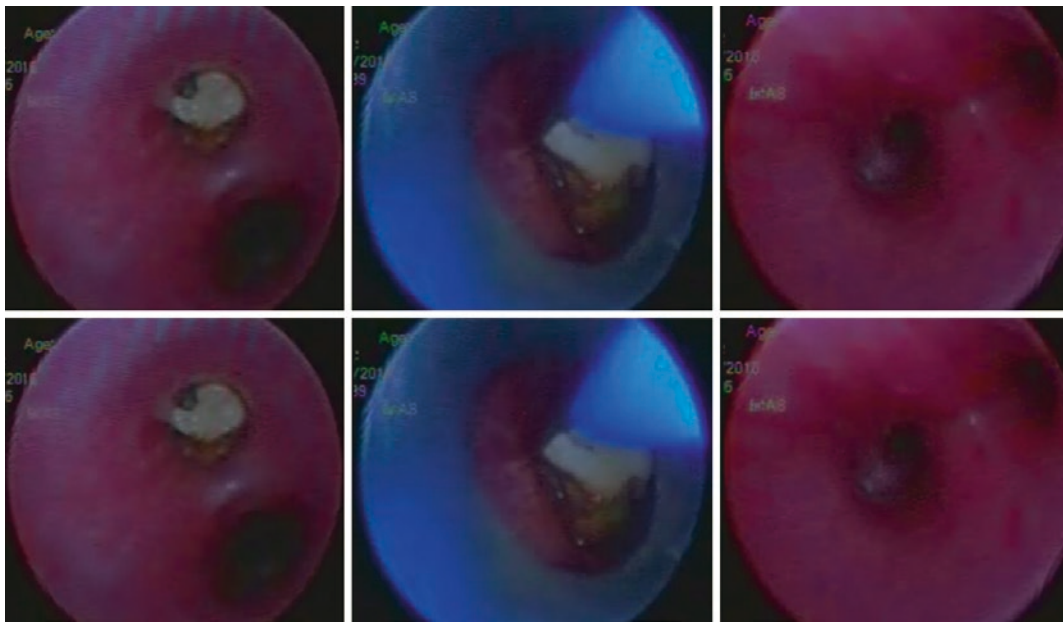

Fig. 9.2 Foreign body in children, a walnut kernel

the lungs to a volume that might exceed their capacity at which point, pneumothorax or barotrauma may occur. So adequate gas ventilation is needed through an endotracheal tube or a rigid bronchoscope.

Evidence-Based Review

Endobronchial Lung Cancer

In endobronchial tumor debulking, the choice of cryotherapy has an evidence level 3 and grade of recommendation D [16]: the same level of recommendation is for electrocautery, argon plasma coagulation, Nd:YAG laser, and stent application, even if each procedure has its safety profile and own indications.

The systematic review by Lee et al. [18] investigated efficacy and safety of endobronchial cryotherapy in lung and bronchial tumor. A total amount of 16 studies were included in the analysis. Patients' population was very diverse, including patients with primary lung cancer, metastatic cancer, benign tumors, and early superficial lung cancer; moreover, due to the variability of methods and the lack of procedure standardization, statistics analyses were not done. Cryotherapy was demonstrated to be effective in approximately 80% of cases and was effective in improving quality of life, symptoms, dyspnea, and pulmonary function especially in inoperable cases.

Maiwand et al. reported 75 cases of advanced tracheobronchial carcinoma (45 squamocellular carcinoma, 7 adenocarcinoma, 18 undifferentiated large cell carcinoma, 5 undifferentiated small cell carcinoma), treated with cryotherapy to relieve symptoms [9]. The majority of patients experienced an improvement of symptoms like stridor, dyspnea, and hemoptysis; 12 patients did not improve, 6 patients worsened, and 1 patient died from nonsurgical cause. Similar results were reported few years later by the same author: in a prospective cohort of 153 consecutive patients, cryotherapy provides effective and rapid control of symptoms caused by tracheobronchial carcinoma and an improved quality of life, with a median survival time of 12.9 months [31]. In this study, a rigid bronchoscope was used except for peripheral smaller tumors that were treated with a flexible bronchoscope.

In an Italian case series, Marasso et al. [33] investigated the therapeutic yield of rigid cryoprobes in 234 patients with malignant and nonmalignant stenosis: 183 patients with malignant tumors (mainly squamocellular carcinoma), 44 nonmalignant stenosis (4 adenoacanthomas, 6 polyps, 16 tracheal granulomas, 12 post-tubercolar heals, 6 leiomyomas and fibroleiomyomas), 4 bronchial carcinoid, and 3 bronchial cylindroma. In patients with malignancy, an improvement of lung atelectasis, hemoptysis, dyspnea, hypoxemia, and sepsis was obtained in 170 cases; in nonmalignant diseases, cryotherapy was also effective, but more settings were necessary to complete the treatment. This study underlined efficacy and safety of cryotherapy compared to other modalities like Nd:YAG laser, limiting its use in nonlife-threatening airway stenosis due to its delayed effect.

