Non-Thermal Cardiac Catheter Ablation Using Photodynamic Therapy

Running title: Kimura et al.; Photodynamic therapy-mediated catheter ablation

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Abstract

**Background** - Radiofrequency (RF) ablation has limitations, largely related to creation of lesions by heating. We herein report the first non-thermal ablation by applying photodynamic therapy (PDT) to cardiac tissues using a custom-made deflectable laser catheter. The present study investigated the feasibility of PDT for cavo-tricuspid isthmus (CTI) ablation in a canine model.

**Methods and Results** - We evaluated the pharmacokinetic profiles of 17 canines following administration of a photosensitizer (talaporfin sodium) by various protocols. We succeeded in maintaining the photosensitizer concentration at a level in excess of the clinically effective dose for humans. Using a 4-polar 7-French deflectable laser catheter, we performed PDT-mediated CTI ablation in 8 canines. PDT caused oxidative injury only to the irradiated area and successfully produced a persistent electrical conduction block. No acute, gross changes such as edematous degeneration, thrombus formation, steam pops, or traumatic injury were observed after irradiation. HE staining of tissues samples also showed well-preserved endothelial layers. Testing of the blood samples taken before and after the procedure revealed no remarkable changes. Lesion size at 2 weeks after the procedure and the temperature data collected during irradiation were compared between the PDT and irrigated RF ablation procedures. A ventricle cross-section revealed a solid PDT lesion, which was as deep as an RF lesion. In addition, endocardial, surficial, and intramural temperature monitoring during the PDT irradiation clearly demonstrated the non-thermal nature of the ablation technique.

**Conclusions** - Non-thermal PDT-mediated catheter ablation is a potentially novel treatment for cardiac arrhythmias.

**Key words**: ablation, atrial flutter, photodynamic therapy, talaporfin sodium
Introduction

Catheter ablation using radiofrequency (RF) energy is an established therapy for cardiac arrhythmias that provides an alternative to the lifelong use of anti-arrhythmia medications. However, the RF ablation of cardiac tissue has several drawbacks related to the mechanism of action being the local generation of heat, occasionally resulting in complications such as local tissue edema\(^1\), thrombus formation\(^2\), and steam pops\(^3\).

Photodynamic therapy (PDT) is a novel, non-thermal ablation method that is not subject to the same limitations encountered with RF energy. PDT is a minimally invasive phototherapy involving application of a photosensitizer that is excited by light to injure targeted cells by promoting the production of highly cytotoxic singlet oxygen molecules and other reactive oxygen species (ROS)\(^4\). The subsequent PDT-induced cell death is restricted to the irradiated area, and systemic effects are negligible given the relatively short half-life of singlet oxygen\(^5\). This method is already used clinically in Japan to treat lung cancers, gastric cancers, and age-related macular degeneration.

In view of these positive attributes of PDT, we developed a custom-made deflectable laser catheter for applying non-thermal PDT to cardiac tissues to explore the feasibility of treating cardiac arrhythmias in a canine model. We chose to first apply PDT for cavo-tricuspid isthmus (CTI) ablation as a classic method established to treat atrial flutter\(^6\). We evaluated the optimal administration route and dose of the photosensitizer, the local temperature changes that occurred during irradiation, the establishment of a conduction block at the CTI, and the complications.
Methods

All of the experimental protocols were approved by the institutional ethics committee.

Photosensitizer

Talaporfin sodium (Laserphyrin™, Meiji Seika Pharma Company Limited, Tokyo, Japan) was used as the photosensitizer. This compound is a second-generation photosensitizer approved by the Japanese government, and its efficacy and associated risks have been evaluated in several clinical studies. The photosensitizer is administered several hours or days prior to irradiation when used in cancer treatment, allowing the compound to accumulate in the tumor tissue. However, for PDT application in cardiac catheter ablation, the talaporfin sodium was distributed in a serum albumin-conjugated form via capillary vessels to the vicinity of the cardiomyocytes. Such distribution actually becomes a determinant of the efficacy of so-called “extracellular PDT” given that the photosensitizer does not accumulate in cardiomyocytes. We therefore monitored the concentration of photosensitizer in the blood samples using a validated high performance liquid chromatography (HPLC) method. According to a previous pharmacokinetic report, the concentration of the photosensitizer remained constant at approximately 20-30 μg/ml during the 4-6 hours after an administration of 1.0 mg/kg to humans with the potential adverse effects listed as cutaneous photosensitivity, coughing, increased sputum, fever, and liver dysfunction.

