

# Development of a Shock-Wave Catheter Ablation System for Ventricular Tachyarrhythmias: Validation Study in Pigs In Vivo

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**Background**—Although radiofrequency catheter ablation is the current state-of-the-art treatment for ventricular tachyarrhythmias, it has limited success for several reasons, including insufficient lesion depth, prolonged inflammation with subsequent recurrence, and thromboembolisms due to myoendocardial thermal injury. Because shock waves can be applied to deep lesions without heat, we have been developing a shock-wave catheter ablation (SWCA) system to overcome these fundamental limitations of radiofrequency catheter ablation. In this study, we evaluated the efficacy and safety of our SWCA system for clinical application to treat ventricular tachyarrhythmia.

**Methods and Results**—In 33 pigs, we examined SWCA in vivo for the following 4 protocols. First, in an epicardial substrate model ( $n=8$ ), endocardial SWCA significantly decreased the sensing threshold (pre- versus postablation:  $11.4\pm 3.8$  versus  $6.8\pm 3.6$  mV;  $P<0.05$ ) and increased the pacing threshold (pre- versus postablation:  $1.6\pm 0.8$  versus  $2.0\pm 1.1$  V;  $P<0.05$ ), whereas endocardial radiofrequency catheter ablation failed to do so. Second, in a myocardial infarction model ( $n=3$ ), epicardial SWCA of the border zone of the infarcted lesion was as effective as ablation of the normal myocardium. Third, in a coronary artery application model ( $n=10$ ), direct application of shock waves to the epicardial coronary arteries caused no adverse effects in either the acute or chronic phase. Fourth, with an epicardial approach ( $n=8$ ), we found that 90 shots per site provided an ideal therapeutic condition to create deep lesions with less superficial damage.

**Conclusions**—These results indicate that our new SWCA system is effective and safe for treatment of ventricular tachyarrhythmias with deep arrhythmogenic substrates. (*J Am Heart Assoc.* 2019;8:e011038. DOI: 10.1161/JAHA.118.011038.)

**Key Words:** animal model • catheter ablation • emerging technology • shock wave • ventricular arrhythmia

Radiofrequency catheter ablation (RFCA) is an established therapy for drug-resistant tachyarrhythmias, including ventricular tachycardia (VT). Although conventional RFCA is quite effective and feasible, the success of RFCA in treatment of acute VT is still limited, especially in patients with structural heart disease (SHD). RFCA has the 3 inevitable weaknesses as a thermal ablation system. First, the lesion depth of RFCA is often insufficient, especially in SHD with thick ventricular myocardium.<sup>1–3</sup> Second, RFCA inevitably causes

myoendothelial damage with thermal damage at the catheter-contact surface, occasionally resulting in thromboembolic complications and steam pop.<sup>4,5</sup> Furthermore, epicardial RFCA for VT sometimes fails because of prohibitive proximity of the target site to the coronary arteries.<sup>6</sup> Finally, RFCA causes a prolonged inflammatory response with subsequent early phase recurrences.<sup>6,7</sup> A shock wave (SW) is an acoustic pressure wave consisting of a compressive phase (overpressure) followed by a tensile phase (negative pressure; Figure 1A). Focused SW, which is currently used for extracorporeal SW lithotripsy, can cause tissue damage at an arbitrary depth without heat generation. Thus, we have been developing a SW catheter ablation (SWCA) system, which we previously demonstrated as a nonthermal system (Figure 1B and 1C).<sup>8,9</sup> The concept of our SWCA system is to make a deeper lesion without severe superficial injury by using focused SWs (Figure 1B and 1C).<sup>8,9</sup> We previously demonstrated that we are able to create a persistent atrioventricular block in pigs in vivo with a prototype SW catheter.<sup>8</sup> Subsequently, we also revealed that compared with conventional RFCA, our SWCA system causes less superficial damage, with rapid recovery from local

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## Clinical Perspective

### What Is New?

- This study is the first to report the electrophysiological feasibility of endocardial shock-wave catheter ablation to the deep myocardium.
- The shock-wave catheter ablation system is effective in the ischemic border zone and is safe for the coronary artery.

### What Are the Clinical Implications?

- These data suggest that our shock-wave catheter ablation system may be able to treat ventricular tachyarrhythmias with deep arrhythmogenic substrates using an endocardial approach alone, even if the substrates are adjacent to the coronary arteries.

inflammation.<sup>9</sup> However, it remains to be examined whether our SWCA system is effective for deep myocardial lesions when used with the endocardial approach or for fibrotic lesions interspersed with viable myocytes, which may be the arrhythmogenic substrates in VT with SHD.<sup>10</sup> It also remains to be elucidated whether our SWCA system is safe for the surrounding tissues (except for myocardium) and whether there is an ideal irradiation protocol for SWCA. In this study, we further examined the feasibility and safety of our SWCA system in pigs in vivo for clinical application to VT treatment in patients with SHD.

## Methods

The data that support the findings of this study are available from the first author on reasonable request.

This study was approved by the Institutional Committee for Use of Laboratory Animals of Tohoku University (nos. 2017MdA-187, 2017MdA-237, and 2018MdA-012) and was conducted according to institutional guidelines.

## SWCA System

Our SWCA system consists of a Q-switched holmium yttrium aluminum garnet (Ho:YAG) laser (pulse energy, 10–25 mJ; pulse width, 100 ns; wavelength, 2.1  $\mu\text{m}$ ; Sparkling Photon Inc), a syringe pump, a main body of catheter, and a SW generator at the tip of catheter. The SW generator consists of an optical fiber and a truncated ellipsoidal brass cavity (SW reflector) with an open end sealed with silicone rubber film. A water supply and drainage system are equipped to remove air bubbles and surplus heat in water inside the cavity of the SW reflector. An SW catheter is a 10.5-French bidirectionally deflectable ablation catheter equipped with an SW reflector

and 2 polar electrodes at the tip to confirm that the catheter is held vertically to the tissue surface with local ECGs (Figure 1B). These 2 electrodes enable us to identify the catheter position using the EnSite NavX mapping system (St. Jude Medical). The SW catheter is connected to a laser generator. An SW was generated by irradiations of a pulse of a Q-switched Ho:YAG laser beam pulse into water through the optical fiber. The tip of the optical fiber was set at the primary focus (F1) of the brass cavity using a precise positioning device. Spherical SWs generated at F1 converge on the secondary focus (F2) after reflection from the wall of the cavity. A material with high acoustic impedance, such as metal, is suitable for the material of the SW reflector because SW reflectivity on the wall of the SW reflector increases in proportion to the difference between water and the material of SW reflector. The brass reflector that we use is robust enough for SWCA. We previously demonstrated that maximal positive pressure of focused SWs at F2 and pulse laser energy were related to positive correlation.<sup>9</sup> Because the maximal positive pressure increases linearly with laser energy, we are able to control the ablation depth by laser energy change. We previously demonstrated that our SWCA system is a nonthermal system.<sup>8</sup> In that report, we applied the focused SW to the thigh muscle and ventricular myocardium with an epicardial approach, and the surface temperature just below the catheter was continuously measured in pigs in vivo.<sup>8</sup> We verified that there was no temperature rise  $>50^\circ\text{C}$  that could cause thermal tissue necrosis.<sup>8</sup> Focused SWs were applied in synchronization with a synchronous ECG signal. An R wave was used as a trigger signal. In case of rapid heart rate  $>150$  beats/min, the pulse repetition frequency of SW irradiation  $>2.5$  Hz was suppressed. Nevertheless, we applied focused SWs at a 1-Hz pulse-repetition frequency with occasional pause so as not to cause overheating of the SW generator. Our SWCA system is able to cause an extensive cavitation phenomenon when observed by the shadowgraph, and we used high-intensity SWs, as reported previously.<sup>9</sup>

