Esophageal Endoscopy Results After Pulmonary Vein Isolation Using the Single Big Cryoballoon Technique

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Esophageal Effects of Single Big Cryoballoon PVI. ***Introduction:*** **Reversible esophageal thermal lesions after cryoballoon pulmonary vein isolation (CB-PVI) have been reported when using variable balloon sizes. The aim of this study was to investigate (1) the incidence of esophageal thermal lesions, and (2) esophageal temperature changes associated with CB-PVI using the single big cryoballoon technique.**

Methods and Results: **Thirty-eight patients with atrial fibrillation underwent successful CB-PVI using only the 28 mm cryoballoon. Luminal esophageal temperature (LET) was continuously monitored by 3 thermocouples. Fluoroscopic distance from cryoballoon to esophagus probe was retrospectively evaluated in RAO 30° and LAO 40° projections. All patients underwent postprocedural esophageal endoscopy. Average minimal LET was lower during freezing at inferior PVs, when compared to superior PVs: 35.4 ± 0.9 (range: 32.6 to 37.4; RSPV); 31.5 ± 7.5 (2.5 to 37.6; RIPV); 32.9 ± 5.2 (8.5 to 36.5; LSPV); and 30.3 ± 8.4°C (−6 to 36.7°C; LIPV); P = 0.001. We found steep temperature gradients over distance (1) from the cryoballoon center (LETs < 10°C confined to a distance of < 15 mm in both RAO 30° and LAO 40° projections), and (2) along the esophagus long axis, underscoring the need for multiple measurement sites. None of the patients showed esophageal thermal lesions at endoscopy after 3 ± 1 (range 1–7) days. No AEF occurred during a follow-up of 125 ± 78 days.**

Conclusion: **In a cohort of AF patients treated by the single big cryoballoon technique, CB-PVI was not associated with thermal esophageal lesions.** *(J Cardiovasc Electrophysiol, Vol. pp. 1-6)*

atrial fibrillation, catheter ablation, esophagus, cryoballoon, pulmonary veins

Introduction

Atrioesophageal fistula (AEF) formation is the most feared complication associated with pulmonary vein isolation (PVI) using radiofrequency current (RFC) ablation due to its high mortality.[1–4] Cryoballoon-PVI (CB-PVI) is an emerging alternative technique with a favorable safety profile that has—as of now—not been reported as a cause of AEF.[5–11] Results from experimental studies suggest that cryothermal energy may be associated with less risk of esophageal ulceration when compared to RFC.[12] Nonetheless, clinical experience with this relatively new approach is limited, and esophageal ulcerations, albeit reversible and without clinical sequelae, have recently been reported in a series of patients utilizing different cryoballoon sizes for PVI.[8] The cryoballoon ablation technique varies among centers, particularly in the use of various balloon dimensions,[5-9] possibly impacting on esophageal lesion development. Here, we report the results of systematic postprocedural esophageal endoscopy in a series of patients with atrial fibrillation (AF) treated exclusively with the single big (28 mm) cryoballoon technique.[9]

Methods

Patients

A total of 38 consecutive patients with paroxysmal (n = 36) or persistent (n = 2) AF were included into the study between August 2008 and November 2009. All patients underwent preprocedural transesophageal echocardiography. Inclusion criteria were as follows: a history of symptomatic AF despite antiarrhythmic drug (AAD) treatment with ≥ 1 AAD and consent to undergo postprocedural esophageal endoscopy. Exclusion criteria were defined as a LA diameter > 55 mm, severe left ventricular hypertrophy (LV wall thickness ≥ 15 mm), LA thrombus, and decompensated heart failure. Patient baseline clinical characteristics are shown in Table 1.

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TABLE 1

Baseline Patient Characteristics (n = 38)

Age (years)	56 ± 12
Male (n)	27 (71%)
Paroxysmal AF	36 (95%)
Persistent AF	2 (5%)
Failed antiarrhythmics (n)	1.4 ± 0.9
AF duration (years)	6 ± 5
LA diameter (mm)	43 ± 5
Hypertension (n)	21 (55%)
Diabetes (n)	1 (3%)
CAD (n)	4 (11%)
GERD (n)	0

CAD = coronary artery disease; GERD = gastroesophageal reflux disease.

