Nonthermal Cardiac Catheter Ablation Using Photodynamic Therapy

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**Background**—Radiofrequency ablation has limitations, largely related to creation of lesions by heating. Here, we report the first nonthermal 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 cavotricuspid isthmus ablation in a canine model.

**Methods and Results**—We evaluated the pharmacokinetic profiles of 17 canines after 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 cavotricuspid isthmus ablation in 8 canines. PDT caused oxidative injury only to the irradiated area and successfully produced a persistent electric conduction block. No acute, gross changes such as edematous degeneration, thrombus formation, steam pops, or traumatic injury were observed after irradiation. Hematoxylin and eosin 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 radiofrequency ablation procedures. A ventricular cross-section revealed a solid PDT lesion, which was as deep as a radiofrequency lesion. In addition, endocardial, surficial, and intramural temperature monitoring during the PDT irradiation clearly demonstrated the nonthermal nature of the ablation technique.

**Conclusions**—Nonthermal PDT-mediated catheter ablation is a potentially novel treatment for cardiac arrhythmias. (Circ Arrhythm Electrophysiol. 2013;6:1025-1031.)

**Key Words:** atrial flutter ■ catheter ablation ■ photochemotherapy ■ talaporfin

Catheter ablation using radiofrequency energy is an established therapy for cardiac arrhythmias that provides an alternative to the lifelong use of antiarrhythmia medications. However, radiofrequency 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, nonthermal ablation method that is not subject to the same limitations encountered with radiofrequency 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.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 nonthermal PDT to cardiac tissues to explore the feasibility of treating cardiac arrhythmias in a canine model. We chose to first apply PDT for cavotricuspid 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.

**Clinical Perspective on p 1031**

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**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 before 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. Therefore, we monitored the concentration of photosensitizer in the blood samples using a validated high performance liquid chromatography method. According to a previous pharmacokinetic report, the concentration of the photosensitizer remained constant at ≥20 to 30 µg/mL during the 4 to 6 hours after an administration of 1.0 mg/kg to humans with the potential adverse effects listed as cutaneous photosensitivity, flushing, 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 (6 animals), 7.5 (6 animals), 5 (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–1D). 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 an SR0 Swartz sheath (St Jude Medical Incorporated, St Paul, MN) was introduced via the right femoral vein. Right atrigraphy was performed to evaluate the anatomy of the ishicus (Figure 2A and 2B). 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 radiofrequency 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 seconds by a point-by-point fashion to prove the nature of nonthermal 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. Therefore, we 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.

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 intracardiac potentials. D, Schematic diagram of the catheter structure. DIV indicates drip infusion of vein.

Evaluation of the PDT-Mediated Ablation

In the acute phase, vital signs were monitored throughout the procedure, and blood sampling was performed before and after each procedure to measure biomarkers (SRL, Incorporated, Tokyo, Japan). A total of 3 canines was euthanized immediately after the procedure to evaluate acute-phase gross changes such as edematous degeneration, thrombus formation, and traumatic injury in Hematoxylin and eosin-stained ablated tissues. For the chronic-phase evaluation, 4 canines were euthanized 2 weeks after the procedure, and an additional animal was euthanized 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 staining.

Temperature Monitoring

To demonstrate the nonthermal 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, CT) mounted on the tip of the catheter in procedures performed on 4 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, whereas the PDT 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 before and after 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 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 cutoff 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 radiofrequency 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 and 2F).

Statistical Methods
Continuous variables were expressed as the mean±SD, and the Wilcoxon signed-rank test was used to compare the numeric data. A P 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 high performance liquid chromatography 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 per hour. 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 >30 minutes. Therefore, we used the infusion protocol for further PDT ablations in the canine model.

