Enlargement of Catheter Ablation Lesions in Infant Hearts With Cryothermal Versus Radiofrequency Energy 
An Animal Study

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Background—Radiofrequency catheter ablation in immature hearts has been associated with marked enlargement of lesions over time, with potential for related late adverse events. It remains unknown whether cryothermal ablation lesions display a similar pattern of growth.

Methods and Results—Ablation lesions (n=384) were performed in 32 infant miniature swine in right and left atria, ventricles, and atrioventricular (AV) grooves preselected by a randomized factorial design devised to compare radiofrequency and cryothermal lesions produced by 7F 4-mm electrode-tip catheters. Animals were euthanized acutely or at 1, 6, or 12 months, according to the randomization scheme. The miniature swine weighed 8.8±1.2 kg and were 63±13 days of age at time of ablation. The minimum temperature during cryoablation was −79.8±3.4°C and the average temperature during radiofrequency ablation was 54.4±5.5°C. On morphometric analyses, no differences in the rate of growth of ablation lesions were noted between the 2 energy modalities in atria (P=0.44), ventricles (P=0.57), or AV grooves (P=0.69). Lesion volumes increased 3.3-fold in atria (95% confidence interval [CI], 2.3 to 4.3; P=0.001) and 2.2-fold in ventricles (95% CI, 1.4 to 3.0; P<0.0001), with the difference between chambers being nonsignificant (P=0.22). Whereas the depth of AV groove lesions increased over time (1.9-fold; 95% CI, 1.5 to 2.3; P<0.0001), lesion volumes did not enlarge significantly (1.5-fold; 95% CI, 0.4 to 2.6; P=0.45).

Conclusions—Ablation lesions produced by cryothermal energy in immature atrial and ventricular myocardium enlarge to a similar extent to radiofrequency ablation. In contrast, AV groove lesion volumes do not increase significantly with either energy modality. (Circ Arrhythm Electrophysiol. 2011;4:211-217.)

Key Words: radiofrequency ablation • cryoablation • cryoenergy • infants • neonates

Large registry data indicate that radiofrequency catheter ablation procedures may be effectively and safely performed in children.1,2 However, infants and toddlers weighing <15 kg have been identified as a subgroup at higher risk of complications.3 Among the concerns raised are late tissue effects related to lesion growth in immature myocardium.4 Indeed, Saul et al5 noted that radiofrequency ablation lesions expand over time in infant sheep, with multiple extensions of fibrous and elastic tissue into surrounding normal myocardium. Clinically, a few cases of sudden death were reported in infants after radiofrequency catheter ablation, with expansive lesions confirmed by autopsy.6,7 It remains unknown whether cryoablation, which involves mechanisms of cellular injury different from thermal energy and produces distinct lesions with preserved tissue ultrastructure, is associated with less propensity for lesion expansion in immature hearts. Our objective, therefore, was to characterize and compare the growth of lesions produced by cryothermal and radiofrequency catheter ablation in infant hearts.

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Methods

Study Design
A randomized, factorial design, summarized in Figure 1, was devised to compare the growth rate of ablation lesions produced by radiofrequency versus cryothermal ablation in 32 infant Yucatan miniature swine 1 to 3 months of age, weighing <10 kg. This animal model was selected for its similarities to human neonates with regard to degree of maturity of the cardiovascular system at birth and its pattern of growth over time.8,9

The transcatheter energy modality, that is, radiofrequency or cryoablation, and time of euthanasia, that is, acute or 1, 6, or 12 months, were randomly allocated. The unit of randomization was the “cardiac chamber,” grouped into 4 categories: right atrium, left atrium, right atrioventricular (AV) groove/right ventricle, and left AV groove/left ventricle. Two ablation lesions were created in each

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right and left atrium, ventricle, and AV groove (posterior and lateral) for a total of 12 lesions per animal. Although both cryothermal and radiofrequency ablation may have been performed in any individual minipig in accordance with the randomization scheme, the same catheter was used for all lesions in a given cardiac chamber. To minimize misclassification errors, AV groove lesions were performed with the same energy modality as the corresponding ventricular lesions. The study was approved by the Montreal Heart Institute Animal Care and Use Committee and conformed to the guiding principles of the Canadian Council on Animal Care and Declaration of Helsinki.