Cryoballoon Ablation

The concept of the "single big cryoballoon" technique for PVI (Arctic Front, 28 mm diameter, Medtronic CryoCath LP, Montreal, Quebec, Canada) has been described in detail previously.[9] No preprocedural imaging, such as CT or MRI, or intraprocedural imaging apart from angiography, such as transesophageal echocardiography,[13] was performed. All procedures were performed under deep sedation using boluses of midazolam and fentanyl as well as a continuous infusion of propofol. Following double transseptal puncture, intravenous heparin was repeatedly administered to maintain an activated clotting time of 250 to 300 seconds. Selective PV angiography was performed to identify the PV anatomy using standard projections (RAO 30°, LAO 40°). Baseline potentials of all PVs were recorded with a Lasso catheter (Biosense Webster, Inc., Diamond Bar, CA, USA). The 28 mm balloon was maneuvered to all PV ostia by use of a steerable 12F sheath (FlexCath, CryoCath) and either a guidewire (Amplatz Stiff Wire, Cook Inc., Bloomington, IN, USA) or a 6-pole spiral catheter (Promap, ProRhythm, Ronkonkoma, NY, USA)[14] inserted through the central canal of the balloon catheter. To assess the exact position of the inflated balloon in relation to the LA–PV junction, contrast medium was injected from the distal lumen of the cryoballoon catheter. Freezing at the LA–PV junction was performed for a target time of 300 seconds. The right phrenic nerve (PN) was constantly paced from the superior caval vein during freezing at the septal PVs. In case of loss of PN capture, freezing was immediately terminated. After each freeze, PV conduction was reevaluated by positioning the Lasso catheter at the same position within the PV as before the cryoballoon application. Alternatively, PV conduction was monitored in real-time by the spiral catheter (11 patients).[14] If the PV was not isolated, the cryoballoon was repositioned and balloon to LA–PV contact reevaluated by angiography before the next freeze. Safety (bonus) applications after PVI were performed with one application at each LA–PV junction in 28 patients or with 2 applications at each LA–PV junction in 10 patients. Ablation endpoint was the loss of all PV potentials as confirmed by the Lasso catheter after a waiting period of 30 minutes.

Esophageal Temperature and Fluoroscopic Distance Measurement

At the start of the procedure and before administration of the heparin bolus a temperature probe (ETP) with 3 thermocouples separated by 10 mm (SensiTherm, St. Jude Medical, Inc., St. Paul, MN, USA; Fig. 1) was inserted into the esophagus transorally under fluoroscopic guidance. In 2 patients the probe could not be placed. Its position was repeatedly adjusted to match the balloon position during freezing. For each cryoballoon application, baseline and minimal LET were recorded. Baseline LET was defined as the lowest temperature measured by any thermocouple before freezing. Minimal LET was defined as the temperature nadir occurring during or shortly after cryothermal energy deployment in any of the thermocouples. In a subgroup of patients (n = 6), temperature readings of all 3 thermocouples were recorded at baseline and at the time of LET nadir. To minimize a stacking effect, LET was allowed to recover before starting the next freeze. Temperature measurements were observational

