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Treatment of Benign Tracheal Stenosis Using Endoluminal Spray Cryotherapy

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IMPORTANCE Tracheal stenosis is a debilitating disorder with heterogeneity in terms of disease characteristics and management. Repeated recurrences substantially alter patients' quality of life. There is limited evidence for the use of spray cryotherapy (SCT) in the management of benign airway disease.

OBJECTIVE To report our early results for the use of SCT in patients with benign tracheal stenosis.

DESIGN, SETTING, AND PARTICIPANTS Data were extracted from the medical records of a consecutive series of patients with benign airway stenosis secondary to granulomatosis with polyangiitis (GPA) (n = 13), prior tracheotomy or tracheal intubation (n = 8), and idiopathic strictures (n = 5) treated from September 1, 2013, to September 30, 2015, at a tertiary care hospital.

MAIN OUTCOMES AND MEASURES Airway narrowing was quantified on a standard quartile grading scale. Response to treatment was assessed by improvement in airway caliber and the time interval for reintervention.

EXPOSURES Delivery of 4 5-second SCT cycles and 2 balloon dilatations.

RESULTS Twenty-six patients (median [range] age, 53 [16-83] years; 20 [77%] female) underwent 48 SCT sessions. Spray cryotherapy was successfully used without any substantial intraoperative or postoperative complications in all patients. In a median (range) follow-up of 11 (1-26) months, all patients had improvement in symptoms. Before the institution of SCT, 23 patients (88%) had grade III or IV stenosis. At the last evaluation after induction of SCT, 4 (15%) had grade III or IV stenosis, with a mean (SD) change of 1.39 (0.51) ($P < .001$). Patients with GPA required significantly fewer SCT procedures (mean [SD], 1.38 [0.96] vs 2.31 [1.18]; $P = .03$) during the study period.

CONCLUSIONS AND RELEVANCE Spray cryotherapy was a safe adjunct modality to accomplish airway patency in patients with benign tracheal stenosis. Although efficacy evidence is limited for SCT, it may be useful for patients who have experienced treatment failure with conventional modalities. Further analysis of this cohort will determine the physiologic durability of the reported short-term changes. Additional trials are warranted for further evaluation of this modality.

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Tracheal stenosis is a debilitating disorder with diverse underlying pathophysiologic mechanisms. Common causes include stenosis secondary to neoplasms, airway trauma (tracheal intubation, prior tracheotomy), collagen vascular diseases (granulomatosis with polyangiitis [GPA], sarcoidosis, and lupus), infectious diseases (tuberculosis), and idiopathic strictures.[1-3] The disease has a high rate of recurrence, and patients often require repeat interventions to maintain airway patency.

Surgical resection with end-to-end anastomosis has therapeutic value in selected patients[4]; however, as good outcomes have been seen with endoluminal therapies, the paradigm has been shifting toward the latter. When open repair is not possible, that is, in patients with long strictures, diffuse inflammatory disorders, and the presence of severe comorbidities, endoluminal therapies can be used to improve airway patency and avoid tracheotomy.[5] Several thermal modalities have been used, such as laser photocoagulation, electrocautery, and photodynamic therapy, and these are usually combined with mechanical dilation using balloon or rigid dilators.[6,7] While effective in many cases, results are inconsistent and there is a concern that heat-based modalities may result in additional scar tissue formation and therefore lead to recurrence.[5] Similarly, airway stents are useful in some situations but are often complicated by formation of granulation tissue, mucus plugging, stent migration, and occasionally stent fracture in the case of metallic stents.[8,9] Given the limitations of current modalities for the treatment of benign tracheal stenosis, there exists a need to explore alternative methods.

