Treatment of Barrett's esophagus with a novel focal cryoablation device: a safety and feasibility study

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Background and aims: Currently, eradication of Barrett's epithelium is preferably achieved using radiofrequency ablation (RFA) or spray cryoablation (SCA). However, both modalities suffer from drawbacks such as the need for sizing, multiple deployment steps, large controller units (RFA), imprecise dosing and need for gas-venting (SCA). The new Cryoballoon Focal Ablation System (CbFAS) may address these limitations. This study assessed the safety, feasibility, and dose response of the CbFAS in patients with flat Barrett's epithelium with or without dysplasia.

Patients and methods: In this multicenter, prospective non-randomized trial, 39 patients were each treated with one or two ablations of 6, 8, or 10 seconds. Symptoms were assessed immediately and 2 days post-cryoablation. Follow-up endoscopy was performed 6–8 weeks post-procedure to assess response. Outcome parameters were incidence of adverse events, pain, esophageal stricture formation, and ablation response by cryogen dose.

Results: Of 62 ablations, 56 (10 with 6 seconds, 28 with 8 seconds, 18 with 10 seconds) were successfully performed. Six ablations failed because of device malfunction (n=3) and procedural or anatomic issues (n=3). Median procedure time was 7 minutes (interquartile range [IQR] 4–10). No major adverse events occurred; six patients experienced a minor mucosal laceration requiring no intervention. Mild pain was reported by 27% of patients immediately after cryoablation and by 14% after 2 days. No strictures were evident at follow-up. Full squamous regeneration was seen in 47 treated areas (6 [60%] of the 6-second areas; 23 [82%] of the 8-second areas; 18 [100%] of 10-second areas).

Conclusions: Focal cryoablation of Barrett's epithelium with the CbFAS is feasible and safe, resulting in squamous regeneration in the majority of patients.

Introduction

Barrett's esophagus harbors a significant risk for the development of esophageal adenocarcinoma. Current guidelines recommend endoscopic treatment for all patients with early Barrett's neoplasia (high grade dysplasia or early esophageal adenocarcinoma) [1,2]. Endoscopic therapy consists of a two-step approach: any visible lesions are resected by endoscopic resection and sent for histopathological evaluation. Subsequently, the remaining flat Barrett's segment is eradicated by ablation therapy to prevent the development of any metachronous neoplasia [3].

Radiofrequency ablation (RFA) is currently the preferred ablation method as it has proven to be highly effective for the eradication of intestinal metaplasia and dysplasia [4,5]. RFA is delivered through either a balloon-based, fully circumferential device or a cap-based focal device (HALO; Covidien, Mansfield, Massachusetts, USA). This heat-based technique aims to eliminate the mucosal tissue, while limiting the damage to the muscularis mucosa to prevent stricture formation [6,7].

Alternatively, spray cryoablation (SCA) is used for the treatment of Barrett's epithelium [8,9]. Deep freezing and slow thawing causes disruption of cells, vascular ischemia, and thrombosis, resulting in necrosis of the superficial esophageal layers [10]. In contrast to heat-based ablation, cryotherapy leaves the tissue architecture intact [11], and may result in less stricture formation.

Although safe and effective, the use of either RFA or SCA is sometimes unwieldy as these methods suffer from certain drawbacks, such as frequent post-treatment pain, the need for precise sizing of the esophageal lumen, multiple deployment

steps, plus large controller units in RFA procedures and imprecise dosing and the need for gas-venting in SCA.

Recently a novel cryoablation technique, the Cryoballoon Ablation System (CbAS), was developed by C2 Therapeutics, Redwood City, California, USA. This cryotherapy device aims to combine the beneficial properties of both RFA and SCA for a compliant, evenly spread ablation therapy with low stricture rate. Earlier studies have assessed the properties of the full circumferential CbAS [12]. For focal cryoablation, a new system, the Cryoballoon Focal Ablation System (CbFAS), has been developed. The aim of this study was to evaluate the safety and feasibility of this novel through-the-scope balloon-based focal cryoablation device for the ablation of Barrett's epithelium.

Fig. 1 The Cryoballoon Focal Ablation System (CbFAS), which consists of a battery-powered handle with a trigger mechanism for which the duration of ablation (in seconds) can be electronically preset; a cartridge containing liquid nitrous oxide that is placed in a compartment in the handle; and, attached to the handle, a 3.6-mm diameter catheter with a compliant balloon probe (30 mm in length) with a single spray hole in the shaft. This through-the-scope device allows for focal ablation (approximately 2 cm^2) by the release of cryogenic fluid into the balloon that adapts to the diameter of the esophageal lumen.

