Feasibility of spray cryotherapy and balloon dilation for non-malignant strictures of the airway

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Objective: Benign airway strictures can be complex and challenging to manage. Although resection is preferred, this is not always feasible, and hence, endoscopic therapies are often performed. However, endoscopic therapies can be problematic, with granulation tissue and fibrosis leading to early failure. Spray cryotherapy (SC) is a new approach that may modulate the healing response leading to less fibrosis and decrease the need or the duration of time to intervention. We report the initial results of SC for benign airway strictures. Methods: Over a 22-month period, 35 patients underwent SC. Median age was 51 (18–81) years. Prior therapy had been undertaken in 14 (41.2%) of patients. Stricture etiology included post intubation (n = 5), prior tracheostomy (n = 6), radiation induced (n = 2), prior surgery (n = 3), other causes (n = 12), or unknown etiology (n = 7). Airway narrowing was graded as follows: 1 = 0–25%, 2 = 26–50%, 3 = 51–75%, and 4 = 76–100%. For the purpose of analysis, this was treated as a continuous variable. The usual treatment algorithm consisted of ≤3–4 SC cycles, followed by balloon dilation, and then by additional SC cycles. Results: Stricture locations were subglottic (n = 18), tracheal (n = 9), and bronchial (n = 8). Seventeen (49%) patients required additional SC therapy, resulting in a total of 63 SC treatment sessions. Only two (3.2%) complications occurred and these included pneumothorax (n = 1) and intra-operative tracheostomy (n = 1). Mean follow-up was available in 33/35 patients at a mean of 8.2 (1–19) months. Twelve (33%) patients (36.4%) were asymptomatic, 16/33 (48.5%) were improved, 4/33 (12.1%) had no improvement or were worse, and 1/33 (3%) patient died from an unrelated cancer. On follow-up bronchoscopy, performed in 28 patients, airway narrowing improved significantly from 3.5 to 2.03 (p < 0.001). Conclusions: Initial experience with SC for benign airway strictures suggests that this can be used safely. This is effective in improving symptoms and reducing the severity of airway narrowing. Re-intervention is still required. Further study should be undertaken to determine factors that may be associated with success or failure as well as the relative efficacy of SC compared with other endoscopic therapies.

Keywords: Cryotherapy; Airway Stricture; Benign

1. Introduction

Benign airway strictures are often complex and challenging to manage. Unlike patients with cancer, patients with benign disease will live longer and may require re-intervention, particularly if an inappropriate therapy was initially used. Surgical resection is the preferred approach for patients with benign airway strictures [5–7]. However, this is not always feasible, given the increasingly complex nature of these patients. Although surgical resection has been associated with improved long-term results, management of recurrent stenosis after resection is an even more challenging problem. Even in experienced centers, scarring and recurrent strictures occur in between 4% and 14% of patients following resection [5–7]. Thus, luminal compromise from non-malignant conditions remains a difficult, time-consuming and, given the increasing use of critical care services, an increasingly common clinical problem.

Traditional endoscopic approaches while often less morbid, are more likely to require re-intervention and may have an impact on the success of subsequent surgery [8]. These modalities include the heat-related modalities such as...
lasers, electrocautery and argon plasma coagulation [9,10], mechanical approaches such as rigid bronchoscopy or balloon dilatation [11], contact probe cryotherapy [12–14], and a variety of airway stents [8,15]. Most endoluminal approaches have produced inconsistent results in their application, and their durability for benign airway strictures. Given the disruption of the extracellular matrix associated with these modalities combined with the initial predilection in these patients for an aberrancy of the wound response, inconsistent results are to be expected. The search for an approach to modify the wound response with an anti-proliferative agent such as topical mitomycin C [9,16] has been employed to dampen the wound response so improving the overall percentage of success, as well as the durability of successful response when this occurs. Nevertheless, the results with these adjuncts remain inconsistent.

Spray cryotherapy (SC) is a new thermal energy platform that has been used extensively in the gastrointestinal tract and more recently reported in the airway [1–3]. Because the integrity of the extracellular matrix remains largely intact at the current dosimetry used with SC [3], and because an intact stroma provides the structural framework for appropriate wound repair, a fundamental shift in the wound response results in a more normative healing process [17,18]. This has been observed in different tissues treated with this technology. Following this type of thermal injury, there is felt to be a more favorable wound response with less long-term scarring, which may be beneficial for patients with benign airway strictures [3,4]. Healing with less fibrosis may allow a reduced number of re-interventions as well as prolong the symptom-free time between interventions. Although the connective network remains intact, it does become malleable at the dosimetry commonly used, allowing for remodeling of the connective matrix while preserving the fundamental architecture of the tissue [19]. This article describes the early experience for patients with benign airway strictures treated with SC. Complications and initial success rates are described below.