Cryotherapy was found to be safe and effective also in a report of 476 consecutive patients with obstructive tracheobronchial tumors [34]: an improvement in hemoptysis, cough, dyspnea, and chest pain was reported and also respiratory function and performance status improved. Survival analysis suggested a possible survival advantage over alternative palliative techniques. Maiwand and Asimakoupoulos [15] reviewed 521 consecutive patients with malignant endobronchial obstruction, not suitable for surgery due to the advanced stage of the disease or the poor clinical condition, which underwent endobronchial cryotherapy for palliation. Rigid probes were used in the trachea and in the main bronchi, and flexible probes were used in peripherally located tumor. There was a symptom improvement in 86% of patients, with a significant improvement in hemoptysis, cough, dyspnea, and chest pain in 76.4%, 69%, 59.25%, and 42.6% of

symptomatic patients, respectively, and there was also a significant improvement in patient's performance status in 63% of cases.

Asimakopoulos et al. [17] investigated the difference in efficacy of cryotherapy in one or two sessions. They reported the data of 329 patients that underwent at least two sessions of endobronchial cryotherapy (group A, $n = 172$) or one session of cryotherapy (group B, $n = 157$) from malignant (primary or metastatic) obstructive lung carcinoma. The most common histologic type of tumor was squamous, followed by adenocarcinoma, small cell carcinoma, and other tumors mainly metastatic. Most of the patients received palliative radiotherapy or chemotherapy, but those treatments were significantly lower in group B. Few patients underwent lung resection, 12 in group A and 8 in group B. About dyspnea, it was improved in both groups: in group A 50.5% of patients improved by at least one NYHA class; less degree of improvement was seen in group B. Similar results in both groups were reported about cough and hemoptysis. About lung function, there was a significant increase in group A in terms of PEF and FVC; the improvement of FEV1 was not significant. An improvement of Karnofsky score was seen in both groups. The mean survival was 15 months in group A and 8.3 months in group B. Patients who had radiotherapy showed longer survival. No particular tumor characteristic was associated with reduction of symptoms. Thus, on the whole, in this study, it was demonstrated that cryotherapy results in symptom relief, respiratory function, and in an improved performance status.

About cryoextraction, Hetzel et al. [3] described a cohort of 60 patients with high-grade airway stenosis from exophytic tumor (51 bronchogenic carcinoma, 4 metastases, 1 carcinoid, 3 granulation tissue and 1 malignant lymphoma). The target tissue was frozen at the tip of the probe and subsequently pooled away with the flexible bronchoscope. The treatment was successful in the 61% of cases, partially successful in the 22% and unsuccessful in the remaining 17% and 14% exhibited local recurrence. About complications, no deaths were recorded, 54 patients had bleeding that was self-limited, and 6 had more intense bleeding (100–300 mL) that was controlled with suction and argon plasma coagulation. In no cases was it necessary to switch to the use of a rigid bronchoscope. More recently, Schumann et al. [35] reported 225 patients with bronchoscopic cryo-recanalization with a flexible cryoprobe. A therapeutic success was achieved in 205 (91.1%) patients. The flexible cryoprobe by means of a flexible scope was used with all patients, and only in 31 cases a rigid bronchoscope was also used. Additional interventional techniques used were endobronchial stents and argon plasma coagulation. Bleeding was the most frequent complication and was mild in 9 patients (treated with ice-cold NaCl or epinephrine solution) and moderate in 18 patients (treated with argon plasma coagulation or bronchus blocker), while severe bleeding never occurred. Finally, Yilmaz and coll. reported similar results [36]: 40 patients with bronchial (primary or metastatic) malignancy were retrospectively included. A successful cryo-recanalization was achieved in 72.5% of patients; authors commented that the success was mainly related to the presence of the distal involvement and the older age of obstruction. Recurrences were observed in 17.2%, with a mean survival of 11 ± 12.7 months. Moderate bleeding occurred in ten patients, which was stopped with an argon plasma coagulator.

Early Stage Lung Cancer

For early stage lung cancer, according to international guidelines [16], the choice of cryotherapy has an evidence level 3 and grade of recommendation D. Only few studies investigated the role of cryotherapy in early stage lung cancer. Deygas and coll. [37] described 35 patients with early superficial bronchogenic carcinoma treated with cryotherapy through a rigid bronchoscope. A therapeutic success was achieved in 91% of cases, local recurrences were observed in ten patients within 4 years, and no complications were observed.

