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The esophageal effects of cryoenergy during cryoablation for atrial fibrillation

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BACKGROUND Cryoenergy is being increasingly used for atrial fibrillation (AF) ablation, but the thermal effect of cryoenergy on the esophagus remains undefined.

OBJECTIVE This study examines the esophageal effects of cryoenergy used during AF ablation.

METHODS Catheter ablation was performed using a cryoballoon catheter in 67 AF patients (Cryoballoon group), and a spot cryocatheter to complete irrigated radiofrequency lesion sets at segments in close proximity to the esophagus in 7 AF patients (Cryo-Focal group). A temperature probe monitored the luminal esophageal temperature (LET) in all patients; LET changes did not guide therapy. Post-procedural endoscopy was performed on 35 of 67 (52%) Cryoballoon and all Cryo-Focal patients.

RESULTS Significant LET decreases (>1°C) occurred in 62 of 67 (93%) Cryoballoon patients. LET continued to decrease after termination of cryoablation before recovering to normal. Temperature decreases were more pronounced during ablation at the inferior (3.1°C) than superior pulmonary veins (1.5°C); the lowest observed temperature was 0°C. Post-procedural endoscopy showed esophageal ulcerations in 6 of 35 (17%) patients. There were no atrial-esophageal fistulas, and all ulcers had healed on follow-up endoscopy. Patients with and without ulceration differed with respect to mean LET nadir, cumulative LET decrease, and number of LETs <30°C. In the Cryo-Focal group, 6 ± 2 spot cryolesions per patient resulted in 1.3 ± 1 LET decreases per patient, and an absolute nadir of 32.5°C.

CONCLUSION Cryoballoon ablation can cause significant LET decreases, resulting in reversible esophageal ulcerations in 17% of patients. No ulcerations occurred with adjunctive spot cryoablation at regions near the esophagus during radiofrequency ablation procedures.

KEYWORDS Atrial fibrillation; Catheter ablation; Arrhythmias; Complications; Esophageal injury

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Introduction

Atrial-esophageal fistula is one of the most feared complications of atrial fibrillation (AF) ablation.[1,2] During radiofrequency (RF) catheter ablation, esophageal temperatures reaching ≥40°C are believed to correlate with thermal injury to the esophagus along its course just posterior to the left atrium (LA).[2] These significant increases in temperature may disrupt the structural integrity of the connective tissue of the esophageal mucosa. Because the site of esophageal submucosal and mucosal injury is contiguous with the posterior LA wall, it is thought that subsequent aberrant healing of the esophagus leads to atrial-esophageal fistula formation.[3]

Although clinical experience with RF catheter ablation numbers in the hundreds of thousands of patients treated, relatively few have been treated with catheter cryoablation. As a result, little is known about the potential for cryoablation to cause thermal injury to the esophagus.[4] To the best of our knowledge, there have been no reported instances of atrial-esophageal fistula formation after catheter cryoablation—including the over 5,000 clinical procedures performed worldwide with the balloon cryoablation catheter. However, given the observed rarity of atrial-esophageal fistula formation after RF ablation, it seems prudent to determine proactively the effect of every ablation technology on the esophagus. This is of particular importance because the use of another ablation technology, using focused ultrasound, has resulted in multiple atrial-esophageal fistulas, of which several were fatal.[5]

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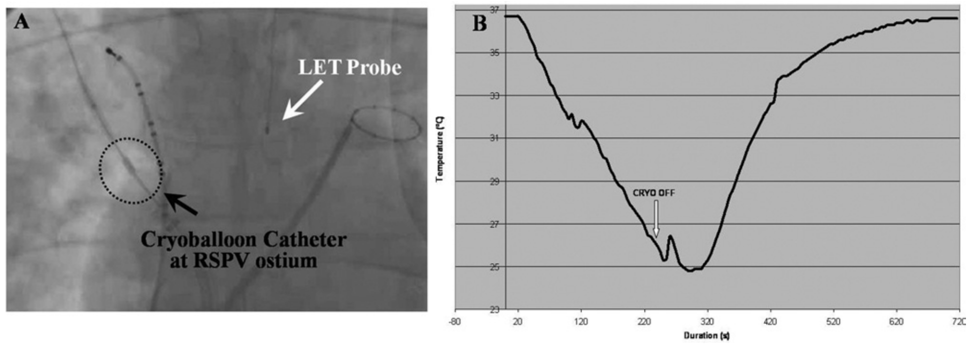

Figure 1 Luminal esophageal temperature monitoring during cryoballoon ablation. **A.** AP view is shown of the Cryoballoon (black arrow) and intraesophageal temperature probe (white arrow) during catheter ablation. **B.** An example of LET is shown as a function of time during balloon cryoablation of the LIPV. Cryoenergy was delivered for 240 seconds (arrow), but the transmural transfer of energy to the esophagus persisted for 50 seconds after the cessation of energy delivery. AP = anteroposterior; LET = luminal esophageal temperature; LIPV = left inferior pulmonary vein; RSPV = right superior pulmonary vein.