## Experimental Protocols

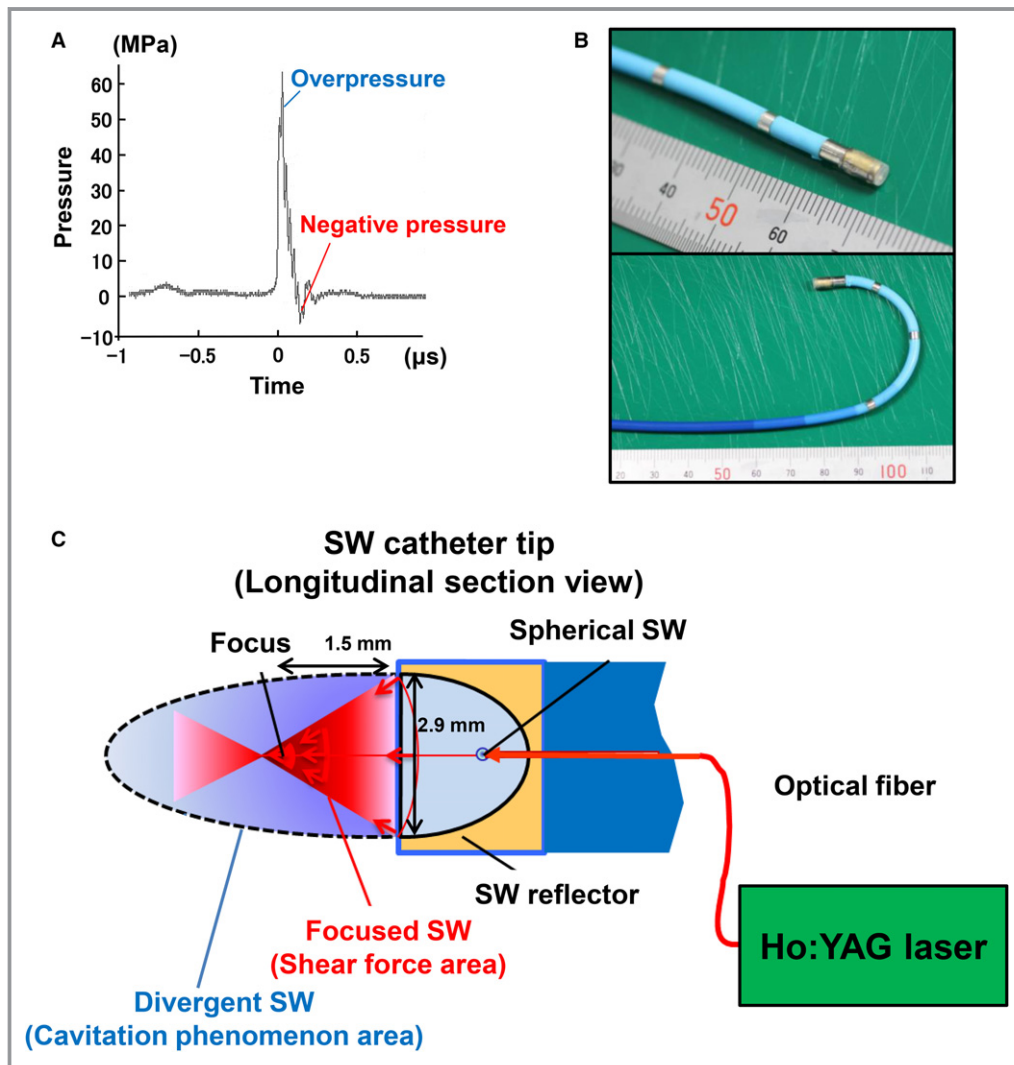
We performed 4 protocols with male domestic pigs in vivo (body weight [BW]:  $44.7\pm 5.7$  kg). All procedures were performed according to the protocols approved by the Institutional Committee for Use of Laboratory Animals of Tohoku University (nos. 2017MdA-187, 2017MdA-237, and 2018MdA-012). The animals were anesthetized with medetomidine (0.05 mg/kg intramuscularly) and midazolam (0.4 mg/kg intramuscularly). After 10 minutes, they were intubated after induction of anesthesia with inhaled 5% sevoflurane and were mechanically ventilated with room air and supplemental oxygen. General anesthesia was maintained with 2.5% to 4.0% sevoflurane. They were continuously

monitored with surface ECGs, percutaneous oxygen saturation measurements, and direct measurements of arterial pressure.<sup>8,9</sup>

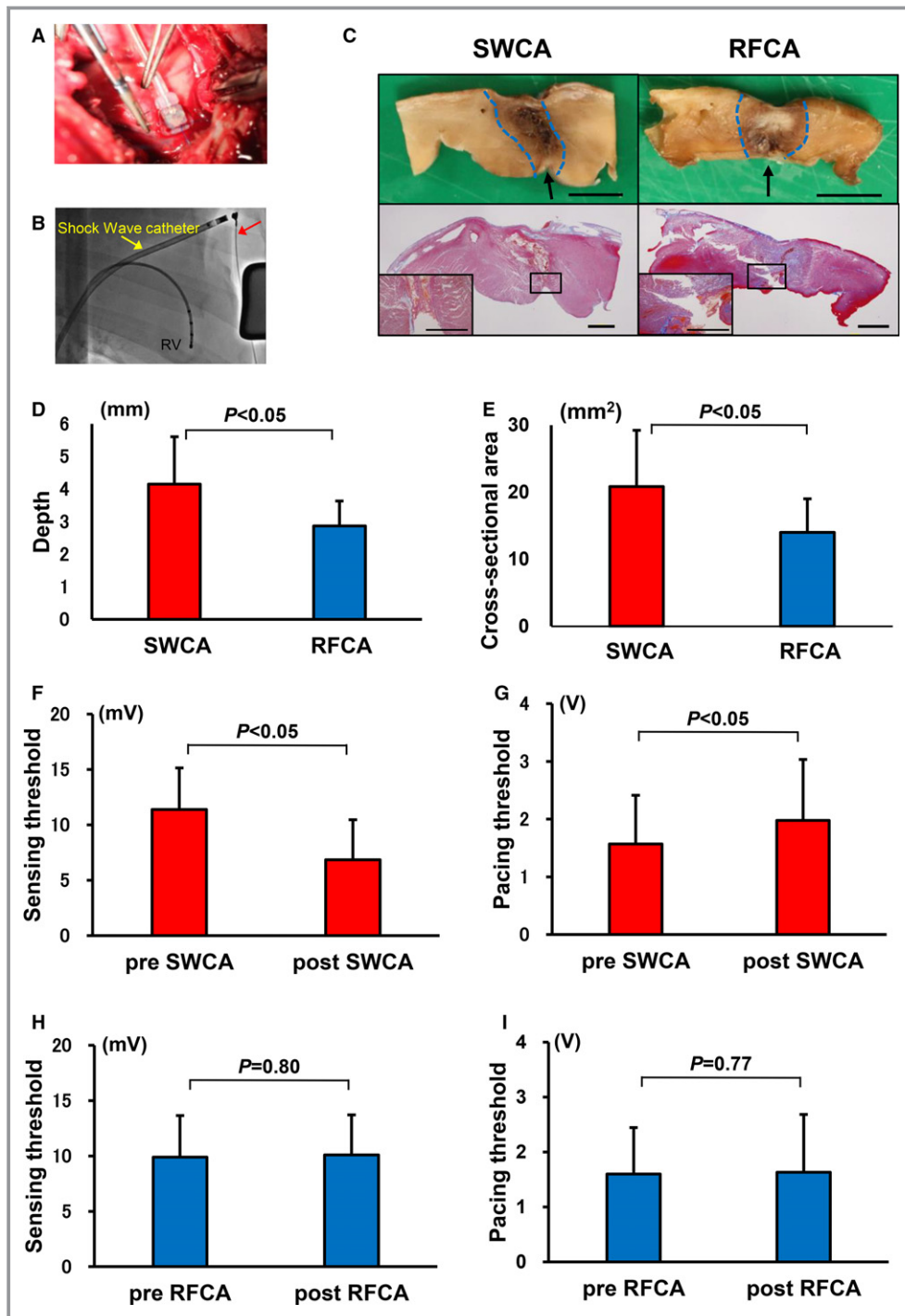
### Protocol 1: Epicardial Substrate Model