Methods

Cryoballoon focal ablation system

The CbFAS is a new ablation device that is comprised of a battery-powered handle with a trigger mechanism for which the duration of ablation (in seconds) can be electronically preset; a cartridge containing liquid nitrous oxide that is placed in a compartment within the handle; and a catheter with a diameter of 3.6 mm, which is attached to the handle, with a compliant balloon probe (30 mm in length, maximum diameter of 36 mm) with a single spray hole in the shaft (**Fig. 1**).

Once deployed through the working channel of a therapeutic endoscope (3.7-mm accessory channel) and positioned at the correct distance within the esophagus, the balloon will inflate at approximately 5 pounds per square inch (psi) and self-size to the diameter of the esophageal lumen after a single 1-second pull of the trigger.

Small puffs of nitrous oxide allow the position of the spray hole in the shaft of the balloon to be determined, and this may then be adjusted by torqueing the catheter. When it has been located in the correct radial position, a continuous pull on the trigger will release a constant flow of nitrous oxide (at −85 °C) until the device automatically stops at the preset duration of ablation (in seconds). The balloon is then deflated. The gas, which develops from the nitrous oxide in the balloon when it comes into contact with the underlying mucosa, is vented back through the catheter and condenses into a sponge in the handle.

This focal cryoablation results in freezing of the superficial layers of the esophageal wall with a surface area for a single ablation of approximately 2 cm^2. Multiple cryoablations (two or three) can be performed from a single nitrous oxide cartridge. Empty cartridges can be exchanged while keeping the catheter in the esophagus. The entire device is designed for single use only.

Patients

This prospective non-randomized study was performed in multiple tertiary centers (five in USA, three in the Netherlands) with extensive expertise in endoscopic treatment of Barrett's epithelium. The institutional review board at each center approved the study protocol. Written informed consent was obtained from all patients entering the study.

Patients were included if they met the following criteria: (i) known Barrett's epithelium; (ii) scheduled for surveillance, endoscopic resection or ablative therapy; (iii) a Prague classification score of at least C ≥ 2 and/or M ≥ 3, and/or a Barrett's epithelium island ≥ 1 cm^2; (iv) a flat treatment area (according to the Paris classification [13]); (v) age 18 – 80 years. Patients were excluded in case of: (i) the presence of active inflammation; (ii) visible nodules within 4 cm of the treatment area at endoscopy; (iii) a stenosis within 4 cm of the treatment area that would prevent advancement of the endoscope; (iv) prior treatment with any energy-based ablation system.

To prevent any active inflammation, acid suppression using double-dose proton pump inhibitors was administered to each patient at enrollment.

Treatment

Conscious sedation was achieved for all patients by the administration of midazolam or monitored anesthesia care using propofol. All endoscopies were performed with a therapeutic endoscope (3.7-mm accessory channel). The esophageal landmarks were recorded and still endoscopic images were obtained of the entire Barrett segment at 1-cm intervals.

After the ablation site at the proximal border of the Barrett's epithelium segment had been determined, a single application of a 6, 8, or 10 seconds of focal cryoablation was given (**Fig. 2**; **Video 1**). In each patient one or two focal areas were treated, depending on the length and shape of the Barrett's epithelium segment. The location of the ablation area(s) was then recorded, and still images and digital videos were obtained. This was followed by a thorough inspection of the esophageal wall for any damage.

Patients did not receive any further endoscopic treatment (endoscopic resection or ablative therapy) during this endoscopy. At discharge additional medication was administered at the discretion of the endoscopist.

Follow-up

For each patient, their symptoms were assessed with a standardized questionnaire at enrollment, on the day of the procedure before and after treatment, and 2 days after the procedure. Pain and swallowing difficulty were scored on a 10-point scale from none (0) to severe (10).