In this study, the esophageal effects of cryoenergy were examined after 1 of 2 AF ablation strategies: (1) pulmonary vein (PV) isolation with a cryoballoon catheter, or (2) wide-area circumferential ablation (WACA) using an irrigated RF catheter, followed by spot cryocatheter ablation at PV regions in close proximity to the esophagus. Luminal esophageal temperature (LET) monitoring was used in all patients to assess the frequency and magnitude of the cryothermal effect. Furthermore, a later consecutive subset of both groups of patients additionally underwent systematic post-procedural endoscopy to assess for esophageal mucosal damage. Of importance, observed changes in LET were recorded only and were not used to interrupt or guide ablation therapy.

Methods

All procedures were performed after obtaining written informed consent according to institutional guidelines at the Massachusetts General Hospital, Boston; Homolka Hospital, Prague; or the Mayo Clinic, Rochester.

Cryoballoon group

In a total of 67 patients with drug-resistant paroxysmal AF, catheter ablation was performed using either a 23-mm or a 28-mm cryoballoon catheter, in 23 (34%) and 32 patients (48%), respectively. Both balloon sizes were needed in 12 (18%) patients to accommodate the variance in intrapatient PV diameters.

The cryoablation balloon system has been described previously.[4] Procedures were performed under either conscious sedation or general anesthesia. The procedures were performed with fluoroscopic and intracardiac ultrasound (ICE; Acunav, Siemens-Ultrasound, Erlangen, Germany) guidance. Intravenous heparin was administered before the transseptal puncture; activated clotting time (ACT) was maintained at >300 s. A multielectrode circular mapping catheter (Lasso, Biosense-Webster, Haifa, Israel) was used to record electrogram activity before and after ablation of each PV–LA junction. Before the delivery of cryoenergy, effective balloon occlusion of the targeted PV was confirmed by injection of contrast.

The esophageal temperature probe was advanced or withdrawn manually during each lesion to ensure proper vertical alignment of the probe's temperature sensor to the balloon ablation catheter (Figure 1A). For each patient, the baseline LET was recorded, along with the nadir for each lesion. For selected energy deliveries, complete temperature curves were documented by recording the temperature changes in 5-s intervals, beginning with the delivery of refrigerant into the inflated balloon (Figure 1B). Each lesion was delivered with a target time of 240 s; those <60s (n = 10) were excluded from analysis. To minimize the chance of long-term electrical reconnection, 1 or 2 "bonus" lesions were delivered to the PV ostia after electrical isolation of the targeted vein had been confirmed using the circular mapping catheter. Bonus lesions were delivered per operator preference, and were typically applied in a different branch of the vein, with a slightly different deflection.

No lesion was stopped prematurely because of observed changes in the LET; premature lesion termination only occurred if there was evidence of impending phrenic nerve damage, or because of poor positioning of the cryoballoon catheter.

Thirty-five (52%) consecutive patients who consented to endoscopy underwent systematic post-procedural endoscopy within 1 week of the procedure. If ulceration were found, patients were prescribed proton pump inhibitors (PPIs), and underwent follow-up endoscopy 1 month post-procedure.

Cryo-Focal group

In a total of 7 patients with paroxysmal (n = 2), persistent (n = 1), or longstanding persistent (n = 4) drug-resistant AF, a spot 4-mm-tip cryoablation catheter (Cryocor, San Diego, CA/Cryocath Inc, Montreal, Canada) was used to complete irrigated RF WACA lesion sets at PV regions close to the esophagus. The determination to use cryoablation was based on: (1) the close vicinity of esophagus to the PV ostium as visualized by electroanatomical mapping and ICE imaging, and/or (2) the rapid increase of the esophageal temperature. General anesthesia was used in all patients.

The LA–PV anatomy was rendered with an electroanatomic navigation system (Carto, Biosense-Webster). A wide-area circumferential ring of ablation lesions was placed, 5 to 15 mm from the PV junctions (RF power range: 25 to 40 W). Additional ablation was undertaken with Lasso guidance to complete venoatrial electrical disconnection. LA linear lesions were placed at the operator's discretion. RF applications were terminated when the LET exceeded 38.0°C, or increased by >0.5°C over the course of 1 to 2 s. For each patient, the anatomical location of cryoenergy delivery was recorded, along with the baseline LET, LET nadir, and duration of cryoablation.

