Contrasting Effects of Convective Flow on Catheter Ablation Lesion Size: Cryo Versus Radiofrequency Energy

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Background: Cryoablation has now become an alternative to treat many cardiac arrhythmias, and may be the treatment of choice in some patient populations. We compared the effects of convective flow on large-tip cryo and radiofrequency (RF) lesions dimensions.

Methods: Cryoablation and RF ablation were performed on porcine heart sections in a saline bath with varying directed flow rates. Cryoablation was performed for 4 minutes on 50 tissue pieces with tip temperature controlled at $-80^\circ$C. RF ablation was performed on 50 tissue pieces for 60 seconds at $60^\circ$C tip temperature. The pieces were placed in culture media for 24 hours, and then sectioned, stained, and measured.

Results: Cryoablation and RF lesion sizes varied significantly with flow such that higher flow rates produced smaller cryoablation lesions and larger RF lesions (mean cryoablation volumes: $854 \pm 402, 808 \pm 217, 781 \pm 217, 359 \pm 114,$ and $292 \pm 117$ mm$^3$ for 0, 1, 2, 3, and 5L/min flow rates, respectively, $P < 0.0005$). Trabeculated pieces had larger cryoablation lesions and smaller RF lesions than nontrabeculated ones at higher flow rate ($P < 0.005$). Cryoablation lesion volume increased as the time to reach $-80^\circ$C decreased ($r^2 = 0.72$).

Conclusion: In contrast to RF ablation, cryoablation lesion size is smaller at high flow rates, and larger at low flow rates due to the warming effects of local convective flow. The effects of high flow are reduced in areas of trabeculation, and the time to reach $-80^\circ$C predicts cryoablation lesion size. (PACE 2008; 31:300–307)

Introduction

Cryoablation has emerged as a treatment alternative for many cardiac arrhythmias, and may be the treatment of choice for certain arrhythmia substrates. Cryoablation has several safety advantages compared to radiofrequency (RF) ablation, with less risk of thrombogenesis, collagen shrinkage, and the ability to perform cryomapping. These aspects are important when performing ablation near the atrioventricular (AV) node or in areas where blood vessel stenosis may be a concern, such as near the pulmonary veins or coronary arteries in children.

While procedural success rates are close to those with RF ablation, cryoablation recurrences continue to be significantly higher than those with RF ablation, and are reported as high as 8–15% in some studies. This may be due to smaller permanent lesions sizes achieved with freezing tissue compared to heating tissue.

The effects of convective cooling on RF ablation are well described in the literature. The goal of this study was to determine the effect of convective flow on cryoablation lesion size, and make a direct comparison to RF ablation lesion size.

Methods

Setup (Fig. 1)

A local meat processor provided freshly removed porcine hearts. The hearts were infused with chilled physiological saline within an hour of excision and transported to the laboratory. Upon arrival, the hearts were sectioned into block-shaped pieces with the endocardial surface exposed ($20 \times 20$ mm, at least 15 mm depth). The tissue pieces were then placed in tissue culture media (Medium 199 [Invitrogen, Carlsbad, CA, USA] with 3% fetal bovine serum and 1% penicillin-streptomycin), and maintained at a temperature of $37^\circ$C. For each ablation, a tissue piece was removed from the medium and placed in an agar–water gel block. The gel block had similar electrical conductive properties ($0.54$ S/m at $500$ kHz, where $1 \text{ S} = 1 \text{ ohm}^{-1}$) to myocardium and simulated surrounding myocardium. The gel block was placed in a temperature-controlled 0.3%...
saline bath with similar thermal and electrical properties to blood (0.67 S/m at 500 kHz and 37°C). The bath temperature was maintained at 37°C using an automatic controller (Haake C1; Haake, Offenburg, Germany). A rigid polyethylene tube (20-mm diameter) located 2 cm from the tissue piece directed flow across the tissue and gel block; the lower tube edge was at the level of the tissue surface. A pump (Mag Drive WMD-20RLT-115, IWAKI, Tokyo, Japan) and flow meter (Model 7200, King Instrument, Garden Grove, CA, USA) were used to maintain and adjust saline flow across the tissue piece. Plastic tubing was used to supply the pump with saline from the bath and connect the pump to the outflow tube. The flow meter and pump were calibrated by injecting a droplet of dye at the inlet of the rigid tube. The wavefront maximum flow velocity was recorded at 30 frames/sec using a digital camera. Flow rates of 1, 2, 3, and 5 L/min corresponded to maximum flow velocities of 5.2, 10.3, 15.5, and 25.8 cm/s, respectively. Velocities around 15.5–25.8 cm/s corresponded to typical high flow velocities measured by Doppler echocardiography in a normal beating heart and have been used in other experiments testing the effect of flow on catheter ablation.

