PRECLINICAL RESEARCH

Septal Reduction Using Transvenous Intramyocardial Cerclage Radiofrequency Ablation

Preclinical Feasibility

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VISUAL ABSTRACT

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors’ institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the JACC: Basic to Translational Science author instructions page.

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HIGHLIGHTS

- Surgical myectomy is morbid and transcoronary alcohol septal ablation can result in geographic miss or occasional nontarget injury.
- We developed a transvenous intraseptal radiofrequency ablation technique (cerclage ablation method) to overcome the shortcomings of surgical myectomy and alcohol septal ablation.
- We delivered dedicated intraseptal radiofrequency ablation catheter into the ventricular septum through the coronary sinus and a septal vein. The ablated volume of myocardium was larger at higher electrode temperatures and using an irrigated-ablation mode in vitro. Cerclage ablation was successful in all in vivo attempts and induced a focal regional wall motion abnormality at later follow-up.
- This study presents in vivo evidence of the feasibility, effectiveness, and safety of cerclage ablation method to debulk interventricular septal myocardium.

SUMMARY

Debulking of left ventricular septal mass is typically accomplished using surgical myectomy, which is morbid, or using transcoronary alcohol septal ablation, which can result in geographic miss and occasional catastrophic nontarget coronary injury. The authors developed and tested operational parameters in vitro and vivo for a device to accomplish transvenous intraseptal radiofrequency ablation to reduce ventricular septal mass using a technique derived from mitral cerclage, which the authors call cerclage ablation. Cerclage ablation appeared feasible in vitro and safe and effective in vivo. Cerclage ablation is an attractive new approach to debulk the interventricular septum in obstructive hypertrophic cardiomyopathy. These data support clinical investigation.

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Hypertrophic cardiomyopathy (HCM) causes heart failure, mitral valve regurgitation, and sudden cardiac death (1–4). Disabling symptoms of left ventricular outflow tract obstruction can be relieved using surgical ventricular septal myectomy (5) and transcoronary alcohol septal ablation. Transcoronary alcohol septal ablation is an attractive alternative offered to older patients at higher risk of complications from surgical myectomy. Transcoronary alcohol septal ablation can result in geographic miss (when available septal perforator arteries fail to subtend the obstructing portion of the septum) and rare, but catastrophic, reflux (to the left anterior descending coronary artery) or spillover (for example, communicating to the posterior descending coronary artery), and more frequent requirement for permanent pacemaker implantation (6–12).

Recently Liu et al. (13,14) reported transthoracic needle radiofrequency (RF) ablation for HCM. Under general anesthesia and transthoracic echocardiography (TTE) guidance, a long 17G RF ablation needle was inserted into the hypertrophied interventricular septum through the chest wall and apical myocardium in 15 patients with HCM. Their approach risks epicardial coronary and myocardial injury, and requires traversing the chest wall and possibly lungs, along with general anesthesia. A transvenous catheter-based approach might be an attractive alternative that would obviate bystander tissue injury and general anesthesia. Our group has proposed a family of catheter procedures that enter the interventricular septum through the coronary veins to treat (mitral loop cerclage [15]), tricuspid valve regurgitation (cerclage tricuspid block [16]), and atrioventricular (AV) conduction failure (cerclage physiological pacing [17]). Coronary vein access also affords a novel opportunity to debulk the interventricular septum using RF ablation, which we describe here.

We developed a simple transvenous catheter approach to overcome the shortcomings of surgical myectomy and transcoronary alcohol septal ablation (Figure 1). We deliver a low-profile ablation catheter into the ventricular septum using the same transvenous coronary sinus technique and trajectory used in mitral cerclage annuloplasty (16,18). Herein we report the in vitro and in vivo evaluation of cerclage...
RF intraseptal ablation using purpose-built catheter prototypes.

**METHODS**

**PROTOTYPE ABLATION DEVICES.** Monopolar (15-mm solenoid electrodes) or multipolar (5 to 6 electrodes spaced 3 mm apart) catheters were manufactured in open-lumen irrigated (5-Fr) and non-irrigated (4-F) forms, and were provided by Tau-PNU Medical (Busan, Republic of Korea) (7,19–22). All incorporated a thermocouple immediately proximal to the electrodes. A dispersive electrode was applied externally to the skin. Irrigation used a commercially available saline pump (SP-8800, AMPall Co., Ltd, Seoul, Republic of Korea) operating 0.5 to 3 ml/min. The ablation catheters were driven by a 400 kHz RF signal generator (Myogen V-1000, RF Medical, Ltd, Seoul, Republic of Korea) (Figure 1). The generator was operated in temperature-controlled mode and set to pause if impedance exceeded a threshold (≥250 ohms).