Patients were scheduled for follow-up endoscopy 6 – 8 weeks after cryoablation. Endoscopic landmarks were again recorded. The cryoablated area was located and any conversion of Barrett's epithelium to neo-squamous epithelium based on the impression at endoscopy was recorded by still images (high definition television [HDTV], white-light imaging and narrow-band imaging [NBI]), and digital video. The treated area was inspected for any evidence of stenosis. One or two biopsies were obtained from

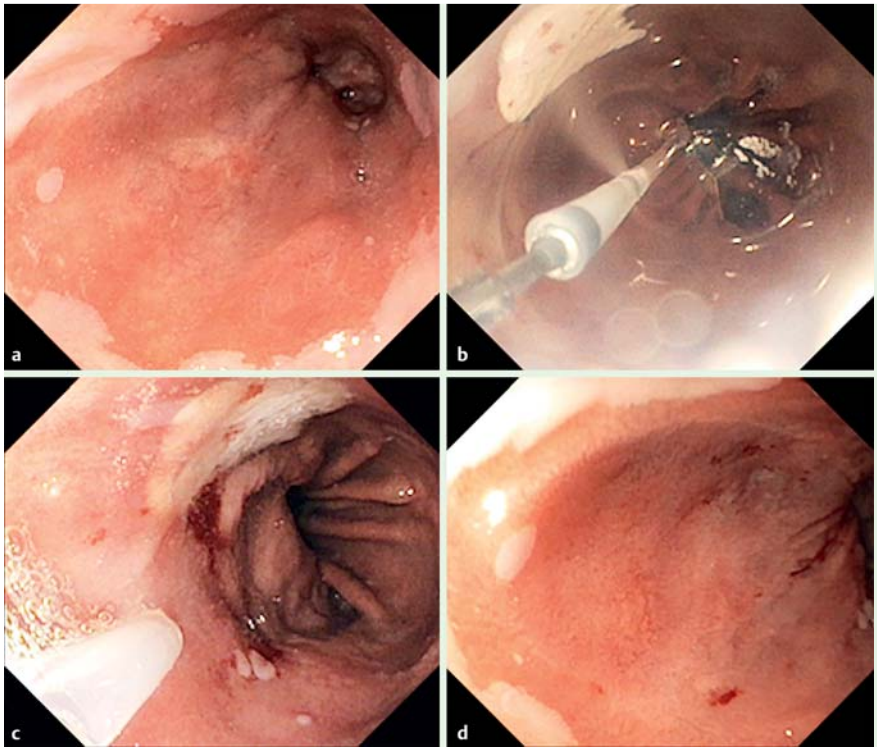

Fig. 2 Endoscopic images of the cryoablation procedure showing: **a** the area that is to be treated before therapy (9 – 11 o'clock); **b** the inflated balloon positioned for the cryoablation procedure; **c** the appearance of the frozen mucosa following deflation of the balloon after the preset duration of ablation; **d** a hyperemic area that remains visible at the location of the cryoablation 30 seconds after completion of the therapy.

the cryoablated area (**Fig. 3**). Further surveillance or treatment of any residual Barrett's epithelium was then continued at the discretion of the endoscopist.

Histology

After they had been fixed in 10% formalin, all biopsies were sent to the USA (Gastrointestinal Pathology, Memphis, Tennessee, USA) for central processing. Biopsies were embedded in paraffin and stained with hematoxylin and eosin (H&E). A gastrointestinal pathologist, blinded for the duration of ablation and location within the esophagus, recorded a detailed description of the presence of any squamous epithelium and/or any residual Barrett's epithelium in every specimen.

Video 1

Video showing focal cryoablation of Barrett's esophagus being performed. Online content including video sequences viewable at: http://dx.doi.org/10.1055/s-0034-1392417

Data monitoring committee

The study was monitored by a data monitoring committee (DMC) consisting of an independent clinician, a committee administrator, a committee chairperson, and a statistician. Based on the safety and effects at follow-up endoscopy, a step-up approach for cryoablation dosing was followed. The first eight subjects were treated with a 6-second focal cryoablation. After approval by the DMC, the duration of cryoablation was increased to 8 seconds in the next 21 patients and the last 10 patients were treated with a 10-second cryoablation.

Outcomes

The primary outcomes were the number of successfully performed ablations, the development of any esophageal stenosis at the location of the cryoablation, and the presence of any adverse events due to cryoablation. Stenoses were graded as none; mild (visible stenosis upon endoscopy, but asymptomatic); moderate (clinical symptoms of dysphagia combined with visible stenosis upon endoscopy); or severe (any stenosis impairing passage of the endoscope).