Ablation Protocol

Acetylsalicylic acid (325 mg/d) was initiated 2 days before ablation and continued until animal euthanization. The miniswine were anesthetized with pentobarbital sodium (25 to 30 mg/kg), intubated, and ventilated with positive-pressure Harvard respirators. An intravenous heparin bolus of 100 IU/kg was administered at the start of the procedure, followed by hourly injections of 15 IU/kg.

Sheath introducers were positioned in the femoral vein. In adherence to the protocol, a 7F cryocatheter (Freezor, Medtronic CryoCath LP, St Paul, MN) and stored on a multigigabyte hard drive and optical disk. Each cryoapplication was maintained for 4 minutes, with a single freeze-thaw cycle. Temperatures were displayed and recorded by a physiology recording system (EP WorkMate System, St Jude Medical, Webster, Inc, Diamond Bar, CA) with a 4-mm distal electrode tip was used for all lesions in a given cardiac chamber. To minimize misclassification errors, AV groove lesions were performed with the same energy modality as the corresponding ventricular lesions. The study was approved by the Montreal Heart Institute Animal Care and Use Committee and conformed to the guiding principles of the Canadian Council on Animal Care and Declaration of Helsinki.

Morphometric Analyses

In accordance with the factorial design, animals were euthanized immediately after the procedure (n=8) or at 1 month (n=8), 6 months (n=8), or at 12 months (n=8) after ablation with a lethal injection of pentobarbital. Heart and lungs were explanted, rinsed, fixed in 10% formalin, and transferred to a pathology laboratory. All personnel were blinded to the ablation modality. Representative sections of epicardial and endocardial surfaces were taken and gross surface maximal lesion length and width measured. Tissue blocks containing the entire ablation lesion with adhering tissue were processed for histology. 

Figure 1. Overview of study design. Time of euthanasia and energy modality for transcatheter ablation were randomly allocated. RA denotes right atrium; LA, left atrium; RV, right ventricle; LV, left ventricle; LAVG, left atrioventricular groove; and RAVG, right atrioventricular groove.

Results

Ablation Lesion Identification and Settings

A total of 384 ablation lesions were systematically created in right and left atria, right and left ventricles, and right and left AV grooves of 32 Yucatan miniature swine weighing 8.8±1.2 kg at 63±13 days of age. A total of 311 (81.0%) lesions were identified macroscopically and processed for

Statistical Analyses

Nonadjusted continuous variables are presented as mean±standard deviation. Given that several ablation lesions were created in each animal, analyses considered the nonindependent data structure. Adjusted summary statistics are presented as estimated marginal means with standard errors. Generalized estimating equations were used to produce marginal regression models for cluster sampling data by specifying link (ie, identity) and distribution (ie, normal functions for continuous outcomes (ie, lesion depth, width, and volume). First-order autoregressive [AR(1)], exchangeable, and unstructured correlation structures were considered. The AR(1) correlation structure was retained since it was associated with the smallest pseudolikelihood under independence model criterion. Cardiac chamber was included as a covariate in models assessing changes in lesion dimensions over time with radiofrequency versus cryoablation. For comparisons of thrombus formation, a binomial distribution was specified with a logit link and an exchangeable correlation structure. Interobserver reliability was assessed by means of an intraclass correlation coefficient. Probability values <0.05 were considered statistically significant. Statistical testing was performed using SAS software Version 9.2 (SAS Institute, Cary, NC). The study was designed to provide >80% statistical power to detect an effect size (difference in mean volume/common standard deviation of volume) of 0.7 at each time point, with an overall significance level of 0.05.
histological analyses. Missing lesions were equally distributed between the two energy modalities (ie, cryothermal 37; radiofrequency 36), with 24 (32.9%) delivered in atria, 14 (19.2%) in ventricles, and 35 (47.9%) at AV grooves. The average temperature recorded during cryoablation was $-73.2 \pm 14.9^\circ C$, with a minimum temperature of $-79.8 \pm 3.4^\circ C$. All lesions were applied for 4 minutes. The average temperature recorded during radiofrequency ablation was $54.4 \pm 5.5^\circ C$, with an impedance of $112.7 \pm 16.5 \Omega$, and power of $26.3 \pm 3.4 W$. The average duration of radiofrequency applications was $59.2 \pm 7.4$ seconds, with 8 of 64 (12.5%) ventricular ablation lesions interrupted prematurely by 5 seconds or more due to ventricular tachycardia or fibrillation. In contrast, no ventricular arrhythmia was induced by cryoablation.

