Increased Incidence of Esophageal Thermal Lesions using the Second-Generation 28mm Cryoballoon

Running title: Metzner et al.: Esophageal Thermal Injury after Cryoballoon-PVI

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Abstract:

**Background** - Pulmonary vein isolation (PVI) is an established treatment option for atrial fibrillation (AF). To date, the incidence and quality of ablation-induced esophageal thermal lesions (ETL) using the recently introduced second-generation cryoballoon (CB, ArcticFront Advance, Medtronic) is unknown.

**Methods and Results** - In patients with drug-refractory paroxysmal AF or short-standing persistent AF, PVI was performed using the second-generation CB. The endoluminal esophageal temperature was monitored via a temperature probe. Following PVI, esophagogastroduodenoscopy (EGD) was performed to assess the incidence of ETL. In 50 patients (18 female, age 61±11 years, left atrial diameter 43±5 mm) successful CB based PVI was performed. Lowest median balloon-temperature and esophageal temperature for the right superior pulmonary vein (PV) was -51°C and 35.8°C, -47°C and 35°C for the right inferior PV, -51°C and 34.4°C for the left superior PV, -48°C and 34.6°C for the left inferior PV and -54°C and 34.5°C for the left common PV, respectively. EGD performed 2±1 days post ablation demonstrated superficial thermal lesions and thermal ulcerations in 1/50 (2%) and 5/50 (10%) patients, respectively. In patients with ETL, during at least 1 freeze cycle the endoluminal esophageal temperature measured less than 3.0°C. All thermal lesions were in the healing process upon repeat EGD 4±2 days after initial endoscopy.

**Conclusions** - Using the second-generation 28mm CB, ETL were detected in 6/50 (12%) patients. All ETL were in the healing process upon repeat EGD. An esophageal temperature safety cut-off may prove valuable in the prevention of ETL and requires further evaluation.

**Key words:** atrial fibrillation, pulmonary vein isolation, cryoballoon, esophageal thermal lesion
Introduction

Pulmonary vein isolation (PVI) using the cryoballoon (CB, ArcticFront, Medtronic Inc.) is an established ablation technology commonly used in patients suffering from drug-refractory paroxysmal atrial fibrillation (AF). Although CB PVI is considered safe and effective, procedure-related complications have been reported. The incidence of esophageal thermal lesions (ETL) using the first-generation CB ranges between 0% to 18% depending on the balloon size utilized. Recently, the first published case of an atrioesophageal fistula following use of the first-generation CB was reported.

The second-generation CB (Arctic Front Advance, Medtronic Inc.) was introduced in 2012. Rather than cooling of only the distal equatorial ring sparing the CB tip, the second-generation CB incorporates a revised refrigerant injection system that allows for more homogeneous cooling of the total distal balloon hemisphere. While these modifications are expected to increase efficacy, enhanced cooling may result in a higher rate of collateral damage to noncardiac tissue. In this context, the current study set out to investigate the incidence of ETL using the second-generation 28 mm CB.

Methods

Inclusion and exclusion criteria

Consecutive patients suffering from symptomatic, drug-refractory paroxysmal atrial fibrillation (PAF) or short-standing persistent AF (persistent AF with a duration of ≤ 3 months) were admitted and eligible for CB-based PVI. Exclusion criteria were prior left atrial (LA) ablation, LA diameter > 55 mm, severe valvular heart disease and contraindications to postinterventional oral anticoagulation. Transeosophageal echocardiography was performed before PVI to assess LA
diameter and to rule out intracardiac thrombi. No additional pre-interventional imaging was performed. Each patient gave written informed consent.