Similar to the Cryoballoon group patients, all 7 Cryo-Focal group patients underwent systematic, post-procedural esophagogastroduodenoscopy (EGD). For 6 of 7 (86%) patients, the endoscopy was performed within 2 days of the procedure; this was not feasible for 1 of 7 patients, who underwent endoscopy at 20 days post-procedure. Six of seven patients additionally underwent high-resolution endoscopic ultrasound for further detection of esophageal thermal injury.

Statistical analysis

Continuous variables are expressed as mean ± SD. For analysis, the Cryoballoon group was divided into 2 subgroups: patients with (Group A, n = 35) and without (Group B, n = 32) post-procedural endoscopy. Group A was then further subdivided: those with (Group A1, n = 6) and without (Group A2, n = 29) esophageal ulceration on post-procedural EGD. The primary end point of the study was 2-fold: the observation of significant LET decreases during cryoballoon ablation of the PVs, and the presence of esophageal ulceration on post-procedural EGD. Means of LET data from Group A1 and A2 were compared with the Student *t*-test, and frequencies with the Fisher exact test. Values of $P < .05$ were considered significant. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the article as written.

Results

Patient characteristics

As shown in Table 1, the mean age of the Cryoballoon group cohort (67 patients) was 57 ± 9 years, and 26 (39%) were female. The left ventricular ejection fraction and LA size were 66% ± 7% and 41 ± 5 mm, respectively. General anesthesia was used in 1 patient. The mean age of the Cryo-Focal group cohort (7 patients) was 59 ± 10 years and 2 (29%) were female; the left ventricular ejection fraction and LA size were 50% ± 12% and 48 ± 6 mm, respectively. The last 35 (52 %) consecutive Cryoballoon group patients and all Cryo-Focal group patients underwent post-procedural endoscopy.

Esophageal temperature changes with cryoablation

Qualitatively, LET monitoring showed a phenomenon similar to the thermal latency observed during RF ablation; that is, the esophageal temperature continued to decrease after termination of the ablation lesion (Figure 1B). Shortly after reaching the nadir, the LET was observed to increase fairly rapidly; in most cases, it approached the baseline temperature before delivery of the subsequent lesion.

Table 1 Patient characteristics

	Cryoballoon group (n = 67)	Cryo-Focal group (n = 7)
Demographic information		
Age (mean ± SD)	57 ± 9	59 ± 10
Female, %	39	29
Medical history		
Hypertension (n, %)	36 (54%)	2 (29%)
CHF (n, %)	0 (0%)	0 (0%)
Atrial flutter (n, %)	23 (34%)	4 (57%)
CAD (n, %)	5 (7%)	1 (14%)
Diabetes (n, %)	6 (9%)	1 (14%)
GERD (n, %)	2 (3%)	0 (0%)
Disease characteristics		
Structurally normal heart (n, %)	62 (93%)	4 (57%)
EF (%, mean ± SD)	66 ± 7	50 ± 12
LA size (mm, mean ± SD)	41 ± 5	48 ± 6
Redo AF ablation (n, %)	1 (1%)	2 (29%)
Medication use		
Failed AADs (n, mean ± SD), no.	1.3 ± 0.6	1.9 ± 0.9

AAD = antiarrhythmic drug; AF = atrial fibrillation; CAD = coronary artery disease; CHF = congestive heart failure; EF = ejection fraction; GERD = gastroesophageal reflux disease; LA = left atrium.

Cryoballoon group

In the patient cohort (n = 67), a total of 763 ablation lesions were delivered. Zero, 1, or 2 bonus lesions were delivered to each PV in 11, 4, and 52 patients, respectively. Overall, a mean of 186 ± 13 lesions were delivered to each vein: left superior pulmonary vein (LSPV), 188; left inferior pulmonary vein (LIPV), 201; right superior pulmonary vein (RSPV), 169; right inferior pulmonary vein (RIPV), 185. Significant (>1°C) LET decreases were observed in 62 (93%) patients (percent LET decreases per vein: LSPV, 43%; LIPV, 57%; left common pulmonary vein (LCPV), 7%; RSPV, 31%; RIPV, 45%; right middle pulmonary vein (RMPV), 33%), with 5 ± 3 significant decreases observed per patient in the total cohort (n = 67). The average baseline LET was 37.4°C ± 0.5°C.