Ablation Lesion Characteristics

On qualitative microscopic analysis, acute cryothermal and radiofrequency ablation lesions were hemorrhagic, with prominent contraction band necrosis. Cryoablation lesions were well delineated, with an endocardial surface that was rarely disturbed. In contrast, radiofrequency ablation lesions were characterized by disruption of the endothelial cell layer and ragged edges less clearly demarcated from underlying normal myocardium. Gross appearance of late lesions are shown in Figure 2 and representative histological examples are portrayed in Figure 3. Except for increasing size, 1-, 6-, and 12-month lesions appeared similar, with normal myocardial cells replaced by dense areas of fibrosis. Multiple extensions of fibrous and elastic tissue appeared as early as one month with both cryothermal and radiofrequency ablation.

Transmural lesions were noted in all locations at all stages of maturity but were more common in the atria (70.1%) than ventricles (38.8%) or AV grooves (36.6%) (overall, $P<0.0001$). The proportion of transmural lesions was similar between cryothermal and radiofrequency ablation ($P=0.96$). Thrombus on the lesion surface was more frequently seen

Figure 2. Epicardial surface 1 year after ablation. Gross appearance of ventricular lesions 1 year after endocardial cryothermal (A) and radiofrequency (B) catheter ablation are shown. Note the large, pale, white lesions on the epicardial surface of the left ventricles. In addition, a pearly white transmural lesion produced in the left atrium by radiofrequency energy may be seen in panel B.

Figure 3. Histological characteristics of cryothermal and radiofrequency ablation lesions. Typical histological characteristics 1 month (A) and 1 year (B) after radiofrequency ablation are shown. All displayed lesions were created in the right ventricle, stained with Masson trichrome, and magnified 16-fold for visual comparison. At 1 month, thrombus is noted on the surface of the radiofrequency (A) but not cryothermal (C) ablation lesion. Twelve-month lesions are devoid of surface thrombosis (B and D). Multiple extensions of fibrous and elastic tissue were observed as early as 1 month after ablation. Note the much larger lesion volumes at 12 months (B and D) compared with 1 month (A and C).
with radiofrequency than cryothermal ablation (27.3% versus 13.6%, \( P = 0.006 \)). It was predominantly observed in the acute setting (ie, 73.3% versus 26.8% with radiofrequency versus cryothermal ablation, \( P < 0.0001 \)) and detected on only 1 radiofrequency and 1 cryoablation lesion at 6 months. All 12-month lesions were devoid of thrombus.

**Ablation Lesion Dimensions**

The minipigs increased in weight from 8.8 ± 1.2 kg at baseline to 62.8 ± 31.2 kg at 12 months. The intraclass correlation coefficient for morphometric analyses was 0.991 (\( P < 0.0001 \)). Dimensions of ablation lesions are summarized in the Table according to time of euthanasia and chamber of ablation. Estimated marginal mean volumes of acute cryoablation versus radiofrequency ablation lesions were 86.4 ± 12.6 mm\(^3\) versus 100.9 ± 15.5 mm\(^3\), respectively (\( P = 0.26 \)). Maximum acute lesion depths were 3.9 ± 0.3 mm with cryoablation and 3.2 ± 0.1 mm with radiofrequency energy (\( P = 0.035 \)). Corresponding maximum widths were 4.9 ± 0.7 mm and 5.4 ± 0.2 mm, respectively (\( P = 0.45 \)). Acute ventricular lesion volumes in atria, AV grooves, and ventricles were 68.3 ± 13.7 mm\(^3\), 78.9 ± 19.1 mm\(^3\), and 105.2 ± 16.1 mm\(^3\), respectively, with a statistically significant difference between atria and ventricles (\( P = 0.007 \)). Lesion volumes were similar in right versus left-sided cardiac chambers (\( P = 0.90 \)).