**Intraprocedural Management**

The procedure was performed under deep sedation using boluses of midazolam, fentanyl, and a continuous infusion of propofol (1%, 10-30ml/hour). Vital parameters (pulse, blood pressure, oxygen saturation, body temperature) were continuously monitored. Prior to transseptal puncture (TP), two diagnostic catheters introduced via a right femoral vein access were placed within in the coronary sinus (CS; 7F, Webster TM, Biosense Webster, Inc., Diamond Bar, CA, USA) and along the His-bundle region (6F, Webster TM, Biosense Webster, Inc.), respectively. Subclavian vein access was attempted only if the CS catheter could not be positioned from the femoral vein. Double TP was performed under fluoroscopic guidance using a modified Brockenbrough technique and two 8.5F transseptal sheaths (TS; SL1, St. Jude Medical, Inc., St. Paul, MN, USA). One TS was exchanged over-the-wire for a 12F steerable TS (Flexcath, Medtronic, Inc., Minneapolis, MN, USA).

Following successful TP, a heparin bolus was administered targeting an activated clotting time of >300 sec. Selective PV angiography aided in identifying the individual PV ostia. A spiral mapping catheter (Lasso, Biosense Webster, Inc.) was positioned at the PV ostium and baseline PV potentials were recorded.

During freeze application at the septal PVs, continuous phrenic nerve (PN) pacing was performed (12mA, 2.9ms) via a diagnostic catheter placed in the superior vena cava. Cryoablation was immediately terminated in the event of loss of PN capture.

**Cryoballoon-based PVI**

In brief, the second-generation CB (Arctic Front Advance, Medtronic, Inc.) is available as a non-
compliant balloon with diameters of 23 mm or 28 mm. Compared to the first-generation CB, it incorporates a modified refrigerant injection system (eight instead of four injection jets; injection jets in a more distal position) providing more homogeneous cooling of the distal hemisphere of the balloon surface. The deflated CB is advanced into the left atrium via a 12F steerable TS using an over-the-wire technique and a stiff wire or a spiral mapping catheter (15 mm or 20 mm diameter; Achieve™, Medtronic, Inc., Minneapolis, MN, USA). The stiff wire or spiral mapping catheter is advanced into the target PV and the CB inflated within the LA before proper positioning at the antral aspect of the target PV. Contrast medium is injected through the central lumen of the CB to verify complete sealing of the balloon-to-PV/left atrial interface. A freezing cycle of 240 sec is applied, while the balloon temperature is automatically stored. In case of successful PV isolation verified by spiral mapping catheter recordings an additional freeze cycle of 240 sec is applied.

In the current study only the 28mm second-generation CB was used irrespective of the PV diameter. The endpoint of cryoablation was achieved once all PVs demonstrated persistent isolation verified by spiral mapping catheter recordings following a 30-min waiting period after the last freeze application.

Temperature Monitoring

An esophageal temperature probe equipped with 3 thermistors (SensiTherm, St. Jude Medical, Inc.) was inserted transorally for continuous observation of esophageal temperature changes during the freeze cycle. The temperature probe was positioned at the level of and the closest distance to the CB during ablation and readjusted as needed using the respective fluoroscopic projection. Only the lowest endoluminal esophageal temperature was recorded for each PV, since the unit does not allow storage of temperature-over-time curves. There was no predefined
temperature cut-off.

Postprocedural Care

All patients underwent transthoracic echocardiography and thoracic fluoroscopy the day after ablation to rule out pericardial effusion and/or pneumothorax, respectively. Following ablation all patients were treated with pantoprazol 40mg twice daily for 6 weeks. Low molecular-weight heparin was administered in patients on warfarin and an INR <2.0 until a therapeutic INR of 2-3 was achieved or until the initiation of a new oral anticoagulant. Anticoagulation was continued for 3 months post ablation and then based on the individual CHA2DS2-VASC score. Previously ineffective antiarrhythmic drug therapy was continued for 3 months.

Esophagogastroduodenoscopy

Two days following ablation, esophagogastroduodenoscopy (EGD) was performed in all patients to assess for the presence and quality of esophageal thermal lesions (ETL). EGD was repeated after 5 days in case of detected ETL. EGD findings were classified as no lesion, superficial thermal lesion (erythema with intact mucosa) or esophageal ulceration.

Follow-up

A blanking period of 3 months post PVI was defined. Outpatient clinic visits at 3, 6 and 12 months including 24h Holter-ECGs were performed. Additionally outpatient clinic visits, ECG and Holter ECG were immediately initiated in case of symptoms suggestive for a recurred arrhythmia.