2. Method

2.1. Technique

SC was performed with the CryoSpray Ablation System (CSA System, Model CC2-NAM; CSA Medical, Inc., Baltimore, MD, USA), which has 510(k) clearance by the US Food and Drug Administration (FDA) as a cryosurgical tool for the destruction of unwanted tissue. The CSA System uses a non-contact method of cryotherapy by applying medical-grade liquid nitrogen (-196 °C), directly to target tissue via a low-pressure, disposable 7-French cryocatheter. This is introduced through the working channel of a therapeutic flexible bronchoscope.

SC was performed under general anesthesia through various techniques. These include: (1) rigid bronchoscopy, (2) suspension laryngoscopy, (3) laryngeal mask anesthesia (LMA), and (4) intubation with an endotracheal tube. Typically, three to four 5-s SC cycles are performed, followed by balloon dilation. Immediately after dilation, another three to four SC cycles are performed. Freeze and thaw techniques were monitored by direct visualization. The exact duration and extent of the cryogen spray to the selected site was at all times under the control of the physician.

Liquid nitrogen changes into a gas after it is sprayed onto tissue. This liquid—gas transformation results in a 700-fold change in volume. For this reason, it is important to deliver the SC above a stricture slightly away from tissue, and to ensure that there is adequate venting of gas proximally as well as to ensure a more even distribution of the liquid nitrogen. With an LMA, after the stricture is visualized with a flexible bronchoscope, the LMA tube is pulled out approximately 1 cm to allow venting of gas through the vocal cords. When an endotracheal tube is used, it is important to ensure that there is a cuff-leak with the endotracheal tube balloon deflated. This is confirmed by handbag ventilation with the ventilator circuit open. If there is no cuff-leak, an alternative method of controlling the airway for SC delivery should be used. Assuming that a cuff-leak is present with the balloon deflated, the patient is disconnected from the ventilator for the duration of the SC cycle. In addition to being able to hear, see, and feel the venting of the gas, the chest is monitored throughout the procedure as well to ensure that there is no rise during the spray cycle, suggesting retention of the gas. It is not unusual to see a drop in the oxygen saturation during SC delivery as nitrogen displaces oxygen from the airway.

It should be noted that although the FDA has approved SC with liquid nitrogen for the destruction of tissue, the present device is currently only approved for use in endoscopic applications. Therefore, use through a bronchoscope is currently off-label.

2.2. Population

A multicenter retrospective study was conducted including 35 patients, who underwent SC for benign airway strictures. HIPAA waiver was obtained for the retrospective analysis. All patients had previously consented for the procedure according to hospital protocols. Patients with malignant strictures were excluded. De-identified data were collected and entered into a Statistical Package for Social Sciences (SPSS) file version 11.0 analysis.

The median age of the subjects was 51 (18–81) years, with 68.6% (24) female. Strictures were treated in a variety of locations including subglottic (n = 18), tracheal (n = 9), and bronchial (n = 8), and were of mixed etiologies (post intubation (n = 5), post tracheostomy (n = 6), post surgical (n = 3), radiation induced (n = 2), other causes (n = 12), and unknown etiology (n = 7)). Fourteen of the patients (41.2%) had undergone prior treatment for the airway stricture with other therapies including stent, laser, steroids, tracheostomy, and tube placement. Prior to treatment, the degree of airway narrowing was visually assessed by bronchoscopy and then graded by the physician according to the following scale: 1 = <25%, 2 = 26–50%, 3 = 51–75%, and 4 = >76%. These were treated as continuous variables for the purpose of analysis.

3. Results

All 35 subjects were assessed prior to treatment. The mean degree of airway narrowing prior to SC treatment was 3.5 (standard deviation (SD) 0.69). Seventeen patients (49%
returned for additional rounds of treatment for a total of 63
treatment episodes in 35 patients (mean 2.2, range; SD 1.2).