**ABLATION IN VITRO (EX VIVO STUDY).** To optimize ablation parameters, we tested the following variables: monopolar versus multipolar; nonirrigated versus irrigated (1 ml/min); ablation time (10, 20, or 30 min); and ablation temperature (65°C, 75°C, or 85°C). Experiments were performed in a constant-temperature 36°C saline-filled tank having a dispersion electrode at the bottom. On the basis of superior performance, temperature and duration experiments were confined to the monopolar irrigated configuration. We tested 6 sample swine heart explants for each of 9 parameters.

**ANIMAL EXPERIMENTS.** Animal experiments were approved by the animal care and use committee policies of the Pusan National Yangsan University Hospital. General anesthesia was induced with alfaxalone 5 mg/kg and xylazine 2 mg/kg intramuscular, and maintained with isoflurane 3%. Amiodarone (150-mg bolus, then 1 mg/min) was administered intravenously as needed to suppress catheter-induced arrhythmia. A total of 11 (nonsurvival n = 4, and then survival n = 7) Yorkshire swine (45 ± 5.4 kg, Orient Bio, Seongnam, Republic of Korea) underwent cerclage RF ablation. The technique was developed and refined in the nonsurvival animals.

The cerclage RF intraseptal ablation procedure is based on the coronary sinus approach of mitral cerclage annuloplasty. After engaging the coronary sinus with a balloon-tipped guiding catheter (Cello catheter, 8-F, Medtronic, Dublin, Ireland), a pressurized radiocontrast venogram is performed to depict and select a target septal perforator vein branch. A commercial 0.014-inch percutaneous transluminal...
coronary angioplasty guidewire (Asahi Sion, Conquest wire, or Astato wire, all Asahi Intecc, Aichi, Japan) are used to engage the target vein with the help of a dual-lumen microcatheter (Crusade catheter, Kaneka Corporation, Tokyo, Japan). Once the wire is inside the myocardium through the septal vein, the wire is intentionally directed toward the target site, which, in most cases, requires the wire to pass through the wall of the septal vein. Traversing the myocardium with the guidewire is done easily with provocation of repetitious ventricular premature contractions. The wire is engaged deeply to provide catheter support, the position is confirmed with TTE, and then the cerclage RF catheter is advanced into position inside the interventricular septum over the wire. By virtue of the high-precision tapered tip together with the pushability-oriented catheter design of the braided shaft, countertraction of the guidewire in the right ventricular cavity was not needed in this study. We further tested the following

(A) Radiofrequency (RF) energy was delivered in temperature-controlled mode for 10 min with or without saline irrigation through the catheter (1 ml/min). (B) The result of ex vivo experiments to determine the relationships between RF ablation and swine myocardial response ($p < 0.05$ in differences among all groups of volume or maximal diameter of volume only except the difference between 75°C irrigation and 85°C nonirrigation groups). Red squares indicate the maximal diameter of the ablated myocardium.
parameters in vivo: ablation temperature, ablation duration, and irrigation versus nonirrigation.

**FOLLOW-UP.** Among survival animals, TTE was performed with a GE Vivid Q (GE Healthcare, Milwaukee, Wisconsin) using a 5 MHz transducer immediately and 2, 4, 6, and 8 weeks after the procedure. Parasternal long-axis and short-axis views were obtained and stored digitally for subsequent off-line analysis. All echocardiographic data were analyzed using an off-line analyzing software (EchoPAC PC v202, GE Healthcare) by an expert cardiologist (J.H. Park) in the core echocardiographic laboratory at the Chungnam National University Hospital). Measurement of myocardial thickness at the basal level was done at the end-diastolic frame more than 3 times, and an average value was used.