As shown in Table 2, the greatest average temperature decrease (3.1°C) was noted in both the LIPV and the RIPV, with LET nadirs of 16.6°C (baseline, 36°C) and ≤0°C (baseline, 36.5°C), respectively. This latter LET decrease was observed during ablation of the RIPV in 1 patient: the first lesion resulted in an LET of 12.5°C (baseline, 36.5°C), and the next 2 reached a nadir of ≤0°C (because the nadir reached a plateau for >10 s, and the LET probe could not display temperatures <0°C, it is likely that a subzero nadir occurred). The maximal absolute LET nadir (0°C) was observed during ablation of the RIPV in 1 patient. The RSPV showed the smallest average temperature change (1.1°C; range, 24.9°C to 37.2°C). The LSPV (range, 21.9°C to 37.2°C) showed an average temperature decrease of 1.9°C and maximum temperature decrease of 14°C. LET

Table 2 Cryoballoon group luminal esophageal temperature data per pulmonary vein

	LSPV	LIPV	LCPV*	RSPV	RIPV	RMPV*
Absolute LET nadir (°C)	21.9	16.6	34.9	24.9	0	35.5
Mean LET decrease (°C)	Δ 1.9	Δ 3.1	Δ 0.6	Δ 1.1	Δ 3.1	Δ 1.1
Maximum LET decrease (°C)	Δ 14	Δ 19.4	Δ 1.5	Δ 11.6	Δ 36.5	Δ 2.9
LET decreases, n (%)	81 (43%)	114 (57%)	1 (7%)	52 (31%)	83 (45%)	2 (33%)

LCPV= left common pulmonary vein; LIPV = left inferior pulmonary vein; LSPV = left superior pulmonary vein; RIPV = right inferior pulmonary vein; RMPV = right middle pulmonary vein; RSPV = right superior pulmonary vein.
*Note that an RMPV was present in 3 patients, and an LCPV in 4 patients.

decreases occurred regardless of the balloon size used (mean LET decrease 23 mm, 2.1°C ± 3.9°C; mean LET decrease 28 mm, 2.3°C ± 4°C; P = .45). With both balloon sizes, the thermal effects were most pronounced during ablation of the inferior PVs (Table 2).

Cryo-Focal group

In the patient cohort (n = 7), a total of 33 ablation lesions were delivered. A mean of 6 ± 2 applications per patient (729 ± 77 s) were delivered (lesions delivered on a per-vein basis: LSPV, 0; LIPV, 4; RSPV, 0; RIPV, 29). Significant (>1°C) LET decreases were observed in 5 (71%) patients, with 1.4 ± 1 significant decreases observed per patient. The mean decrease in LET was 1.9°C ± 1.2°C. The maximal temperature nadir was 32.5°C.

Esophageal endoscopy after cryoablation

For 35 (52%) patients in the Cryoballoon group, endoscopy was performed 1 ± 2 days post-procedure (range, 1 to 5 days), revealing esophageal ulcerations in 6 of 35 (17%) patients. No patient or procedural characteristics were found to be statistically significant predictors of the incidence of ulceration (Table 3). When comparing patients with and without ulceration, a statistically significant difference was found for: (1) the mean absolute LET nadir, (2) the mean number of lesions resulting in LETs <30°C, and (3) the cumulative LET decrease (Figure 2). However, no threshold temperature value was found to predict ulceration.

All patients presenting with esophageal ulceration were asymptomatic and without clinical sequelae. The ulcerations were observed at the retrocardiac esophageal location, the characteristic site of ulcer formation in RF ablation (Table 4). In 2 patients, ulcerations were also seen on the posterior esophageal wall (Figures 3A and 4). In 1 patient, this was also accompanied by inflammation of the esophageal wall, resulting in thickening of the LA esophageal wall to 9 mm (normal approximately 4 mm) (Figures 3A and

Table 3 Comparison of patient characteristics for patients with and without esophageal ulceration as observed on post-procedural endoscopy

	Post-procedural EGD: ulceration (n = 6)	Post-procedural EGD: no ulceration (n = 29)	P value
Demographic information			
Age (mean ± SD)	61 ± 8	56 ± 10	.19
Female, %	50	34	.65
Medical history			
Hypertension (n, %)	2 (33%)	16 (56%)	.4
CHF (n, %)	0 (0%)	0 (0%)	1
Atrial flutter (n, %)	4 (67%)	9 (31%)	.17
CAD (n, %)	0 (0%)	2 (7%)	.98
Diabetes (n, %)	0 (0%)	6 (21%)	.56
GERD (n, %)	1 (17%)	1 (3%)	.29
Disease characteristics			
Structurally normal heart (n, %)	6 (100%)	28 (97%)	.83
EF (%, mean ± SD)	66 ± 2	67 ± 6	.51
LA size (mm, mean ± SD)	42 ± 6	39 ± 5	.32
Redo AF ablation (n, %)	0 (0%)	1 (3%)	.83
Medication use			
Failed AADs, no. (mean ± SD)	1.3 ± 0.5	1.4 ± 0.7	.85
Procedure characteristics			
Pre-procedural TEE (n, %)	3 (50%)	11 (38%)	.66
General anesthesia (n, %)	1 (17%)	0 (0%)	1
Bonus lesions per PV, no.			
0	0 (0%)	0 (0%)	1
1	1 (17%)	3 (10%)	.55
2	5 (83%)	26 (90%)	.55

AAD = antiarrhythmic drug; AF = atrial fibrillation; CAD = coronary artery disease; CHF = congestive heart faiulre; EF = ejection fraction; EGD = esophagogastroduodenoscopy; GERD = gastroesophageal reflux disease; LA = left atrial; PV = pulmonary vein; TEE = transesophageal echocardiograph.

