Comparison of Cryothermia and Radiofrequency Current in Safety and Efficacy of Catheter Ablation within the Canine Coronary Sinus Close to the Left Circumflex Coronary Artery

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Cryoablation Versus RF in the Canine CS Close to LCx. Introduction: A canine model was used to compare cryoablation and radiofrequency ablation (RFA) within the coronary sinus (CS) in the ability to create a transmural CS myocardial (Trans-CSM) lesion and risk of coronary artery stenosis.

Methods: After CS and left circumflex (LCx) coronary angiography, an intravascular ultrasound (IVUS) probe was placed in LCx in 29 dogs. An irrigated RFA catheter (8 dogs) or N 2O cryoablation catheter (21 dogs) was inserted into the CS and positioned within 2 mm of LCx, confirmed by IVUS. RF (30–50W) was applied for 60 seconds at 10 CS sites. Cryoablation (−75°C) was performed with one (n = 7) or two (n = 14) 4-minute applications. Dogs were sacrificed at 1 week (8 RFA and 13 cryoablation) or 3 months (8 cryoablation).

Results: During RFA, IVUS showed wall thickening and LCx narrowing in 9 of 10 sites. Angiography at 5-minute post-RFA identified LCx narrowing (25–90%) at 6 of 10 sites and 25–75% narrowing at 4 of 9 sites at 1-week post-RFA. During cryoablation, IVUS showed reversible ice ball compression of LCx, and no LCx narrowing by angiography at 5 minutes, 1 week, or 3 months. Histology showed Trans-CSM lesion at 10 of 10 RFA sites and 20 of 21 cryoablation sites. RFA produced LCx medial necrosis at 7 of 10 sites, involving 20–50% (median 32.5%) of LCx circumference with loss of intima at 5 of 7 sites. Single and twice 4-minute cryoablation produced LCx medial necrosis at 2 of 7 and 8 of 14 sites (5–40%, median 25% circumference). Intima was preserved at 1 week (13/13) with minor proliferation (without narrowing) at 2 of 8 sites at 3 months.

Conclusions: Cryoablation in CS within 2 mm of LCx produces Trans-CSM lesions similar to RFA with lower risk of LCx stenosis than RFA. (J Cardiovasc Electrophysiol, Vol. 16, pp. 1218-1226, November 2005)

Introduction

Catheter ablation within the coronary sinus (CS) or coronary veins, such as the middle cardiac vein (MCV), is desirable for ablation of epicardial posteroseptal accessory AV pathways and for completion of linear left atrial lesions to the mitral annulus for ablation of atrial fibrillation or macroreentrant left atrial tachycardia.1-7

Epicardial posteroseptal or left posterior accessory AV pathway often results from a connection between an extension of the CS myocardial coat along the MCV or posterior coronary vein and the epicardial surface of ventricle.8 Due to extensive connections between the CS myocardial coat and the atria,9-11 ablation is most effective when targeting the extension of the CS myocardial coat from within the MCV or posterior coronary vein.9 We recently found a significant coronary artery located within 2 mm of the ideal ablation site in the CS, MCV, or posterior coronary vein in 65% of patients, and radiofrequency ablation (RFA) within 2 mm has a 66% risk of coronary artery stenosis.12 The mechanism of radiofrequency-induced coronary arterial stenosis may be heat-induced shrinkage of collagen fibers in the media of the artery.13,14 Studies in dogs and sheep have shown that epicardial surgical cryoapplications directly over a coronary artery in a normothermic heart does not produce stenosis of the coronary artery at 6 months or 2 years.15,16 Therefore, we postulated that catheter cryoablation within the coronary venous system would be capable of creating a transmural lesion in the CS myocardium with a low risk of coronary artery stenosis. The purpose of this study was to use a previously tested canine model17 to compare cryoablation and RFA in the CS within 2 mm of the left circumflex (LCx) coronary artery in efficacy (transmural CS lesion) and safety (risk of coronary artery stenosis).
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Figure 1. Radiographs (left anterior oblique projection) during coronary sinus (CS) angiography and left circumflex (LCx) coronary arteriography before and after radiofrequency ablation. A: Retrograde CS angiography was performed using the balloon occlusion technique, identifying the CS, great cardiac vein (GCV), middle cardiac vein (MCV) and posterior coronary vein (PCV). B: LCx arteriography. C: Location of the radiofrequency (RF) ablation catheter in the CS and the intravascular ultrasound (IVUS) probe in the LCx. Note the RF ablation catheter is positioned within 2 mm of the LCx arterial wall, verified by IVUS as shown in Figure 2. D: LCx angiogram 5 minutes after RF ablation (50 W, 60 seconds) in the CS, showing 90% stenosis of the LCx adjacent to the CS ablation site. E: LCx angiogram 30 minutes after RF ablation, showing 75% stenosis. F: LCx angiogram 1 week after RF ablation, showing similar level of stenosis (75%).