We examined whether endocardial SWCA of the ventricular myocardium could cause an electrophysiological effect on the opposite epicardial side, using an epicardial substrate model in pigs. Eight male domestic pigs (BW:  $42.1 \pm 1.5$  kg) were pretreated with amiodarone (400 mg/day orally) for 5 days to prevent RFCA-induced ventricular arrhythmias (VAs) because

pigs are highly vulnerable to RFCA and easily establish VAs, unlike humans.<sup>11</sup> After vascular access, intravenous lidocaine (50 mg bolus followed by 1 mg/kg per hour continuous infusion) was administered, and an additional bolus of nifekalant (0.3 mg/kg) was injected when malignant VAs were noted. We performed medial sternotomy and attached the epicardial pacemaker lead to the surface of the right ventricular myocardium (Figure 2A). After 30 minutes, we measured the sensing and pacing thresholds. Then, we performed the SWCA or RFCA to the opposite endocardial site of epicardial lead tip by transvascular approach (SWCA 13



**Figure 1.** Characteristics of the SWCA system. **A**, SW pulses form in the focal zone; a SW is an acoustic pressure wave consisting of a compressive phase (overpressure) followed by a tensile phase (negative pressure). **B**, The 10.5-French SW catheter (upper panel). The catheter is bidirectionally steerable (lower panel) and equipped with bipolar electrodes for recording local ECGs and 4-ring electrodes for a 3-dimensional mapping system. **C**, Schematic diagram of the SWCA system; the spherical SW is generated in a water-filled semiellipsoidal reflector attached to the catheter tip by irradiation of a Ho:YAG laser beam through quartz optical fiber. The SW is then reflected by the reflector and converged on the outer focus. Ho:YAG indicates holmium:yttrium aluminum garnet; SW shock wave; SWCA, shock-wave catheter ablation.



**Figure 2.** Threshold change of the epicardial pacemaker lead by endocardial ablation. **A**, We performed medial sternotomy and attached the epicardial pacemaker lead to the surface of the right ventricular myocardium in pigs in vivo. **B**, We applied SWCA or performed RFCA to the opposite site of the lead tip using an endocardial approach. Red arrow indicates epicardial pacemaker lead. **C**, Representative transmural lesion of the right ventricle with endocardial SWCA and RFCA (upper panels). Arrow indicates shock wave or radiofrequency application site. Scale bar=5 mm. Masson’s trichrome staining of the same lesion (lower panels). Scale bar=2 mm and 1 mm for inserted panels. **D** and **E**, Comparison of the lesion depth and cross-sectional area between endocardial SWCA (n=13) and RFCA (n=10). **F** and **G**, Change in the sensing and pacing thresholds by SWCA. **H** and **I**, No change in the sensing and pacing thresholds by RFCA. RFCA indicates radiofrequency catheter ablation; SWCA, shock-wave catheter ablation.

sites, RFCA 10 sites) (Figure 2B). The SW catheter was located as perpendicularly as possible to the right ventricular wall under the guidance of fluoroscopy and right ventriculography (Figure 2B). The focused SW was applied for 360 shots per site with a heartbeat-synchronized method and occasional pause so as not to cause overheating of the laser generator, as mentioned earlier. RFCA was performed at 50°C and maximum power output of 30 W for up to 60 seconds and limiting impedance decrease of 10  $\Omega$  (EZ STEER; Biosense Webster, Inc). We paced from the epicardial lead tip at twice the pacing threshold during endocardial ablation. At 30 minutes after SWCA or RFCA, we again measured the thresholds.

### **Protocol 2: Myocardial Infarction Model**

We examined whether our SWCA system could cause an ideal ablation lesion even in the abnormal myocardium using a myocardial infarction (MI) model. Four domestic male pigs (BW: 39.3±1.5 kg) were treated with amiodarone (400 mg/day orally) and aspirin (100 mg/day orally) for 3 days before the infarction procedure. First, we performed left ventriculography and administered lidocaine (50 mg bolus followed by 1 mg/kg per hour continuous infusion) to prevent malignant VAs during myocardial ischemia.<sup>12,13</sup> Then, we occluded the distal left anterior descending coronary artery for 90 minutes by using a 2.5×12-mm coronary angioplasty balloon to create MI (Figure 3A).<sup>13</sup> Acute MI was confirmed by coronary angiography during the occlusion and by ECG showing ST-segment elevation. In case of malignant VAs, we provided defibrillation and injected nifekalant (0.3 mg/kg intravenously). After monitoring of hemodynamic state and malignant VAs for 1 hour from reperfusion, animals were recovered from anesthesia and survived for 4 weeks. Then we performed general anesthesia and medial sternotomy. We confirmed the region of MI with the left ventriculography and macroscopic myocardial tissue changes. We applied the focused SW to the epicardial surface of the left ventricular myocardium (normal region: 4 sites; border region: 10 sites; scar region: 6 sites) for 360 shots per site with the heartbeat-synchronized method and an occasional pause so as not to cause overheating of the laser generator. The SW catheter was located perpendicularly to the left myocardium under direct vision.

### **Protocol 3: Influence of SWCA on the Coronary Artery**

We examined whether our SWCA system causes harmful effects on the coronary arteries with an epicardial approach. We used 9 male domestic pigs (acute-phase study, n=6, BW: 46.3±3.4 kg; chronic-phase study, n=3, BW: 40.3±2.1 kg). We performed general anesthesia, as mentioned earlier, and medial sternotomy. We performed coronary angiography after intracoronary administration of nitroglycerin (1 mg). Then we