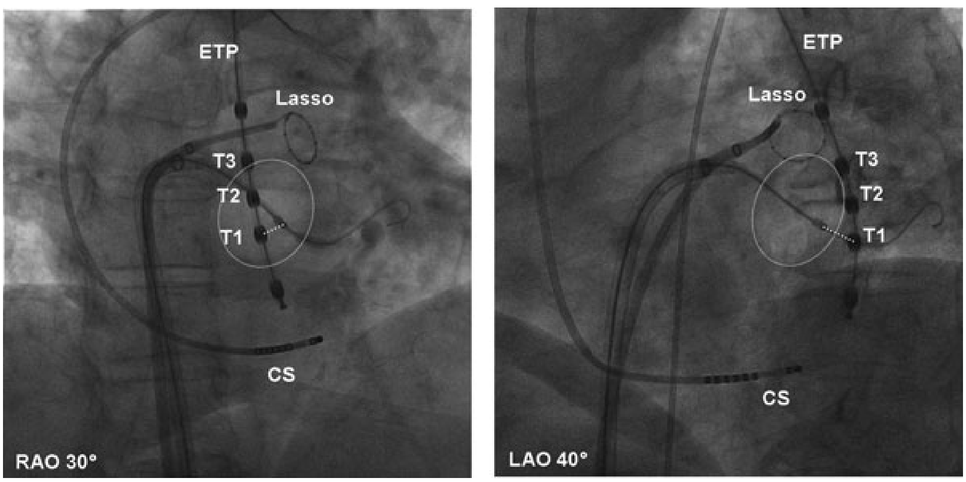

Figure 1. *Cryoballoon and esophageal temperature probe (ETP) position during freezing at the left inferior pulmonary vein in the patient with an LET nadir of −6.0°C. Fluoroscopic views in right anterior oblique (RAO) and left anterior oblique (LAO) projections are shown. The 3 thermocouples of the ETP separated by 10 mm (T1–3) can be seen. At the time of LET nadir, temperature readings were: 6.6 (T1), −6.0 (T2), and 20.0°C (T3). Punctuated lines represent fluoroscopic distance of the cryoballoon refrigerant injector to the thermocouple in closest proximity (RAO: 7 mm; LAO: 9 mm). Lasso = Lasso catheter in left superior pulmonary vein; CS = coronary sinus catheter.*

only and did not influence cryoballoon applications. The refrigerant injector near the distal cryoballoon pole was used as a fluoroscopic marker to measure the distance (mm) between the cryoballoon and the esophageal probe thermistor in closest proximity in RAO 30° and LAO 40° projections (Fig. 1).

Postprocedural Care and Follow-Up

All patients underwent postprocedural transthoracic echocardiography and chest X-ray to rule out pericardial effusion or pneumothorax. Patients were bridged with low molecular weight heparin (enoxaparin), and oral anticoagulation (phenprocoumon targeting an INR value of 2.0–3.0 for at least 3 months) was initiated the following day. Proton-pump inhibitor therapy was not routinely prescribed. All patients underwent gastroesophageal endoscopy within 7 days following ablation. In addition, patients were scheduled for outpatient clinic visits or contacted by telephone 1, 3 and 6 months after ablation.

Statistics

Continuous data were presented as mean ± standard deviation. The Friedman test was used to compare average minimal LETs measured during freezing at the 4 anatomical PVs (data on superior and inferior branches of a left common trunk were included into LSPV and LIPV group, respectively). Confidence intervals (CI) of proportions were calculated from the binomial distribution. A correlation coefficient was calculated to asses the relationship between minimal LET and maximum temperature difference measured between 2 thermocouples of the esophageal probe. A P-value of < 0.05 was considered statistically significant.

Results

Cryoballoon Ablation

In 38 patients a total of 149 PVs were identified including a short left common trunk (LCPV) in 3 patients. Mean angiographic diameters measured in RAO 30° (septal PVs) or LAO 40° (lateral PVs) were: 18 ± 3 (range: 12–24): RSPV, 17 ± 3 (10–25): RIPV, 18 ± 3 (10–23): LSPV, 17 ± 2 (12–21): LIPV, and 28 ± 4 mm (25–33 mm): LCPV. In the 2 patients with persistent AF, sinus rhythm was restored by external cardioversion before ablation. A total of 399 cryoballoon (including bonus) applications were applied; RSPV: 3 ± 1 (total: 97), RIPV: 3 ± 1 (total: 109), LSPV: 2 ± 1 (total: 84), LIPV: 3 ± 2 (total: 97), and LCPV: 4 ± 0 (total: 12). All PVs were successfully isolated using only the 28 mm balloon. Procedure duration was 176 ± 32 minutes, radiation time was 31 ± 11 minutes.

Esophageal Temperature Changes

Average minimal LET during freezing varied with treated PV, with lower LETs observed during freezing at inferior PVs when compared to superior PVs (Fig. 2, Table 2): 35.4 ± 0.9 (RSPV); 31.5 ± 7.5 (RIPV); 32.9 ± 5.2 (LSPV); and 30.3 ± 8.4°C (LIPV); $P < 0.001$ for comparison between all groups. The number of freezes with minimal LETs < 10°C was: 0 (RSPV), 3 (RIPV), 1 (LSPV), and 4 (LIPV). The absolute minimal LET achieved in any patient according to treated PV was as follows: 32.6 (RSPV), 2.5 (RIPV), 8.5 (LSPV), and −6.0°C (LIPV), which was the lowest LET and the only freeze with subzero LET observed in this study. The fluoroscopic position of the cryoballoon in relation to the esophageal probe during this application is shown in Figure 1 (7 mm in RAO 30°; 9 mm in LAO 40°). The first freeze at the LIPV in this patient resulted in a LET decrease from 36.8 to 14.6°C and the second freeze (bonus application) resulted in a LET decrease from 35.2 to −6.0°C.