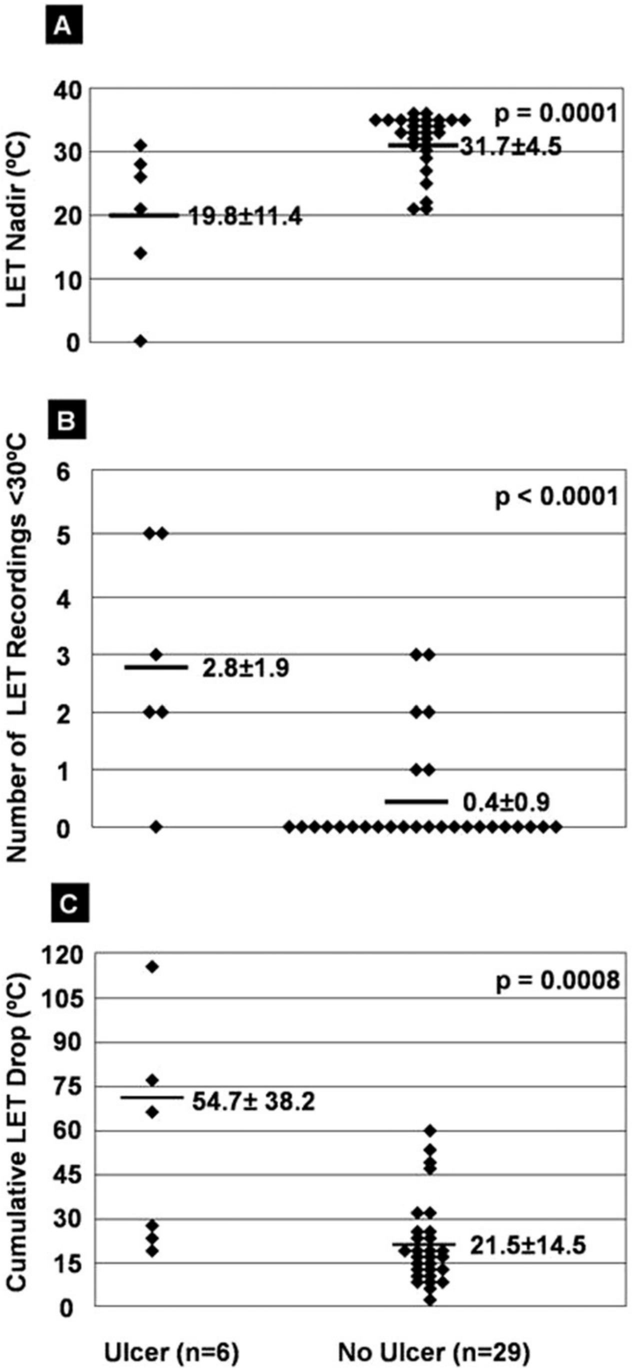

Figure 2 Comparison of LET data for patients with and without esophageal ulceration as observed on post-procedural EGD. **A.** Observed LET nadirs are depicted for patients with and without ulceration as observed with post-procedural endoscopy; mean values: 19.8°C ± 11.4°C and 31.7°C ± 4.5°C, respectively (P = .0001). **B.** The number of lesions with observed LET <30°C is depicted; mean values: 2.8 ± 1.9 and 0.4 ± 0.9 in patients with and without esophageal ulceration, respectively (P < .0001). **C.** The cumulative LET decrease is depicted for each patient, grouped by the presence or absence of ulceration as observed with post-procedural endoscopy; mean values: 54.7°C ± 38.2°C and 21.5°C ± 14.5°C, respectively (P = .0008). The cumulative decrease represents the sum of LET decreases observed for each lesion delivered to that patient. ♦, individual data point; —, mean value; EGD = esophagogastroduodenoscopy; LET = luminal esophageal temperature.

3B). Because of the severity of the damage, the patient also underwent computed tomography (CT) scanning, which showed a soft tissue prominence containing hyperdensities and foci of air along the right lateral aspect of the esophagus at the level of the LA (Figure 3C). Because this was interpreted as suspicious for inflammation surrounding a focal perforation, a barium swallow was performed to assess for an esophageal leak. There was no contrast extravasation, and esophageal motility was normal.

For the Cryo-Focal group patients, endoscopy showed normal esophageal mucosa. Endoscopic ultrasound imaging showed no esophageal mucosal erosions or muscular disruption.