Methods

The experimental protocol was approved by the University of Oklahoma Institutional Animal Care and Use Committee. Twenty-nine mongrel dogs weighing 24–39 kg (median 28 kg) were anesthetized with sodium pentobarbital and mechanically ventilated. The left carotid artery and left jugular vein were cannulated. Heparin (5,000 units) was administered. Angiography was performed using a digital biplane system. Retrograde CS angiography was performed using the balloon occlusion technique (Fig. 1A). LCx arteriography was performed after nitroglycerin administration (0.1 mg i.c.) to identify the anatomy of the LCx and its relationship to the CS (Fig. 1B). A 40-MHz intravascular ultrasound (IVUS) probe (Atlantis SR, Boston Scientific, MN, USA) was advanced over a 0.014-inch guidewire into the posterior or posterolateral LCx (Fig. 1C).

Radiofrequency Ablation

In 8 of 29 dogs, a 7F deflectable RFA catheter with a 3.5-mm saline irrigated tip electrode (ThermoCool, Biosense Webster, CA, USA) was inserted into the posterior or posterolateral CS. The tip was positioned within 2 mm of the LCx wall, confirmed by IVUS (Figs. 1C and 2A). During saline irrigation at 30 mL/minute, radiofrequency energy was delivered for 60 seconds in CS at 1 site (6 dogs) or 2 sites (2 dogs) at 30 W (4 sites), 40 W (4 sites), or 50 W (2 sites) for a total of 10 sites in the 8 dogs. IVUS imaging of the LCx was performed continuously for at least 5 minutes following each radiofrequency application (Fig. 2A-D). The IVUS probe was removed and LCx angiography (with nitroglycerin 0.1 mg i.c.) was performed at 5 minutes and 30 minutes following ablation (Fig. 1D,E). Angiographic narrowing of the LCx was measured using the criteria established by the American Heart Association. Retrograde CS angiography was repeated and the dogs were recovered from anesthesia.

One week after ablation, seven of eight dogs were anesthetized and CS angiography and LCx angiography (nitroglycerin 0.1 mg i.c.) was performed (Fig. 1F). The seven dogs were sacrificed and the hearts were fixed in formalin. The one remaining dog died 3 days after ablation due to aortic dissection resulting from the arterial cannulation. The heart was excised and fixed in formalin.

Cryoablation

In 21 of 29 dogs, a 7F deflectable catheter with a 4-mm cryoablation tip electrode (Freezor™, CryoCath Technologies, Quebec, Canada) was inserted into the posterior or posterolateral CS and positioned within 2 mm of the LCx wall, confirmed by IVUS in 19 dogs (Figs. 3C and 4A) and angiography in all 21 dogs (Fig. 3B).

The cryoablation catheter uses nitrous oxide for the refrigerant. The transformation from liquid to gas produces rapid cooling of the tip electrode to −75°C. Cryoablation (−75°C) was performed at only one CS site in all 21 dogs.
A single 4-minute cryoapplication was used in seven dogs. In 14 dogs, a second 4-minute cryoapplication was delivered at the same site, beginning as soon as the electrode temperature increased to approximately 30°C following the first application (two sequential 4-minute applications). IVUS imaging of the LCx was performed during and following cryoablation in 19 of 21 dogs (Fig. 4). LCx angiography (nitroglycerin 0.1 mg i.c.) was performed at 5 minutes and 30 minutes following cryoablation in all 21 dogs (Fig. 3D,E). Retrograde CS angiography was repeated and the dogs were recovered from anesthesia.