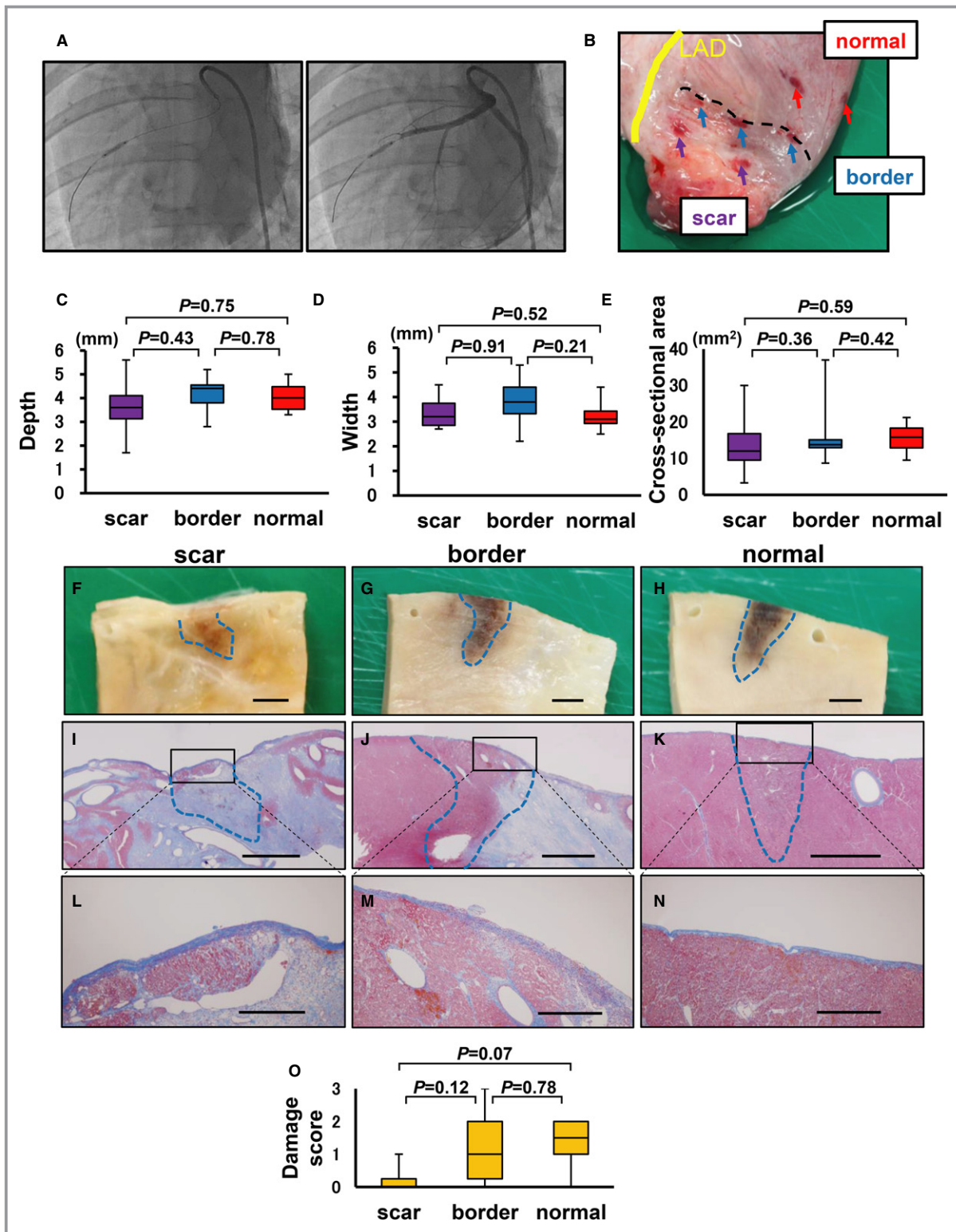
directly applied the focused SW to the coronary arteries for 180 shots per site with the heartbeat-synchronized method and an occasional pause to prevent overheating the laser generator. We performed coronary angiography during SW application to confirm that the SW catheter was located on the coronary artery by stopping coronary flow at the SWCA site. We administered epicardial SWs with an occasional pause to prevent overheating the SW generator, and the coronary flow was resumed during the pause. However, we considered that long ischemia would be harmful for pigs and decided to irradiate SWs for 180 shots per site. We targeted the middle portion of the left anterior descending, proximal portion of the first diagonal artery or the proximal portion of the left circumflex artery (acute-phase study: 12 sites, sham 4 sites; chronic-phase study: 6 sites, sham 2 sites). Then we performed coronary angiography just after the epicardial SWCA in the acute-phase study. After intravenous administration of nitroglycerin (1 mg), we performed coronary angiography again. We evaluated the degree of stenosis by quantitative coronary angiography analysis. In the chronic-phase study, we performed coronary angiography and quantitative coronary angiography analysis in the same manner after intracoronary administration of nitroglycerin (1 mg) and at 4 weeks. In this study, we did not use RFCA as a control because of its excess invasion. Pigs are highly vulnerable to RFCA and easily develop malignant VAs, unlike humans.<sup>11</sup> Moreover, there is a risk of coronary complications when ablating coronary arteries. Consequently, in the present study, we simply examined the safety of SWCA.

### **Protocol 4: Dependency on Irradiation Number for Lesion Depth or Superficial Damage**

We previously examined the efficacy of epicardial SWCA for 180 shots per site, and we already knew the approximate lesion size. However, relatively strong interstitial hemorrhage was noted in some cases. In the present study, we aimed to investigate the ideal shot number for maintaining efficacy and reducing complications. In 8 male domestic pigs (BW: 50.4±7.0 kg), we performed general anesthesia and medial sternotomy, as mentioned earlier, and applied the focused SW to the left ventricle for 45, 90, or 135 shots per site using an epicardial approach (14 sites each). Then we analyzed the correlation between the number of irradiation times and the lesion depth or degree of superficial damage.

### **Histological Analysis**

After euthanasia, the heart was extracted and subsequently fixed in 10% buffered formalin. We sectioned the center of lesions of the fixed heart to the perpendicular direction and embedded in paraffin. The tissue specimens were stained with hematoxylin-eosin and Masson's trichrome. All



**Figure 3.** Evaluation in an MI model. **A**, Induction of MI with a balloon catheter. **B**, After 4 weeks, we performed epicardial SWCA to the normal myocardium (normal), ischemic border zone (ischemic), and scar region (scar). Arrows indicate epicardial shock-wave application sites of the 3 zones. **C–E**, The lesion depth, lesion width, and cross-sectional area of the 3 zones. **F–H**, Macroscopic views of the 3 zones. Scale bar=2 mm. **I–K**, Masson’s trichrome stainings of the 3 zones. Scale bar=2 mm. **L–N**, Magnified images of panels **I–K**. Scale bar=500  $\mu$ m. **O**, Histological grading of epicardial injury. LAD indicates left anterior descending artery; MI, myocardial infarction; SWCA, shock-wave catheter ablation.

histopathological slides were examined by light microscopy (Olympus BX51; Olympus America Inc). The lesion depth, lesion width, and cross-sectional area were measured macroscopically and were validated microscopically using ImageJ (US National Institutes of Health). The extent of superficial tissue damage was evaluated by the microscopic grading score, as described previously; *intact* (no changes, score 0), *mild* (wavy change with preservation of thickness, score 1), *moderate* (thinning or partial detachment of the epicardium, score 2), and *severe* (disruption or loss of epicardium, score 3).<sup>8</sup>

## Statistical Analysis

Continuous data were expressed as mean±SD. We assessed normality using a histogram stratified by groups and normal Q-Q plot. The Mann–Whitney *U* test was used to compare each threshold's change in the epicardial substrate model. Similarly, the Mann–Whitney *U* test was used to compare the lesion depth, lesion width, and cross-sectional area in the MI model experiments. One-way ANOVA was used to compare data for statistically significant differences among the SWCA and sham groups at each time course. The Student *t* test was used to compare the lesion depth and superficial damage at each irradiation time.  $P<0.05$  was considered statistically significant. All statistical analyses were performed with JMP Pro 13.1.0 (SAS Institute).

## Results

### Protocol 1: Epicardial Substrate Model

We examined whether the endocardial SWCA system could exert electrophysiological effects on the deep myocardium using an epicardial substrate model in pigs. The endocardial SWCA system created macroscopically visible lesions in each application site. Macroscopic analysis showed that the SWCA lesions appeared as dark violet and extended to the pacemaker lead tip, as compared with RFCA lesions, which appeared semicircular in shape (Figure 2C). Histological examination showed that SW-induced myocardial lesions were spheroidal shape with the infiltration of neutrophils and mononuclear cells. The strongest tissue degeneration, including myocardial fiber disruption, interstitial hemorrhage, and contraction band necrosis, was noted in the center of the lesion, and relatively mild tissue injury characterized by eosinophilic myocyte and infiltration of inflammatory cells was noted in the superficial site of the lesion (Figure 2C). In contrast, severe myocardial degeneration starting from the catheter contact surface was noted in the radiofrequency-induced lesions (Figure 2C). Transmural lesions were noted in 6 of 13 lesions (46%) with SWCA

and 2 of 10 lesions (20%) with RFCA ( $P=0.38$ ). The mean lesion depth of endocardial SWCA versus RFCA was  $4.2\pm 1.5$  versus  $2.6\pm 0.6$  mm, respectively ( $P<0.05$ ; Figure 2D). The mean cross-sectional area was  $20.9\pm 8.4$  versus  $14.0\pm 5.0$  mm<sup>2</sup>, respectively ( $P<0.05$ ; Figure 2E). The endocardial SWCA significantly decreased the sensing threshold (pre- versus postablation:  $11.4\pm 3.8$  versus  $6.8\pm 3.6$  mV,  $P<0.05$ ; Figure 2F), and increased the pacing threshold (pre- versus postablation:  $1.6\pm 0.8$  versus  $2.0\pm 1.1$  V,  $P<0.05$ ; Figure 2G). In 1 animal, transient pacing failure occurred from the epicardial lead tip during SWCA but was improved soon after temporary pacing. In contrast, endocardial RFCA caused no change of each threshold (pre- versus postablation: sensing threshold:  $9.9\pm 2.2$  versus  $10.1\pm 3.3$  mV,  $P=0.80$ ; pacing threshold:  $1.6\pm 0.7$  versus  $1.6\pm 0.6$  V,  $P=0.77$ ; Figure 2H and 2I). The mean ablation time was longer for endocardial SWCA than RFCA ( $23.8\pm 5.6$  versus  $0.9\pm 0.2$  minutes). In the SWCA group, no remarkable complications (eg, malignant VAs or cardiac tamponade) were noted, even in the animals with transmural lesions. In contrast, in the RFCA group, 1 pig collapsed from ventricular fibrillation during the RFCA but recovered with cardiac defibrillation and injected nifekalant (0.3 mg/kg). In that animal, because the recurrence of malignant VAs was anticipated, we reduced the ablation time by 30 seconds.