Secondary outcomes were the proportion of cryoablations that resulted in the endoscopic impression of the Barrett's epithelium having been converted to neo-squamous epithelium (defined as 'no conversion' if < 20% of the total ablated area appeared to have been converted; 'partly converted' if > 20% and < 80%; and 'full conversion' if > 80%), confirmation of the endoscopic impression by squamous epithelium being identified in biopsies, the number of device malfunctions, and the presence of pain symptoms after cryoablation.

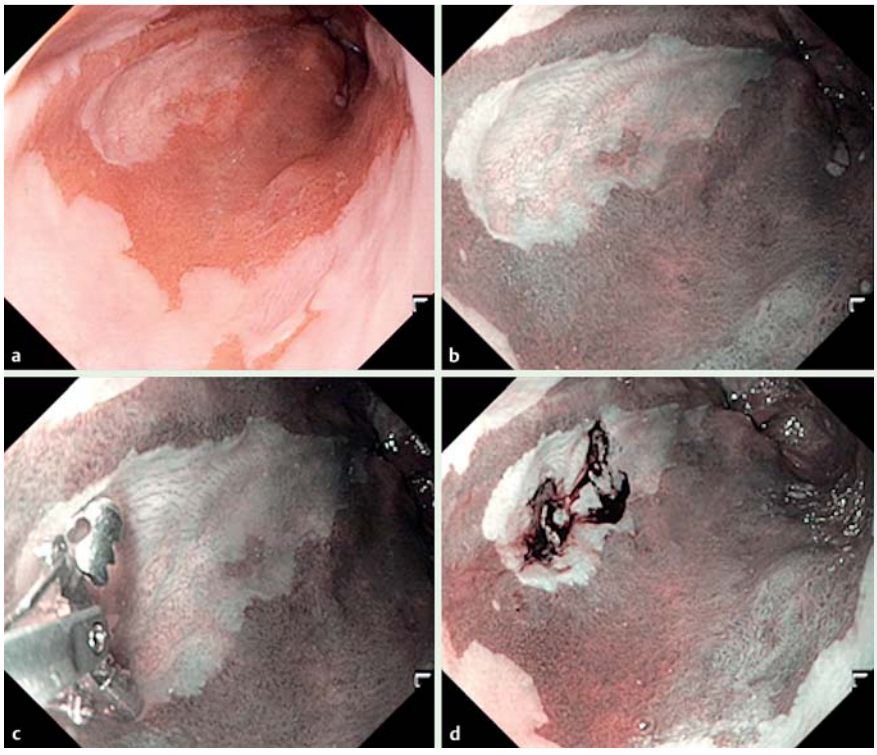

Fig. 3 Endoscopic images of the results of the cryoablation procedure from a follow-up endoscopy after 6 – 8 weeks showing regeneration of the Barrett's epithelium with neo-squamous epithelium visible on **a** white-light imaging; **b** narrow-band imaging. **c, d** The appearance after collection of biopsies for histopathological analysis.

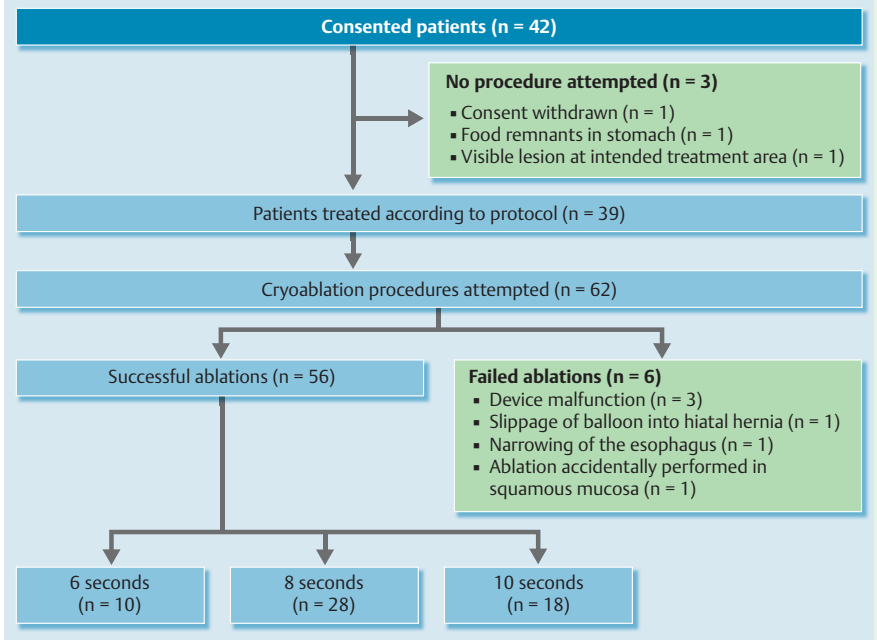

Fig. 4 Flow diagram of the study showing the 56 cryoablation procedures that were successfully performed in 37 patients (maximum two ablations per patient) and the reasons for the six failed ablations, which were attempted single ablations in two patients and second ablations in four patients.