One week (13 dogs) or 3 months (8 dogs) following cryoablation, CS angiography and LCx angiography (nitroglycerin 0.1 mg i.c., Fig. 3F) were repeated and the dogs were sacrificed. The hearts were excised and fixed in formalin.

Histological Examination

After fixation, the region surrounding the ablation site(s) was sectioned perpendicular to the mitral annulus. Hematoxylin-eosin and trichrome stained sections were examined microscopically for CS myocardial wall necrosis and LCx injury.

Statistical Analysis

Values are expressed range and median. The significance of the difference between RFA and cryoablation in incidence of transmural CS necrosis, and LCx stenosis (angiography and IVUS), medial necrosis, and segmental loss of the intima was assessed by chi-square analysis or Fisher’s exact test. The extent of transmural CS necrosis and LCx medial necrosis (measured as percentage of circumference) was compared between RFA and cryoablation using the two-tailed Student’s t-test. The value $P < 0.05$ was considered significant.

Results

Radiofrequency Ablation

IVUS demonstrated increased echogenicity and thickening of the LCx wall during 9 of 10 radiofrequency applications in the CS. The IVUS changes in the LCx wall started in the region surrounding the ablation electrode, beginning 10–45 seconds (median 25 seconds) after onset of the radiofrequency application (Fig. 2). The increase in echogenicity and thickening of the arterial wall extended circumferentially, followed by luminal narrowing. At the end of the radiofrequency application, the cross-sectional area of LCx lumen (measured by IVUS) was decreased by 12–82% (median 30%) at 9 of 10 ablation sites. LCx luminal narrowing occurred in 3 of 4 applications at 30 W (12–50% narrowing of the cross-sectional area), 4 of 4 at 40 W (15–37% narrowing), and 2 of 2 at 50 W (71% and 82% narrowing, Fig. 5A).

Angiography 5 minutes after RFA showed LCx stenosis (greater than 25%\textsuperscript{18} at 6 of 10 ablation sites. Angiographic LCx narrowing at 5 minutes occurred in two of four
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Figure 3. Radiographs (left anterior oblique projection) during CS angiography and LCx arteriography before and after cryoablation. A: Retrograde CS angiography was performed using the balloon occlusion technique. The balloon is located distal to the MCV which is filling in the antegrade direction from collaterals. B: LCx arteriography showing the proximity of cryoablation catheter within CS. C: Location of the cryoablation catheter in the CS and the intravascular ultrasound (IVUS) probe in the LCx. The cryoablation catheter is positioned within 2 mm of the LCx arterial wall, verified by IVUS as shown in Figure 4. D–F: LCx arteriograms 5 minutes (D), 30 minutes (E) and 3 months (F) following cryoablation (−75°C, twice for 4 minutes) showing no LCx stenosis.

applications at 30 W (25% and 25% narrowing), in two of four at 40 W (25% and 25% narrowing), and in two of two at 50 W (75% and 90% narrowing, Fig. 5B). At 30 minutes after ablation, angiographic LCx narrowing was present at same six sites. The degree of narrowing was unchanged (25%) for the four sites at 30 W and 40 W, but decreased from 75% to 50%, and 90% to 75% in the two 50-W ablation sites (Fig. 5B).

One week after ablation, angiography showed no LCx narrowing at the three 30-W application sites, the same degree of narrowing (25%) at the same two 40-W sites, and a further decrease in narrowing at one of the two 50-W sites (50% to 25%, Fig. 5B).