Statistical analysis

Continuous data are shown as mean and standard deviation in case of normally distributed data and as median, interquartiles, minimum and maximum otherwise. Differences in esophageal and balloon temperatures between patients with and without esophageal thermal lesions were tested.
with the Wilcoxon–Mann Whitney test. The Kolmogorov-Smirnov and Shapiro-Wilk tests on normal distribution were used. Additionally Q-Q plots of the data were applied.

For associations between continuous variables, the nonparametric correlation coefficient of Spearman was calculated. Receiver Operating Characteristic (ROC) curves, which represent false and right positive rates for all cutpoint-values of a continuous variable, were used to achieve ideal cut-point-values for esophageal and balloon temperatures in order to predict the presence or absence of lesions. The cutpoint-values were optimized for specificity. The rate of right positives and right negatives for these values are mentioned in the text.

All p-values are two-sided and a p<0.05 was considered significant. All calculations were performed with the statistical analysis software SAS (SAS Institute Inc., version 9.2, Cary, NC, USA).

All authors have read and agreed to the manuscript as written.

Results

Patient characteristics

Fifty patients (18 female, mean age 61±11 years, mean LA-diameter 43±5mm) with a history of PAF (36/50 patients [72%]) or short-standing persistent AF (14/50 patients [28%]) underwent CB-based PVI using exclusively the 28mm second-generation CB. Thirty-seven of 50 (74%) patients, 6/50 (12%) patients and 8/50 (16%) patients had a known history of arterial hypertension, stable coronary artery disease and diabetes mellitus, respectively. None of the patients had a previous left atrial ablation attempt. The mean creatinine level measured in the patient cohort was 0.9±0.2 mg/dl (range: 0.7 – 1.4 mg/dl).

Ablation Results

In 50 patients a total of 192 PVs was identified. 191/192 (99%) PVs were isolated successfully.
using only the second-generation CB. One of 50 (2%) right inferior PVs (RIPVs) was not targeted due to loss of phrenic nerve (PN) capture during CB ablation of the ipsilateral RSPV. Electrical PVI during the first cryo-application was achieved in 46/50 (92%) RSPVs, 41/50 (82%) RIPVs, 37/42 (88%) left superior PVs (LSPVs), 42/42 (100%) left inferior PVs (LIPVs), and in 4/8 (50%) left common PVs (LCPVs), respectively. The mean number of cryo-applications resulting in PVI was 1.1±0.5, 1.3±0.6, 1.1±0.3, 1.0±0 and 1.5±0.5 for the RSPV, RIPV, LSPV, LIPV and LCPV, respectively. In all PVs, one safety cryo-application was applied after successful PVI. Mean total number of CB applications including the safety freeze cycle was 2.2±0.5, 2.2±0.7, 2.1±0.3, 2.0±0 and 2.5±0.5 for the RSPV, RIPV, LSPV, LIPV and LCPV, respectively.

Median minimal balloon-temperature was: RSPV -51 (-54 - -45; q1-q3)°C, RIPV -47 (-52.3 - -43)°C, LSPV-51 (-55 - -189 45)°C, LIPV -48 (-52 - -44)°C and LCPV -54 (-57 - -47.5)°C. (table 1).

Median procedure and fluoroscopy times were 135 (125-154; q1-q3) min and 25 (21-29) min, respectively. The median fluoroscopy dose-area product was 5077 (3001-8048) cGy×cm². The mean amount of contrast used per patient was 174±55 ml.

**Esophageal Temperatures**

The median minimal esophageal temperature during cryo-application was: RSPV 35.8 (34.8-36.3; q1-q3)°C, RIPV 35 (31.5-36)°C, LSPV 34.4 (32.6-35.8)°C, LIPV 34.6 (25.8-35.3)°C and LCPV 34.5 (30.2-35.1)°C, respectively. During 6 freeze cycles in 5 patients endoluminal esophageal temperature was measured <0°C (range -1.5°C to -14.0°C); in these patients below zero temperatures were recorded during cryoablation of the LIPV (table 2). The absolute minimal esophageal temperature assessed in any patient according to treated PV was: RSPV
23.3°C, RIPV 2.9°C, LSPV 5.9°C, LIPV -14.0°C and LCPV 7.2°C, respectively.