The concept of cryosurgery for laryngotracheal strictures dates back to the late 20th century with the work by Strome[10,11] and others. Contact probe cryotherapy as a nonthermal modality was first used in the human trachea in 1986 to relieve symptoms associated with advanced carcinoma.[12] Advances have been made in the delivery system of this technology in the form of spray cryotherapy (SCT), is which liquid nitrogen is delivered through a 7F disposable catheter, causing tissue ablation by flash freezing.[13] The use of this modality has been reported for ablation of esophageal lesions with good long-term outcomes.[14] Therefore, some centers already using SCT for gastrointestinal procedures investigated this modality for ablation of airway strictures.[15] The initial multicenter study evaluating the role of SCT in malignant airway obstruction reported substantial complications.[16] It is thought that these complications were the result of insufficient egress of the nitrogen gas that forms as a result of large-volume expansion during the phase transformation of liquid nitrogen. In contrast to gastrointestinal procedures in which this evacuation can be achieved with active suctioning, an additional catheter is not practical in the airway and passive venting of the nitrogen gas remains the only option for adequate egress.[17,18]

In 2012, the advanced truFreeze device was approved by the US Food and Drug Administration for cryogenic destruction of tissue using liquid nitrogen spray requiring either active or passive ventilation during surgical procedures.[19] Hence, the use of this device in the airway is now considered on-label. Browning et al[20] in their recent experience have shown safety of this device in the management of neoplasm-related strictures and did not experience any of the complications reported by Finley and colleagues.[16] In this study, we report our initial results for the use of SCT as an adjunct to balloon dilatation in a cohort of patients with benign tracheal stenosis using the new truFreeze system.

Key Points

Question Is spray cryotherapy safe in patients with benign tracheal stenosis?

Findings In this case series, spray cryotherapy was successful in improving airway patency in all patients, and no substantial intraoperative or postoperative complications were observed.

Meaning Spray cryotherapy is a safe adjunct modality to accomplish airway patency in patients with benign tracheal stenosis and seems to prolong intervention-free interval.

Methods

Patients

This is a retrospective study of a consecutive series of patients with benign tracheal stenosis who gave informed consent and underwent SCT treatment between September 1, 2013, and September 30, 2015, at a single institution. The majority of these patients had failure or poor response to prior therapies. Individual patient characteristics (age, sex, etiology, prior airway procedures, follow-up) were extracted from each patient's record. The study design and methodology were reviewed and affirmed exempt by the Icahn School of Medicine Institutional Review Board.

The extent of airway stenosis was evaluated on a quartile grading scale (1 = <25%, 2 = 25%-50%, 3 = 51%-75%, 4 = >75%) from endoscopic evaluation of airway diameter before and after the therapy and graded by a panel of 4 reviewers (S.R., A.M.A.-A., and 2 others). The frequency and time to reintervention between subsequent SCT sessions was noted and compared with prior treatment modalities.

All data management and analyses were done using IBM Statistical Package for Social Sciences (SPSS), version 19. Differences between the preoperative and postoperative grades and the mean number of interventions before and after SCT were assessed by using the paired-sample t test. A $P < .05$ was considered significant.

Technique

All procedures were performed under general anesthesia. For upper and mid tracheal lesions (44 procedures), the larynx was suspended using a Dedo laryngoscope in a standard fashion and a ventilating pin was used for intermittent apneic oxygenation. For distal tracheal lesions (4 procedures), endotracheal intubation (using at least a size 8.5F tube) was used. After a complete endoscopy, preprocedural photographic documentation was obtained. The truFreeze System spray cryotherapy machine (CSA Medical) was used to apply liquid nitrogen spray through a flexible catheter passed though the working channel of a therapeutic bronchoscope. The spray application was