Follow-up

There were no occurrences of atrial esophageal fistula. Of the 6 patients showing ulcerations, 5 received PPI treatment. Follow-up endoscopy at 1 month showed complete resolution of all ulcerations in 5 of 6 (83%) patients; for the patient with LETs ≤0°C, complete resolution of the ulcerations was not observed until a 3-month endoscopy.

Incidental findings

In the Cryoballoon group, other incidental endoscopy findings included Barrett esophagus in 1 patient. In another, Candida was observed along the length of the esophagus, presumably resulting use of a steroid inhaler. This resolved after treatment with antifungal medications. Endoscopic ultrasonography of the Cryo-Focal group showed a small pleural effusion in 1 patient and a moderate right pleural effusion in another.

Discussion

This study showed that significant changes in esophageal temperature are common during cryoablation, and are particularly pronounced during balloon cryoablation of the inferior PVs. This is consistent with the PV anatomy because the inferior veins are anatomically posterior, and therefore closer to the esophagus.

After ablation with the cryoballoon catheter, a statistically significant correlation was found between the incidence of esophageal ulceration as identified by post-procedure endoscopy and the LET nadir, the number of LETs <30°C, and the cumulative LET decrease. No other patient or procedural characteristics, including the number of bonus lesions delivered to each PV, were found to be statistically significant predictors of ulceration. There was also no significant difference in esophageal temperature decreases between use of the 23-mm and 28-mm balloon catheters. Perhaps most importantly, routine post-procedural endoscopy showed a 17% incidence of esophageal ulceration. Despite this, no atrial-esophageal fistula or other clinical sequelae, including symptoms of dysphagia, were observed. And importantly, all ulcers healed during follow-up.

The study also suggests the safety of using spot cryoablation at PV regions determined to be close to the esophagus when placing WACA RF lesion sets. In the 7 patients

Table 4 Patients showing esophageal ulceration: LET and EGD data

Patient	I	II	III	IV	V	VI
Baseline LET	35.7°C	35.8°C	35.6°C	36.6°C	36.1°C	36.5°C
LET nadir (ΔLET)	20.9 °C (14.8°C)	13.8°C (22°C)	25.6°C (10°C)	28°C (8.6°C)	30.7°C (5.4°C)	0°C (36.5°C)
Significant LET decreases, no.	6	6	2	6	11	13

EGD = esophagogastroduodenoscopy; LET = luminal esophageal temperature.

undergoing this ablation strategy, systematic post-procedural EGD and high-resolution endoscopic ultrasonography showed no esophageal mucosal erosions, muscular disruption, or atrial-esophageal fistula formation.

Prior studies

Cummings et al[2] documented changes in esophageal temperature during RF ablation, and the possible correlation of these changes with injury to the esophagus. They reported that the intensity of power applied to PV ostia adjoining the esophagus was not a reliable predictor of such damage; instead, the appearance of microbubbles on ICE, which approximately correlated with esophageal temperatures ≥40°C, was an indicator of esophageal damage. Similarly, in a study of 81 patients undergoing RF ablation, we compared the incidence of esophageal ulceration in patients for whom LET monitoring was not used and those in whom LET monitoring was used to titrate power <38.5°C.[6] Esophageal injury was observed more frequently (36% vs. 6%, P <.006) in the cohort without LET monitoring. It is therefore reasonable to assume that: (1) LET-guided RF ablation, combined with a strategy of using spot cryoablation at pre-identified PV regions close to the esophagus, and thus more likely to result in thermal conduction to the esophagus, would further reduce the incidence of esophageal injury; and (2) the observed injury to the esophagus after cryoballoon ablation is likely caused by the multiple significant changes in LET. Given a significantly larger ablative surface and the ability to temporarily occlude PV blood flow, it follows that the esophageal impact of balloon cryoablation would be significantly greater than that observed with spot cryoablation.

Ripley et al[7] performed a study on 16 calves with direct application of both RF and cryoenergy to the cervical esophagus. Analysis of esophageal tissues at 1, 4, 7, and 14 days post-ablation showed esophageal ulceration, the number and depth of which peaked at 4 days post-ablation, using both forms of energy. No significant differences were observed in lesion width, depth, or volume between the 2 energy sources. Transmural ulcers, however, were only observed with the application of RF energy. This may be because of the preservation of the structure of the connective tissue and basement membranes when ablating with cryoenergy.[8] Although important, this study only examined the effect of direct applications of cryoenergy using a spot cryocatheter on the esophagus for 30 seconds, a strategy not comparable to clinical applications with the cryoballoon catheter. Furthermore, the study suggested that esophageal ulceration peaks at 4 days post-ablation. Although this may limit our sensitivity for detecting esophageal ulceration (15 of 29 patients in the Cryoballoon group underwent endoscopy 1 day post-ablation), it does not change the significance of our findings; namely, that cryoenergy does injure the esophagus, albeit reversibly. Finally, the study by Ripley et al[7] showed that although RF ablation lesions chronically resulted in replacement of the esophageal muscular layer with fibrotic tissue, the cryoablated tissue chronically looked indistinguishable from nonablated tissue. This may again be because of the nature of cryoenergy, which is believed to affect only the cellular components, while largely preserving the connective tissue matrix.