**Endoscopic findings**

EGD was performed in all patients 2±1 days post ablation. Superficial thermal lesions and thermal ulcerations were found in 1/50 (2%) and 5/50 (10%) patients, respectively (figure 4). In 2/50 (4%) patients, signs of gastric hypomotility were detected, including one patient with a thermal ulceration. All patients with ETL were asymptomatic. In patients with superficial thermal lesions or ulcerations, repeat EGD performed 4±2 days after the initial pathologic endoscopy demonstrated healing lesions.

Median minimal balloon temperature in patients with and without ETL was -57 (-54.8 - -50.8; q1-q3)°C and -50 (-53 - -43)°C (p=0.43), -46 (-51 - -40.5)°C and -48 (-52.8 - -57)°C (p=0.74), -56 (-58 - -54)°C and -49 (-54 - -43)°C (p=0.013), -51.5 (-56 - -47.5)°C and -48 (-52 - -43)°C (p=0.066) for the RSPV, RIPV, LSPV, LIPV, respectively (figure 1). Median minimal balloon temperature for the LCPV was -54 (-57 - -47.5)°C. None of the patients with an LCPV developed ETL.

Median minimal endoluminal esophageal temperature in patients with and without ETL was 35.9 (34.8-36.4)°C and 35.7 (34.8-36.3)°C (p=0.74), 36.0 (35.6-36.3)°C and 34.6 (31.0-34.5)°C (p=0.37), 33.2 (28.6-34.5)°C and 34.8 (33.0-35.8)°C (p=0.045), and -0.45 (-5.8-13.0)°C and 34.6 (29.8-35.3)°C (p=0.019), respectively (figure 2). Median minimal endoluminal esophageal temperature for the LCPV was 34.5 (31.0-35.0)°C. All patients with detected ETL had a minimal endoluminal esophageal temperature of ≤2.9°C during ≥1 freeze cycle (range -2.9°C to -14°C). This occurred in 5/6 (83%) patients along the LIPV and 1/6 (17%) along the RIPV (table 3). All ETL were located at the opposite side of the posterior LA.

No ETL was detected if the minimal endoluminal esophageal temperature was ≥ 3.0°C.
Complications

Despite continuous stimulation of the PN throughout the freeze cycle targeting the right-sided PVs, PN-palsy occurred in 1/50 (2%) patients. Loss of PN capture was noted during the second freeze cycle targeting the RSPV. Although cryoenergy application was immediately stopped, PN-palsy persisted throughout the procedure. No thromboembolic events, no pericardial effusion or pericardial tamponade or severe groin complications occurred in the study population.

Follow-up

Forty-four of 50 (88%) patients had completed the blanking period. One of 44 (2%) patients outside the blanking period was lost to FU. During a median FU of 147 (132-169; q1-q3) days, 35/43 (81%) patients remained free of any symptomatic and/or documented AF episode following a single CB procedure and including a 3-month blanking period. A symptomatic and/or documented AF episode was observed in 7/43 (16%) patients. In 1/43 (2%) patients both AF and right isthmus-dependent atrial flutter was documented. Nine of 35 (26%) patients without recurrent AF were still using antiarrhythmic drug therapy.

Discussion

The current study reports on the results of acute PVI using the second-generation 28mm CB. The study found that 1) the incidence of CB-induced ETL is 12%, 2) there is a statistically significant correlation between endoluminal esophageal temperature and the incidence of ETL, and 3) a suggested esophageal temperature cut-off of +10°C may prevent the occurrence of ETL demonstrating a sensitivity of 100% and a specificity of 93%.