### Protocol 2: MI Model

We examined whether the SWCA could cause ideal ablation lesions even in the abnormal myocardium with fibrotic and normal myocardial tissues. We created an MI model in pigs, except for 1 animal that developed ventricular fibrillation repeatedly during coronary occlusion and was subsequently euthanized. The range of MI was macroscopically distinguishable because the scar region was pale and smooth (Figure 3B). We compared the extent of epicardial SWCA lesions between the ischemic border zone and normal myocardium. There were no significant differences between the 2 areas in lesion depth ( $4.4\pm 0.8$  versus  $4.0\pm 1.0$  mm,  $P=0.78$ ), lesion width ( $3.8\pm 1.1$  versus  $3.1\pm 0.5$  mm,  $P=0.21$ ), or cross-sectional area ( $13.8\pm 2.2$  versus  $15.8\pm 5.4$  mm<sup>2</sup>,  $P=0.42$ ; Figure 3C–3G). Similarly, there was no significant difference between the 2 areas in the histological grading score for epicardial injury ( $1.2\pm 1.0$  versus  $1.3\pm 0.7$ ,  $P=0.78$ ; Figure 3I–3O). SW lesions in the scar region were relatively unclear macroscopically, but infiltration of inflammatory cells and interstitial hemorrhage were evident histologically. In the border zone and normal myocardium, the lesions were well demarcated and myocardial tissue disruption or contraction band necrosis were noted inside the lesions (Figure 3F through 3N). No remarkable complications (e.g. malignant

VAs and cardiac perforation) were noted during epicardial SWCA.

### Protocol 3: Influence of SWCA on the Coronary Artery

We examined the safety of our SWCA system by directly applying the focused SW to the coronary arteries in pigs in vivo. In the acute-phase study, although mild coronary stenosis was noted at the SW application site, the extent of stenosis was not significant (pre- versus postablation: 0% versus  $4.1 \pm 11.0\%$ ,  $P=0.15$ ) and disappeared in response to intracoronary nitroglycerin, indicating the involvement of coronary vasoconstriction (Figure 4A and 4B). When comparing the extent of stenosis after ablation, there were no differences between the SWCA and sham groups (6.4% versus 22.3%, respectively;  $P=0.15$ ; Figure 4C). In the acute-phase study, vascular lumen of the coronary artery was well preserved macroscopically (Figure 4D), and no obvious damage was noted histologically in the vascular system (eg, smooth muscle or endothelium; Figure 4E), whereas the SW lesion reached beyond the coronary artery (Figure 4D). The average lesion depth was  $5.1 \pm 1.8$  mm. In the chronic-phase study, the vascular lumen was also preserved (SWCA versus sham: 0.4% versus  $-0.5\%$ ,  $P=0.49$ ), and no thrombus or neointimal proliferation was noted (Figure 4F). SWCA caused no coronary spasm or other complications, and no sudden death was noted during the follow-up period.

### Protocol 4: Dependency on Irradiation Number for Lesion Depth or Superficial Damage

We compared the lesion depth and the superficial damage by altering the irradiation number to identify the ideal SWCA protocol in the condition with perpendicular contact of the catheter tip and myocardium. Ninety and 135 shots per site created significantly deeper lesions than 45 shots per site ( $6.5 \pm 2.8$  and  $6.5 \pm 2.2$  versus  $4.3 \pm 1.6$  mm, both  $P<0.05$ ; Figure 5A, 5E–5G). Similarly, 90 and 135 shots per site created significantly wider cross-sectional area of lesions compared with 45 shots per site ( $22.7 \pm 12.3$  mm<sup>2</sup> and  $22.4 \pm 11.3$  mm<sup>2</sup> versus  $13.6 \pm 7.1$  mm<sup>2</sup>, both  $P<0.05$ ; Figure 5B, 5E–5G). There were no significant differences among the 3 groups regarding the lesion width (45 shots/site:  $3.3 \pm 1.4$  mm; 90 shots/site:  $3.6 \pm 1.1$  mm; 135 shots/site:  $3.9 \pm 1.6$  mm;  $P=0.55$ ; Figure 5C, 5E–5G). In contrast, 45 and 90 shots per site caused less superficial damage than 135 shots per site (histological grading score;  $1.6 \pm 1.0$  and  $1.6 \pm 1.2$  versus  $2.6 \pm 0.5$ , both  $P<0.05$ ; Figure 5D, 5H–5M). Histological analysis showed that epicardial tissue was relatively preserved in 45 and 90 shots per site, whereas thinning and detachment of the epicardium were noted with

135 shots per site. Thus, we decided to use 90 shots per site to create deep lesions with less superficial damage.