Present study

Cryoballoon group

Although the limited number of patients with esophageal ulceration precludes robust conclusions from this study, a statistically significant correlation was found between the incidence of esophageal ulceration after cryoballoon ablation and: (1) the LET nadir observed per patient (P = .0001), (2) the number of LETs <30°C observed per patient (P <.0001), and (3) cumulative LET decrease per patient (P = .0008). No patient or procedural characteristics were found to be predictors of the incidence of ulceration. However, because of the limited sample size, these cannot be removed definitively as factors or cofactors in the incidence of ulceration. Further studies may show significant benefit to systematic LET monitoring during cryoablation, as has become common during RF ablation, with similar early termination of lesions when significant temperature changes are observed.

Cryo-Focal group

It is similarly difficult to draw robust conclusions because of a small sample size, but the high incidence of esophageal ulceration typically associated with RF ablation was not observed in this cohort of patients. This was determined by both post-procedural endoscopy and high-resolution ultrasound in the majority of patients. However, it cannot be stated definitively that the lack of esophageal ulcerations was caused by the strategy of completing RF WACA lesion sets with spot cryoablation, rather than the use of LET-guided RF ablation alone.

Clinical implications

The clinical implications of the temperature changes observed with both spot and balloon cryoablation, and the esophageal ulcerations observed with cryoballoon ablation, remain unclear. On the one hand, not only were there significant esophageal temperature decreases in 93% of the Cryoballoon group and 71% of the Cryo-Focal group, but also there was evidence of macroscopically visible esophageal damage in 1 of every 6 patients undergoing balloon cryoablation. On the other hand, because lesion application was not prematurely terminated when the esophageal temperature decreased, it is reasonable to consider the observed ulceration the worst-case scenario. And despite this, all patients were asymptomatic and the ulcers were reversible. When combined with the aforementioned experimental animal data indicating that esophageal cryolesions heal completely, the clinical importance of these ulcerations can reasonably be questioned. No compelling evidence has been presented to warrant any change in clinical practice at this point. In particular, no threshold LET value was found that might be used to guide future cryoablation procedures. Nevertheless, although there are no conclusive data available to support the use of PPIs, there are few complications to treatment with PPIs, and we use this as standard practice after balloon cryoablation. Perhaps with advances in esophageal temperature monitoring, finding a threshold value may become feasible.

This study also suggests the importance of an awareness of clinical findings that may be mistaken for evidence of esophageal perforation. As shown in Figure 3C, the periesophageal soft tissue prominence containing hyperdensities and foci of air noted on the post-procedure CT was misinterpreted as focal esophageal perforation. However, this actually represented the coincidental ablation of lung tissue adjacent to the right inferior PV ostium.

Furthermore, despite the favorable data from the Cryo-Focal group, a sample size of only 7 patients precludes any argument for the alteration of clinical practice at this time. More data are needed to determine the comparative statistical significance of ulceration rates associated with this strategy. This is particularly pressing given the increased procedural costs associated with the use of an additional ablation catheter per patient. Of course, the additional cost associated with a combined RF/cryoablation strategy may not be problematic if safety and efficacy data become compelling.

Study limitations

Although not observed either in this study or in the authors' clinical experience, the LET probe may be associated with its own risks.[6] In addition, although vertical alignment of the esophageal temperature probe with the site of ablation was verified with fluoroscopy, the horizontal position of the