Ablation was performed using either an 8-mm tip cryocatheter (Freezor Max 5; CryoCath, Kirkland, Canada) or a 10-mm tip RF ablation catheter (Blazer II XP; Boston Scientific, Natick, MA, USA). The catheter was positioned perpendicular to the endocardial surface and placed at the center of the tissue piece. Trabeculation presence or absence was documented. Presence of trabeculation was defined as the catheter tip sitting within an area of trabeculation that contained at least one-third of the catheter tip. The cryocatheter was also advanced through a 40-cm polyethylene tube filled with saline at 37°C to simulate the catheter coursing through the body. A 15-g piece of copper was attached to the catheter to provide consistent tissue contact pressure. Cryoablation was performed using a CryoCath console. RF power was supplied by a commercial cardiac ablation generator (EPT-1000XP; Boston Scientific). During RF ablation, a piece of aluminum foil (15 × 10 cm) was placed in the saline bath more than 20 cm from the ablation catheter to provide electrical grounding.

### Ablation Protocol

**Cryoablation**

Cryoablation was performed on 50 tissue pieces for 4 minutes with temperature controlled to −80°C. External flow rate (0, 1, 2, 3, and 5 L/min) was selected randomly before each application, and tissue trabeculation presence was recorded for each piece. The time to reach −80°C was also recorded for each cryoablation. After ablation, the lesion center was marked by two small perpendicular incisions that crossed at the lesion center and the tissue pieces were placed in culture media (Medium 199 with 3% fetal bovine serum and 1% penicillin-streptomycin) for 24 hours.

**RF Ablation**

Temperature-controlled RF ablation was performed on 50 tissue pieces for 60 seconds, at a target temperature of 60°C and maximum power set at 100 watts (W). External flow rate (0, 1, 2, 3, and 5 L/min) was selected randomly before each application. Trabeculation presence was recorded for each piece. After ablation was complete, the tissue sample was placed in tissue culture (Medium 199 with 3% fetal bovine serum and 1% penicillin-streptomycin) for 24 hours.

### Tissue Processing

All the tissue samples were sectioned perpendicular to the endocardium, through the center of the lesion, and along the direction of flow. Each lesion was stained with nitroblue tetrazolium. Each lesion was photographed with a digital camera (PowerShot A510, Canon, Lake Success, NY, USA), and the image was downloaded to a computer. Image processing software (Paint Shop Pro 5.0, Corel Corporation, Ottawa, Canada) was used to approximate the lesion boundary by drawing an ellipse over the lesion image. The ellipse dimensions (long and short axes), lesion width, and lesion depth were measured using Image J v1.37 software (National Institutes of Health, Bethesda, MD, USA). Lesion volume was calculated using a general equation of volume for a partial ellipsoid that was derived using calculus (Fig. 2).

### Statistics

All variables are reported as mean ± standard deviation (SD). Analysis of variance (ANOVA) was
Figure 2. Stained cryo lesion with ellipse approximating the lesion border; the dimensions measured and the equation of volume for a partial ellipsoid. $V = \frac{(3a-h)b^2h\pi}{3a}$

used to determine significant changes in lesion dimensions (width, depth, and volume) with flow rate. Student’s $t$-test was used to compare RF and cryo lesions dimensions at each flow rate. Student’s $t$-test was also used to compare each lesion dimension with and without trabeculation presence. Simple linear regression was used to evaluate, individually, the relationship of flow and time to $-80^\circ$C with lesion dimensions. ANOVA, with analysis of covariance, was used to evaluate the combination of flow and trabeculation as predictors of lesion dimensions. Multiple linear regression analysis was also used to evaluate the contribution of flow to time to $-80^\circ$C as predictors of lesion dimensions. Statistical significance was considered at $P$ values smaller than 0.05.

**Results**

A total of 100 lesions were produced (50 cryoablation and 50 RF ablation). All lesions measured underwent ablation for the full application period. During RF ablation, there was no popping noted. Statistical significance in difference of lesion dimensions between Cryo and RF lesions is indicated in Figures 2–4.