Sample size estimation and statistical analysis

This study was the first human prospective feasibility trial, for which 40 patients each receiving up to two ablation treatments was considered to be a sufficient sample size.

Statistical analysis was performed with the Statistical Software Package version 20.0.0.1 for Windows (SPSS, Chicago, Illinois, USA). For descriptive statistics, the median with interquartile range (IQR) was used for variables with a skewed distribution. Comparison of endoscopic regeneration between different duration categories was analyzed with a chi-squared test for trend analysis.

Results

Patients and procedure

Between November 2012 and March 2014 a total of 42 consecutive patients were enrolled in this study. Three patients consented for the study did not undergo cryoablation because of withdrawal of informed consent (n = 1), food remnants in the stomach during endoscopy (n = 1), and the presence of a visible lesion in the intended treatment area (n = 1) (**Fig. 4**).

Therefore, 39 patients were evaluable and had been treated according to the protocol. The baseline characteristics of these patients are displayed in **Table 1**. A total of 56 focal ablations (90.3 %) were successfully performed in 37 patients (two ablation

Table 1 Baseline demographic and disease-specific characteristics of the enrolled patients who underwent attempted cryoablation procedures.

Patients, n			39	
Age, median (IQR), years			66 (57 – 69)	
Men, n (%)			35 (90 %)	
Reported use of proton pump inhibitors prior to enrollment, n (%)			35 (90 %)	
Barrett length (Prague classification)				
Circumferential extent, median (IQR), cm			2 (2 – 4)	
Maximum extent, median (IQR), cm			5 (3 – 7)	
Worst pre-cryoablation diagnosis[1], n (%)	Total cohort	6 seconds	8 seconds	10 seconds
No dysplasia	9 (23 %)	2 (25 %)	6 (29 %)	1 (10 %)
Indefinite for dysplasia	1 (3 %)	0 (0 %)	0 (0 %)	1 (10 %)
Low grade dysplasia	9 (23 %)	1 (13 %)	3 (14 %)	5 (50 %)
High grade dysplasia	9 (23 %)	3 (38 %)	4 (19 %)	2 (20 %)
Early adenocarcinoma	11 (28 %)	2 (25 %)	8 (38 %)	1 (10 %)
Pre-cryoablation EMR, n (%)	12 (31 %)	2 (25 %)	9 (43 %)	1 (10 %)
Time between EMR and cryoablation, median (IQR), days			67 (51 – 128)	

IQR, interquartile range; EMR, endoscopic mucosal resection.
[1] All visible lesions with adenocarcinoma and high grade dysplasia were removed by endoscopic resection before the cryoablation treatment.

Table 2 The effect of cryogenic ablation duration on conversion of Barrett's epithelium to neo-squamous epithelium at follow-up endoscopy after 6 – 8 weeks.

Areas with evidence of conversion[1], n (%)	Length of ablation			*P* value[2]
	6 seconds	8 seconds	10 seconds	
No conversion (< 20 %)	3 (30 %)	2 (7 %)	0 (0 %)	
Partly converted (20 % – 80 %)	1 (10 %)	3 (11 %)	0 (0 %)	0.04
Full conversion (> 80 %)	6 (60 %)	23 (82 %)	18 (100 %)	

[1] Assessment based on the impression of the endoscopist at the time of endoscopy and a secondary check of the endoscopic images.
[2] Chi-squared test for trend analysis.

areas in 19 patients, a single ablation area in 18 patients). In the two remaining patients, the focal cryoablation procedure failed. In four of the 18 patients with a successful single cryoablation, a second attempt at cryoablation failed. This resulted in a total of six failed cryoablations (9.7 %) for a variety of reasons (**Fig. 4**): in one patient a stenosis in the treatment area became apparent after inflation of the balloon; one intended treatment area was too close to the esophagogastric junction; one ablation was accidently performed in squamous mucosa; and three device malfunctions occurred (in one patient the balloon did not properly make contact with the esophageal wall despite continuous suction during cryoablation; in two other patients the device gave an "error" signal when trying to inflate the balloon).

