Cryotherapy in pulmonology today and tomorrow

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The analgesic and anti-inflammatory properties of ice have been known for several centuries. But it was as recent as 1961, that Cooper and Lee [1] reported a cryothalamectomy, and introduced the closed tip cryoprobe, using liquid nitrogen as a coolant source, thus allowing local application of freezing for the treatment of cancer in many different areas. Many medical specialties use cryosurgery, but the treatment of airway strictures and malignant tumours of the tracheobronchial tree is a new application of this technique [2-7], made possible by the miniaturization of the probes.

The technique utilizes a nitrous oxide cryoprobe, which employs the Joule-Thomson effect (cooling of a gas upon sudden expansion from a high to a low pressure region). The entire probe is isolated, except the distal tip. The temperature obtained at the tip of the cryoprobe is -80°C but the tissues are frozen at -40°C. With the French probes, a combined impedance meter measures variations of resistance of tissues during the process of freezing and thawing [8].

The cryolesion is well known; two factors contribute to the tissue destruction, namely physical and vascular. The physical effect is predominant, with cellular dehydration and intracellular crystallisation contributing to cell death [9, 10]. Mazur [11, 12] has suggested that the presence of intracellular ice and its crystallisation has a destructive effect on intracellular membranes. An electron microscopic study of bronchial, lung and pleural tissues recently confirmed this [13]. Complex biochemical effects secondary to cellular dehydration and an increase in intracellular electrolyte concentration contribute to the denaturation of lipoproteins in cell membranes. A cryothrombosis due to several factors completes the destruction: vaso-constriction, modification of the vascular epithelium, increase in permeability of the vascular walls and increase in blood viscosity.

Nevertheless, histopathological findings are not modified by freezing when biopsies are made immediately after cryotherapy. The secondary cellular changes in the days following cryotherapy result in a cellular necrosis: bronchial biopsy usually shows a necrotic eosinophilic substance; tumour tissue is no longer visible and therefore entirely destroyed [5].

Experimental studies [14, 15] showed that following application of temperatures of -80°C for 60 s to the tracheal epithelium of animals, a superficial ulcer formed within 48 h, which was completely re-epithelialized within four days. The initial regenerated epithelium is a simple columnar layer, but within six weeks it differentiates to a more normal appearing tracheal epithelium.

Some authors consider [16-18] that cryosurgery may induce an immunological effect: it is still only a hypothesis and no definite conclusion has yet been possible.

The major indication of bronchoscopic cryotherapy is tumour destruction. For malignant tumours, cryotherapy does serve as a good alternative for palliative tumour control. It is an efficient method for destroying benign tumours, and the destruction of tracheal granulomatous tissues appears to be simple and offers a complete cure. Indications appear to be the same as laser therapy; nevertheless, the result is delayed, and the technique is not useful for acute respiratory distress. However, it is cheap and easier to use than laser therapy, and tumour lesions seem to grow slower than after laser therapy [7]. Other applications have been described: treatment of in situ carcinoma, and of tracheal or bronchial stenosis [19].

Pleural and lung cryobiopsies during thoracoscopy are a new application of the technique [20]. The cryoprobe is passed via a trocar and applied to the area of pleura (partial or visceral) to be biopsied under direct vision. During the parietal cryobiopsy the patients do not complain of any pain, which reinforces the well known analgesic effect of freezing. The risk of haemorrhage or pneumothorax is reduced. The microscopic findings are not modified by freezing and the quality of biopsy specimen is equivalent to surgical biopsy.

Cryanalgesia appears to offer a practical technique for controlling pain after thoracotomy. Freezing intercostal nerves at the end of the operation gives a reversible nerve block with no undesirable sequelae [21-23]. After thoracotomy, cryanalgesia has an important role in the prevention of pulmonary complications, allowing early mobilisation with physiotherapy. It appears to be a simple method, and offers advantages not achieved by any other available technique.

Another use of freezing has been described in China, namely local excision of tumours at thoracotomy [24, 25]. This technique is indicated for patients with poor pulmonary or cardiac function, when lobectomy or radiotherapy are excluded, for lung metastasis and when the tumour found during thoracotomy is too extensive for resection. The tumour is held by a special ring forceps; a plastic cylinder of corresponding size is placed against the tumour surface within the ring forceps and liquid nitrogen is then poured into the cylinder. A large frozen

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portion of tumour is then easily enucleated, the residual tumour is also frozen but left in place.

Interesting advances are being made both with development of the apparatus, and with the application of cryotherapy. The cryoprobes are now safe, efficient and robust. It is still necessary to use a rigid bronchoscope, and bronchial lesions of upper lobes are often inaccessible. Thus it is advantageous to use flexible probes. German and French ones will be commercially available in a few months. Prototypes have been used for the past two years [26, 27], and can be passed through fiberoptic bronchoscopes. A modified impedance meter connected to a processor, will probably facilitate manipulation of the apparatus. Cryotherapy is now well known in France: at the end of 1988, a study group was formed and research is currently in progress. Immunological studies are being carried out by Vergnon (personal communication), whereby bronchial tumours are transplanted on to “nude” mice and cryotherapied. Veterinary surgeons have been working on the same subject [28]. It seems that radiotherapy and chemotherapy may be more effective after cryotherapy, and a multicentre study is in progress to evaluate the association of cryo-radiotherapy in France. Anti-metabolic drugs would appear to concentrate in the tumour site immediately after cryotherapy [29, 30]; this is being tested in an isolate study using bleomycin marked with 32P, in a small group of patients [31]. Electron micrographs may aid the understanding of cryodestruction of bronchial tumours.

Other research in cryotherapy is being carried out in other countries but in different specialities (e.g. phlebology, dermatology, heart surgery, urology) and more cross-fertilisation is needed between specialities. At present there is very little being written about this technique in the chest literature and the most recent studies have all come from Europe [4, 5, 7, 27, 32].

Acknowledgement: I would like to express my thanks to N.J. Bell (M.D. Oxford, England) for reviewing the text.

References
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