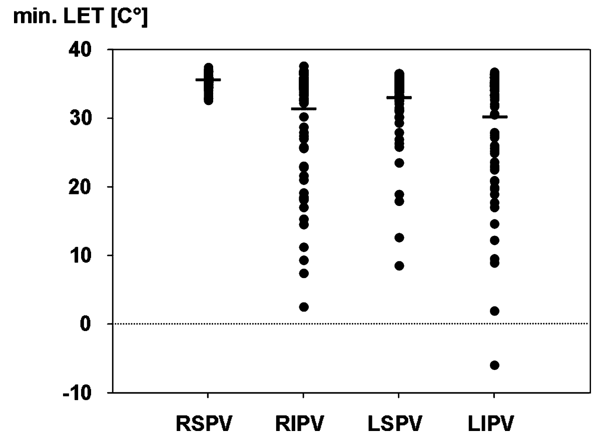

Figure 2. *Minimal luminal esophageal temperature (LET) measurements per vein treated. Solid bars indicate group means. RSPV = right superior pulmonary vein; RIPV = right inferior pulmonary vein; LSPV = left superior pulmonary vein (including data on 3 superior branches of a left common PV); LIPV = left inferior pulmonary vein (including data on 3 inferior branches of a left common PV).*

The temperature distribution among the 3 thermocouples at the time of absolute LET nadir in a subgroup of patients is shown in Table 3. The maximum temperature difference measured between 2 thermocouples correlated well with the absolute LET nadir ($r = -0.982$, $P < 0.001$); thus, differences were more pronounced when freezing near the esophagus. The highest temperature gradient (26°C) was measured in the patient with subzero LET between T2 (−6°C) and T3 (20.0°C). Thus, with the thermocouples spaced 10 mm apart, subzero LET was confined to a small area (Fig. 1, Table 3).

Average and absolute minimal LETs according to the fluoroscopic distance between the cryoballoon center (refrigerant injector) and the esophageal temperature probe during freezing at any PV are shown in Table 4. These data demonstrate a steep temperature gradient over distance from the cryoballoon with lowest LETs (< 10°C) confined to a distance of < 15 mm in both RAO 30° and LAO 40° projections (Table 4).

Gastroesophageal Endoscopy and Follow-Up

Endoscopy was performed 3 ± 1 (range 1–7) days following ablation. Thirty-seven out of 38 patients (including the patient with subzero LET during cryoablation) were free of any detectable lesion of the esophageal mucosa. In 1 patient, endoscopy at the first postprocedural day revealed 2 longitudinal, fissural lesions confined to the top of mucosal folds in a region beginning 35 cm from the incisor teeth and reaching down to the esophagogastric junction. These lesions were interpreted to be of mechanical origin by the investigator, possibly due to preprocedural transesophageal echocardiography or manipulation with the temperature probe. In this patient, proton-pump inhibitor therapy was initiated and a

TABLE 2

Luminal Esophageal Temperature Measurements

	RSPV	RIPV	LSPV	LIPV
Average minimal LET (°C)	35.4 ± 0.9*	31.5 ± 7.5*	32.9 ± 5.2*	30.3 ± 8.4*
Absolute minimal LET (°C)	32.6	2.5	8.5	−6.0
Minimal LET < 30°C (n)	0	21	10	25
Minimal LET < 10°C (n)	0	3	1	4
Average LET decrease (°C)	0.2 ± 0.9	2.7 ± 5.5	2.8 ± 5.3	5.3 ± 8.1

Data for LSPV and LIPV include 3 superior and inferior branches of a left common pulmonary vein, respectively. RSPV = right superior pulmonary vein; RIPV = right inferior pulmonary vein; LSPV = left superior pulmonary vein; LIPV = left inferior pulmonary vein; LET = luminal esophageal temperature; *P < 0.001 for comparison among all groups (Friedman test).

control endoscopy 6 days later showed a normal esophageal mucosa. In summary, the incidence of thermal esophageal lesions was 0% (95% CI: 0–9.3%). The incidence of any esophageal lesion was 2.6% (95% CI: 0.07–13.8%).

During a follow-up of 125 ± 78 days, no atrioesophageal fistula occurred.