We aimed to reproduce this human blood concentration in our canine model by evaluating the pharmacokinetic profiles of 17 canines after administering the photosensitizer by various protocols. Doses of 10 mg/kg (6 animals), 7.5 mg/kg (6 animals), 5 mg/kg (4 animals), and 2.5 mg/kg (1 animal) were administered by bolus infusion, based on unpublished data. The resulting
data were used to determine the appropriate photosensitizer administration protocol for PDT ablation in our canine model.

**Laser catheter**

We used a newly developed laser generator that can produce red laser light with a wavelength of 663 nm (Optical Fuel™, Sony Company Limited, Tokyo, Japan) to excite the photosensitizer. We developed a 4-polar 7-French deflectable ablation catheter with a 20-mm bending radius (Figure 1b-d). The catheter was attached to the laser generator, and the laser light was delivered through a silica optical fiber to the distal tip of the catheter, with an output diameter of 1.4 mm.

**Ablation procedure**

A total of 8 canines weighing 20.3 ± 1.4 kg were sedated by infusion of 0.5 mg/kg pentobarbital. Canines in the supine position were intubated and ventilated with room air using a constant-volume cycled respirator (Model SN-480-3, Shinano Incorporated, Tokyo, Japan). The general anesthesia was maintained during the procedure using 1.5% halothane. A forefoot was used to deliver normal saline and photosensitizer. Blood pressure monitoring, electrocardiography, and pulse oximetry were performed during the procedure. An 8-French sheath (Terumo Incorporated, Tokyo, Japan) was introduced via the jugular vein, and a SR0 Swartz™ sheath (St. Jude Medical Incorporated, St. Paul, MN, USA) was introduced via the right femoral vein. Right atriography was performed to evaluate the anatomy of the isthmus (Figure 2a, b). A 10-polar electrode lumen catheter or a 20-polar electrode deflectable catheter (St. Jude Medical) was then introduced into the coronary sinus, and contrast medium was injected into the electrode lumen to ensure that it was securely inserted and to reveal the position
of the ostium (Figure 2c). A custom-made 4-polar 7-French deflectable laser catheter was placed at the isthmus and manipulated as for the RF ablation procedure and reported in previous studies. Because our previous study showed that a total of 300 J/cm² was required to obtain the acute conduction block in a porcine model, we set the irradiance to 10 W/cm² and the duration of each irradiation to 30 sec by a point-by-point fashion to prove the nature of non-thermal ablation. According to previous reports, intercaval and connected transverse lesions were required to ensure the establishment of a CTI conduction block in the canine atrial flutter ablation model. We therefore added a posterior wall ablation if the expected conduction delay was not evident after CTI ablation. Differential pacing was also performed to confirm the bidirectional conduction block. Four skilled physicians performed the PDT ablations to additionally evaluate the versatility of this procedure.

**Evaluation of the PDT-mediated ablation**

In the acute phase, vital signs were monitored throughout the procedure and blood sampling was performed prior to and following each procedure to measure biomarkers (SRL, Incorporated, Tokyo, Japan). A total of three canines were sacrificed immediately following the procedure to evaluate acute-phase gross changes such as edematous degeneration, thrombus formation, and traumatic injury in HE-stained ablated tissues.

For the chronic-phase evaluation, four canines were sacrificed 2 weeks after the procedure, and an additional animal was sacrificed 1 month after the ablation. Before sacrifice, blood sampling and an electrophysiological study were performed to confirm the chronic conduction block at the CTI. The pathology of the excised heart was evaluated by AZAN
Temperature monitoring