The primary endpoint of the animal experiments was technical feasibility of RF delivery into the intraseptal myocardium of the basal septum without

### TABLE 1 The Average of Ablated Myocardial Volume and Maximum Diameter of Volume According to Parameters in Ex Vivo Tests

| Group               | Watts  | Average Resistance, Ω | Ablated Myocardial Maximum Diameter of Volume, mm | p Value | Ablated Myocardial Volume, mm³ | p Value |
|---------------------|--------|------------------------|--------------------------------------------------|---------|--------------------------------|---------|
| Type of catheter, 75°C, 10 min | 4-F multipolar | 1,571 | 93 | 5 ± 1 | 0.004 | 290 ± 60 | 0.004 |
|                     | 4-F monopolar | 2,185 | 68 | 8 ± 1 | 0.004 | 550 ± 50 | 0.004 |
| Catheter size, 75°C, 10 min | 4-F monopolar | 2,185 | 68 | 8 ± 1 | 0.004 | 550 ± 50 | 0.004 |
|                     | 5-F monopolar | 2,343 | 63 | 9 ± 1 | 0.126 | 820 ± 90 | 0.006 |
| Ablation time, 75°C, 5-F monopolar | 10 min | 2,343 | 63 | 9 ± 1 | 0.126 | 820 ± 90 | 0.006 |
|                     | 20 min | 4,060 | 70 | 10 ± 1 | 1,110 ± 150 | 1,070 ± 180 | 0.001 |
|                     | 30 min | 5,512 | 63 | 10 ± 1 | 1,110 ± 150 | 1,070 ± 180 | 0.001 |
| Temperature, 10 min, 5-F monopolar | 65°C | 1,323 | 69 | 5 ± 0 | <0.001 | 280 ± 60 | <0.001 |
|                     | 75°C | 2,343 | 63 | 9 ± 1 | 280 ± 60 | <0.001 |
|                     | 85°C | 3,141 | 63 | 12 ± 1 | 1,620 ± 130 | 1,620 ± 130 | 0.001 |
| 65°C, 10 min, 5-F monopolar | No irrigation | 1,323 | 69 | 5 ± 0 | 0.002†‡§ | 280 ± 60 | <0.001†‡§ |
|                     | Irrigation on, 1 ml/min | 4,134 | 73 | 10 ± 0 | 1,430 ± 200 | 1,430 ± 200 | <0.001†‡§ |
| 75°C, 10 min, 5-F monopolar | No irrigation | 2,343 | 63 | 10 ± 1 | <0.001 | 820 ± 90 | <0.001 |
|                     | Irrigation on, 1 ml/min | 4,798 | 72 | 13 ± 1 | 2,000 ± 210 | 2,000 ± 210 | <0.001†‡§ |

* Differences in volume or diameter according to temperature when performed with irrigation. † Differences in volume or diameter according to temperature when not performed with irrigation. ‡ Difference in volume or diameter at 65°C depending on whether saline irrigation was used or not. § Difference in volume or diameter at 75°C depending on whether saline irrigation was used or not. k Difference between groups of 4.

### FIGURE 3 Representative Porcine Septal Venograms

The average diameter of the septal veins was 1.5 ± 0.4 mm, and the average length was 6.6 ± 2.4 mm (n = 10).
major adverse events. Secondary endpoints of the survival animal experiments were safety and septal thinning during follow-up.

In the analysis of the wall-thinning data, >40% reduction was arbitrarily applied as the successful criteria of wall thinning on the basis of Liu’s human data (13). One animal underwent contrast-enhanced cardiac computed tomography (CT) 8 weeks after ablation. After euthanasia, cardiac explant specimens were formalin-fixed, paraffin-embedded, and then stained with hematoxylin and eosin for microscopic examination.

**STATISTICAL ANALYSIS.** Continuous variables are presented as mean ± SD or median (25th to 75th percentiles) as determined by Kolmogorov-Smirnov normality test. Data were compared using Mann-Whitney U test, analysis of variance, or Welch Two Sample t-test as appropriate. Analyses were conducted using Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, version 21.0, released 2012, IBM Corp., Armonk, New York). A p value <.05 was considered statistically significant.

**RESULTS**

**IN VITRO ABLATION PARAMETERS.** In swine heart tissue treated in vitro, the impact of ablation parameters on tissue necrosis is summarized in Table 1. Monopolar and irrigated catheter prototypes caused larger ablation fields than multipolar and nonirrigated prototypes (550 ± 50 mm³ for monopolar vs. 290 ± 60 mm³ for multipolar, at 75°C for 10 min; p = 0.004). Ablation volume progressively increased after ablation durations increased from 10 to 20 min (820 ± 90 mm³ vs. 1,110 ± 150 mm³; p = 0.010, respectively), but not longer. Higher temperature and irrigation caused further incremental volume and diameter of ablation (1,430 ± 200 mm³ with irrigation vs. 280 ± 60 mm³ without irrigation, at a flow rate of 1 ml/min at 65°C; p < 0.001; 2,000 ± 210 mm³ with irrigation vs. 820 ± 90 mm³ without irrigation, at a flow rate of 1 ml/min at 75°C; p < 0.001) (Table 1, Figure 2). Regarding the diameter of the ablated tissue, the largest diameter was seen on temperature-controlled mode at 75°C with irrigation compared with the smallest diameter, which was seen on low temperature (65°C) controlled without irrigation using 5-F monopolar ablation for 10 min (13 ± 1 mm vs. 5 ± 0 mm; p < 0.001). The ablated diameter at 85°C without irrigation was between the value of the 75°C temperature control and 65°C under irrigation (12 ± 1 mm vs. 13 ± 1 mm vs. 10 ± 0 mm).