In 2 patients, gastroesophageal endoscopy at day 3 after the procedure showed food retention despite overnight fasting. In patient 1, pyloric spasm was also shown. Both patients reported mild abdominal discomfort and distention, but were able to continue food intake. Repeat gastroesophagoscopy was performed 1 week after the procedure in both patients, demonstrating normal gastric emptying and pyloric function in patient 1, with complete resolution of symptoms. In patient 2, impaired gastric emptying was still demonstrated. However, with conservative treatment the patient was successfully discharged on almost normal diet at 1 week.

Complications

Right PN palsy (PNP) occurred in 2 patients despite immediate cessation of the cryoballoon application upon loss of PN capture. In 1 patient PNP occurred during the third cryothermal application (2nd bonus) at the RSPV (max. diameter: 22 mm). Thus, despite a relatively small PV diameter, cumulative tissue cooling ultimately led to PNP. This patient felt dyspnea on exertion, which resolved within 7 months after ablation. Repeat chest fluoroscopy demonstrated normal diaphragm movement at that time. In the other patient, PNP occurred during the first cryothermal application at a large RIPV (max. diameter: 25 mm) and persisted until discharge. This patient was asymptomatic and refused further chest fluoroscopy. No other complication occurred during procedure or follow-up.

TABLE 3

LET Measurements from 3 Thermocouples at the Time of Absolute LET Nadir

Vein	T1 [°C]	T2 [°C]	T3 [°C]	Δmax [°C]	Pt
LSPV	35.7	36	33.1*	2.9	39
LIPV	22.1*	25.6	32	9.9	37
LIPV	19.7*	23.9	31	11.3	31
LIPV	22.5*	26.6	33.9	11.4	32
RIPV	33.6	24.5	18.5*	15.1	38
LIPV	6.6	−6*	20	26	29

RIPV: right inferior pulmonary vein; LSPV = left superior pulmonary vein; LIPV = left inferior pulmonary vein; LET = luminal esophageal temperature; *absolute LET nadir; T1-T3 = individual thermocouples; Δmax = maximum temperature difference between 2 thermocouples; pt = patient number.

Discussion

The main new findings of this study are (1) the absence of esophageal thermal lesions in a cohort of 38 patients undergoing CB-PVI using only the big (28 mm) balloon, and (2) restriction of lowest LET to a small area as demonstrated by the use of multiple thermocouples, as well as a steep temperature gradient over the distance between cryoballoon center and temperature probe such that LET decreases to < 10° C occurred in a small subset of patients (n = 5) with a distance of < 15 mm in both RAO 30° and LAO 40° projections (Table 4).

Previous Studies

There is one previously published study reporting on postprocedural esophageal endoscopy following cryoballoon PVI. The authors found a 17% incidence (6 out of 35 patients) of reversible esophageal thermal ulcerations associated with CB-PVI.[8] The ablation technique differed from our approach in that both available balloon dimensions (23 and 28 mm) were employed for PVI, with the use of a 23 mm cryoballoon in 52% of patients.[8] The authors found no difference in mean LET decrease associated with the use of the 23 mm as opposed to the 28 mm balloon. However, a single thermocouple was used for LET measurement and esophageal thermal lesions in this cohort were observed over a wide range of minimal LETs (0–30.7°C), such that no temperature limit could be found to distinguish between patients with and without lesions.[8] On the other hand, we could show that minimal LET during LA cryoablation close to the esophagus is localized to a small area when using multiple thermocouples (Fig. 1, Table 3). Accordingly, measurement by a single thermocouple likely decreases sensitivity to detect maximum temperature changes in the esophagus.[15] Thus, it is currently not clear whether the use of a 23 mm cryoballoon may result in lower esophageal temperatures when compared to the use of a 28 mm balloon.

Possible Impact of Balloon Size

The use of a small as opposed to a big balloon at a given PV diameter may have several effects on collateral structures. A deeper position within the vein could result in the combined effect of (1) close proximity to adjacent tissue, and (2) deeper freezing temperatures due to less convective heating of the balloon by atrial blood flow.