For the 56 cryoablations successfully performed, the duration of ablation was 6 seconds (n = 10), 8 seconds (n = 28), or 10 seconds (n = 18). The median treatment duration from introduction to retraction of the CbFAS was 4 minutes (IQR 2 – 7) in patients with a single ablation. In patients with two ablations, the median procedure time was 8 minutes (IQR 4 – 13).

In six patients (15 %), a minor esophageal mucosal laceration occurred, with all the durations of ablation being affected (6 seconds [n = 2], 8 seconds [n = 2], 10 seconds [n = 2]), but no patients required any further intervention.

Pain scores

None of the patients reported pain at baseline (score of 0/10 on a visual analog scale [VAS]). Immediately after the procedure, the median pain score in the treatment area in all 37 patients was 0 (IQR 0 – 2); however, for the 10 patients (27 %) who did report pain in the treatment area, the median score was 2.5 (IQR 2 – 3). None of these patients required any additional pain medication.

During follow-up assessment after a median 2 days (IQR 2 – 2), five patients (14 %) reported pain in the treatment area (median score 4 [IQR 3 – 6]) and with swallowing (median 4 [IQR 2 – 5]). Three of the 37 patients (8 %) used additional pain medication (nonsteroidal anti-inflammatory drugs [n = 2] and acetaminophen [n = 1]) on the days following the cryoablation procedure.

Follow-up

The median duration between the cryoablation procedure and the follow-up endoscopy was 54 days (IQR 49 – 62). During this period no adverse events occurred in any of the patients. Follow-up endoscopy showed that none of the patients had developed a stenosis.

Full conversion of Barrett's epithelium to neo-squamous epithelium was observed significantly more frequently with increasing durations of ablation: in 60 % of the ablated areas with a 6-second ablation duration; in 23 areas (82 %) after an 8-second ablation; and in 100 % of the areas after 10 seconds of ablation ($P = 0.04$). The conversion data are listed in **Table 2**.

All treatment areas considered partly or fully regenerated with neo-squamous epithelium at endoscopy were histologically confirmed by the presence of squamous epithelium in the biopsies. Of the five treatment areas that were considered "failures", one did not contain any squamous epithelium in the biopsies, two consisted of mixed squamous and Barrett's epithelium, and two areas were not biopsied.

Discussion

Over the past decade, ablation therapy has become one of the core approaches for the endoscopic treatment of Barrett's esophagus. Several ablation techniques such as RFA, SCA and photodynamic therapy are currently available [4, 5, 9, 14, 15]. Recently the novel CbAS was developed, which aims to combine the beneficial properties of the SCA and RFA techniques [16]. In an earlier study, the circumferential CbAS appeared safe and feasible for the ablation of esophageal mucosa. In the current study, we found the new CbFAS to be safe and feasible for the focal treatment of Barrett's epithelium.

Over several decades, cryotherapy has been successfully used in a variety of medical applications. Two mechanisms facilitate the effects of this therapy: direct and indirect damage. The direct effect of freezing is characterized by ice crystallization in both extracellular and intracellular spaces with electrolyte shifts, damage to cell membranes, and eventually cell death. The indirect effect is achieved by endothelial defects in capillary walls with subsequent edema, microvascular stasis, and thrombosis, which results in ischemia and cell death. The severity of injury is dependent on the target temperature, the length of freezing, and the number of freeze-thaw cycles, although studies have shown that, at tissue temperatures of below −50 °C, cells are sufficiently damaged in a single freeze-thaw cycle [10].

At present, available cryotherapy for the treatment of Barrett's epithelium consists of devices with spray application of liquid nitrogen or carbon dioxide onto the mucosa. Only a few studies have assessed the efficacy of cryoablation. A retrospective study by Shaheen et al. [9] showed that 87 % of the 60 patients undergoing complete cryoablation treatment had complete eradication of dysplasia and 57 % had compete eradication of intestinal metaplasia after a follow-up of 10.5 months. In another retrospective study [14], complete eradication of intestinal metaplasia persisted after a follow-up of 2 years in 84 % of the 32 patients with initial HGD in Barrett's epithelium.

