Electrical superior vena cava isolation using photodynamic therapy in a canine model

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Aims
With the new era of multi-tip radiofrequency or balloon ablation catheters replacing the point-to-point ablation strategy, we aimed to determine the feasibility of a ring—laser catheter ablation technology to electrically isolate the superior vena cava (SVC) by exploring the advantages of the limitless catheter tip size possibly with the photodynamic therapy (PDT)-mediated ablation.

Methods and results
We developed a first-generation prototype of a circular-laser-mapping catheter by fitting a 7 cm plastic optical fibre onto a circular variable-loop Lasso™ mapping catheter. Following SVC venography, both the laser catheter and another ring catheter for monitoring the SVC potentials were placed at the SVC. After the systemic infusion of a photosensitizer (tala-porfin sodium), we initiated the irradiation with an output of 1 W in three canines and 0.3 W in four. The creation of electrical isolation as well as occurrence of phrenic nerve injury, sinus node injury, and SVC stenosis were evaluated before, immediately after, and 1 month after the procedure. A PDT-mediated SVC isolation was successfully performed in all seven canines. The isolation was completed with a laser irradiation of 70.4±71.4 J/cm under 30.9±5.0 μg/mL of a photosensitizer without any sinus node injury, phrenic nerve palsy, or SVC stenosis in both the acute and chronic evaluations. The minimum isolation time of 270 s was not correlated with the laser input power or the photosensitizer concentration.

Conclusion
The electrical SVC isolation was successfully and instantly achieved using the PDT laser—ring catheter without any complications.

Keywords
Superior vena cava isolation • Photodynamic therapy • Cardiac catheter ablation • Talaporfin sodium

Introduction
Photodynamic therapy (PDT) creates non-thermal tissue injury mediated by the generation of a singlet oxygen species using oxygen, a photosensitizer, and laser irradiation.1 The clinical use of PDT has already been proved in the field of cancer, including for malignant brain tumours,2 oesophageal cancer,3 and lung cancer.4 Previously, we demonstrated the effectiveness of PDT-mediated cardiac catheter ablation by using a four-polar laser-irradiating catheter in a canine model.5 Capitalizing on the non-thermal characteristic of this technology and based on the added advantage of a limitless catheter tip size, we sought to further apply the PDT ablation to the instantaneous electrical isolation of caval veins. We then evaluated the feasibility of the electrical isolation of the superior vena cava (SVC) using PDT with a newly developed circular-laser-mapping catheter.

We chose the canine SVC as a linear electrical isolation model because of its anatomical resemblance to humans. In addition, the SVC is a known source of arrhythmogenic foci, and the electrical isolation of the SVC alone is an established treatment for atrial fibrillation (AF) to reduce the incidence of recurrences.6 Furthermore, the electrical isolation of the SVC with radiofrequency (RF) catheter ablation may be accompanied by complications. For instance, the reported prevalence of phrenic nerve injury after RF catheter...
What’s new?
- We aimed to create an electrical isolation of the superior vena cava (SVC) using a ring-laser catheter ablation technology for a photodynamic therapy (PDT)-mediated ablation.
- We developed a first-generation prototype of a circular-laser-mapping catheter by fitting a plastic optical fibre onto a variable-loop circular-mapping catheter.
- The PDT-mediated SVC isolation was successfully performed in all canines without any sinus node injury, phrenic nerve palsy, or SVC stenosis during both the acute and chronic evaluations.
- Capitalizing on the non-thermal characteristic of this technology and based on the added advantage of a limitless catheter tip size, the PDT-mediated, non-thermal linear ablation may become a promising alternative ablation technology.

Methods
A total of seven canines weighing 21.7 ± 2.0 kg were used in this study. The institutional ethics committee approved all the study protocols, which conformed to the Position of the American Heart Association on Research Animal Use.

Laser catheter
The development of our prototype of a circular-laser-mapping catheter for the electrical isolation of the SVC involved attaching a plastic optical fibre (\( \varphi = 0.25 \text{ mm}, \text{ outer diameter} = 0.48 \text{ mm}, \text{ baud transmission rate} = 60%) to a variable loop Lasso\textsuperscript{TM} circular mapping catheter (Biosense Webster, Inc., Diamond Bar, CA, USA), with the aim of recording the potentials at the laser-irradiating site and obtaining contact across the entire periphery of the ablation site (Figure 1A–D). A laser with a wavelength of 663 nm (Optical Fuel\textsuperscript{TM}, Sony Company Limited, Tokyo, Japan) was used to excite the photosensitizer. The laser was irradiated uniformly from the distal 7 cm tip to cover the entire circular portion of the Lasso\textsuperscript{TM} catheter. The initial input power was set to 1 W for the first three canines, so that the input power per unit length was 0.14 W/cm, according to our previous report.\textsuperscript{5} Then, the input power was decreased by one-third to 0.3 W for the four remaining canines.