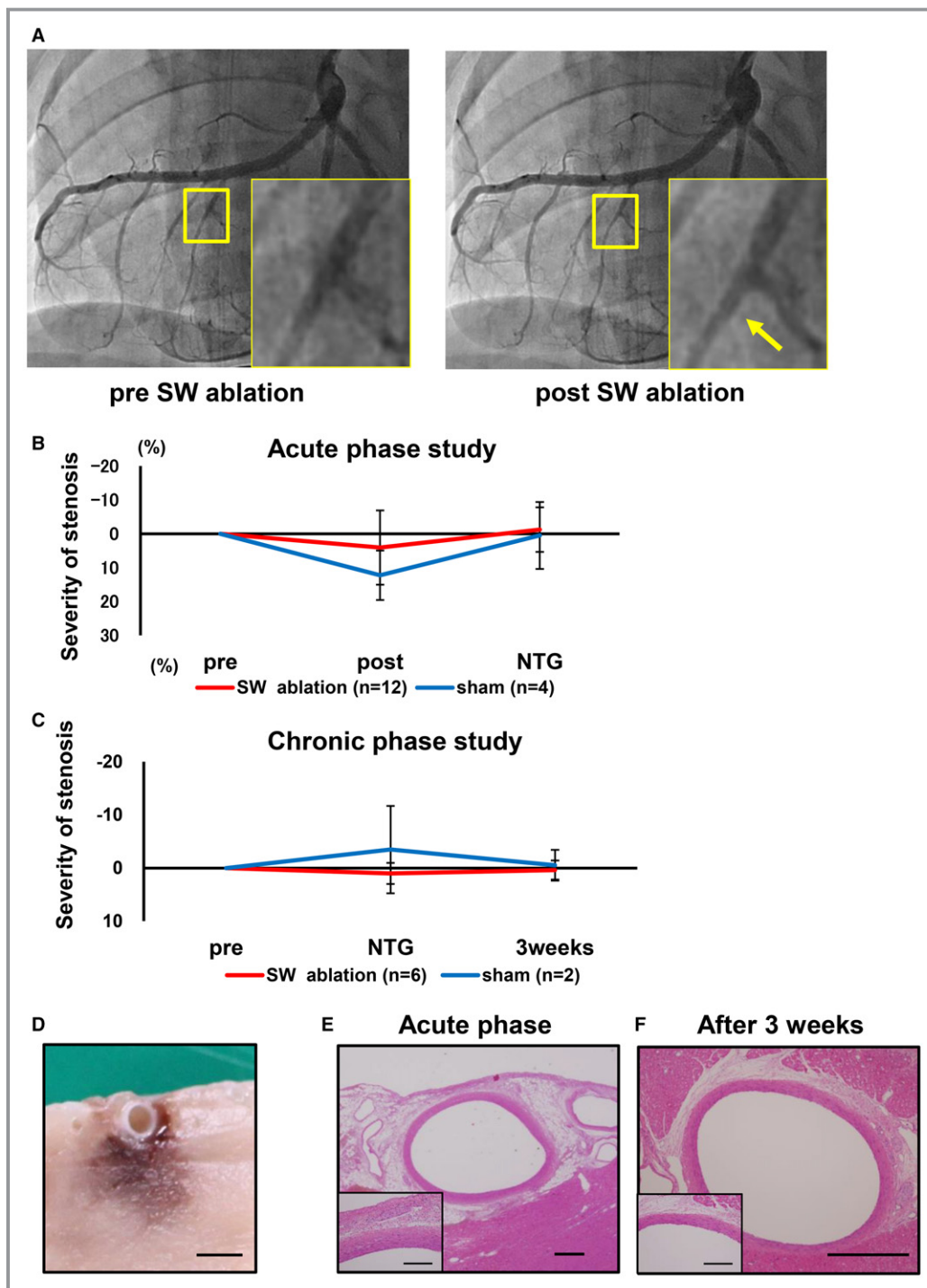
## Discussion

The major findings of this study in pigs in vivo were as follows: (1) Our SWCA can reach the deep myocardium of the left ventricle and affect its electrophysiological property; (2) SWCA at the ischemic border zone is as effective as in the normal myocardium; (3) SWCA causes no damage to the coronary artery, even when directly irradiated at the artery; and (4) irradiation number of 90 shots/site was sufficient to create deep lesions with less superficial damage.

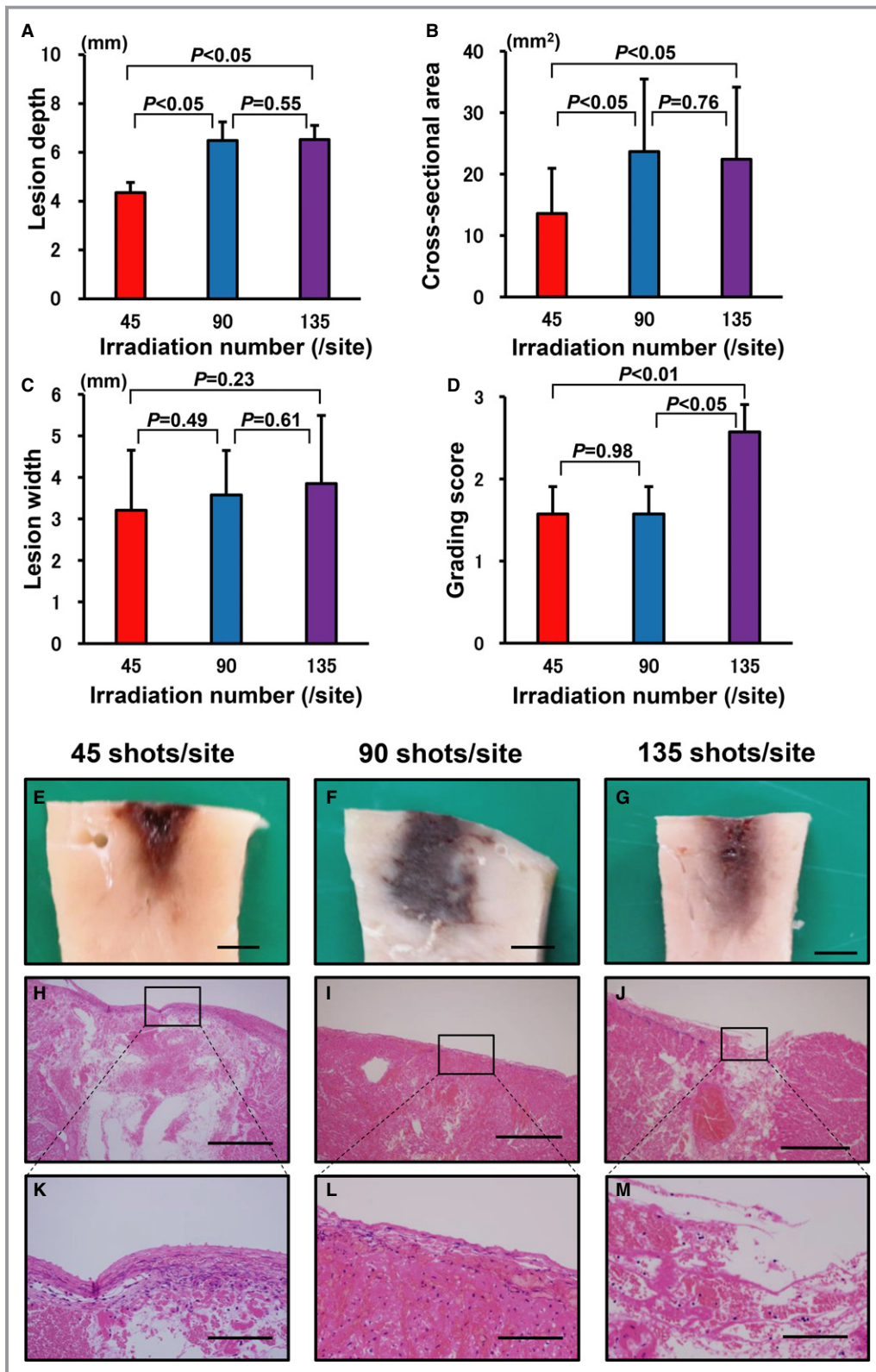
### Feasibility of SWCA for VT with Deep Substrate

Conventional RFCA for VT in patient with SHD is associated with increased recurrence rate as high as 50% at 6 months.<sup>14–19</sup> The main reasons for this limited success rate are related to the presence of an epicardial origin and the proximity of lesions to the vital structure such as coronary arteries. Thus, advanced approaches have been sought, such as cardiac radioablation<sup>20</sup> and needle catheter ablation.<sup>21,22</sup> Although cardiac radioablation is a promising noninvasive ablation method, it has some limitations; this system is unable to confirm local potential during the treatment, and long-term safety for the surrounding organs or arrhythmogenicity around the target lesion remain to be elucidated. Similarly, needle ablation is suitable for creating deep lesions, but there are concerns about the coronary complications, thromboembolisms, and early recurrence because the system uses Joule heat, as in the case of conventional RFCA. In the protocol of the epicardial substrate model, we demonstrated that our nonthermal SWCA system could electrophysiologically affect the deeper myocardium than RFCA without any complications. During the endocardial SWCA, we performed ventricular pacing from the epicardial pacemaker lead in some pigs. We confirmed that pacing failure occurred in 1 pig during SWCA. This indicates that endocardial SWCA can cause electrophysiological effects in the deep myocardium. Currently, to create deep lesions with RFCA, we need to increase the contact force, output, and/or ablation time, which increases complications. The safety of radiofrequency ablation has been improving with various techniques, such as irrigated radiofrequency ablation systems. However, it is reported that the incidence of silent cerebral events after irrigated radiofrequency ablation is 6.8% to 24%.<sup>23</sup> Furthermore, Seiler et al previously reported the frequency of the steam pops during endocardial open-irrigated radiofrequency ablation for VT.<sup>24</sup> With 4107 ablation lesions in 145 patients, steam pops occurred in 62 radiofrequency lesions (1.5%) in 38 patients





**Figure 4.** Influence of SW catheter ablation on the coronary artery. **A**, Coronary angiography before and after SW ablation in the acute-phase study. Arrow indicates SW ablation site. **B**, Severity of stenosis after SW ablation and after intracoronary NTG in the acute-phase study. **C**, Severity of stenosis immediately after NTG and 3 weeks after SW ablation in the chronic-phase study. **D**, Macroscopic view of the SW application site in the acute-phase study. The lesion reaches beyond the coronary artery. Scale bar=2 mm. **E** and **F**, Hematoxylin-eosin stainings of SW-ablated coronary artery in the acute- and chronic-phase studies, respectively. Scale bar=500 and 200  $\mu$ m for inserted panels. NTG indicates nitroglycerin; SW, shock wave.