**CERCLAGE RFABLATION IN VIVO.** Efficacy. The cerclage RF ablation was successful in all swine (nonsurvival n = 4, survival n = 7). The average angiographic diameter of septal veins was 1.5 ± 0.4 mm, and the length was 6.6 ± 2.4 mm (Figure 3). Cerclage intraseptal RF application immediately induced akinesia in the target myocardium, which persisted through follow-up (Table 2). The 75°C or

### Table 2: Echocardiographic Features in Survival Group After RF Ablation

| Subject # | Catheter | Experimental Condition | Watts | Average Resistance, (Ω) | Wall Thickness, mm | Wall Motion | QRS Width, ms |
|-----------|----------|------------------------|-------|-------------------------|-------------------|-------------|--------------|
| 1         | 4-F multipolar | 15 min, 65°C 4 weeks follow-up | 570   | 108                      | 10.3              | Thinning (+) | II | 106          |
| 2         | 4-F multipolar | 40 min, 65°C 8 weeks follow-up | 2,396 | 73                       | 11.5              | Thinning (+) | II | NA           |
| 3         | 4-F multipolar | 60 min, 85°C 8 weeks follow-up | 3,219 | 86                       | 11.4              | Thinning (+) | III | 67          |
| 4         | 4-F monopolar | 30 min, 80°C 6 weeks’ follow-up | 1,329 | 141                      | 11.9              | Thinning (+) | II | 100          |
| 5         | 5-F monopolar | 30 min, 85°C 8 weeks’ follow-up | 2,259 | 65                       | 11.6              | Thinning (+) | III | 107          |
| 6         | 5-F monopolar | 45 min, 55°C 8 weeks’ follow-up | 8,114 | 87                       | 12.5              | Thinning (+) | II | 92           |
| 7         | 5-F monopolar | 15 min, 75°C Sudden death at 2 weeks Performed with irrigation | 1,608 | 57                       | 11.7              | Thinning (+) | III | 97           |

The wall motion of visual estimation in echocardiography subjectively determined, where – = no abnormality, /+ = mild abnormality, I = abnormality length was shorter than catheter length, II = abnormality length same length of the catheter, and III = abnormality length was longer than catheter length. Thinning (+) was defined as a reduction of a septal thickness, <30% in the baseline at last follow-up. Thinning (++) was defined as reduction of septal thickness by 30% or greater than baseline at last follow-up.

NA = not available due to technical problems; RF = radio frequency.
higher temperature-controlled mode with the 5-Fr irrigated monopolar catheter system showed more obvious wall thinning at 8 weeks’ follow-up.

Two representative echocardiography-guided ablations in swine # 5 are shown in Figure 4. In all cases, ablation immediately induced a hyperechogenic tissue appearance and a regional wall motion abnormality that persisted at follow-up (Table 2, Figure 4). The wall motion score index by TTE decreased in 6 of the 7 swine in the survival group, after the procedure. Cardiac CT imaging also showed the ablation-induced septal thinning at 8 weeks’ follow-up.

**Safety.** During technical development experiments, ablation induced frequent ventricular premature contractions and/or ventricular fibrillation requiring defibrillation but were suppressed thereafter using parenteral amiodarone.

One animal (#7) died suddenly at 2 weeks, attributed to electrical instability from a large infarction. No other animals exhibited important physiological complications. Two animals (29%) exhibited transient AV block during RF ablation (n = 2). One animal (15%) exhibited QRS prolongation >20% (Table 2, Figure 5). No animal exhibited high-grade AV conduction block.