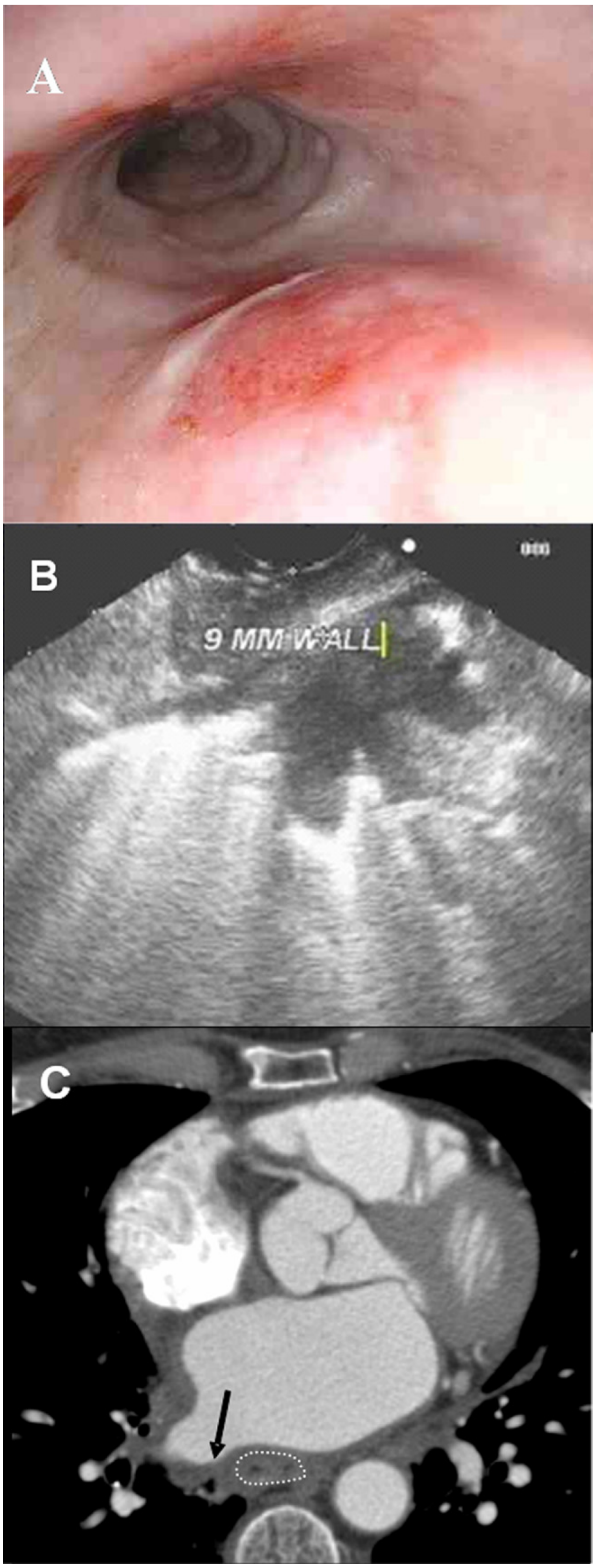

Figure 3 Patient with anterior and posterior ulceration: post-ablation EGD image of ulceration, echocardiographic image of esophageal wall, and CT images of chest. **A.** Image from post-procedural EGD showing injury noted both anteriorly and posteriorly, accompanied by wall thickening. **B.** Esophageal endoscopic ultrasound imaging during the post-cryoablation EGD of patient II indicating, in the region of esophageal ulceration, wall thickening to 9 mm with periesophageal fluid, and pockets of air. **C.** A CT image showing air foci that were mistakenly believed to be indicative for esophageal perforation; instead, they likely represent ablated contiguous lung tissue. CT = computed tomography; EGD = esophagogastroduodenoscopy.

Figure 4 Esophageal ulceration observed after absolute temperature nadir observed in total patient cohort. Marked anterior and posterior ulceration observed after LETs $\leq 0°C$. LET = luminal esophageal temperature.

temperature probe may be away from the site of ablation and therefore suboptimal. Thus, the LETs obtained do not represent the actual temperature changes in the esophagus, but rather an underestimation of the degree of temperature decrease.[6] This may be improved in the future with advances in LET monitoring, including the use of probes with multiple thermocouples.

Another limitation of this study was the lack of pre-procedural endoscopy. Therefore, it is impossible to state definitively that the observed esophageal ulcerations resulted completely from the ablation procedure. However, it is very unlikely that these ulcerations existed previously: when present, the ulcerations were always noted at the retrocardiac esophageal location (clearly noted by the cardiac pulsations), a characteristic similar to RF ablation–related esophageal damage. As noted above, no statistically significant correlation was found between a medical history of acid reflux and the incidence of ulceration (P = .29) or pre-procedural transesophageal echocardiography (P = .66) (Table 3).

Conclusion

In those patients undergoing ablation with the cryoballoon, the effects of cryothermal energy on the esophagus were most pronounced during ablation of the inferior PV. Of those patients undergoing cryoballoon ablation, routine post-procedural endoscopy showed a 17% incidence of acute esophageal injury, but with no occurrence of clinical symptoms or atrial-esophageal fistula. Furthermore, statistically significant correlation was found between the incidence of esophageal ulceration and: (1) the LET nadir observed per patient, (2) the number of LETs $<30°C$ observed per patient, and (3) cumulative LET decrease per patient. In patients undergoing a strategy of combined RF and cryoablation, no esophageal injury was observed in any patient. Future studies are required both to corroborate this experience and to assess whether the absence of atrial-esophageal fistula formation is related to a potentially distinct post-ablation healing process that occurs with cryoenergy.

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