However, the SCA technique harbors some drawbacks. First, an equal distribution in the application of the cryogenic fluid onto the esophageal mucosa is difficult. Secondly, contact between the cryogenic fluid and the esophageal tissue results in the development of gas that needs direct ventilation using an orogastric tube to prevent complications such as perforations due to gastric distension [17]. The balloon-based system of the CbFAS allows for a controlled cryoablation in a single freeze-thaw cycle at −70 °C (mucosal temperature) at a single target area, with removal of the gas produced back through the catheter [16].

The CbFAS may carry some potential advantages over focal RFA for the treatment of Barrett's epithelium. The focal RFA device, mounted at the tip of the endoscope, may hinder introduction of the endoscope and the approach to the target area. In contrast, the CbFAS is easily introduced and advanced through the accessory channel of the endoscope. In addition, current protocols with focal RFA advocate double applications per area with cleaning of the ablated area and the focal device in between applications, requiring multiple introductions of the endoscope. Although requiring a therapeutic endoscope, the CbFAS appears to successfully target focal ablation areas with one freeze-thaw cycle per location, obviating the need for multiple introductions of the endoscope.

In this study 56 ablations were successfully performed in the Barrett's epithelium confirming the feasibility of the CbFAS. Multiple endoscopists from different tertiary care centers for the treatment of Barrett's epithelium were able to correctly apply focal cryoablation with the CbFAS. Six procedures failed: three because of device malfunction and three related to procedural or anatomic issues. Future device improvements and increased user experience may reduce the number of failed ablations as well as the procedure times reported.

After RFA treatment for Barrett's epithelium, most of the patients experience some degree of chest pain [4, 18]. In contrast, patients in this study reported few complaints of chest pain or issues with swallowing immediately after treatment or during follow-up. Pain scores did not differ between the groups with different ablation durations. This limited amount of pain is consistent with the previous circumferential CbAS study and other cryoablation studies [9, 12, 19]. The rationale is that cooling of the tissue and the surrounding nerves during cryotherapy provides an anesthetic effect inhibiting pain sensations [20].

At follow-up endoscopy 6 – 8 weeks post-cryoablation, none of the patients had developed a stenosis. Even in the 15 patients in whom two areas were cryoablated at the same distance to the incisors, but in different radial positions, no stenoses developed. Although stenosis formation after focal ablation is not expected, stenosis after cryoablation in general appears scarce [9, 19]. Cryotherapy is minimally destructive to the structural components of tissue, such as collagen, whereas heat-based ablation techniques irreversibly destroy proteins, thereby affecting the architecture of the collagen matrix [11].

After successful cryoablation, a small longitudinal mucosal laceration was observed in six patients when deflating the balloon, but no additional treatment was needed for these incidents. In the focal balloon-ablation system used in this trial, the average balloon inflation pressure was 5.3 psi (maximum 6.2 psi). A new generation of the CbFAS using lower inflation pressures is currently under development, which may possibly reduce the number of mucosal lacerations.

In the light of the limited pain scores, the absence of stenosis, and the absence of major bleeding or perforations, the CbFAS seems a safe focal ablation tool for the eradication of Barrett's epithelium. Moreover, the conversion rate of Barrett's epithelium to neo-squamous epithelium of 100 % in the group with 10-second ablations seems promising for focal cryoablation with the CbFAS.

This study has certain limitations. First, although we found low pain scores and no stenosis formation, only a limited number of patients underwent two focal ablations. While it cannot be ruled out that treatment of more extensive areas with cryoablation will increase the occurrence and severity of these complications, earlier studies have shown that post-cryoablation pain is often mild [9, 21] and this method leaves the extracellular matrix intact so has a low risk of stenosis formation [11]. Second, at this point a 10-second ablation seems optimal for regeneration of Barrett's epithelium to neo-squamous epithelium without compromising safety; however, the number of procedures in each category of ablation duration was limited, and further assessment of the efficacy of 10 seconds as the optimal duration for focal ablation is required.

In conclusion, this study showed that the novel CbFAS appears safe and feasible for the focal treatment of Barrett's epithelium. Treatment with the CbFAS was well tolerated, and repeat endoscopies revealed no stenosis. A focal ablation duration of 10 seconds seems to result in full squamous regeneration without compromising safety, although a study using this duration in a larger cohort is warranted.