CTI 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 through 2F. 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.15 The conduction block was confirmed in all of the canines after 16±7 applications of irradiation with a total laser energy of

Figure 2. Fluoroscopy images and cavotricuspid isthmus (CTI) conduction block. Right angiography (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 (RF) ablation catheter (Therapy) were placed next to the ablation site to monitor thermal changes. Representative images captured during CTI ablation in the RAO (E) and LAO (F) views. The SensiTherm probe was inserted into the esophagus. G, Surface ECG of the lead I, II, and aVF, and potentials of the tricuspid annulus (TA) are shown together with data from the ablation catheter (ab) for a typical CTI ablation. After the photodynamic therapy ablation (post), the sequence of the TA was changed compared with the baseline data (pre). The potential of the ablation catheter was delayed from 18 to 80 ms, suggesting that a CTI block was successfully created (black arrows). Ab indicates ablation; CS, coronary sinus; d, distal; ESO, esophageal thermometer; IVC, inferior vena cava; p, proximal; RAA, right atrial appendage; RV, right ventricle; and uni, unipolar.
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 ms before ablation, and this increased to 76±5 ms after the CTI block. In 2 of the animals, the local potential delay remained only 30 and 40 ms after the initial ablation, respectively, and the block was only obtained after an additional ablation at the posterior wall.13 Differential pacing14 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 versus after, 6328±2250 versus 5175±2939 cells/μL, P=0.141; hemoglobin level, 11.4±0.8 versus 12.4±0.4 g/dL, P=0.083; platelet count, 194±36×10³ versus 234±50×10³ cells/μL, P=0.068), coagulation and fibrinolysis status (activated partial thromboplastin time, 20.3±6.7 versus 22.2±3.7 seconds; P=0.257 and fibrinogen level, 299±72.9 versus 249±53.7 mg/dL; P=0.144), kidney function (creatinine, 0.8±0.1 versus 0.7±0.1 mg/dL; P=0.173), liver function (aspartate amino transferase, 23.8±9.3 versus 23.3±8 IU/L; P=0.524), creatine kinase level (91.8±22.9 versus 118.7±20.4 IU/L; P=0.173), lactate dehydrogenase level (47.2±16.1 versus 49.3±4.4 IU/L; P=0.463), C-reactive protein level (0±0 versus 0±0 mg/dL; P=0.157), or haptoglobin level (69.5±27.2 versus 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 3 canines euthanized immediately after the treatment. Hematoxylin and eosin 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 before sacrifice of the animals revealed no reconnection of the isthmus block. The blood samples collected before and 2 weeks after the procedure showed no remarkable changes attributable to PDT ablation; similar results were obtained for the preablation and postablation samples with respect to creatine kinase (91.8±22.9 versus 176.0±104.7 IU/L; P=0.180), lactate dehydrogenase (47.2±16.1 versus 58.5±12.0 IU/L; P=0.180), and

![Figure 3](http://circep.ahajournals.org/)

**Figure 3.** Pathological evaluation. **A**, Endothelial layer from an animal that was euthanized immediately after irradiation showing good preservation by Hematoxylin and eosin 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 (photodynamic therapy [PDT], 10 W/cm² 30 sec) photosensitizer infusion and those induced by radiofrequency (RF) ablation (35 W for 30 seconds). **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 indicates 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; and TV, tricuspid valve.
C-reactive protein levels (0±0 versus 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 postablation (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 Nonthermal Ablation

The temperature data are shown in Table 1. The surface monitoring revealed a temperature increase (\( \Delta ^\circ C \)) at the PDT catheter tip of 4.8±0.5\(^\circ C \) when PDT was applied at 10 W/cm\(^2 \) for 30 seconds. The \( \Delta ^\circ C \) of the irrigated radiofrequency catheter tip under 35 W for 30 seconds with a 50\(^\circ C \) cutoff and 27 mL/min of saline irrigation was 23.3±8.9\(^\circ C \), whereas the \( \Delta ^\circ C \) for the preinstalled thermometer inside of the tip was 9.3±4.3\(^\circ C \). The \( \Delta ^\circ C \) as detected by the infrared thermal camera was only 3.0±1.6\(^\circ C \) during PDT, compared with 34.8±8.5\(^\circ C \) during radiofrequency 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 \( \Delta ^\circ C \) at the PDT tip of only 0.9±0.1\(^\circ C \), and no temperature increase (<0.1\(^\circ C \)) was detected by either an radiofrequency ablation catheter or an esophageal thermometer placed next to the PDT catheter. In the irrigated radiofrequency ablation catheter, \( \Delta ^\circ C \) values for the tip, the monitor radiofrequency catheter next to the ablation catheter, and the esophageal thermometer adjacent to the ablation site were 7.7±2.2\(^\circ C \), 7.9±1.2\(^\circ C \), and 6.7±2.3\(^\circ C \), respectively. The intramural monitoring revealed only 2.1±0.9\(^\circ C \) and 1.8±1.0\(^\circ C \) of temperature increase at 3 and 7 mm into the thigh muscle, respectively. During the PDT-mediated CTI ablation, there was no temperature increase (<0.1\(^\circ C \)) as measured using an esophageal thermometer placed in the esophagus. A ventricular cross-section revealed a solid PDT lesion with a depth of 7 mm (Figure 3I), which was as deep as an radiofrequency lesion (Figure 3J), and no heat injury was caused by the irradiation in the absence of photosensitizer (Figure 3H).