Photosensitizer
We used talaporfin sodium (Meiji Seika Pharma Company Limited, Tokyo, Japan) as a photosensitizer.\textsuperscript{11} Blood samples collected to measure the photosensitizer concentration by high-performance liquid chromatography (HPLC) were centrifuged and kept at −20°C immediately after sampling. The dosing regimen was decided according to our previous pharmacokinetic report in a canine.\textsuperscript{9} A bolus of 2.5 mg was administered at the beginning of the procedure in association with a continuous infusion at a speed of 2.93 mg/kg/h for six canines. A higher concentration was used in the remaining canine by administering a continuous dose of 3.9 mg/kg/h (Table 1, Case 6).

Ablation procedure
The canines were sedated with pentobarbital at a dose of 0.5 mL/kg, and then infused with normal saline from the foreaarm to compensate for any fluid loss. The blood pressure, electrocardiogram, and pulse oximetry (SpO\textsubscript{2}) recordings were monitored throughout the procedure. The canines were intubated and ventilated with room air (Excel 1105E, Dartex/omeda, Model SN-480-3, Shinano, Incorporated, Tokyo, Japan). The general anaesthesia was maintained by using 1.5% halothane. After isodine sterilization, both femoral veins were cut down, and a 10 Fr Swartz\textsuperscript{TM} right SR0 sheath (St Jude Medical, Incorporated, St. Paul, MN, USA) was introduced from the right femoral vein for the laser-ablation catheter. An 8 F French Swartz\textsuperscript{TM} right SR0 sheath was also introduced from the left femoral vein with the Lasso\textsuperscript{TM} catheter (Biosense Webster) to monitor the SVC potentials. After the SVC–right atrium (RA) junction was identified by SVC venography, both the ablation and mapping catheters were positioned to record the RA and SVC potentials. The mapping catheter was placed just above the ablation catheter as horizontally parallel as possible (Figure 1E and F). Once the positioning was fixed, both catheters were widened as much as possible to ensure direct and full contact with the SVC wall. The sinus node recovery time (SRT) was measured as a pre-procedural evaluation using a 30-s pacing train from the mapping catheter with a heart rate from 160 to 220 bpm incremented by 20 bpm. Any phrenic nerve capture around the entire periphery of the SVC was also confirmed before the procedure with pacing at an output of 9.9 V from each electrode of the mapping catheter.

Irradiation was initiated 15 min after the administration of the photosensitizer. Upstream phrenic nerve pacing with a cycle length of 1200 ms from the mapping catheter electrode was applied throughout the laser irradiation to monitor for any acute phrenic nerve injury.\textsuperscript{15} The termination of the irradiation was decided upon the SVC isolation. The irradiation was discontinued and reinitiated after rotating the catheter position, when the physicians decided that there was no potential delay observed for >5 min during the irradiation. Several skilled physicians carried out the procedure to minimize any interphysician variability.

Evaluation
In the acute evaluation, the SVC isolation was confirmed by the loss of both SVC potentials and dormant conduction under a rapid injection of adenosine triphosphate (ATP) 20 mg.\textsuperscript{13} The phrenic nerve capture was then confirmed, and the SRT was re-measured. The blood samples were tested for a complete blood cell count, liver function, haemolysis markers, and inflammatory markers (SRL, Incorporated, Tokyo, Japan).

In the chronic evaluation, the canines were maintained alive for 1 month for electrophysiological and microscopic evaluations. Before the intubation, the diaphragmatic movement was monitored under floroscopy and evaluated for respiratory movement. After the general anaesthesia was maintained as described above, the left jugular vein was cut down, and an 8 Fr sheath (Terumo, Inc. Tokyo, Japan) was introduced and advanced to the SVC for venography to evaluate for any stenosis.
The circular mapping catheter was placed in the SVC to confirm the maintenance of the SVC isolation. The SRT was also measured and phrenic nerve pacing was applied to confirm the lack of any phrenic nerve injury. The animals were then sacrificed, and cross-sections of the SVC were stained with a haematoxylin–eosin and Masson’s trichrome stain.

Safety demonstration for any phrenic nerve injury

Direct irradiation to the phrenic nerve during open chest surgery was performed to demonstrate the safety of avoiding any acute phrenic nerve injury in a canine. The photosensitizer (2.5 mg + 2.93 mg/kg/h) was administered under direct pacing upstream from the phrenic nerve, and direct irradiation with 10 W/cm² was applied using the 7 Fr laser catheter 5 15 min later. The irradiation was continued for 9 min and the phrenic capture was monitored.