**Lesion Dimensions**

**Width** (Fig. 3A)

Cryoablation lesion width decreased with increasing flow rate ($P < 0.01$), while RF lesion width increased with increasing flow rate ($P < 0.01$).
Cryoablation lesion width was significantly larger than RF lesion width at flow rates between 0 and 2 L/min \((P < 0.01)\), with no significant difference at 3 L/min. Cryolesion width was significantly smaller than RF lesion width at 5 L/min \((P < 0.05)\).

**Depth (Fig. 3B)**

Cryoablation lesion depth did not significantly change with flow rate as an overall trend. However, lesion depth was significantly smaller at high flow rates (3 and 5 L/min) than at low flow rates \((0–2 \text{ L/min})\) \((P < 0.05)\). RF lesion depth increased with increasing flow rate \((P < 0.05)\). Cryoablation lesion depth was significantly larger at 0 L/min \((P < 0.05)\), and was significantly smaller at 3 and 5 L/min \((P < 0.05)\) compared to RF lesion depth. There was no significant difference at 1 and 2 L/min flow rates.

**Volume (Fig. 3C)**

Calculated cryoablation lesion volume decreased with increasing flow rate \((P < 0.005)\) while RF lesion volume increased with increasing flow rate \((P < 0.005)\). Cryoablation lesion volume was significantly larger than RF lesion volume at 0 L/min and 1 L/min \((P < 0.05)\), and significantly smaller at 3 and 5 L/min \((P < 0.05)\) compared to RF lesion volume. There was no significant difference at 2 L/min flow rate.

**Lesion Shape**

Cryoablation lesions were shaped like a partial oblate (flow rates 1 and 1 L/min) or partial prolate ellipsoid (flow rates 2-5 L/min), and had a well-demarcated lesion border (Figs. 4 and 6). The maximum lesion width occurred at the tissue surface. In contrast, RF lesions were shaped like a partial oblate ellipsoid and had a lesion border that was not as well demarcated (Figs. 5 and 6). The maximum RF lesion width occurred several millimeters below the tissue surface.

**Trabeculations (Fig. 7)**

The presence of trabeculations did not significantly affect cryo lesion size at low flow rates \((0–2 \text{ L/min})\). However, at high flow rates (3 and 5 L/min), cryoablation lesions made in trabeculations were significantly larger than lesions made in nontrabeculated areas. Analysis of covariance revealed that the overall trend of increasing cryoablation lesion size in the presence of trabeculation was significant with all dimensions measured (width, depth, and volume; \(P < 0.01\) for all dimensions). The combination of trabeculation and flow was also predictive of cryoablation lesion volume, width, and depth \((P < 0.005)\). RF lesions were smaller in the presence of trabeculations at higher flow rates 2, 3, and 5 L/min \((P < 0.01)\). The presence of trabeculations had no significant effect on RF lesion volume at 0 and 1 L/min flow rates. Average RF power increased with increasing flow rate \((P < 0.005)\) and was significantly less for all flow rates in the presence of trabeculations except at 0 L/min (Fig. 8).

**Time to \(-80°C\)**

Time to \(-80°C\) ranged from 14 seconds to 30 seconds (Fig. 9) and a minimum temperature of \(-80°C\) was achieved for all 50 cryoablations. Cryoablation lesion volume decreased as the time to \(-80°C\) increased \((r^2 = 0.72)\). Lesions with times
Figure 6. Ellipsoid graphs comparing the average lesion dimensions for cryoablation and RF ablation at each respective flow rate. The series shows decreasing lesion dimensions with increasing flow rate for cryoablation ($P < 0.005$) and increasing lesion dimensions for increasing flow rate for RF ablation ($P < 0.005$). Note the partial prolate ellipsoid shape of cryoablation lesions and the partial oblate ellipsoid shape of the RF ablation lesions.

greater than 24 seconds had a mean volume of $313 \pm 150 \text{ mm}^3$ while lesions with times less than 24 seconds had a mean volume of $841 \pm 306 \text{ mm}^3$. Linear regression analysis revealed that time to $-80^\circ\text{C}$ was predictive of lesion volume and width, but not depth ($r^2 = 0.63, 0.72,$ and $0.33$, respectively). The addition of flow to this regression did not add any predictive value ($r^2 = 0.63, 0.74,$ and $0.33$, respectively). The mean time to $-80^\circ\text{C}$ was 16 seconds for 0 L/min and 27 seconds for 5 L/min for nontrabeculated tissue pieces.