**Figure 5.** Effects of different numbers of shock waves on lesion dimension. **A–D**, Lesion depth, cross-sectional area, lesion width, and grading score of the epicardium. **E–G**, Macroscopic views of irradiated myocardium. Scale bar=2 mm. **H–J**, Hematoxylin-eosin stainings of irradiated myocardium. Scale bar=1 mm. **K–M**, Magnified images of panels H–J. Scale bar=200 μm.

(26.8%).<sup>24</sup> This indicates that even if we use the irrigated radiofrequency catheter, steam pop is an inevitable complication. Consequently, we consider that the risk of thromboembolisms and steam pops during the irrigated radiofrequency ablation is higher than expected. In contrast, because our SWCA system is nonthermal, we believe that complications would not increase even if we tried to make deeper lesions with SWCA.

In the present study, the radiofrequency setting was slightly underpowered, and the mean lesion depth of endocardial RFCA was shallow ( $2.6\pm 0.6$  mm), partly because of the use of the nonirrigated RFCA system. Moreover, pigs are more highly vulnerable to RFCA than humans in general.<sup>11</sup> They easily develop malignant VAs when we increase the power output or ablation time; therefore, we performed RFCA with the settings at 50°C for temperature and maximum power output of 30W for up to 60 seconds, which is slightly underpowered compared with the RFCA settings targeting human left ventricular myocardium. In the previous reports on needle ablation, Sapp et al reported that the lesion depth of conventional RFCA was  $5.3\pm 1.2$  mm, whereas the ablation setting was 65°C for temperature and 120 seconds for duration, which could increase the risk of steam pop.<sup>22</sup> Moreover, because target tissue was left ventricular myocardium, the cooling effect of the blood stream might be more effective with RFCA.<sup>22</sup> Miyagi et al reported that the lesion depth of endocardial RFCA is similar to our setting.<sup>25</sup> They targeted the left atrium and controlled radiofrequency energy at 60°C to 70°C for 60 seconds. The lesion depth of endocardial RFCA was  $3.0\pm 1.4$  mm, which is consistent with our findings. We previously demonstrated that SWCA achieved remarkably deep lesions extending about  $7.8\pm 0.9$  mm when overpressure exceeded 75 MPa. Moreover, the deepest lesion created by epicardial SWCA was 12.5 mm in the present study. This indicates that SWCA has the potential to treat deep arrhythmogenic substrate compared with irrigated RFCA. To achieve the same lesion depth using irrigated RFCA, it has been reported that contact force of 30 to 50 g is needed and that steam pop occurred in 50% to 63% of radiofrequency applications in a canine model.<sup>26</sup>

### Feasibility of SWCA for VT in SHD

SW is considered to cause tissue injury through the combination of 2 different mechanical stresses: shear force and the cavitation effect.<sup>8</sup> We previously examined the characteristics of the SW lesion by varying maximal positive overpressure of SWs.<sup>8</sup> When the maximal overpressure exceeded 40 MPa at the focal site, myocardial injury was also noted at the prefocal zone, where the overpressure was <30 MPa. In contrast, focused SW <30 MPa caused no

tissue injuries, even at the focal site. These results indicate that myocardial injury at the prefocal zone was caused not only by a compression effect but also by other effects, such as the cavitation effect, as suggested by the basic study with a shadowgraph.<sup>8</sup> We also took a shadowgraph of high- and normal-intensity SWs with a high-speed camera in room air bubbled with extracellular fluid buffer.<sup>9</sup> High-intensity SW cause a more extensive cavitation phenomenon compared with normal-intensity SW.<sup>9</sup> Thus, we consider that the cavitation phenomenon is substantially related to the creation of the SW lesion. Koor et al reported that there were no significant differences in the radiofrequency lesion depth between normal myocardium and the ischemic border zone in dogs in vivo.<sup>27</sup> However, it remains to be elucidated whether our SWCA system also could create macroscopically visible lesions in scarred myocardium. It is possible that the cavitation phenomenon in heterogeneous tissues (eg, ischemic border zone) is more attenuated than in homogeneous tissue. When a SW passes through the interface of 2 media, its reflection factor is defined as follows:

$$\frac{Z_a - Z_b}{Z_a + Z_b} \times 100 (\%)$$

$Z_a$  and  $Z_b$  represent the specific acoustic impedance of each medium. Saijo et al previously reported the specific acoustic impedances of normal myocardium, degenerated myocardium, and fibrosis, using infarcted myocardial specimens obtained from autopsy.<sup>28</sup> In this report, the specific acoustic impedances of normal and degenerated myocardiums were  $1.75 \times 10^6$  Ns/m<sup>3</sup> and  $1.69 \times 10^6$  Ns/m<sup>3</sup>, respectively.<sup>28</sup> Therefore, the reflection factor of interface between these 2 media is calculated as 1.74%. This means that myocardial degeneration does not affect propagation characteristics of SWs. In fact, the present study showed that the lesion depth of normal myocardium was equivalent to that of the ischemic border zone. Furthermore, because we were able to create electrophysiological effects at deeper myocardium with SWCA but not RFCA, endocardial SWCA would be feasible for treating VT in patients with SHD.

Jauregui-Abularach et al previously compared epicardial cryoablation and irrigated RFCA in a porcine model of MI.<sup>29</sup> In this report, the lesion depths of cryoablation and RFCA in the infarct border zone were  $4.5\pm 2.3$  mm and  $5.0\pm 1.6$  mm, respectively, and the volumes of the infarct border zone were  $171.7\pm 173.1$  mm<sup>3</sup> and  $77\pm 53.5$  mm<sup>3</sup>, respectively.<sup>29</sup> In contrast, the lesion depth of the present study was  $4.4\pm 0.8$  mm. Assuming that the epicardial SWCA lesion was an inverse conical shape, the lesion volume calculated is 16.6 mm<sup>3</sup> in the present study. This means that our SWCA system does not increase the lesion volume unnecessarily compared with cryoablation or RFCA at the same lesion

depth. Consequently, our SWCA system may have no harmful effect on cardiac function after VT treatment.

### Safety and Superiority of SWCA for Arrhythmogenic Substrates Near the Coronary Artery

Coronary arterial injury due to RFCA is rare, but once it happens, it is a serious complication, especially in the epicardial ablation.<sup>30</sup> Viles-Gonzalez et al reported that both intimal and medial thickening of the coronary artery was noted when epicardial RFCA was performed in proximity to the arteries in pigs *in vivo*.<sup>31</sup> Cryoablation may be safer than RFCA, but Lustgarten et al reported that epicardial cryoablation of the coronary arteries could cause MI, and coronary neointimal proliferation was commonly noted in dogs *in vivo*.<sup>32</sup> To avoid this complication, a distance >5 mm between the ablation catheter and an epicardial artery is recommended for epicardial RFCA.<sup>33</sup> However, the arrhythmogenic substrate exists in the immediate vicinity of the coronary artery, resulting in the failure of epicardial RFCA in some cases. Indeed, Tung et al previously reported that epicardial ablation was withheld given the proximity to the coronary artery in 2 of 55 epicardial procedures in patients with nonischemic cardiomyopathy and in 5 of 20 epicardial procedures in those with idiopathic VAs.<sup>34</sup> However, in the present study, because direct application of SW to the coronary artery caused no coronary lesions, our SWCA system appears to be safer than RFCA to treat arrhythmogenic substrate even if it exists near the coronary artery.