Competing interests: This study was supported by C2Therapeutics, Inc. (Redwood City, California, USA).

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References

1 *Shaheen NJ, Richter JE.* Barrett's oesophagus. Lancet 2009; 373: 850–861
2 American Gastroenterological Association. *Spechler SJ, Sharma P* et al. American Gastroenterological Association medical position statement on the management of Barrett's esophagus. Gastroenterology 2011; 140: 1084–1091
3 *May A, Gossner L, Pech O* et al. Local endoscopic therapy for intraepithelial high-grade neoplasia and early adenocarcinoma in Barrett's oesophagus: acute-phase and intermediate results of a new treatment approach. Eur J Gastroenterol Hepatol 2002; 14: 1085–1091
4 *Shaheen NJ, Sharma P, Overholt BF* et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. NEJM 2009; 360: 2277–2288
5 *Pouw RE, Wirths K, Eisendrath P* et al. Efficacy of radiofrequency ablation combined with endoscopic resection for Barrett's esophagus with early neoplasia. Clin Gastroenterol Hepatol 2010; 8: 23–29
6 *Ganz RA, Utley DS, Stern RA* et al. Complete ablation of esophageal epithelium with a balloon-based bipolar electrode: a phased evaluation in the porcine and in the human esophagus. Gastrointest Endosc 2004; 60: 1002–1010
7 *Dunkin BJ, Martinez J, Bejarano PA* et al. Thin-layer ablation of human esophageal epithelium using a bipolar radiofrequency balloon device. Surg Endosc 2006; 20: 125–130
8 *Greenwald BD, Dumot JA, Abrams JA* et al. Endoscopic spray cryotherapy for esophageal cancer: safety and efficacy. Gastrointest Endosc 2010; 71: 686–693
9 *Shaheen NJ, Greenwald BD, Peery AF* et al. Safety and efficacy of endoscopic spray cryotherapy for Barrett's esophagus with high-grade dysplasia. Gastrointest Endosc 2010; 71: 680–685
10 *Gage AA, Baust J.* Mechanisms of tissue injury in cryosurgery. Cryobiology 1998; 37: 171–186
11 *Evonich RF3rd, Nori DM, Haines DE.* A randomized trial comparing effects of radiofrequency and cryoablation on the structural integrity of esophageal tissue. J Interv Cardiac Electrophysiol 2007; 19: 77–83
12 *DeMeester SR, Awais O, Bergman JJ* et al. Initial human experience with a novel through-the-scope cryoballoon device for mucosal ablation. Gastroenterology 2012; 142 Suppl 1: S1038
13 Endoscopic Classification Review Group. Update on the Paris classification of superficial neoplastic lesions in the digestive tract. Endoscopy 2005; 37: 570–578
14 *Gosain S, Mercer K, Twaddell WS* et al. Liquid nitrogen spray cryotherapy in Barrett's esophagus with high-grade dysplasia: long-term results. Gastrointest Endosc 2013; 78: 260–265
15 *Overholt BF, Lightdale CJ, Wang KK* et al. Photodynamic therapy with porfimer sodium for ablation of high-grade dysplasia in Barrett's esophagus: international, partially blinded, randomized phase III trial. Gastrointest Endosc 2005; 62: 488–498
16 *Friedland S, Triadafilopoulos G.* A novel device for ablation of abnormal esophageal mucosa (with video). Gastrointest Endosc 2011; 74: 182–188
17 *Verbeek RE, Vleggaar FP, Ten Kate FJ* et al. Cryospray ablation using pressurized carbon dioxide gas for the ablation of Barrett's esophagus with early neoplasia. Gastrointest Endosc 2012; 75: AB453
18 *Shaheen NJ, Frantz DJ.* When to consider endoscopic ablation therapy for Barrett's esophagus. Curr Opin Gastroenterol 2010; 26: 361–366
19 *Johnston MH, Eastone JA, Horwhat JD* et al. Cryoablation of Barrett's esophagus: a pilot study. Gastrointest Endosc 2005; 62: 842–848
20 *Erinjeri JP, Clark TW.* Cryoablation: mechanism of action and devices. J Vasc Interv Radiol 2010; 21: 187–191
21 *Greenwald BD, Dumot JA, Horwhat JD* et al. Safety, tolerability, and efficacy of endoscopic low-pressure liquid nitrogen spray cryotherapy in the esophagus. Dis Esophagus 2010; 23: 13–19