Table 1. Patient Characteristics

Patient No./Sex/Age	Indication	Rituximab Therapy	Prior Airway Procedures	Duration of Prior Procedures, mo	SCT Sessions	SCT Grade Before	SCT Grade After	Time Since Induction of SCT, mo
1/F/10s	GPA	Yes	1	8	1	4	3	8
2/F/30s	GPA	Yes	3	8	1	4	2	11
3/F/30s	GPA	No	2	3	1	3	2	10
4/F/30s	GPA	Yes	1	1	4	2	1	13
5/M/30s	GPA	Yes	32	72	3	4	2	19
6/F/40s	GPA	No	7	72	1	3	1	1
7/F/50s	GPA	No	8	96	1	3	2	8
8/F/50s	GPA	No	2	84	1	3	1	12
9/F/50s	GPA	Yes	7	23	1	4	3	11
10/F/60s	GPA	Yes	4	91	1	4	2	11
11/F/60s	GPA	Yes	3	29	1	3	2	9
12/F/60s	GPA	No	2	28	1	3	2	4
13/F/80s	GPA	Yes	3	17	1	3	1	11
14/M/20s	PT/PI	NA	2	2	3	4	2	11
15/M/40s	PT/PI	NA	1	5	3	2	1	24
16/F/40s	PT/PI	NA	0	NA	1	3	1	2
17/F/50s	PT/PI	NA	5	21	5	2	1	26
18/F/50s	PT/PI	NA	1	2	3	3	2	14
19/M/50s	PT/PI	NA	1	5	2	4	2	26
20/F/50s	PT/PI	NA	2	4	1	4	2	1
21/F/60s	PT/PI	NA	1	8	2	3	1	20
22/F/50s	Idiopathic	NA	4	17	1	4	2	1
23/F/50s	Idiopathic	NA	3	8	2	4	3	18
24/M/60s	Idiopathic	NA	8	56	3	4	2	22
25/M/60s	Idiopathic	NA	12	76	3	4	2	25
26/F/60s	Idiopathic	NA	3	24	1	4	3	5

Abbreviations: GPA, granulomatosis with polyangiitis; NA, not applicable; PT/PI, posttracheotomy or postintubation; SCT, spray cryotherapy.

monitored in real time on the video monitor. Our procedures included 2 initial 5-second sprays of liquid nitrogen followed by deploying a tracheal balloon also monitored in real time. A second cycle was performed, for a total of 4 5-second spray cycles and 2 balloon repairs.

Our spray cycle commenced when mucosal frost formation was visualized on the monitor. Cryospray was applied circumferentially along the area of stenosis (**Video**, "spray cryotherapy application"). Egress of nitrogen gas was confirmed by feel and by visual inspection. In patients with endotracheal intubation, the endotracheal tube cuff was deflated and the tube disconnected from the respiratory circuit while egress of gas was confirmed. All patients had continuous monitoring of vital signs, heart rhythm, and respiratory volumes and pressures after the anesthesia circuit was reconnected. An arterial line was not used.

After completion of the procedure, all patients were extubated in the operating room and transferred to the postanesthesia care unit. They were discharged home within 24 hours. Patients were observed regularly at the outpatient otolaryngology and/or thoracic surgery clinic to assess response and for evaluation of need to repeat the intervention. At follow-up visits, patients were queried about subjective improvement in symptoms.

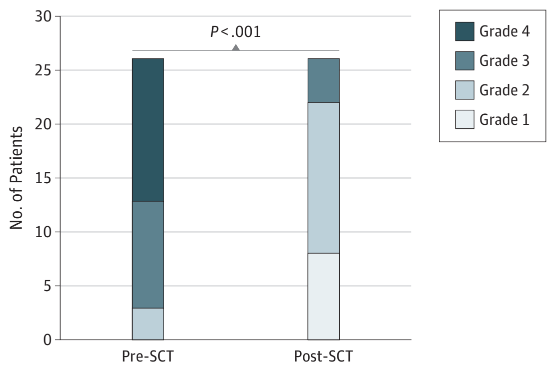
Results

A total of 48 cryotherapy sessions performed on 26 patients were identified during the study period. The median age was 53 years (range, 16-83 years), and 20 patients (77%) were female. Granulomatosis with polyangiitis was the most common cause of stenosis (n = 13), followed by tracheal intubation or prior tracheotomy (n = 8) and idiopathic stenosis (n = 5). Twenty-five patients (96%) had undergone prior endoscopic treatments before the institution of SCT. Patient characteristics are summarized in **Table 1**.

In a median follow-up of 11 months (range, 1-26 months), all patients reported an overall subjective improvement in breathing. Before the institution of SCT, 23 patients (88%) had grade III or IV stenosis. At the last evaluation after induction of SCT, 4 patients (15%) had grade III or IV stenosis and the mean (SD) change in grade of stenosis was 1.39 (0.51) ($P < .001$) (**Figures 1** and **2**).