### Discussion

Here, we present the first study of nonthermal 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 radiofrequency ablation. Because of the nonthermal nature of PDT-mediated ablation, lesion creation without an additional cooling system induced no edema, thrombus formation, or

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<th>RF</th>
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<td>Steam pop</td>
<td>-</td>
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N/A indicates not applicable; PDT, photodynamic therapy; and RF, radiofrequency.

### Table 2. Advantages and Disadvantages of PDT Ablation vs RF Ablation

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<tr>
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<td>Local blood flow</td>
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<td>No</td>
<td>Risk of systemic adverse effects</td>
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steam pops. A comparison between the features of radiofrequency 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 attributable 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.12 Because infrared thermal cameras are subject to errors attributable 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 attributable to any sudden temperature increase.16,17 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.18 Even for sites with high impedance, which often leads to unsuccessful treatment with radiofrequency 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 radiofrequency ablation may be the maximum lesion size. We limited the irradiance to 10 W/cm² with the nonthermal 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,19 whereas delayed apoptosis results from irradiation-induced activation of various messenger proteins in a mechanism that is strongly dose and time dependent.20 Previous cancer-related studies showed a time-dependent increase in lesion size associated with apoptosis in a rat glioma model.21 How the conduction block achieves acute efficacy during irradiation22 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 radiofrequency ablation. PDT catheter ablation in the canine CTI model required 8±4 minutes of irradiation time with 16±7 applications in this experiment, whereas the conventional radiofrequency catheter required 14.7±5.2 minutes energy delivery time with 8.9±7.2 applications in human,23 and 3 to 4.5 minutes of 25 W radiofrequency energy delivery in a canine atrial flutter model with a surgical posterior line in advance.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 nonthermal PDT–induced cardiac catheter ablation holds potential as a novel treatment for cardiac arrhythmias.

Conclusions
Nonthermal PDT–mediated catheter ablation is a potentially novel treatment for cardiac arrhythmias.

Disclosures
None.

References


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**CLINICAL PERSPECTIVE**

Radiofrequency (RF) energy is routinely used in catheter ablation to treat cardiac arrhythmias. However, the RF ablation of cardiac tissue has several drawbacks that stem from the fact that its mechanism of action is the local generation of heat. Photodynamic therapy (PDT) is a novel, nonthermal ablation method that is not subject to the limitations encountered with RF energy. We developed a custom-made deflectable laser catheter for applying nonthermal PDT to cavotricuspid isthmus ablation to explore the feasibility of treating cardiac arrhythmias in a canine model. PDT caused oxidative injury only to the irradiated area and successfully produced a persistent electric conduction block without edema, thrombus formation, temperature rise, or lethal complications. Various temperature monitoring successfully revealed the nonthermal nature of PDT-mediated ablation. A ventricular cross-section also revealed a solid PDT lesion as deep as an RF lesion. PDT ablation can also be safely applied in blood-flow–rich sites given that the endothelial layer is intact in our acute evaluation. 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. Although we limited the irradiance with the nonthermal proof as a priority, deeper lesions should be possible by establishing more appropriate conditions. This study first demonstrated that nonthermal PDT-induced cardiac catheter ablation holds potential as a novel treatment for arrhythmia. PDT ablation can overcome the limitations of RF ablation and is expected to become a next-generation cardiac ablation therapy.
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