CS angiography at 30 minutes following RFA showed narrowing of the CS at 2 of 10 sites (50% and 90%). One week

Figure 4. IVUS images of the LCx before, during and after cryoablation within the CS (−75°C, twice for 4 minutes). Same dog as Figure 3. A: Before cryoablation, the ablation electrode within the CS is located adjacent to the LCx wall (<1 mm). B: Six seconds after onset of cryo application, a large ice ball (low echogenetic mass) is formed around the ablation electrode, compressing the LCx. C: Only 7 seconds after termination of the cryo application (rewarming), ice ball and compression of the LCx is resolved. Note the LCx luminal diameter and the thickness and echogenicity of the LCx are unchanged from preablation (Panel A).
after ablation, CS narrowing was observed at three of nine sites (25%, 25%, and 75%).

Histological examination at 3 days (1 dog) or 1 week (7 dogs) after ablation showed transmural coagulation necrosis of the CS myocardial wall at all 10 RFA sites. Necrosis extended around 5–100% (median 45%) of the circumference of the CS myocardial wall (Figs. 6A and 7A, B). The lesions extended to the LCx in 7 of 10 sites. The seven LCx lesions had medial necrosis extending around 20–50% (median 32.5%) of the circumference of the LCx (Figs. 6B and 7). Endothelial cells (intima) were lost in the region of medial necrosis in five of seven LCx lesions (1 of 4 radiofrequency lesions at 30 W, 2 of 4 lesions at 40 W, and 2 of 2 lesions at 50 W, Fig. 7B,C), and the elastic lamina was disrupted in two of these five lesions.

Cryoaiblation

IVUS imaging during cryoaiblation in 19 of 21 dogs showed ice ball formation around the ablation electrode (a low echogenic mass) in 16 of 19 dogs (Fig. 4B). The time to onset of ice ball formation was 5–10 seconds (median 6 seconds). The ice ball compressed the LCx wall in 13 of these 16 dogs. On rewarming, the ice ball resolved quickly and compression of artery disappeared (Fig. 4C). The time to complete disappearance of the ice ball was 4–15 seconds (median 7 seconds). After cryoaiblation, IVUS showed no increased echogenicity, wall thickness, or luminal narrowing of the LCx (P < 0.01 compared to RFA, Figs. 4C and 5A).

Angiography showed no LCx narrowing in any of the 21 dogs at 5 minutes and 30 minutes after cryoaiblation (21 dogs), any of the 13 dogs studied at 1 week, or any of the 8 dogs studied at 3 months (Figs. 3 and 5B).

CS angiography performed 30 minutes after cryoaiblation (21 dogs) and 1 week after cryoaiblation (13 dogs) showed no CS narrowing. At 3 months after cryoaiblation, CS narrowing was observed in 2 of 8 dogs. In these 2 dogs, the CS diameter was decreased by 90%.

Histological examination showed transmural necrosis of the CS myocardial wall in 20 of 21 dogs. This included 6 of 7 dogs with a single 4-minute cryoapplication and all 14...
Figure 7. Histology at 1 week following an RF application in the CS at 50 W for 60 seconds (trichrome stain). Same dog as Figures 1 and 2. A: Low magnification showing transmural necrosis of the CS myocardial wall (100% circumference) and extension of the lesion to the LCx. B: Higher magnification of the LCx showing segmental medial necrosis (50% of the circumference, dashed line). C: Further magnification of a segment of the LCx showing full thickness coagulation necrosis of the media and adventitia with loss of endothelial cells (intima).

dogs with two sequential 4-minute cryoapplications. For all 21 dogs, transmural necrosis extended around 0–100% (median 40%) of the circumference of the CS myocardial wall (Figs. 6A, 8A, and 9A). The incidence and extent of transmural CS myocardial (Trans-CSM) necrosis was similar to the radiofrequency lesions (Fig. 6A).

Cryoablation produced LCx medial necrosis at 10 of the 21 (48%) sites, extending around 5–40% (median 25%) circumference. Of the 13 hearts examined 1 week after ablation, LCx medial necrosis was present at 2 of 7 sites with a single 4-minute cryoapplication (involving 5% and 25% of the LCx circumference) versus 6 of 6 sites (15–40%, median 25% of the LCx circumference) with two sequential 4-minute cryoapplications (Figs. 6B and 8). Of the 14 lesions produced by two 4-minute cryoapplications, LCx medial necrosis was present in all 6 lesions examined at 1 week compared to only 2 of 8 lesions examined at 3 months (Figs. 6B and 9A).