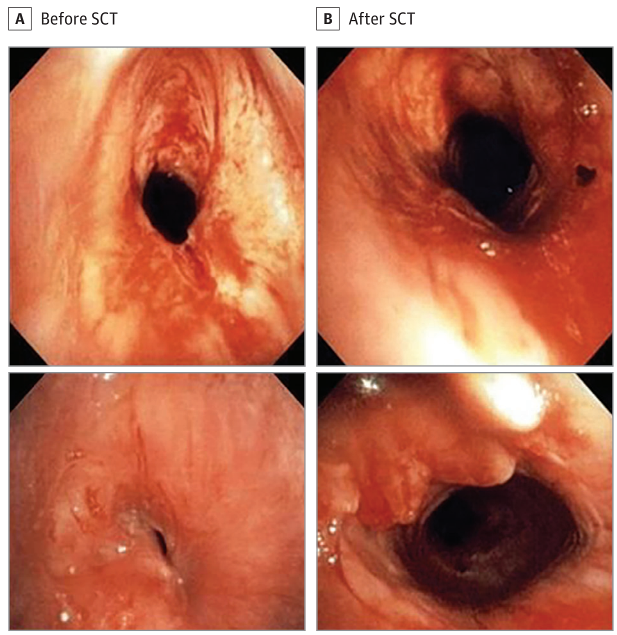
The mean (SD) number of SCT procedures per patient for the overall cohort was 1.85 (1.16). Patients with GPA underwent fewer SCT procedures during the study period compared with patients with traumatic or idiopathic strictures (mean [SD], 1.38 [0.96] vs 2.31 [1.18]; $P = .03$). Twenty

Figure 1. Change in Grade of Stenosis Before and After Spray Cryotherapy (SCT)



Post-SCT grade was obtained at the last available outpatient follow-up (range, 1-26 months).

Figure 2. Bronchoscopic Evaluation of Airway Caliber Before and After Spray Cryotherapy (SCT) Application



patients had a follow-up of 6 months or greater after the induction of SCT, and we calculated the mean number of interventions per year before and after the introduction of SCT for this group. The mean (SD) intervention rate decreased from 3.8 (3.4) per year prior to induction of SCT to 1.6 (0.8) per year after the institution of SCT (P = .004) (**Figure 3**). Cryospray outcomes are summarized in **Table 2**.

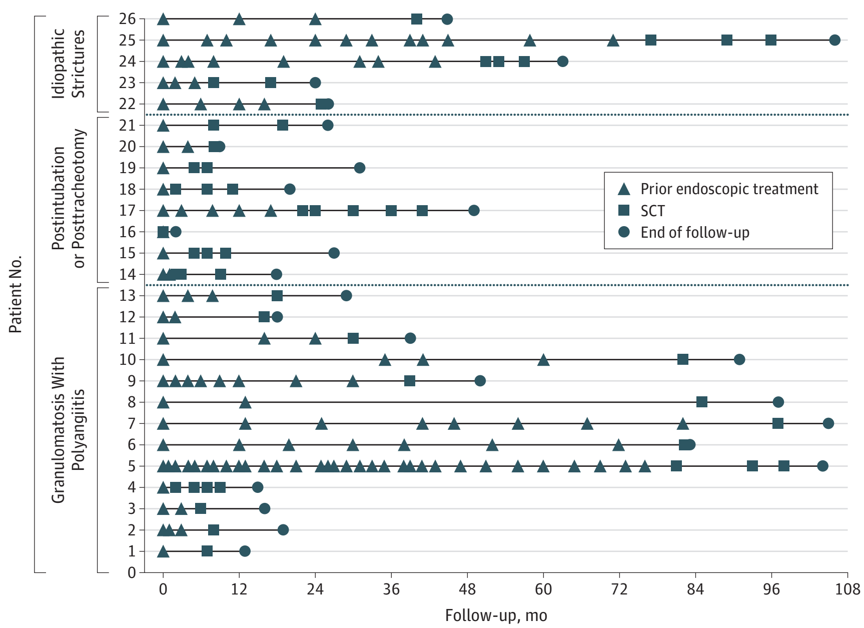
There was no substantial morbidity or mortality associated with the procedure except for 1 patient who had transient hypotension during the procedure.