Metastatic Disease

No guidelines state a level of recommendation for metastatic endobronchial tumor. Few report

described this application: [20, 25] reported the first use of cryotherapy in 35 patients with endobronchial metastases from extrapulmonary tumor. The 85% of patients improved their symptoms; in over half of the patients, endoluminal patency improved by ≥50% and survival ranged is from 10 days to 4 years and 8 months, with a median survival of 34 weeks. One-year survival was 37.5%. No complications were observed.

Benign and Rare Tumor

Lipomas: A retrospective multicenter study [26] reviewed the role of bronchoscopic techniques in the management of endobronchial lipomas. Out of 38 patients, 29 underwent laser therapy and mechanical debulking, cryotherapy and mechanical debulking in 7 patients, and mechanical debulking alone in 2 cases.

Hamartoma: Sarioglu et al. [27] reported a case of a man with a polypoid mass arising from the posterior wall of the anterior segment of the right lower lobe. The histopathologic diagnosis was lipomatous hamartoma, and it was resected with an electrosurgical snare, and subsequently cryotherapy was applied to residual lesion on the surface of the bronchus. Ucar [38] reported a case of hamartoma first cauterized using snare electrocautery probe and then removed with cryoextraction. Two other similar cases were reported by Sim et al. [39] using flexible bronchoscopy without complications.

Schwannoma: Le Rouzic et al. [28] reported a case of a patient with a tracheal mass at the CT scan; bronchoscopy revealed an endobronchial multi-lobular tumor with a moderate degree of vascularization. The patient underwent complete resection with a rigid bronchoscope followed by cryotherapy. No relapse was seen during the follow-up period.

Tracheobronchial carcinoid tumors: Dalar et al. [29] investigated the role of endobronchial treatment in patients with tracheobronchial carcinoid tumors. Twenty-nine patients with carcinoid tumor underwent endobronchial endoscopic treatment with diode laser or argon plasma coagulation. Cryotherapy was applied consecutively in patients for whom there were good bronchoscopic visualization of the distal and basal tumor margins and no evidence of bronchial wall involvement. There was no tumor-related death and no recurrence during the following 49 months. There was no difference for survival or recurrence between the surgical and the endobronchial treatment group of patients. Bertoletti et al. [40] studied safety and efficacy of cryotherapy via rigid bronchoscope for the treatment of isolated endoluminal typical carcinoid tumors. Eighteen patients were analyzed: all underwent a complete removal of the tumor and received cryotherapy on the implantation base. Only one patient had a recurrence after 7 years. Thus, cryotherapy was found to be safe and effective in adjunct to endobronchial mechanical resection. Finally, a recent case report by Chawla et al. [41] reported a case of carcinoid tumor successfully biopsied and treated with cryo-recanalization.

Foreign Body Removal

Fruchter et al. [42] investigated the cryo-adherence of various commonly aspirated objects. Organic objects like chicken and fish bones were adherent to cryoprobe, and inorganic objects like safety pin and paper clip were not retrievable by cryo-adhesion. Conversely, several inorganic objects like dental cup despite their low water content were cryo-adhesive. Authors proposed to test the cryo-adherence of the aspirated body before performing the procedure on the patient, if the nature of the aspirated body is not known.

To our knowledge, Sriratanaviriyakul and coworkers [32] described one of the largest case series. They reviewed 38 cases of patients with nonneoplastic tracheobronchial obstruction: the cryoprobe successfully reestablished airway patency in 32 of cases (84%), 24 blood clots, 4 mucous plugs, 2 foreign bodies, and 2 plastic bronchitis. In 68% the procedure resulted in an improvement in oxygenation or ventilation. No complications related to the procedure occurred, only one related to sedation. Lee et al. [31] described a case of a 66-year-old woman admitted

for acute respiratory failure due to an obstruction of the left main bronchus from large blood clots. Flexible bronchoscopy failed to remove the clots, and they were removed using bronchoscopic cryotherapy at bedside in intensive care unit. Grosu et al. [34] reported a case of critical airway obstruction due to pseudomembranous Aspergillus tracheitis: cryotherapy removed successfully a 4 cm piece of tissue and the airway patency was restored. A successful cryoextraction of a chewing gum was reported by Rubio et al. [31]. Maiwand and coworkers [33] described a series of 16 patients with airway complications arising from granulation stenosis after heart-lung transplantation: cryotherapy was an effective treatment for excessive granulation tissue and reduced the need for endobronchial stenting and limited recurrences.