Statistical analysis

Continuous variables are expressed as the mean ± standard deviation, and a Mann–Whitney’s U test was used to compare the numerical data.
Pearson’s correlation test and simple linear regression analysis were used. A P-value of <0.05 was considered to indicate statistical significance.

**Results**

**Acute electrophysiological findings**

The electrical isolation of the SVC was successfully performed in all canines without any major complications. The details of each case are summarized in Table 1. Figure 1G represents a typical example of an SVC isolation. The SVC potentials gradually delayed during the irradiation and finally it was isolated, accompanied by the presence of automaticity. A loss of any dormant conduction was also confirmed under a concentration of the photosensitizer of 30.9 ± 2.3 μg/mL in the six initially dosed canines, and 55.2 ± 2.3 μg/mL in the canine administered with a high dose of photosensitizer. The average time for a successful acute SVC isolation was 710 ± 388 s, and the average energy required was 70.4 ± 51.3 J/cm with 1.1 ± 0.4 catheter repositionings. The minimal irradiation time was 270 s with an initial positioning of the catheter, whereas the longest isolation time was 1353 s, involving two bouts of irradiation due to catheter repositioning because there was no remarkable potential delay for >5 min (No. 3). Figure 2 shows the changing potentials in canine No. 3. A local potential delay was initiated within 1 min, and a partial conduction block was completed within 5 min after the initiation. Since no further delay was confirmed, the ablation catheter was rotated clockwise so that the middle portion of the ablation catheter was placed so it could record the earliest conduction site. Then, following the occurrence of 2 to 1 conduction, the isolation was accomplished with an extra 294 s with upstream pacing applied for continuous phrenic nerve capture (Figure 3A). No sinus node dysfunction was observed, and no prolongation of the SRT was observed between that obtained before and after the procedure (pre vs. post, 495 ± 6 vs. 490 ± 13 ms, P = 0.524). There was no significant difference in the time required for the SVC isolation between the irradiation with an input power of 1 W and that with 0.3 W (922.7 ± 505.5 vs. 552.0 ± 231.3 s, P = 0.400). In the high-dose administered canine, the isolation time was not relatively shorter compared with that in the others.

**Safety demonstration of any acute phrenic nerve injury**

The concentration of the photosensitizer during the direct irradiation to the left phrenic nerve was 25.8 ± 3.9 μg/mL. A total of 9 min of irradiation at 10 W/cm² and 5400 J/cm² induced no acute phrenic nerve palsy.

**Discussion**

**Main findings**

The PDT-mediated electrical isolation of the SVC was successfully performed in all seven canines tested in this study using our first-generation prototype of the circular-laser-mapping catheter. The isolation was completed with 70.4 ± 71.4 J/cm of laser irradiation under a concentration of the photosensitizer of 30.9 ± 5.0 μg/mL without any sinus node injury, phrenic nerve palsy, or SVC stenosis during both the acute and chronic evaluations.

**Critical factors for an isolation**

The PDT-mediated linear ablation was successfully demonstrated in this study. The effectiveness of the PDT reaction is basically determined by the three required components: oxygen, photosensitizer, and laser. Our canines were ventilated with room air, and the pulse oximetry remained stable throughout the procedure, and the photosensitizer concentration was set to a human clinical pharmaceutical dose, which was constant at ~20–30 μg/mL during 4–6 h after the administration of 1.0 mg/kg. Theoretically, the PDT-mediated lesion depth is influenced by the drug concentration; however, we found no shortening of the isolation time by simply

<table>
<thead>
<tr>
<th>No.</th>
<th>Input power (W)</th>
<th>BW (kg)</th>
<th>Concentration (mean, range)</th>
<th>Time (s)</th>
<th>Total energy (J/cm)</th>
<th>Catheter rotation</th>
<th>SNI</th>
<th>PNI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>20.6</td>
<td>31.9 ± 4.5</td>
<td>1049</td>
<td>149.9</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>23</td>
<td>32.9 ± 5.1</td>
<td>366</td>
<td>52.3</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>24.4</td>
<td>33.0 ± 5.1</td>
<td>1353</td>
<td>193.3</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>0.3</td>
<td>22.6</td>
<td>29.6 ± 4.6</td>
<td>661</td>
<td>31.2</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>0.3</td>
<td>18.8</td>
<td>36.3 ± 12.2</td>
<td>270</td>
<td>11.6</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>0.3</td>
<td>20</td>
<td>55.2 ± 2.3</td>
<td>474</td>
<td>20.3</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>0.3</td>
<td>22.8</td>
<td>21.8 ± 4.2</td>
<td>803</td>
<td>34.4</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