The first generation CB was initially developed as a single-shot device, which should overcome limitations of conventional RFC based PVI. It is easy to handle, effective and safe. The over-the-wire system permits safe access to the respective PV. Acute and long-term results
are comparable to RFC based procedures. The incidence of procedure-related complications such as ETL is favorable for the 28mm CB when compared to the 23mm device. The zone of optimal cooling in the first-generation CB is a ring around the equator of the balloon providing less effective cooling along the distal pole. However, depending on the individual PV anatomy and PV size this cooling characteristic eventually demanded different ablation techniques such as the “cross-talk” for successful PVI or even RF touch-up had to be performed. The second-generation CB was modified to overcome these limitations by incorporating an improved refrigerant injection system. It uses eight injection jets at a more distal position of the balloon shaft and thus provides homogeneous cooling of the complete distal balloon-hemisphere. This improved cooling results in an impressive ice cap formation of the distal CB-pole (figure 3). A recently published case-report even described a remaining ice cap after deflation of the CB at the end of the freeze cycle. The massive and homogeneous ice formation allows for an effective cooling of variable PV diameters. Even smaller PVs in which isolation could be challenging when using the first-generation CB can be effectively treated with the modified device. The previously described “cross-talk” phenomenon which was occurring in a high percentage of procedures when treating the left-sided PVs due to ineffective freezing of the inferior portion of the LSPV is rare when using the second-generation CB since even a non-coaxial position of the balloon will result in homogeneous cooling of the complete PV circumference. Consequently, in the current study 170/192 (89%, Table 1) PVs were successfully isolated with the first CB-freeze. No RF touch-up was necessary in any PV. This improved device efficacy in combination with a shorter freezing duration of 240 sec. per application further reduces procedure times.

However, increased efficacy may result in greater collateral damage to non-cardiac structures. The incidence of ablation-related ETL has been previously investigated and published
for different ablation-systems and different energy-sources: up to 18% for RFC-based PVI \(^8,9\), 18% for endoscopic PVI utilizing laser-energy\(^17\), and between 0% to 18% for cryothermal energy using the first-generation CB, depending on balloon-size utilized.\(^4,5\) For the first-generation CB an atrio-esophageal fistula was recently reported.\(^6\) However, the incidence of ablation-related ETL using the second-generation CB was unknown. As discussed in one of our previous studies we could not detect any ETL when using the first-generation 28mm CB.\(^4\) In the current study an identical ablation approach and endoscopic follow-up were performed. However, using the second-generation CB the cryo-freeze duration was reduced from 300 sec. to 240 sec. But despite that the incidence of ETL significantly increased to 12 %. All patients were completely asymptomatic and all lesions resolved upon repeat endoscopy under treatment with pantoprazol twice daily. The critical absolute esophageal temperature predictive for occurrence of ETL in our patient cohort was \(\leq 2.9^\circ C\). In all patients with ETL minimal esophageal temperatures of \(\leq 2.9^\circ C\) were measured during at least one cryo-application either along the LIPV or the RIPV. None of the patients with a minimal endoluminal esophageal temperature in any PV of \(\geq 3.0^\circ C\) developed ETL. An endoluminal esophageal temperature of \(3^\circ C\) as a cut-off value predictive for occurrence of ETL has a sensitivity of 100% and a specificity of 100%. However, based on our experience esophageal temperatures may further drop for up to \(4^\circ C\) after cessation of cryo-application. To have a safety margin we therefore recommend an esophageal temperature cut-off of \(10^\circ C\) (sensitivity 100%, specificity 93%). The total number of cryoenergy applications one could have abandoned early adhering to the defined temperature cut-off of \(10^\circ C\) is 0 for RSPVs, 1 for RIPVs, 1 for LSPVs, 12 for LIPVs (8 patients) and 2 for LCPVs (1 patient). However, the cut-off temperature of \(10^\circ C\) may only be reached at the end of the respective freezing cycle, resulting in a significant number of already successfully isolated PVs without the need for
additional cryoenergy application. In case of non-isolation, a different balloon position should be attempted. Alternatively, a second freezing cycle could be applied adhering to the defined cut-off temperature. In summary, additional studies are needed to evaluate the impact of a predefined esophageal temperature cut-off.

Mechanical damage to the esophagus caused by manipulation of the temperature probe cannot be ruled out with certainty. However, all esophageal lesions were detected in patients with low esophageal temperatures and not in patients without a significant endoluminal drop in esophageal temperature. Furthermore, all esophageal lesions abutted the posterior LA wall, implying thermal rather than mechanical injury.