Discussion

Spray cryotherapy has evolved from contact cryoprobes that have been used in the aerodigestive tract for more than a decade. In contact cryotherapy,[7,21] nitrogen gas is released from the tip of a probe and as it expands, the temperature is brought down to −40°C by the Joule-Thomson effect. This is followed by formation of extracellular ice crystals, dehydration, and tissue necrosis. The tissue response from this cold injury ranges from inflammation to total destruction, depending on the severity of freezing. Unlike the cryoprobe, SCT uses a noncontact spray of liquid nitrogen at −196°C, causing flash freezing and intracellular crystal formation. With the onset of ice formation, water is extracted from within the cells, followed by cell shrinkage and damage to the intracellular matrix due to high salt content. As the temperature approaches −15°C and below, lethal intracellular ice begins to form. In a structurally constrained space, the expanding ice front may destroy cells of the capillary endothelial lining, rendering the vascular tree impaired after thawing and imparting its hemostatic properties.[22] With SCT tissue destruction is associated with preservation of extracellular matrix and regenerative growth of the tissue, which may allow healing with decreased or minimal fibrosis.[13,23] The major benefits of cryotherapy in neoplasm-related strictures appear to be its dual antiproliferative and hemostatic properties. When applied to benign strictures, it may cause "remodeling" of the connective tissue matrix, which makes it more malleable and allows easier and more atraumatic dilation of the stricture.[24,25] However, the exact mechanism is less clear and additional research is required to enhance our understanding of the pathophysiologic mechanism of this modality.

Use of SCT in patients with airway stenosis is fairly recent. Krimsky et al[15] evaluated the feasibility of SCT in 21 patients with lung cancer and reported regeneration of histologically normal epithelium with its use. Another multicenter study[16] described the use of SCT in 80 patients with neoplasm-related strictures. They reported improved luminal patency in all but 1 patient. However, substantial complications were observed including 21 (26%) intraoperative events (hypotension, bradycardia, tachycardia, ST-segment changes, and desaturation), 3 pneumothoraces, and 2 intraoperative and 3 postoperative deaths. This study raised concerns for the safety of SCT in the airway. In addition, a clinical trial (NCT00747461) was initiated in 2008 to investigate its role in benign airway disease. According to company records (CSA Medical), this trial was undertaken using the previous-generation device (CSAM2). Serious adverse effects were noted in the first accruals, and the trial was therefore terminated prematurely. Several modifications were made in the delivery and flow characteristics of the device. The new truFreeze system was released in 2012 and received expanded clearance from the Food and Drug Administration including cryogenic destruction of tissue necessitating active and passive ventilation. A recent study investigated the safety of this device in 27 patients with malignant airway strictures and observed 3 complications (all transient hypoxia) in 80 procedures.[20] The authors concluded that SCT can be safely used in the airway by ensuring adequate passive venting and allowing for adequate oxygenation between spray applications. The evidence for the use of SCT

Figure 3. Individual Patient Treatment Timeline for All Patients Who Underwent Application of Endoluminal Spray Cryotherapy (SCT)



The timeline starts at first treatment and ends at last follow-up. Each symbol represents a procedure.