**Enlargement of Ablation Lesions**

Figure 4 portrays the rate of enlargement of lesions produced by radiofrequency and cryothermal energy according to site of ablation. On morphometric analyses, no differences in the rate of growth of ablation lesions were noted between the 2 energy modalities in atria (\( P = 0.44 \)), ventricles (\( P = 0.57 \)), or AV grooves (\( P = 0.69 \)). As summarized in the Table, increases in lesion depth and width were likewise similar with radiofrequency and cryothermal ablation. Over a 12-month period, ablation lesion volumes increased 3.3-fold in atria (95% confidence interval [CI], 2.3 to 4.3; \( P = 0.001 \)) and 2.2-fold in ventricles (95% CI, 1.4 to 3.0; \( P < 0.004 \)), with the difference between the 2 chambers being nonsignificant (\( P = 0.22 \)). Whereas the depth of AV groove lesions increased over time (1.9-fold; 95% CI, 1.5 to 2.3; \( P < 0.0001 \)), lesion volumes did not enlarge significantly (1.5-fold; 95% CI, 0.4 to 2.6; \( P = 0.45 \)).

**Discussion**

Although radiofrequency catheter ablation is occasionally indicated in infants and small children, the increased rate and severity of complications have led some to recommend reserving these interventions for dire circumstances.\(^3\)\(^6\)\(^11\)\(^13\)\(^14\) In a series of 18 radiofrequency ablation procedures in children weighing <15 kg, complications included pericardial effusion, mitral regurgitation, and myocardial infarction.\(^16\) These appeared to be related to the dose of radiofrequency energy received, as indexed by body size. Substantial late tissue effects have occasionally been observed in the young, with rare cases of sudden death.\(^6\)\(^7\) Autopsies revealed myocardial cavitation at the presumed site of ablation, with marked lesion expansion.\(^6\)\(^7\)

Such observations prompted Saul et al\(^5\) to systematically assess acute and late effects of radiofrequency lesion production in immature myocardium. Under fluoroscopic guidance,
Radiofrequency ablation lesions were created in all 4 cardiac chambers of 19 infant sheep (10.9±1.4 kg). Lesion sizes and histological characteristics were assessed acutely (n=5), at 1 month (n=5), and at 8.5 months (n=9). Whereas Saul et al primarily focused on lesion width and depth, we further extended these findings by performing detailed histological 3-dimensional morphometric analyses of lesion volume. Such an approach overcomes limitations of formula-based estimates (eg, prolate ellipsoid)\textsuperscript{17} and yields highly consistent results.\textsuperscript{18,19} Using this methodology, we confirmed the observation by Saul et al that radiofrequency ablation in immature myocardium results in substantial enlargement of atrial and ventricular lesions but not AV groove lesions over time. Although underlying mechanisms remain unknown, it was speculated that expansion of radiofrequency ablation lesions may be driven in part by the serrated bordering zones\textsuperscript{18,20,21} that produce multiple extensions of fibrous and elastic tissue into surrounding normal myocardium.\textsuperscript{5,22}

The main focus of the current study was to determine whether cryoablation in immature myocardium would result in a comparable degree of lesion enlargement to radiofrequency ablation. Because the 2 energy modalities produce cellular effects through different mechanisms and result in lesions that are histologically distinct, we speculated that lesion expansion in immature myocardium would likewise differ. By virtue of the fact that cryolesions are more homogeneous, with clearer and smoother demarcations from underlying normal myocardium,\textsuperscript{20,23} and that ultrastructural tissue integrity is maintained,\textsuperscript{24} with lesser propensity to rupture or form aneurysms,\textsuperscript{25,26} we hypothesized that cryolesions would enlarge to a lesser degree. Our hypothesis was tested using a rigorous randomized factorial design with a previously validated end point (intraclass correlation coefficient of 0.991) that is robust to irregularities in lesion morphology. Moreover, because the unit of randomization was the cardiac chamber as opposed to the animal, the study design allowed for coexisting radiofrequency and cryoablation lesions within the same minipig. This approach was combined with generalized estimating equations analyses to isolate the impact of energy modality and limit animal-specific outlier effects.

Acute ablation lesion characteristics observed, proportion of missing lesions, and greater thrombogenic potential with radiofrequency energy are consistent with prior reports.\textsuperscript{18,19,27} Acute lesion sizes and the extent of variability obtained by 4-mm electrode-tip radiofrequency and cryothermal ablation catheters, with cryoablation producing nonsignificantly smaller lesion volumes, are likewise compatible with prior observations in mature animals.\textsuperscript{18,19} It is worth noting that although the study was powered to compare expansion rates of ablation lesions according to energy modality, analyses that further divide lesions into multiple subgroups (eg, by cardiac chamber and time of euthanasia) are limited by smaller sample sizes.