Due to the close proximity of the right-sided PN and the right-sided PVs, PN-palsy is a characteristic complication of CB-based PVI. Using the first-generation 23mm CB an incidence of PN-palsy of 12.4% was described, as compared to 3.5% using the 28mm CB. In the current study no 3D-reconstruction of the left atrium and the pulmonary veins with pace-identification of the course of the PN was performed. However, in order to stay as antral as possible and as far away from the PN as possible during cryoablation of the septal PVs we only use the 28mm CB. In addition the PN is continuously stimulated during ablation of the septal PVs. In case of loss of PN capture the energy application is immediately stopped. However, PN-palsy occurred in 1/50 (2%) patients during ablation of a RIPV and was persistent during the procedure. Upon 2-month follow-up the patient symptoms had improved, while repeat fluoroscopic evaluation is currently pending. In another 1/50 (2%) patients hypomobility of the diaphragm occurred during procedure although permanent pacing and capture of the right-sided PN was obtained. We cannot explain the mechanism. However, the hypomobility of the diaphragm was still present 2 days post ablation. No pericardial effusion or tamponade and no severe groin-complications occurred.
in our study population.

In the current study double TP was performed in case we had to switch from the endoluminal spiral catheter to a stiff wire due to insufficient mechanical support. In this case, the second TP was used for a standard spiral catheter to check for PVI after cryo-application. However, in our experience the endoluminal spiral catheter provides sufficient mechanical support for most PVs and we currently perform CB-based procedures with a single TS.

The improved efficacy of the second-generation CB may justify further reduction in the freeze cycle duration or abandonment of an additional “safety” freeze cycle after successful PVI. Shortening the cryo-energy application time will result in shorter procedure times and may further contribute to reduce complications. This hypothesis needs to be evaluated in future studies.

Limitations

The current study focused on acute success rates and peri- and postprocedural complications when using the second-generation 28mm CB. No comparison-group using the first-generation CB or another energy source is included. However, the incidence and quality of esophageal thermal injury for the first-generation CB as well as for other ablation systems and energy sources has been investigated and described in detail in previous publications from our laboratory.4-10,17 Our temperature unit measuring the endoluminal esophageal temperature does not store temperature-over-time curves. Consequently only the minimal esophageal temperature is provided. Although extreme caution was undertaken to position the temperature probe at the level of and in closest proximity to the CB during ablation, failure to measure the true lowest esophageal temperature cannot be excluded.

The procedures were performed in an electrophysiology laboratory equipped only with a
monoplane fluoroscopy system. During ablation of the septal PVs only the RAO 30°-projection and during ablation of the lateral PVs only the LAO 40°-projection were used. Consequently, the exact anatomical relationship between the esophagus and the target PV was not assessed.

Conclusions

As compared to the first-generation CB the incidence of ETL increased to 12 % when using the second-generation 28mm CB. ETL only occurred if the intraluminal esophageal temperature was ≤2.9°C. All ETL resolved completely upon repeat EGD.

Conflict of Interest Disclosures: KH Kuck received a research grant and speaker's honoraria from Medtronic. A Metzner and E Wisser received speaker's honoraria from Medtronic. All others have none.

References:


Table 1: Ablation results

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<th>RIPV</th>
<th>LSPV</th>
<th>LIPV</th>
<th>LCPV</th>
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<td>no. of PVs (n)</td>
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<td>50</td>
<td>42</td>
<td>42</td>
<td>8</td>
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<td>Isolated PVs, n (%)</td>
<td>50/50 (100)</td>
<td>49/50 (98)</td>
<td>42/42 (100)</td>
<td>42/42 (100)</td>
<td>8/8 (100)</td>
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<td>Isolation with first Cryo-appl. n (%)</td>
<td>46/50 (92)</td>
<td>41/50 (82)</td>
<td>37/42 (88)</td>
<td>42/42 (100)</td>
<td>4/8 (50)</td>
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<td>No. of Cryo-application until PVI, mean±SD</td>
<td>1.1±0.5</td>
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<td>Minimal balloon temperature, median (q1-q3) (°C)</td>
<td>-51</td>
<td>-47</td>
<td>-51</td>
<td>-48</td>
<td>-54</td>
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<td>PV = Pulmonary Vein; PVI = PV Isolation; RSPV = Right Superior PV; RIPV = Right Inferior PV; LSPV = Left Superior PV; LIPV = Left Inferior PV; LCPV = Left Common PV</td>
<td></td>
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Table 2: Endoluminal Esophageal Temperatures