Summary and Recommendations: Highlight of the Development During the Last 3 Years (2013 on)

To date, cryotherapy is an effective and safe technique to treat endobronchial obstruction, both from malignant and nonmalignant diseases. Compared with other treatments, cryotherapy has had a limited role due to its delayed effect and due to the need in some cases to perform a second procedure to achieve an optimal result. Despite this disadvantage, it is safer and cheaper compared to other techniques like Nd:YAG laser, electrocautery, or photodynamic therapy [5]. The introduction of flexible probes that can be used through a flexible scope made the procedure more familiar, and also the access to distal endobronchial lesions was possible. Cryo-recanalization offered a new horizon, allowing the tumor removal immediately without the need of further procedures and with a low complication rate. New devices or new applications of cryotherapy or cryoextraction have been proposed.

Spray cryotherapy consists of a minimally invasive device that delivers extremely cold liquid nitrogen spray through a small catheter to freeze structures inside the airways. Using a flexible bronchoscope, after choosing the target tissue, the operator inserts a special spray cryotherapy 7F catheter through the scope and sprays liquid nitrogen on the diseased or obstructed tissue, with a temperature of -196°C [36]. However, a rigid scope or an endotracheal tube is needed to allow the nitrogen gas to come out. Nitrogen retention is dangerous for two reasons [43]: firstly, it has the potential to displace oxygen, and this could lead to severe desaturation, especially in patients with underlying respiratory failure; secondly, the nitrogen gas expands the lungs to a volume that might exceed their capacity, and this could lead to barotrauma and pneumothorax. The knowledge and the recognition of these side effects are mandatory for the patient's safety. The nitrogen gas during spray cryotherapy is passively removed from the airways: if an endotracheal tube is used, it should always be disconnected from the ventilator and the cuff deflated prior to the procedure, in order to let nitrogen go passively out. A visual assessment should be done, monitoring the chest movements and the frosting mist venting from the mouth or from the endotracheal tube. Browning et al. reported recently [44] 27 patients with malignant airway disease. Eighty procedures were performed in the central airways, with either the truFreeze system or with the G2 CryoSpray Ablation System, alone or in combination (n = 31 procedures) with other therapeutic modalities, also in patients with stent (n = 45 procedures). The truFreeze is an adjustable lower flow setting that allows for a wider margin of safety in the airways by delivering the liquid nitrogen at a slower rate, allowing more time to recognize the buildup of trapped nitrogen gas and make adjustments to the spray and/or the gas ventilation route. Out of 27 patients, 3 complications occurred (transient hypoxemia). The same authors [47] described a case series in which spray cryotherapy with truFreeze was successfully used in malignant and nonmalignant stenosis. Two patients with central tracheobronchial tumor were successfully treated with spray cryotherapy in conjunction with chemotherapy and radiation therapy. In two patients, cryotherapy was used to unblock an airway stent from tumor tissue and from granulation tissue and to prevent

relapses. One patient with cough caused by extensive infiltrating tumor throughout the trachea and the main bronchi was also successfully treated with repeated application of spray cryotherapy. Moreover, spray cryotherapy was also effective in a patient with post-intubation stenosis, in conjunction with balloon dilatation. No complications were reported in all four patients. The only prospective study about cryotherapy, to our knowledge, is still ongoing: the study is performed in the Netherlands [45] and aims to investigate the feasibility, the efficacy, and the safety of spray cryotherapy with the truFreeze system, in malignant and nonmalignant central airway diseases.

Another proposed use of cryoprobes in the airways is in place of endobronchial biopsy to sample exophytic and flat airway lesions. A randomized clinical trial [46] concluded that endobronchial cryobiopsy is a safe technique with superior diagnostic yield in comparison with conventional forceps biopsy: out of 593 patients randomized, in 281 forceps biopsy was done and in 282 cryobiopsies through a flexible bronchoscope. The diagnosis was achieved in 85.1% of patients randomized to conventional forceps biopsy and 95.0% of patients who underwent cryobiopsy and there was no difference in complications (bleeding). Recently, in the study of Rubio et al. [47], cryobiopsy allowed sampling of exophytic and flat lesions located centrally or distally in the airways; specimens were larger when compared with standard forceps biopsy.

Cryotherapy has been shown to have effects also in systemic treatment, such as chemo- and radiation therapy, making the tumor more susceptible to those treatments [19–22].

Finally, an interesting study by Chudasama and coworkers [48] investigated the impact on circulating tumor cell spread after cryotherapy: they enrolled 20 patients scheduled for endobronchial cryotherapy and sampled circulating tumor cells at the baseline and post cryotherapy. An increased level of circulating tumor cells was observed after cryotherapy in the 75% of patients.

In conclusion, the use of new devices and the proposed new applications of cryotherapy make the procedure versatile, and in the near future, there could be the possibility to extend the indications and to minimize the complication rates.

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