TABLE 4

LET According to the Fluoroscopic Balloon-to-Esophagus Probe Distance

CB-ETP (mm) LAO 40°	**CB-ETP (mm) RAO 30°**								
	0–4	**5–9**	**10–14**	**15–19**	**20–24**	**25–29**	**30–39**	**40–49**	**50–59**
0–4	#	#	5.7 (1.9)	21.6 (19.7)	26.4 (25.8)	#	#	34.3 (34.3)	#
5–9	#	4.3 (−6.0)	#	21.5 (17.7)	31.4 (25.2)	33.5 (33.1)	35.2 (35.0)	#	#
10–14	10.8 (2.5)	26.3 (18.1)	#	18.8 (18.5)	#	33.0 (32.1)	34.5 (34.0)	34.8 (34.8)	#
15–19	27.2 (21.0)	27.0 (18.1)	#	#	#	33.1 (32.1)	35.0 (34.8)	35.2 (33.9)	#
20–24	35.6 (35.4)	#	#	34.8 (34.8)	#	34.8 (33.1)	35.5 (34.1)	35.0 (34.6)	36.1 (35.7)
25–29	34.9 (34.6)	34.2 (32.6)	#	#	35.7 (32.9)	35.1 (33.3)	35.5 (35.2)	34.7 (34.3)	#
30–39	34.0 (33.6)	31.7 (30.2)	35.8 (35.5)	#	34.2 (34.1)	35.3 (34.8)	34.8 (33.5)	36.2 (36.0)	35.1 (35.0)
40–49	#	#	#	35.0 (34.6)	35.4 (35.3)	36.0 (35.9)	34.9 (34.6)	35.9 (35.9)	36.1 (35.9)
50–59	#	#	#	#	35.5 (35.3)	#	34.9 (34.9)	35.9 (35.5)	#
60–69	#	#	#	#	#	#	35.9 (35.9)	#	34.5 (34.5)

Average and absolute minimal luminal esophageal temperature (LET [°C]) is shown as a function of fluoroscopic distance to the cryoballoon in both RAO 30° and LAO 40° projections. The refrigerant injector of the cryoballoon was used as a fluoroscopic marker. Values in parentheses represent absolute minimal LET. CB = cryoballoon; ETP = esophageal temperature probe.

Anatomical and imaging studies have shown that in ~60% of patients the esophagus passes close to the pulmonary venoatrial (VA) junction, most often on the left side.[16–18] In fact, the shortest distance between the LA endocardium and the esophageal wall was found at the left VA junction.[16] Due to the posterior course of the inferior PVs as opposed to the more anterior course of the superior PVs,[19] the shortest distance to the border of the esophagus has been described for the inferior PVs.[18] These anatomical findings are well reflected by our LET measurements during cryoablation at individual PVs (Fig. 2, Table 2). In some patients, the esophagus is crowded into a space surrounded by the LIPV, the spine, and the descending aorta.[18] Thus, especially during cryoablation at the LIPV, a relatively distal balloon position may result in close contact to the esophagus. Moreover, due to a steep temperature gradient in close proximity to the cryoballoon (Table 4), even a small difference in balloon-to-esophagus distance, such as might be brought about by the use of a small balloon, may greatly impact on LET when freezing near the esophagus.

In contrast, in this patient cohort treated exclusively with the 28 mm balloon, we did not observe thermal esophageal lesions. Thus, esophageal temperature measurement did not provide incremental safety benefit in this study. Further research is needed to confirm the study results in a larger cohort.

Complications

While reversible PNP is a well-recognized complication of cryoballoon ablation,[5–9,20] delayed gastric emptying has to the best of our knowledge not yet been reported in association with CB-PVI. Several cases of acute pyloric spasm and gastric hypomotility have been described following RFC ablation for AF,[21] probably due to damage of the periesophageal vagal plexus, some of which required corrective interventions. The 2 patients described in this study had mild or transient symptoms with successful conservative treatment. Further research is required to determine whether this complication takes a generally benign course following CB-PVI.

Limitations

This study has several limitations. (1) The study did not include a control group. Thus, the hypothesis that exclusive use of the 28 mm balloon is associated with a lower risk for esophageal lesions compared to ablation strategies involving the 23 mm balloon needs to be tested in a randomized trial. (2) Digital temperature readings were registered manually, thus exact LET-time curves could not be analyzed. (3) The relationship or time course between esophageal lesions detected at endoscopy and manifest AEF is unclear. Furthermore, it cannot be excluded that thermal esophageal lesions became manifest after endoscopy was performed. However, clinical and experimental studies indicate thermal esophageal lesion development by cryoablation well within the time frame of this study.[8,12]

Conclusions

In a cohort of AF patients treated by the single big (28 mm) cryoballoon technique, CB-PVI was not associated with thermal esophageal lesions. LET measurement by multiple thermocouples revealed high temperature gradients along the esophagus during cryoablation, underscoring the role of multiple measurement sites.

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