Vasospasm is another serious side effect that could occur during RFCA as a direct thermal effect.<sup>35</sup> The right coronary artery and the left circumflex coronary artery are adjacent to the valvular annuli and are likely to suffer when radiofrequency energy is delivered to accessory pathways, cavotricuspid isthmus, and mitral isthmus.<sup>35</sup> In the present study, only mild coronary vasoconstriction occurred just after SW application, and no severe vasospasm occurred even if we directly applied SW to the coronary arteries. Furthermore, in case of RFCA, the cooling effect of the coronary artery could attenuate its effectiveness.<sup>36</sup> However, our SWCA system could create macroscopically visible lesions beyond the coronary arteries. The mean lesion depth ( $5.1 \pm 1.8$  mm) was equivalent to that in the normal myocardium. Because SWCA is a nonthermal system, it could create ideal lesions regardless of blood stream around the catheter tip. This may enable us to treat arrhythmogenic substrate just below the coronary arteries that is hard to ablate safely with epicardial RFCA. Although a number of alternative ablation methods have been under development,<sup>20–22</sup> none of them have this advantage. Thus, our SWCA system may be superior to other

ablation systems for arrhythmogenic substrates near the coronary artery.

### Ideal Irradiation Protocol for SWCA

We previously demonstrated a significant positive correlation between SW intensity and lesion depth.<sup>9</sup> In this study, we also demonstrated that maximal positive pressure of focused SW and pulse laser energy were positively correlated.<sup>9</sup> Thus, we were able to control the ablation depth by changing laser energy. In that protocol, irradiation number was uniformly 180 shots per site. Recently, deep irradiation with a lower irradiation number has been available in our SWCA system with the improvement of the laser generator. In the present study, we examined the feasibility and safety of epicardial SWCA with variable irradiation numbers and found that the best irradiation number was 90 shots per site. However, we must note that the epicardial approach with thoracotomy is the favorite condition for SWCA. This is because the epicardial surface is smooth, unlike the endocardium, and we can manually locate the SW catheter perpendicularly so that the entire edge of the reflector at the SW catheter tip can contact target tissue. Therefore, the ideal SWCA protocol might be different when used in the endocardial approach. Indeed, in the present study, the lesion depth of endocardial SWCA tended to be shallow compared with the epicardial approach. This is because our SW catheter and sheath are underdeveloped. Operability and flexibility of these devices need to be improved, as we had some difficulties in holding the SW catheter perpendicular to the endocardium. Moreover, the tip of the SW catheter moved a little with heart beats. We continue to improve the operability of the SW catheter and the SW generator, so we will be able to treat deeper myocardium with endocardial SWCA in the future. We consider that the ideal irradiation protocol is determined by SW intensity and irradiation number under the same stable condition that can maintain both efficacy and safety when used in the endocardial approach.

### Study Limitations

Several limitations should be mentioned for the present study. First, the SW catheter needs to be located as perpendicularly as possible to the myocardium in principle, which is often difficult given the catheter's thickness and/or flexibility. Therefore, we need to improve the quality of the sheath and SW catheter to deliver SW energy freely in the narrow cardiac chamber. Conversely, to obtain maximal ablation depth, the ablation electrode has to be perpendicular to the myocardium. However, it is sufficient that the ablation target is positioned in the propagation direction of the focused SW, namely, the extending direction of the central axis of the SW reflector. It is

possible to position the catheter tip, as mentioned earlier, using a catheter navigation and mapping system such as EnSite. Moreover, our goal is to ablate deep myocardium with an endocardial approach alone. We do not aim at epicardial application of our SWCA system with an open-chest surgical procedure in the clinical setting. We continue to improve our system for this goal and believe that endocardial SWCA will be able to treat every arrhythmogenic substrate even if it locates in the deep myocardium. Second, in the present study, an irrigated radiofrequency catheter was unavailable. If we could have used an irrigated radiofrequency catheter, the pacing and sensing threshold might have changed in the epicardial substrate model experiment. In the present study, we did not compare the incidence of thromboembolisms using magnetic resonance imaging. Sasano et al reported 2 phases of thrombogenesis caused by RFCA.<sup>37</sup> The acute phase of thrombogenesis is considered to be caused by hemostasis from the placement of the intravascular catheters. The late phase of thrombogenesis is caused by endothelial damage from application of the radiofrequency current. This late phase of thrombogenesis peaked 3 days after the procedure.<sup>37</sup> We previously demonstrated that SWCA caused less superficial damage than RFCA.<sup>9</sup> In the present study, we performed only endocardial SWCA or RFCA as an acute-phase study. Even if we had used magnetic resonance imaging after the protocol 1 procedure, it would be difficult to compare the risk of thrombogenesis in the late phase. Furthermore, Matsudaira et al previously demonstrated that electrode temperature of the part-to-tissue interface often exceeded the temperature of other parts of the system, and thrombus developed without an impedance rise at interface temperatures as low as 80°C.<sup>38</sup> Saline-irrigated radiofrequency ablation may reduce the incidence of thrombogenesis to some extent. However, it has been reported that the incidence of silent cerebral events after irrigated radiofrequency ablation is 6.8% to 24% in reality.<sup>23</sup> We will compare safety between SWCA and irrigated radiofrequency ablation in a clinical trial in the near future. Third, it took a relatively longer time for SWCA compared with RFCA. We applied the focused SW with an occasional pause to prevent overheating the laser generator, with resultant relatively longer ablation time; however, this method was necessary to prevent overheating the laser generator. We believe that we will be able to solve this limitation by improving the SWCA system devices. Fourth, since we performed only the acute study in the epicardial substrate model experiment, the SWCA lesions were not homogenous fibrotic lesions. Thus, it was possible to pace by epicardial pacing lead, even after SWCA with an endocardial approach. Similarly, because we did not examine SW lesions in the chronic phase in the MI model, we were unable to confirm that the SW lesion was present in fibrotic tissue. We previously demonstrated the histological features of SWCA

lesions, including initial myocardial disruption with interstitial hemorrhage and contraction band necrosis, followed by infiltration of inflammatory cells with resultant formation of homogeneous fibrotic lesions.<sup>9</sup> If we performed a chronic phase study in the epicardial substrate model experiment and MI model experiment, pacing would be more difficult or the SW lesion at ischemic border zone would be more homogeneous fibrotic lesion. Fifth, although the heart-beat synchronized equipment was attached to the SW catheter in the present study, the temperature of the SW generator elevated quickly, and its performance deteriorated when the animal's pulse was fast. Sixth, although our SWCA system caused no serious complications when applied directly to the coronary arteries, we did not examine the influence of the endocardial approach on the coronary arteries. Because the distance between the reflector and the focus point was 1.5 mm, shear stress created by focused SW had no influence on the coronary arteries. However, it remains to be examined whether the cavitation phenomenon could damage the coronary arteries. Seventh, because the diameter of the SW catheter is thick, we need to pay more attention to vascular complications of the catheter access site. Eighth, the lesion depth of SWCA varied depending on the period. Indeed, when we applied the focused SW to the normal myocardium for 360 shots per site using an epicardial approach in the infarction model experiment, the lesion depth reached  $4.0 \pm 1.0$  mm. In contrast, in the irradiation number-optimization experiment, the lesion depth reached  $\approx 6.5$  mm even if we applied only for 90 or 135 shots per site. This is in part because the lesion depth of SWCA is influenced by various factors. Thus, we need to improve the stability of the SW generator.

## Conclusions

In this validation study in pigs *in vivo*, we were able to demonstrate that our SWCA system is effective and safe for both the deep myocardium and the ischemic border zone and that the system causes no coronary complications even when applied directly to the arteries. Thus, our SWCA system may be a promising option for VT treatment in patients with SHD.

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## Disclosures

Hirano, Yamamoto, and Shimokawa have stocks of the Shock Wave Medical, Inc. The remaining authors have no disclosures to report.

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