To demonstrate the non-thermal nature of the ablation technique, we used SensiTherm™, Therapy™ dual-8™ ablation catheters (St. Jude Medical), an infrared thermal camera (Avio TVS-500; Nippon Avionics, Limited, Tokyo, Japan), and a thermocouple wire (K-type, Omega Engineering Incorporated, Stamford, USA) mounted on the tip of the catheter in procedures performed on four canines to monitor the endocardial, surficial, and intramural temperature increases during irradiation. In the endocardial monitor, the SensiTherm™ probe was introduced via the jugular vein through a 10-French sheath, while the Therapy™ catheter and the PDT catheter were introduced via the left femoral vein and the right femoral vein, respectively. The PDT catheter was then placed in direct contact with the SensiTherm™ probe and the Therapy™ catheter (Figure 2d), and the temperature change resulting from a 30-second, 10-W/cm² irradiation applied prior to and following photosensitizer administration was monitored. The surficial temperature change was monitored by the PDT catheter and an infrared thermal camera via a median sternotomy. The intramural temperature was monitored by inserting the 21G hypodermic needle thermocouple probe (HYP2-21-1-1/2-K-G-48-OST-M, Omega Engineering) to depths of 3 mm and 7 mm into the thigh muscle during a 30-second, 10-W/cm² irradiation. We also monitored the temperature change using a Safire BLU™ (St. Jude Medical)-irrigated ablation catheter (35 W for 30 seconds with a 50°C cut-off under 27 ml/min of saline irrigation). Lesion size at 2 weeks after the procedure and the temperature data collected during irradiation were compared between the PDT and RF ablation procedures. During the CTI ablation, the
SensiTherm™ probe was also introduced into the esophagus to monitor the temperature of adjacent organs during the procedure (Figure 2e, f).

**Statistical methods**

Continuous variables were expressed as the mean ± standard deviation, and the Wilcoxon signed-rank test was used to compare the numerical data. A probability value of < 0.05 was considered statistically significant.

**Results**

**Pharmacokinetics of the photosensitizer**

The concentration profile of talaporfin sodium over time was measured under various infusion protocols by HPLC as shown in Figure 1a. We succeeded in maintaining a concentration of 30.6 ± 3.6 μg/ml during the entire ablation procedure by administering a bolus infusion of 2.5 mg/kg in conjunction with a continuous infusion of 2.7 ± 0.5 mg/kg/h. None of the tested bolus-alone protocols were able to maintain the photosensitizer concentration at a level in excess of 20 μg/ml, which is the clinically effective dose for humans, for more than 30 minutes. We therefore used the infusion protocol for further PDT ablations in the canine model.

**Cavo-tricuspid isthmus ablation**

Using our custom-made 4-polar 7-French deflectable laser catheter, 8 canines were subjected to CTI ablation using the catheter configuration shown in Figure 2a-f. The vital signs were stable during the procedure. The oximetry measurements decreased to 94.7 ± 0.8% of baseline after photosensitizer administration; however, the actual oxygen saturation has previously been
reported to be unchanged\textsuperscript{15}. The conduction block was confirmed in all of the canines after 16 ± 7 applications of irradiation with a total laser energy of 94.7 ± 37.0 J. A representative case is shown in Figure 2g. Under pacing from the coronary sinus ostium, the conduction time to the ablation catheter placed on the lateral side of the CTI was 12 ± 4 msec prior to ablation, and this increased to 76 ± 5 msec following the CTI block. In two of the animals, the local potential delay remained only 30 and 40 msec following the initial ablation, respectively, and the block was only obtained following an additional ablation at the posterior wall\textsuperscript{13}. Differential pacing\textsuperscript{14} was successfully performed to demonstrate the bidirectional block of the isthmus in all canines.

Testing of the blood samples taken before and after the procedure revealed no remarkable changes in the complete blood cell count (white blood cell count, before vs. after: 6328 ± 2250 vs. 5175 ± 2939 cells/\mu l, \( P = 0.141 \)); hemoglobin level: 11.4 ± 0.8 vs. 12.4 ± 0.4 g/dl, \( P = 0.083 \); platelet count: 194 ± 36 × 10\(^3\) vs. 234 ± 50 × 10\(^3\) cells/\mu l, \( P = 0.068 \)), coagulation and fibrinolysis status (activated partial thromboplastin time: 20.3 ± 6.7 vs. 22.2 ± 3.7 sec, \( P = 0.257 \)); fibrinogen level: 299 ± 72.9 vs. 249 ± 53.7 mg/dl, \( P = 0.144 \)), kidney function (creatinine: 0.8 ± 0.1 vs. 0.7 ± 0.1 mg/dl, \( P = 0.173 \)), liver function (aspartate amino transferase: 23.8 ± 9.3 vs. 23.3 ± 8 IU/l, \( P = 0.524 \)), creatine kinase level (91.8 ± 22.9 vs. 118.7 ± 20.4 IU/l, \( P = 0.173 \)), lactate dehydrogenase level (47.2 ± 16.1 vs. 49.3 ± 4.4 IU/l, \( P = 0.463 \)), C-reactive protein level (0 ± 0 vs. 0 ± 0 mg/dl, \( P = 0.157 \)), or haptoglobin level (69.5 ± 27.2 vs. 73.3 ± 29.3 mg/dl, \( P = 0.345 \)). In addition, no acute, gross changes such as edematous degeneration, thrombus formation, or traumatic injury were observed after irradiation in the three canines sacrificed immediately following the treatment. HE staining of tissues samples taken immediately after irradiation.
showed well-preserved endothelial layers, suggesting an absence of acute vascular injury (Figure 3a).