**HISTOLOGICAL FINDINGS.** Histologic examinations were done at 8 weeks’ late follow-up (2 swine in survival), and a case of sudden death at 2 weeks (1 swine in survival). The specimen of late follow-up (survival #5 at 8 weeks) showed a large area of coagulated necrotic regions with borders that distinguished these regions from the surrounding normal healthy myocardial tissue (Figure 6). In subject #7, which showed sudden death at 2 weeks from excessive RF energy with respect to its baseline septal thickness, the pathological finding showed an acute ischemic injury pattern of the myocardium with consistent remote damage of the adjacent septal perforators up to 2.5 cm away from the direct ablation zone. Despite damage to the septal perforators, the epicardial left anterior descending artery was completely intact. In all specimens, tissue at the endocardial site appeared to be less damaged by RF injury.

**DISCUSSION**

This study shows that targeted cerclage intraseptal RF ablation accomplishes septal debulking via a transvenous approach, without inducing high-grade
AV block. Endocardial RF ablation has been described previously for HCM treatment (23–28), and it usually, if not universally, induces high-grade AV conduction block requiring permanent pacing. Other approaches to RF ablation have important shortcomings. Endocardial ablation using 7- to 8-F right- or left-ventricular cardiac electrophysiology catheters requires multiple points of ablation contact that may be discontinuous, may ablate excessive nontarget myocardium, and confers a high risk of high-grade AV conduction block (29). Recently, Liu et al. (13) reported transapical needle intraseptal RF ablation, which is unattractive in requiring protracted transthoracic transapical needle access to the basal septum despite cardiac and respiratory motion.

Our transvenous cerclage intraseptal RF ablation approach has other potential advantages. Because it is “right-sided,” it does not risk thromboembolic complications including stroke. And guidewires are navigated through coronary veins to intended targets. This characteristic of flexible manipulation of wire navigation to the intended target cannot deny the benefit of suitable anatomy of the septal perforator vein for an easier procedure compared with the case of having a poor septal vein. The target territory can be confirmed when the guidewire or catheter is visualized via echocardiography before ablation.
PROTOTYPE OF ABLATION CATHETER AND METHODS OF RF DELIVERY. Our prototype 4- to 5-F cerclage ablation catheters were easily advanced to intraventricular septal targets without using accessories beyond guiding sheaths, catheters, and guide wires, analogous to techniques used to introduce cardiac resynchronization therapy electrodes.

With this system (Table 1), we are able to ablate a large volume of myocardium (up to 1,624.1 ± 131.1 mm³) along the axis of the ablation catheter. As expected, ablation performance is superior using monopolar prototypes, with irrigation, and with longer and higher temperature settings. We predict this performance will allow better access to the basal septum compared with current (endocardial and transcoronary alcohol septal) ablation techniques.

As for imaging guidance for this procedure, a pre-procedural cardiac CT scan usually can show the anatomy of the septal vein very well and should be an important imaging tool to determine and plan the procedure beforehand (15). The whole procedure can be done under fluoroscopic guidance only. However, TTE or transesophageal echocardiography guidance is very useful to check the guidewire position during the procedure, which is important in order to have a successful and safe procedure.

POTENTIAL APPLICATION OF CERCLAGE RF ABLATION. The novel approach of our study can be applied, not only to HCM treatment, but also to other
diseases that mandate septal reduction or ablation (8,17). For instance, obstructive sigmoid septum without hypertrophied septum for focal RF ablation, ventricular tachycardia ablation in the basal interventricular septum, or preemptive septal reduction for relieving left ventricular outflow tract obstruction risk in transcatheter mitral valve replacement could be considered as potential indications of this approach.

**STUDY LIMITATIONS.** First, because we do not have an animal model of the hypertrophied septum, the normal septum was tested in our study. However, hypertrophied septum might have more room for placement of the ablation catheter and theoretically would also be more tolerant to the risk of conduction system damage. Second, this study was done only for proof of our concept for procedural feasibility with a handful of animal experiments; the actual response and long-term follow-up would be different in real-world clinical use in patients. Dosimetry data from the ex vivo study for looking at the relationship between ablation parameters and amount ablation tissue may not match with the in vivo study. It should be kept in mind that the amount of ablated tissue achieved in perfused tissue in a living organ is known to be approximately 30% lower than that of nonperfused ex vivo tissue (30). Devices used in this study are not the final mature model for human translation.

**CONCLUSIONS**

The findings confirm the feasibility, effectiveness, and safety of transvenous ventricular septal RF ablation along a mitral cerclage trajectory to debulk interventricular septal tissue. This promising preclinical result supports further investigation to debunk or prevent left ventricular outflow tract obstruction such as in hypertrophic cardiomyopathy or transcatheter mitral valve implantation.

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**AUTHOR RELATIONSHIP WITH INDUSTRY**

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