Table 2. Spray Cryotherapy (SCT) Outcomes and Comparison Based on Etiology

Parameter	Overall (N = 26)	GPA (n = 13)	Posttrauma (n = 8)	Idiopathic Stenosis (n = 5)
Age, y, median (range)	53 (16-83)	51 (16-83)	51 (20-68)	65 (52-66)
Previous airway treatments, median (range)	3 (0-32)	3 (1-32)	1 (0-5)	4 (3-12)
SCT sessions, No. (%)	48 (100)	18 (37)	20 (41)	10 (20)
SCT sessions required per patient, mean (SD)	1.85 (1.16)	1.38 (0.96)	2.50 (1.31)	2.00 (1.00)
Grade of stenosis, mean (SD)				
Before SCT	3.37 (0.68)	3.37 (0.63)	3.16 (0.84)	4.00 (0)
After SCT	1.98 (0.66)	1.96 (0.69)	1.69 (0.54)	2.45 (0.55)
Change	1.39 (0.51)	1.40 (0.52)	1.47 (0.52)	1.25 (0.55)
Interventions per year, mean (SD)[a]				
Before SCT	3.78 (3.43)	3.65 (3.65)	4.57 (3.95)	2.70 (1.56)
After SCT	1.64 (0.76)	1.52 (0.78)	1.96 (0.90)	1.47 (0.15)

Abbreviation: GPA, granulomatosis with polyangiitis.

[a] Calculated for patients with follow-up of at least 6 months.

in benign airway disease is limited. A multicenter, retrospective study[24] assessed its clinical utility in 35 patients with benign airway strictures using the previous-generation device. In a mean follow-up of 8.2 months, SCT was effective in improving symptoms in 85% of patients. There were 2 (6%) complications including 1 pneumothorax and 1 intraoperative tracheostomy.

In this study, we have analyzed both the safety and short-term efficacy of SCT as an adjunct to balloon dilatation and compared it with our standard technique, which includes endoscopic ablation with bipolar cautery or mechanical scar incisions and mechanical dilatation with or without steroid injections. We observed improvement in symptoms in all patients without experiencing any substantial complications with the new truFreeze device. Our study also shows significant improvement in luminal caliber after SCT and in most patients a longer period before reintervention. Interestingly, we observed that patients with strictures secondary to GPA were responsive to SCT and were able to maintain airway patency for longer periods after the first procedure.

In comparison with previous studies[16,24] in which complication rates of up to 6% to 19% were reported, we experienced no substantial procedure-related morbidity or mortality. Important safety measures need to be carried out with the use of SCT due to rapid expansion of nitrogen gas and potential risk of barotrauma.[17] Our record of safety is attributable to use of a team approach (including a thoracic surgeon [F.Y.B.], an otolaryngologist [R.S.L.], and an experienced anesthetist), meticulous attention to egress, and enhancements in the flow characteristics of the new cryospray system. These include delivery through a nonpulsatile and adjustable low-flow system that releases nitrogen spray at a slower rate, allowing more time to recognize the buildup of nitrogen gas and make adjustments accordingly to the spray and/or the gas ventilation.[17] Our technique of laryngeal suspension in most cases may also provide an additional safety margin by providing rapid egress.

Our study is limited by its retrospective nature, small sample size, and short follow-up. In addition, systemic biologics such as rituximab have been shown to be effective for otolaryngologic manifestations of GPA.[26] Although we have included information on the use of rituximab for our patients, data about the treatment regimens and duration are lacking. Despite these limitations, to our knowledge this is the largest single-center study of the use of SCT in patients with benign tracheal stenosis with the longest follow-up reported in the literature. Moreover, we also compared the utility of SCT in patients whose conditions stemmed from rare etiologies such as GPA and idiopathic strictures, an area not previously well studied in the literature. Another strength of our study is that each patient serves as his or her own control, with SCT as an adjunct to balloon repair being the new variable as compared with other modalities previously used in these patients in combination with balloon dilatation.

Conclusions

Our results demonstrate that SCT is a safe adjunct modality to accomplish airway patency in patients with benign tracheal stenosis. Although efficacy evidence is limited for SCT, it may be particularly useful for those who have experienced treatment failure with conventional modalities. Further analysis of this cohort will determine the physiologic durability of the reported short-term results. In addition, prospective, multicenter, open-label trials with long-term outcomes are warranted for further evaluation of these observations and to improve our understanding of the pathophysiologic mechanism and role of this modality in the management of airway stenosis.

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Critical revision of the manuscript for important intellectual content: Ayub, Forleiter, Huang, Alshehri, Rehmani, Al-Ayoubi, Lebovics.
Statistical analysis: Ayub, Forleiter, Rehmani, Raad.
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