BW, body weight; PNI, phrenic nerve injury; SNI, sinus node injury.
applying a higher drug concentration. Therefore, the laser condition remained as the only adjustable factor for achieving an effective ablation, with dependence on the input power, duration of the irradiation, and light penetration. Among these factors, the input power should be maintained as low as possible because increasing the input power shortens the isolation time and could potentially increase the risk of injury to adjacent organs. Therefore, the uniformity of the light penetration determined the lesion formation, which was governed by both the optical design of the catheter and the level of the catheter-tissue contact. The variable loop Lasso™ catheter is designed to make contact across the entire periphery of the veins; however, as shown in Figure 3G, part of the catheter was visible floating in the SVC. The myocardial sleeve at the SVC–RA junction was confirmed for the entire periphery; however, an electrical connection between the SVC and RA might consist of deviated bundles associated with the position of the ostium of the azygous vein. Also, the distal end of the laser-irradiating fibre might be distant from the proximal part of the laser fibre, potentially creating a gap in the laser irradiation. Varieties in both the contact and uniformity might explain why the rotation of the catheter succeeded in creating a successful SVC isolation. Thus, developing a second-generation laser catheter will require a design that ensures uniform laser diffusion with constant contact across the entire periphery of the SVC. A major benefit of the catheter design, allowing it to be tailor-made based on 3D images of pre-scanned cardiac computed tomography, and thus contributing to the efficacy of the PDT ablation.

Reconnection of the isolation is correlated with the clinical outcome, and the acute dormant conduction revealed by an ATP infusion and observed in 36.3% of successful RF isolations, which was recognized as the independent predictor of recurrence.15 Our PDT-mediated ablation induced successful isolations in all cases without any dormant conduction or reconnections at 1 month, and resulted in the creation of transmural lesions along the entire periphery of the vein. Since the PDT-mediated lesion creation was based on a mixture of acute singlet oxygen species-derived cell injury and chronic apoptosis,16 it is completely different from RF catheter ablation, after which the resting potential of the incompletely ablated and remaining myocardium becomes partially depolarized and shallow, triggering a conduction block. The mechanism of dormant conduction has been attributed to the restoration of the repolarized and deep resting membrane potentials induced by the activation of the ATP-activated inward rectifier potassium current (\(I_{KAdo}\)) that produces the transient reconnections of isolated veins.17 The characteristics of the membrane potentials after the PDT ablation remain to be clarified; hence, ATP is not suitable for evaluating the acute reconnections of isolated veins. In either case, no acute or chronic recurrence of the SVC conduction was observed with the PDT ablation.

![Figure 2](https://example.com/figure2.png)

**Figure 2** Electrical changes during the irradiation. The time course of the surface ECG, as well as the potentials from the distal (d) through proximal (p) electrodes of the superior vena cava (SVC) and ablation (Abl) catheters, is shown. The initiation of a local potential delay was marked within a minute. A partial conduction block was completed within 5 min (asterisk). However, there was no further delay for the next 3 min.
PDT-mediated lesion size potentially expanded in the chronic phase due to delayed apoptosis, which might have contributed to the persistent conduction block. Therefore, although the mechanism remains unknown in the cancer field, a PDT-mediated cardiac lesion control should be evaluated in further experiments.

Safety profile

An instantaneous procedure for isolating veins is attractive; however, complications associated with energy-derived problems cannot be ignored. Since the PDT-mediated lesion was induced non- thermally...
and might be controllable by the laser penetration, the shape of the laser catheter should be studiously planned and designed with a high safety profile. The safety margin attained here might be enough when considering the average energy required for the SVC isolation was 70.4 ± 71.4 J/cm, which was converted into 405.2 ± 221.6 J/cm², assuming that the baud transmission rate of the prototype was 60%, and no acute phrenic nerve injury was induced by a total of 5400 J/cm² of irradiation. There was a risk that PDT-mediated lesions could enlarge over time, based on a previous report; however, the phrenic nerve was intact electrophysiologically and histologically at 1 month after the procedure. The difference in the degree of tissue injury might be due to the sensitivity among organs to PDT-induced injury. A safety profile to prevent any nerve injury might also be beneficial for preventing phrenic nerve injury during PV isolation and ablation on the RA free wall or the left atrial appendage, as well as vagus nerve injury causing gastroparesis. Further evaluation for the safety of organs in close proximity to the targeted veins should also be performed.

Following a modification of the laser catheter to improve the contact and simplicity, PDT-mediated non-thermal linear ablation might become a promising alternative ablation procedure.

Limitations
The number of animals used in this study was too small to elucidate the efficacy and disadvantages statistically. When the specifications of the laser catheter are fixed after modifying the prototype, sufficient data for the efficacy and safety should be collected.

Conclusions
Photodynamic therapy with a circular-laser catheter successfully achieved the electrical isolation of the SVC instantly and without any complications.

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Conflict of interest: T.K. has a patent regarding this technology pending.

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