The incidence and extent (percent of circumference) of LCx medial necrosis was not significantly different between cryoablation and RFA examined at 1 week (8/13 vs 7/10, respectively, Fig. 6B). However, the LCx medial necrosis at 1 week produced by RFA showed coagulation necrosis (with no cell structure, Fig. 7C), while medial necrosis produced

Figure 8. Histology (trichrome stain) at 1 week following cryoablation in the CS (−75°C, twice for 4 minutes). A: Low magnification showing transmural necrosis of the CS myocardial wall (95% circumference) and segmental medial necrosis of the LCx (15% of the circumference, dashed line). B: Higher magnification of segmental medial necrosis of the LCx, showing cellular infiltration of fibroblasts. The intima is preserved.
by cryoablation was associated with infiltration of fibroblasts and somewhat preserved structure (Fig. 8B). The intima was preserved at the site of LCx medial necrosis in all eight cryoablation lesions (Fig. 8B).

At 3 months after cryoablation, only two of eight lesions exhibited LCx medial necrosis (involving 30% and 35% of the LCx circumference, Figs. 6B and 9A). The intima was preserved in both lesions. However, there was minor proliferation of the intima (2–3 layers of endothelial cells) involving 10–20% of the LCx circumference (Fig. 9B).

Discussion

This study used intravascular echocardiography as well as angiography and histology to view the immediate, acute and chronic effects of radiofrequency and cryoablation within the CS very close (within 2 mm) to the LCx coronary artery. Transmural necrosis of the CS myocardial coat was produced equally by cryoablation and RFA. After rewarming, cryoablation did not produce LCx narrowing by IVUS imaging or angiography, while RFA frequently (90%) produced some degree of LCx narrowing. Despite a comparable incidence of LCx medial necrosis, cryoablation was not associated with the loss of intima in the LCx lesions (in contrast with a 50% loss of intima in the LCx lesions produced by RFA).

This study also describes the dynamics of acute narrowing of the coronary artery for both ablation energy sources. During cryoablation, IVUS identified ice ball formation compressing the coronary arterial wall and decreasing the luminal diameter by up to 40% (Fig. 4B). During rewarming, the compression quickly resolved with no echocardiographic change in the arterial wall (Fig. 4C). In a recent study testing larger cryoelectrodes (6- and 30-mm lengths) directly on coronary arteries in the canine pericardium, angiography showed mild-to-severe arterial narrowing (20–100% diameter) of the lumen diameter during cryoapplication with rapid return to TIMI III flow on rewarming. This observation is consistent with ice ball compression. During RFA, IVUS demonstrated increased echogenicity and thickening of the LCx wall. These changes in the arterial wall occurred initially near the ablation electrode and then extended circumferentially, followed by luminal narrowing. Angiography at 5 minutes and 30 minutes after ablation showed a decrease in the degree of narrowing for the two radiofrequency applications at 50 W, but no change for the eight applications at 30 W and 40 W.

The mechanism of coronary artery narrowing produced by RFA has not been clarified. The acute narrowing is unlikely to be the result of spasm, because it was not prevented by the intracoronary administration of nitroglycerin. Cryoablation was not associated with narrowing of the coronary artery, despite an incidence and extent of LCx medial necrosis similar to RFA. This suggests that the occurrence of coronary artery narrowing with radiofrequency energy is more related to heat-induced shrinkage of collagen than medial necrosis. During surgical laser ablation in rabbits, Gorisch et al. found the extent of heat-induced shrinkage of the vessel correlated with the amount of the heat-induced denaturation of collagen fibers in the vessel wall. The loss of LCx intima in radiofrequency lesions may also be related to heat, since this was not observed in cryoablation lesions.

The LCx medial necrosis at 1 week after cryoablation was already associated with the infiltration of fibroblasts (Fig. 8B). This suggests that cryoablation lesions have a quick healing process compared to the radiofrequency lesion and may account for the preservation of the overall structure of
the artery. LCx medial necrosis was identified in only two of eight dogs which were studied at 3 months following two 4-minute cryoapplications, compared to six of six dogs studied at 1 week (P < 0.01, Fig. 6B), despite transmural CS necrosis in all dogs in both groups.