For our evaluation of the chronic phase, repeated electrophysiological measurements made prior to sacrifice of the animals revealed no reconnection of the isthmus block. The blood samples collected prior to and 2 weeks following the procedure showed no remarkable changes due to PDT ablation; similar results were obtained for the pre- and post-ablation samples with respect to creatine kinase level (91.8 ± 22.9 vs. 176.0 ± 104.7 IU/l, P = 0.180), lactate dehydrogenase level (47.2 ± 16.1 vs. 58.5 ± 12.0 IU/l, P = 0.180), and C-reactive protein level (0 ± 0 vs. 0 ± 0 mg/dl, P = 1.000). The extracted hearts showed no evidence of macroscopic injury such as thrombus formation or pericarditis; however, the characteristic linear, brownish scar lesion was identified at the CTI in all of the canines 2 weeks after the procedure (Figure 3b). Vertical sections of the isthmus were subjected to pathological examination with AZAN staining, which revealed the transmural scar lesion along the isthmus 2 weeks post-ablation (Figure 3c). The transmural lesion was replaced by fibrous tissue 1 month after the procedure (Figure 3d). The average lesion size in the isthmus was 22.4 ± 4.8 mm in length and 6.9 ± 1.7 mm in depth.

Proof of non-thermal ablation

The temperature data are shown in Table 1. The surface monitoring revealed a temperature increase (Δ°C) at the PDT catheter tip of 4.8 ± 0.5°C when PDT was applied at 10 W/cm² for 30 seconds. The Δ°C of the irrigated RF catheter tip under 35 W for 30 seconds with a 50°C cut-off and 27 ml/min of saline irrigation was 23.3 ± 8.9°C, whereas the Δ°C for the pre-installed thermometer inside of the tip was 9.3 ± 4.3°C. The Δ°C as detected by the infrared thermal
camera was only 3.0 ± 1.6°C during PDT, compared with 34.8 ± 8.5°C during RF ablation, which caused a steam pop that produced a very large hole in the right ventricle (Figure 3g).

There was no surficial heat injury such as edema, thrombus formation, or steam pops caused by the laser irradiation without a photosensitizer (Figure 3e) or by PDT (Figure 3f). The endocardial monitoring revealed a Δ°C at the PDT tip of only 0.9 ± 0.1°C, and no temperature increase (< 0.1°C) was detected by either an RF ablation catheter or an esophageal thermometer placed next to the PDT catheter. In the irrigated RF ablation catheter, Δ°C values for the tip, the monitor RF catheter next to the ablation catheter, and the esophageal thermometer adjacent to the ablation site were 7.7 ± 2.2°C, 7.9 ± 1.2°C, and 6.7 ± 2.3°C, respectively. The intramural monitoring revealed only 2.1 ± 0.9°C and 1.8 ± 1.0°C of temperature increase at 3 mm and 7 mm into the thigh muscle, respectively. During the PDT-mediated CTI ablation, there was no temperature increase (< 0.1°C) as measured using an esophageal thermometer placed in the esophagus. A ventricle cross section revealed a solid PDT lesion with a depth of 7 mm (Figure 3i), which was as deep as an RF lesion (Figure 3j), and no heat injury was caused by the irradiation in the absence of photosensitizer (Figure 3h).