| Table 1 | demonstrates the number of repeat cryotherapy treatment sessions 
| related to initial stricture severity. The mean follow-up was 8.2 months (range 1—19) 
| and was available in 33/35 patients. There were no
| periprocedural deaths, but complications occurred after 
| two procedures and included the need for a tracheostomy in
| one patient, and pneumothorax in another. The tracheostomy 
| was undertaken in a morbidly obese patient, who developed 
| glottic edema proximal to the site of a tracheal 
| stricture that had been treated with SC. She had undergone 
| resection of a large goiter a few days prior to this and had a 
| difficult intubation for her initial procedure because of the
| previously undiagnosed stricture. The second patient, who 
| developed a pneumothorax, had a subglottic stenosis 
| treated with SC. Following this, but during the same 
| anesthesia, a second area of narrowing in the left main 
| bronchus was also treated. The patient developed a right 
| pneumothorax that was treated with a chest tube. It is 
| believed that the pneumothorax occurred because of 
| impaired egress of gas during the SC of the second distal 
| lesion. At the time of follow-up, 12/33 (36.4%) were 
| asymptomatic, 16/33(48.5%) were improved, 4/33(12.1%) 
| had no improvement or were worse, and 1/33(3%) patient 
| died from an unrelated cancer. Follow-up bronchoscopy was 
| performed in 28 patients. The mean follow-up stricture 
| narrowing was 2.03 (SD 1.37), which was significantly 
| improved (Student’s paired t-test, \( p < 0.001 \)) compared 
| with the pre-treatment findings.

4. Discussion

The results described here demonstrate that SC is a 
relatively safe therapy that was effective in eliminating or 
improving symptoms in 84.9% of patients. This is in a high-risk 
patient group, who in 41% cases had failed prior therapies. Of 
a total of 63 cryospray treatments that were performed, only 
two cases resulted in adverse outcomes of which only one 
(the pneumothorax) was related to the cryospray technique. 
As discussed earlier, this was felt to be related to impaired 
egress of nitrogen when treating a distal stricture in the face of 
a more proximal stricture. This case emphasizes the need 
to pay attention to adequate proximal venting when 
performing SC.

SC differs from the more commonly used method of 
counter cryotherapy. Contact cryotherapy (with an endo-
cryoprobe) uses the ‘Joule—Thompson effect’. This process 
involves the compression of gas (carbon dioxide or argon) 
through a narrow aperture with the resulting expansion of 
that gas causing a concomitant temperature drop, cooling the 
probe. This is a relatively inefficient way to deliver the 
cryogen to tissue and requires local contact of the probe with 
the tissue. The tissue is cooled in a radial fashion from the 
area of contact. SC allows a more even and linear distribution 
of the cryogen over a large area and the biological effect will 
be more pronounced.

Although surgical resection is the preferred approach 
for benign airway strictures, this is not always feasible and 
a variety of other approaches have been used. Other 
ablative approaches, such as laser combined with dilation, 
are a favored approach by many otolaryngologists; however, the success rate of this drops for higher-grade 
lesions and particularly lesions longer than 3 cm [9]. 
Airway stents are another popular approach; however, self-
expanding metal stents, which are generally easier to 
place, should be avoided because of a higher complication 
rate [8]. Silicone stents are better tolerated, particularly 
in the lung transplant population where successful stent 
placement and removal has been reported in up to 69% of 
anastomotic strictures [20]. In a study involving 209 
patients with benign tracheal stenoses, patients were 
divided into simple stenosis (<1 cm; \( n = 167 \)) and complex 
stenoses (>1 cm; \( n = 42 \)) [21]. Sixteen silastic stents were 
placed in the simple stenosis group, of which one patient 
required subsequent resection. In the complex stenosis 
group, 34 stents were placed and 12 subsequently had 
recurrence after stent removal. Eight patients also 
required stent repositioning after stent migration, demonstrating the need for repeated interventions in these 
patients.

The major limitation of our study is the use of a 
retrospective cohort with somewhat variable follow-up. The 
effect of the therapy can also be exaggerated in 
observational studies. The strengths of our study include 
analysis of data obtained from both community and 
academic centers as well as a relatively large number of 
patients treated with this modality. Future investigation 
should ideally be undertaken comparing this approach to 
other common endoscopic approaches, such as dilation or 
stenting with silastic stents, with careful classification of 
stenosis severity/type to determine success rates with 
each therapy. However, an important advantage with SC 
may be that this modality will not adversely affect future 
intervention (in particular, surgery) because of the 
favorable wound response [3,4] although, this is spec-
ulative.

In conclusion, these preliminary results with SC suggest 
that it is both safe and effective for the treatment of benign 
airway strictures. Further prospective studies are, however, 
needed to confirm and better characterize these results.

| Table 1 | Number of spray cryotherapy procedures undertaken based on initial 
| stricture severity. 

<table>
<thead>
<tr>
<th>Narrowing</th>
<th>76–%</th>
<th>51–75%</th>
<th>26–50%</th>
<th>0–25%</th>
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<td>Number pre-procedure</td>
<td>21</td>
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<td>5</td>
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<td>1 – n = 6</td>
<td>1 – n = 4</td>
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<tr>
<td></td>
<td>5 – n = 2</td>
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