**Discussion**

This study demonstrates the effects of convective flow on cryoablation lesions and provides a comparison between cryoablation and RF ablation at different flow conditions. The most important findings of this study are: (1) cryoablation lesion size decreases with increasing flow rate, (2) cryoablation lesions are larger than RF lesions at low flow rates and smaller than RF lesions at high flow rates, using comparable catheter tip sizes, (3) cryoablation lesion geometry is different than RF lesion geometry, and (4) the time to $-80^\circ\text{C}$ predicts cryoablation lesion size. The study also confirmed that RF lesion size increases with increasing flow rate. Taken together, these findings have important implications for the clinical application of cryo and RF ablations in humans.

A recent study showed that cryoablation lesion size is smaller at high flow compared to no flow. The data in this study compliment this finding, and provide a comparison at varying flow conditions. Cryoablation lesion size declined with increasing flow, with lesion volume being more than twice as large at no flow compared to maximum flow. While lesion width decreased with every increase in flow rate, there was not a significant
RF VERSUS CRYO VERSUS CONVECTION

Figure 7. (A) Graph of the average cryoablation lesion volume for trabeculated and nontrabeculated tissue pieces at each respective flow rate. (B) Graph of the average RF lesion volume for trabeculated and nontrabeculated tissue pieces at each respective flow rate. *P < 0.05 between trabeculated and nontrabeculated volumes. Error bars represent one standard deviation.

decrease in lesion depth until a flow rate of 3 L/min was reached (Fig. 3). This may be explained by the melting ice ball at the tissue surface. As the flow rate increases, the width of the ice ball decreases sequentially, exposing a wider tissue surface to the warming effects of flow. The lesion depth, however, is measured from a position that is directly below the catheter tip. The catheter shields this area of tissue from convective warming, requiring higher flow rates to achieve an effect on lesion depth.

This study also directly compares cryoablation lesion size with RF lesion size at varying flow rates. Conversely to cryoablation lesions, RF lesions became larger with increasing flow rates (Figs. 3 and 6). In areas of low flow (0 and 1 L/min), cryoablation created larger lesions, and in areas of high flow (3 and 5 L/min), RF ablation created larger lesions (Figs. 3 and 6). The smaller ice ball size during cryoablation at higher flow rates could be directly visualized in this ex vivo model (Fig. 10).

In situations where maximum lesion size is desirable, these results may be helpful in deciding between large-tip RF and cryoablation based on the anticipated local blood flow characteristics in the area of ablation. In areas of expected or documented low flow, such as in a Fontan atrium or in trabeculated areas, large-tip cryoablation may be superior to large-tip RF ablation unless the RF catheter uses an active cooling system, such as closed-loop irrigation or open irrigation. However, when a large lesion is desired in an area of high flow rate, such as along the AV groove or in the

Figure 8. Graph of the average power for the RF ablations at each respective flow rate. *P < 0.05. Error bars represent one standard deviation.

Figure 9. Scatter plot of all the cryoablation lesion volume samples versus the time to −80°C with an exponential curve fit and $r^2 = 0.72$.
right ventricular outflow tract (RVOT), a large-tip RF catheter is likely to be more efficacious. These findings also suggest that if cryoablation is performed in areas of high flow, decreasing the flow rate (such as with balloon occlusion of the blood flow proximal to the ablation site) may improve lesion creation in a clinically significant manner.

Increasing lesion size with increasing convective cooling is well described for RF ablation with normal-tip sized (4-mm length) catheters. Cooling the RF catheter tip allows the application of higher power by cooling the catheter and tissue surface. The higher applied power pushes the area of resistive heating deeper into the tissue, and creates larger RF lesions. In contrast, convective flow warms the cryocatheter and myocardium during cryoablation. While the inside of the cryocatheter, where the tip temperature sensor is located, is kept at \(-80^\circ\mathrm{C}\) by cryogenic cooling, convective warming of cryocatheter surface and tissue surface reduces tissue temperatures, therefore decreasing the lesion size. Increased convective warming at higher flow rates therefore results in larger differences between catheter tip temperature and tissue temperatures, making tip temperature not a good predictor of lesion size at varying flow rates. The dependence of lesion size on convective flow would also likely apply to the 6-mm cryocatheter, with reduced lesion size due to the smaller tip surface area.