**Discussion**

Herein we present the first study of non-thermal PDT ablation of cardiac tissues using a custom-made deflectable laser catheter in a canine model. Acute-phase and chronic-phase results with the PDT were compared with animals undergoing RF ablation. Due to the non-thermal nature of PDT-mediated ablation, lesion creation without an additional cooling system induced
no edema, thrombus formation, or steam pops. A comparison between the features of RF ablation and PDT is shown in Table 2. It should be noted that irradiation-induced heat was generated as a consequence of laser light diffusion at the lens tip due to optical factors. In our previous report, a successful PDT-mediated conduction block using a simple silica optical fiber with 208 J/cm² of irradiation induced a maximum temperature increase of 12.8°C measured by an infrared thermal camera. Because infrared thermal cameras are subject to errors due to the use of red laser light, we used various temperature monitors in this study and developed a new PDT laser catheter, which also enabled us to monitor backscattering of the laser and avoid blood charring due to any sudden temperature increase. The present study clearly demonstrated that lesion induction by PDT was not mediated by heat.

PDT ablation can also be safely applied in blood-flow-rich sites given that the endothelial layer was intact in our acute evaluation and that intracoronary PDT was also reported to reduce intimal proliferation. Even for sites with high impedance, which often leads to unsuccessful treatment with RF catheter ablation, PDT ablation might be more easily applied to the target area and thus produce the best treatment outcome. The real clinical limitation of RF ablation may be the maximum lesion size. We limited the irradiance to 10 W/cm² with the non-thermal proof as a priority, deeper lesions should be possible by establishing more appropriate conditions. Because the size of the PDT-mediated lesion was governed by the degree of light penetration, increasing the irradiance output might be a solution for achieving depth of penetration, although the limitation of light penetration could also become a disadvantage. In addition, lesion size could potentially be expanded because the tissue injury is caused by a combination of necrosis and
apoptosis. Necrosis is caused immediately by photosensitizers in the plasma membrane during light exposure\textsuperscript{19}, whereas delayed apoptosis results from irradiation-induced activation of various messenger proteins in a mechanism that is strongly dose- and time-dependent\textsuperscript{20}. Previous cancer-related studies showed a time-dependent increase in lesion size associated with apoptosis in a rat glioma model\textsuperscript{21}. How the conduction block achieves acute efficacy during irradiation\textsuperscript{22} is not yet clear, because the precise mechanism of PDT-mediated tissue injury has not been fully elucidated even in the field of cancer research. Further evaluation of the optimal conditions for maximizing the acute tissue injury and the lesion size is needed.

One disadvantage of PDT ablation is the longer time required compared with RF ablation. PDT catheter ablation in the canine CTI model required $8 \pm 4$ min of irradiation time with $16 \pm 7$ applications in this experiment, whereas the conventional RF catheter required $14.7 \pm 5.2$ min energy delivery time with $8.9 \pm 7.2$ applications in human\textsuperscript{23}, and $3-4.5$ min of $25$ W RF energy delivery in a canine atrial flutter model with a surgical posterior line in advance\textsuperscript{13}. Systemic adverse effects are also potential disadvantages of PDT ablation.

The study has some limitations. The number of animals was small and may not have been sufficient to fully characterize all aspects of the PDT procedure. The follow-up period was also too brief to identify any long-term effects of PDT. The potential effects on adjoining organs in the very late phase were not evaluated. The underlying differences between species are generally potential limitations of canine model experiments. As our laser catheter was only capable of forward irradiation, it was also occasionally difficult to ablate the site where the distal tip recorded the most appropriate potential.
Taken together, our results demonstrated that non-thermal PDT-induced cardiac catheter ablation holds potential as a novel treatment for arrhythmia.

**Conclusions**

Non-thermal PDT-mediated catheter ablation is a potentially novel treatment for cardiac arrhythmias.

**Conflict of Interest Disclosures:** None.

**References:**


**Table 1:** Proof of non-thermal PDT ablation by temperature monitoring

<table>
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<th>Surface Monitor</th>
<th>Endocardial Monitor</th>
<th>Intramural Monitor</th>
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<tr>
<td><strong>Type</strong></td>
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<td>PDT</td>
<td>RF</td>
</tr>
<tr>
<td><strong>Power</strong></td>
<td>10 W/cm²</td>
<td>10 W/cm²</td>
<td>35 W</td>
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<tr>
<td><strong>Irradiation (sec)</strong></td>
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<td>30</td>
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<td><strong>Ablation catheter tip</strong></td>
<td>(Δ°C) 5.2 ± 0.5</td>
<td>4.8 ± 0.5</td>
<td>23.3 ± 8.9</td>
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<td><strong>RF catheter next to ablation catheter</strong></td>
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<td><strong>Infrared thermal camera</strong></td>
<td>(Δ°C) 3.7 ± 0.1</td>
<td>3.0 ± 1.6</td>
<td>34.8 ± 8.5</td>
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<tr>
<td><strong>Steam pop</strong></td>
<td>—</td>
<td>—</td>
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Table 2: Advantages and disadvantages of PDT ablation versus RF ablation