The intima of the LCx was preserved in all dogs after cryoablation. There was minor proliferation of the intima in two of eight dogs examined at 3 months following cryoablation. The long-term significance of the intimal proliferation is unknown. Previous studies in multiple animal models have shown that epicardial surgical cryoapplications placed directly over a coronary artery in the beating heart or during normothermic cardiopulmonary bypass, did not produce narrowing of the coronary artery at 6 months and 2 years. Histological examination in these studies showed minor proliferation of the intima without significant narrowing of the coronary artery. However, epicardial surgical cryoapplications over a coronary artery during cold cardiopulmonary bypass have been shown to result in significant intimal hyperplasia associated with coronary artery narrowing. These data suggest that the warm blood flow through the coronary artery prevents severe cooling of the arterial wall and stenosis.

Clinical Implications

Catheter ablation within the CS, a coronary vein, or within the pericardial space (epicardial ablation) may be effective for a number of arrhythmias when endocardial ablation is unsuccessful. These arrhythmias include some epicardial accessory pathways, atrial tachycardias, ventricular tachycardias, and atrial fibrillation. In patients with atrial fibrillation, ablation across the mitral isthmus is challenging. Because of the CS musculature and its connection to the left atrium, ablation within the CS may be required to produce complete mitral isthmus block. Similarly, ablation of epicardial posteroseptal accessory pathways, resulting from a connection between an extension of the CS myocardial coat along the MCV (or other branch of the CS) and the ventricle, usually requires ablation within the MCV. A coronary artery is located within 2 mm of the ideal ablation site in the MCV in 65% patients with epicardial accessory pathways and delivering radiofrequency current within 2 mm of the adjacent coronary artery has a high risk of some degree of coronary artery narrowing. Coronary artery injury during RFA has occurred with irrigated and nonirrigated electrodes. The results of this study suggest that cryoablation is safer than RFA within the CS or a coronary vein when close to a coronary artery.

Study Limitations

A limitation of this study is the relatively short follow-up. Significant luminal narrowing and histological lesions were already evident within 1 week following RFA. Cryoablation was not associated with luminal narrowing at up to 3 months. However, the significance over years of the segmental medial necrosis and mild intima proliferation is unknown.

This study examined the effects of ablation on a large coronary artery (LCx). Cryoablation may produce greater injury to smaller arteries. The risk of arterial injury may increase with larger cryoelectrodes, lower temperature, and longer application time.

Another limitation of this study is that RF ablation was not tested at low power (<30 W). The risk of arterial injury during RF ablation will increase with increasing RF power as found in this study. Higher RF power (up to 50 W) can be delivered within the coronary venous system by using several ablation electrodes, including an 8- to 10-mm electrode, an internally irrigated electrode, and an externally irrigated electrode (as tested in this study). In our clinical experience, we have observed significant arterial narrowing at RF power <30 W when delivered very close (<2 mm) to a coronary artery. There was no ST segment elevation, enzyme elevation, or symptoms of ischemia unless the coronary artery was completely occluded. In addition, we have found asymptomatic arterial stenosis (>50%) in several patients referred after ablation within the coronary venous system at low RF power. These observations suggest that asymptomatic coronary artery stenosis may be more common than expected following ablation within the coronary vein, even at low power.

Conclusions

In this canine model, cryoablation and RFA within the coronary sinus close to LCx coronary artery produced similarly effective lesions (transmural necrosis of CS myocardium), but RFA frequently produced LCx coronary artery narrowing. The absence of coronary artery narrowing in the cryolesions despite a similar incidence of LCx medial necrosis as in the radiofrequency lesions, suggests that coronary artery narrowing may be more related to heat-induced collagen shrinkage than medial necrosis.

Acknowledgments: Hiroshi Aoyama and this manuscript won Honorable Mention in the 2003 Young Investigator Award Competition of the North American Society of Pacing and Electrophysiology (Heart Rhythm Society).

References