As previously reported, cryoablation in this study produced lesions with a better demarcated border compared to RF lesions (Figs. 4 and 5). Lesion geometry was also different between cryoablation and RF ablation. Cryoablation produced lesions with a partial prolate (at high flow rates) or oblate ellipsoid shape (at low flow rates), and maximum lesion width at the tissue surface (Fig. 6). RF ablation created lesions with a partial oblate ellipsoid shape and maximum lesion width a few millimeters below the tissue surface (Fig. 6). This difference in lesion geometry is likely explained by thermodynamic differences between the two modalities. While during RF ablation, convective flow provides direct cooling of both the tissue surface and catheter, during cryoablation an ice ball protects the catheter and endocardium from the direct effects of blood flow (Fig. 10). The endocardial surface is therefore “protected” by the ice ball from convective effects.

In addition to convective flow, trabeculation had a direct impact on lesion dimensions. At high flow rates, larger lesion size for cryoablation and smaller lesion size for RF ablation was observed in the presence of trabeculations (Fig. 7). This study shows that the combination of flow rate and trabeculation presence was a good predictor of lesion size. However, without direct visualization of the catheter tip, detailed knowledge of trabeculation depth can be elusive to the catheter operator. Advances in imaging, such as three-dimensional transthoracic, transesophageal, and intracardiac echocardiography, might aid in assessing local flow and structure characteristics in the future.

Another clinically useful observation of this study is that the time to \(-80^\circ\mathrm{C}\) predicts lesion size (Fig. 9). This was true across all flow rates and in the presence or absence of trabeculation. Time to \(-80^\circ\mathrm{C}\) provides an easily observable variable during clinical procedures to help evaluate whether a specific lesion will likely be adequate for a given cryoablation application. In particular, when the time to \(-80^\circ\mathrm{C}\) is larger than 30 seconds, the resulting cryo lesion is unlikely to be of adequate size. This observation could be used along with other ablation endpoints to help predict cryoablation success and recurrence. It can also be used to guide decisions on the need for insurance lesions or possible flow reduction measures to improve lesion creation and size. If the time to \(-80^\circ\mathrm{C}\) is consistently elevated despite all efforts, RF ablation may be required to achieve the elimination of the arrhythmia substrate. In such situations, a catheter capable of performing both cryoablation and RF ablation would have high utility. In certain high flow situations like ablation near the AV node, the cryoablation safety profile may be very desirable. In these cases, the time to \(-80^\circ\mathrm{C}\) could be used as an aid with other endpoint data to predict cryoablation success and recurrence.

Limitations

The study was performed using an ex vivo model at constant flow rates. In clinical ablation settings, the cardiac cycle produces pulsatile blood flow. It is unclear how significant in vivo pulsatile flow would be when averaged over an ablation time of one or four minutes. In vivo tissue perfusion would also likely result in smaller lesion
sizes due to tissue warming during cryoablation and tissue cooling during RF ablation from coronary blood flow. Catheter tissue contact and direction were controlled in this study by application of a consistent tip pressure and angulation. In vivo, the catheter tip pressure and angulation may be highly variable, depending on many factors, some of which might affect the consistency of lesion dimensions produced by any catheter or technique. During cryoablation the catheter tip freezes to the tissue, prohibiting catheter tip movement. During RF ablation, however, the catheter tip is not stuck to the tissue, allowing for small movements between the tissue and catheter during in vivo ablation. This movement was not present in our in vitro setup and could affect the size of RF lesions dimensions produced in comparison to an in vivo ablation. In addition, saline was used in our experiment to simulate blood flow. This prohibited monitoring for blood boiling, charring, and coagulum formation, all of which are serious concerns during RF ablation.24

Conclusions
Convective cooling due to varying perfusate flow rates significantly affects lesion size for both cryoablation and RF ablation. At low flow rates, large-tip cryoablation catheters create larger lesions while at high flow rates, large-tip RF catheters create larger lesions. Cryoablation and RF lesion geometries are different. In the presence of high flow, trabeculations significantly affect lesion size such that cryo lesions are larger and RF lesions are smaller. In addition, the time to −80°C predicts lesion size for cryoablation. It should be noted that the operator must be aware of the potential complications as well as the benefits of large ablation lesions.

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References