<table>
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<th>RF</th>
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<td>Heat</td>
<td>Independent</td>
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<td>Cooling</td>
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<td>Required</td>
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<td>Edema</td>
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</tr>
<tr>
<td>Steam pop</td>
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<td>Local blood flow</td>
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<td>High impedance sites</td>
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<td>Lesion Size</td>
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<td>Governed by temperature</td>
<td>Light penetration limitations</td>
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<td>Potential late expansion of the lesion</td>
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<td>Photosensitizer</td>
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<td>No</td>
<td>Risk of systemic adverse effects</td>
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Figure Legends:

**Figure 1**: Photosensitizer metabolism and configuration of the laser catheter. A. The concentration profile of talaporfin sodium over time was measured under various infusion protocols by high performance liquid chromatography. B. We developed a custom-made 4-polar 7-French deflectable ablation catheter. C. Laser light was emitted from the distal tip and 4-polar electrodes were able to record intracardial potentials. D. Schematic diagram of the catheter structure.

**Figure 2**: Fluoroscopy images and cavo-tricuspid isthmus (CTI) conduction block. A, B. Right atriography (RAG) in the right anterior oblique (RAO) (a) and left anterior oblique (LAO) (b) views. C. Imaging of the coronary sinus was performed by venography using a 10-polar electrode lumen catheter. D. An esophageal thermometer (SensiTherm™) and a radiofrequency ablation catheter (Therapy™) were placed next to the ablation site to monitor thermal changes. E, F. Representative images captured during CTI ablation in the RAO (e) and LAO (f) views. The SensiTherm™ probe was inserted into the esophagus. G. Surface electrocardiogram of the lead I, II, and V₆, and potentials of the tricuspid annulus (TA) are shown together with data from the ablation catheter (ab) for a typical CTI ablation. Following the PDT ablation (Post), the sequence of the TA was changed compared to the baseline data (Pre). The potential of the ablation catheter was delayed from 18 msec to 80 msec, suggesting that a CTI block was successfully created (black arrows). Ab: ablation; Ab uni: unipolar; CS: coronary sinus; d: distal; ESO: esophageal thermometer; IVC: inferior vena cava; p: proximal; RAA: right atrial appendage; RF: radiofrequency ablation catheter; RV: right ventricle
Figure 3: Pathological evaluation. A. Endothelial layer from an animal that was sacrificed immediately after irradiation showing good preservation by HE staining. B. The pathological evaluation performed 2 weeks after ablation revealed no gross damage. A linear, brownish scar lesion was identified at the isthmus (white arrows). C. AZAN staining of a vertical tissue section through the isthmus revealed a transmural lesion along the isthmus (black and white arrows). D. A month after the procedure, the transmural scar lesion was replaced by a fibrotic scar (black arrows). E–G. Acute macroscopic changes to the ventricle were compared between those induced by laser irradiation before (Laser only) and after (PDT, 10 W/cm² 30 sec) photosensitizer infusion, and those induced by radiofrequency ablation (RF, 35 W for 30 sec). H–J. Cross sections taken 2 weeks after Laser only, PDT, or RF ablation were compared. The black and white scale bar shows 1 cm. Each lesion is shown encircled by white and black arrows.

CS: coronary sinus; IVC: inferior vena cava; IVS: interventricular septum; RA: right atrium; RAA: right atrial appendage; RV: right ventricle; RVFW: free wall of the right ventricle; SVC: superior vena cava; TV: tricuspid valve
Talaporfin sodium concentration (μg/ml) vs. Time (min)

- 10 mg/kg
- 7.5 mg/kg
- 5 mg/kg
- 2.5 mg/kg
- 2.5 mg/kg + DIV
E  Laser only
F  PDT 30 W/cm² 30 sec
G  RF 35 W 30 sec

Macroscopic change

Cross section
Non-Thermal Cardiac Catheter Ablation Using Photodynamic Therapy
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