In adult animals, cryoablation lesions have not been noted to expand over time and are considered mature by 7 days, with sharp borders, dense areas of fibrotic tissue, and contraction band necrosis.\textsuperscript{18,19} The postablation healing response is somewhat slower with radiofrequency energy, as replacement fibrosis is confined to the outer margin of lesions at 7 days, with lingering intralesional hemorrhage.\textsuperscript{18,19} Radiofrequency ablation lesions become densely fibrotic by 1 month.\textsuperscript{28} We had speculated that differences in the pathophysiology of acute injury and healing processes associated

![Figure 4](http://circep.ahajournals.org/)

**Figure 4.** Growth of ablation lesions in atria, ventricles, and AV grooves with cryothermal versus radiofrequency energy. Ablation lesion volumes produced by cryothermal (blue) and radiofrequency (red) energy in atria (A), ventricles (B), and atrioventricular grooves (C) are depicted by straight lines with surrounding 95% CIs, according to time of euthanasia. No significant differences between cryothermal and radiofrequency energy were observed. Note that lesion volumes at the AV grooves did not increase significantly over time. *Probability values are derived from generalized estimating equations analyses that include the time interval between ablation and animal euthanasia, energy modality, and first-order interaction between time and energy modality.
with cryothermal and radiofrequency ablation may produce different effects on immature myocardium. Contrary to our hypothesis, the enlargement of cryolesions was similar to radiofrequency lesions in all cardiac chambers. These results suggest that ablation lesion enlargement in immature atrial and ventricular myocardium is independent of the energy modality by which they were produced.

It may be speculated that lesion growth is predominantly determined by enlargement of the fibrous core that is common to radiofrequency and cryothermal lesions. Unlike fetal wound healing, which is characterized by absence of scar, transforming growth factor-β1 is a ubiquitous cytokine with potent postnatal fibrogenic effects. Indeed, neonatal fibroblasts express particularly high levels of latent transforming growth factor-β1 and insulin-like growth factor binding protein-3, with upregulation of connective tissue growth factor and collagen type I. In a newborn mouse model, both connective tissue growth factor and transforming growth factor-β1 were strikingly upregulated 1 week after induced myocardial infarction in fibroblasts and within the thin layer of surrounding surviving myocytes. The 2 ligands colocalized with fibronectin and were clearly related to the development of fibrosis. This rapid fibrogenic response is compatible with our observation of multiple extensions of fibroelastic tissue as early as 1 month after ablation.

### Conclusion

As the immature myocardium grows, atrial and ventricular lesions produced by cryothermal and radiofrequency ablation enlarge to a similar degree, refuting the notion that cryoablation should be favored on the basis of lesion expansion. In contrast, AV groove lesion volumes do not increase significantly with either energy modality. Further studies are required to elucidate the pathogenesis of ablation lesion growth in immature myocardium, identify potential therapeutic targets to limit lesion expansion, and assess the efficacy of preventive approaches.

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### Disclosures

Dr Dubuc is a consultant for Medtronic CryoCath LP. Dr Roy was chairman of a clinical adjudicating events committee for a trial sponsored by Medtronic CryoCath LP (STOP-AF).

### References


**CLINICAL PERSPECTIVE**

Catheter ablation in infants and small children, though once reserved for life-threatening or drug-refractory arrhythmias, is increasingly performed. However, radiofrequency ablation lesions may expand considerably over time, and occasionally result in sudden death. Cryoablation has an attractive safety profile and involves mechanisms of tissue injury distinct from radiofrequency ablation. It was unknown whether cryoablation is associated with a similarly propensity for lesion expansion in immature hearts. We therefore randomly assigned 32 infant miniature swine (63±13 days of age; 8.8±1.2 kg) to catheter ablation by radiofrequency or cryothermal energy. A total of 384 ablation lesions were created in all cardiac chambers and atrioventricular grooves. Animals were euthanized acutely or at 1, 6, or 12 months, according to the randomization scheme. Atrial and ventricular ablation lesion volumes produced by cryothermal energy increased 2- to 3-fold within a year, in a manner similar to radiofrequency ablation. In contrast, atrioventricular groove lesion volumes did not increase significantly with either energy modality. These results suggest that lesion enlargement in immature myocardium is independent of the type of energy used for ablation and may be predominantly determined by growth of the fibrous core. Late tissue effects, therefore, remain a real concern with either energy modality and should be considered when balancing risks and benefits of catheter ablation in infants and small children.
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