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<tr>
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<td>Minimal esophageal temp., median (q1-q3) (°C)</td>
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<td>Lowest esophageal temp. (°C)</td>
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<td>2.9</td>
<td>5.9</td>
<td>-14.0</td>
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<td>No. of applications with esophageal temp. &lt;0°C, n</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6</td>
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PV = Pulmonary Vein; RSPV = Right Superior PV; RIPV = Right Inferior PV; LSPV = Left Superior PV; LIPV = Left Inferior PV; LCPV = Left Common PV
**Table 3: Procedural characteristics of patients with ablation-related esophageal thermal injury**

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<th>Quality of lesion</th>
<th>Pat. #10</th>
<th>Pat. #14</th>
<th>Pat. #21</th>
<th>Pat. #23</th>
<th>Pat. #36</th>
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<td>Superficial thermal lesion</td>
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</tr>
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</table>

**RSPV:**

| No. of appl. | 2 | 2 | 2 | 2 | 2 | 2 |
| Minimal balloon temp. [°C] | -57 | -65 | -54 | -52 | -47 | -53 |
| Minimal esophageal temp. [°C] | 34.8 | 36.5 | 35.9 | 36.3 | 32.9 | 35.6 |

**RIPV:**

| No. of appl., mean±SD | 2 | 4 | 4 | 2 | 2 | 2 |
| Minimal balloon temp. [°C] | -52 | -64 | -40 | -53 | -47 | -48 |
| Minimal esophageal temp. [°C] | 34.6 | 36.3 | 35.9 | 36.3 | 32.9 | 35.9 |

**LSPV:**

| No. of appl., mean±SD | 2 | 2 | 2 | 2 | 2 | 2 |
| Minimal balloon temp. [°C] | -50 | -56 | -59 | -63 | -57 | -57 |
| Minimal esophageal temp. [°C] | 24.9 | 25.5 | 34 | 32.4 | 34.4 | 27.8 |

**LIPV:**

| No. of appl., mean±SD | 2 | 2 | 2 | 2 | 2 | 2 |
| Minimal balloon temp. [°C] | -61 | -51 | -54 | -52 | -59 | -46 |
| Minimal esophageal temp. [°C] | -2.8 | -14 | -1.5 | -11.7 | 35.3 | 3.8 |
Figure Legends:

**Figure 1**: Correlation between incidence of esophageal thermal lesions and minimal Cryoballoon temperature. PV = Pulmonary Vein; RSPV = Right Superior PV; RIPV = Right Inferior PV; LSPV = Left Superior PV; LIPV = Left Inferior PV; LCPV = Left Common PV

**Figure 2**: Correlation between incidence of esophageal thermal lesions and lowest esophageal temperature. LET = Lowest esophageal temperature; PV = Pulmonary Vein; RSPV = Right Superior PV; RIPV = Right Inferior PV; LSPV = Left Superior PV; LIPV = Left Inferior PV; LCPV = Left Common PV

**Figure 3**: The second-generation Cryoballoon provides homogeneous cooling of the complete northern balloon-hemisphere whereas the first-generation Cryoballoon is characterized by an anular equatorial cooling zone.

**Figure 4**: Esophageal ulceration in patient #10 two days post pulmonary vein isolation using the second-generation 28mm Cryoballoon. Lowest endoluminal esophageal temperature was -2.8°C during cryo-application along the left inferior pulmonary vein.
Increased Incidence of Esophageal Thermal Lesions using the Second-Generation 28mm Cryoballoon

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