Lower Incidence of Thrombus Formation With Cryoenergy Versus Radiofrequency Catheter Ablation

Paul Khairy, MD, MSc; Patrick Chauvet, MSc; John Lehmann, MD, MPH; Jean Lambert, PhD; Laurent Macle, MD; Jean-François Tanguay, MD; Martin G. Sirois, PhD; Domenic Santoianni, BEng; Marc Dubuc, MD

***Background*—**Radiofrequency (RF) catheter ablation is limited by thromboembolic complications. The objective of this study was to compare the incidence and characteristics of thrombi complicating RF and cryoenergy ablation, a novel technology for the catheter-based treatment of arrhythmias.

***Methods and Results*—**Ablation lesions (n=197) were performed in 22 mongrel dogs at right atrial, right ventricular, and left ventricular sites preselected by a randomized factorial design devised to compare RF ablation with cryocatheter configurations of varying sizes (7F and 9F), cooling rates (−1°C/s, −5°C/s, and −20°C/s) and target temperatures (−55°C and −75°C). Animals were pretreated with acetylsalicylic acid and received intraprocedural intravenous unfractionated heparin. Seven days after ablation, the incidence of thrombus formation was significantly higher with RF than with cryoablation (75.8% versus 30.1%, $P=0.0005$). In a multiple regression model, RF energy remained an independent predictor of thrombus formation compared with cryoenergy (OR, 5.6; 95% CI, 1.7, 18.1; $P=0.0042$). Thrombus volume was also significantly greater with RF than with cryoablation (median, 2.8 versus 0.0 mm^3; $P<0.0001$). More voluminous thrombi were associated with larger RF lesions, but cryolesion dimensions were not predictive of thrombus size.

***Conclusions*—**RF energy is significantly more thrombogenic than cryoenergy, with a higher incidence of thrombus formation and larger thrombus volumes. The extent of hyperthermic tissue injury is positively correlated with thrombus bulk, whereas cryoenergy lesion size does not predict thrombus volume, most likely reflecting intact tissue ultrastructure with endothelial cell preservation. **(*Circulation*. 2003;107:●●●-●●●.)**

Key Words: ablation, radiofrequency ■ cryoablation ■ cryoenergy ■ thrombus ■ thromboemboli

Radiofrequency (RF) catheter ablation has become the treatment of choice for a wide variety of arrhythmias. Coagulation and tissue necrosis induced by hyperthermia, however, are associated with an inherent risk of thrombus formation. Clinically, a 0.6% to 0.8% incidence of thromboembolic events has been estimated.[1] This complication rate increases further when RF ablation is performed in systemic cardiac chambers (1.8% to 2.0%) and for ventricular tachyarrhythmias (2.8%). Moreover, use of intravenous heparin and temperature feedback to control RF current do not appear to eliminate thromboembolic risk.[1–3] More recently, percutaneous cryoenergy catheters have been used successfully in ablating atrioventricular nodes[4] and supraventricular tachycardias[5] in humans. The hypothermic tissue injury induced by this alternate ablation modality is thought to be nonthrombogenic.[6] Indeed, preliminary data suggest the absence of histologically identifiable thrombus formation at the site of cryoenergy injury.[7] The objective of this study was, therefore, to prospectively compare the incidence and characteristics of thrombi complicating RF and cryoenergy catheter ablation and to identify predictors of the presence and extent of thrombus formation.

Methods

The experimental protocol was approved by the Montreal Heart Institute Animal Care and Use Committee following the guidelines of the Canadian Council on Animal Care. Ablation lesions were performed in 22 mongrel dogs at sites preselected by a randomized factorial design devised to compare RF ablation with cryocatheter configurations of varying sizes (7F and 9F), cooling rates (−1°C/s, −5°C/s, and −20°C/s), and target temperatures (−55°C and −75°C). Lesions were created in the right atrium and both ventricles of each animal with 1 predetermined ablation setting per chamber (ie, energy type, catheter size, cooling rate, and target temperature). Acetylsalicylic acid 325 mg/d was initiated 7 days before ablation and continued until the animal was euthanized. Dogs 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, followed by hourly injections of 15 IU/kg.

Sheath introducers were placed in the femoral artery and vein. In adherence to the protocol, a 7F or 9F cryocatheter (Freezor,

Received September 19, 2002; revision received December 19, 2002; accepted January 3, 2003.

From the Department of Medicine, Montreal Heart Institute, Montreal, Quebec, Canada.

Correspondence to Marc Dubuc, MD, Chief, Department of Electrophysiology, Montreal Heart Institute, 5000 Bélanger St E, Montreal, Quebec, Canada, H1T 1C8. E-mail dubuc@icm.umontreal.ca

Circulation is available at http://www.circulationaha.org DOI: 10.1161/01.CIR.0000058706.82623.A1

CryoCath Technologies Inc) or 7F quadripolar RF catheter (Biosense Webster, Inc) with a 4-mm distal electrode tip was positioned under fluoroscopic guidance. Surface and intracardiac ECG recordings were displayed on a multichannel oscilloscope (Electronics for Medicine, VR-12, Honeywell Inc) and stored on a VHS tape recorder. Each cryoapplication was maintained for 4 minutes. Temperatures were displayed and recorded by a CryoCath console with ±1°C accuracy over the range of +40°C to −80°C at a sampling rate of 10/s. Average and maximum cooling rates and average and minimum temperatures were calculated with a customized Matlab program. RF ablations were maintained for 60 seconds at 50 W with a target temperature of +70°C. Maximum impedance and maximum and mean temperature and power were displayed on the generator (EP Technologies Inc).

Animals were killed at 7 days 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 treatment modality. Representative photographs of epicardial and endocardial surfaces were taken, and gross surface maximal lesion length and width were measured. Tissues were dehydrated and embedded in paraffin. Specimens were serially sectioned perpendicular to the endocardial surface in 1000-μm increments at a thickness of 6 μm with a motorized microtome (Olympus 4060E). Sections were stained with Masson's trichrome. A calibrated light microscope using Scion image 1.60 software for CG-7 (Scion Corp) was used for morphometric measurements of thrombus volume and lesion depth. Thrombus was defined as being present if its volume exceeded 0.1 mm^3.

Statistical Analyses

Given that several ablation lesions were created in each animal, all analyses took into consideration the nonindependent nature of the data structure. For binary outcomes (eg, presence or absence of thrombus), generalized estimating equations, which are robust to an assigned correlation configuration, were used to produce multiple regression marginal models for cluster sampling data by specifying link and distribution functions. For continuous outcomes (eg, thrombus volume), both generalized estimating equations and mixed regression models with prespecified covariance matrix assumptions were used. Analyses were performed with and without potential outliers and influential observations. Two-tailed probability values <0.05 were considered statistically significant. Statistical testing was performed using SAS software Version 8 (SAS Institute).

Results

Baseline Characteristics

A total of 197 RF and cryoenergy lesions were created systematically in the right atrium and both ventricles of 22 mongrel dogs (7 males, 15 females). Of these lesions, 176 (89.3%) were identified macroscopically and processed for histological analysis. Of the 21 missing lesions, 15 (71.4%) were created by 7F cryocatheters, 2 (9.5%) by 9F cryocatheters, and 4 (19.0%) by RF ablation. These lesions were dispersed uniformly within the right atrium (n=6) and right (n=8) and left ventricles (n=7). Moreover, missing lesions created by 7F cryocatheters were distributed evenly among the various ablation settings.

Subdivision of lesions according to energy modality, catheter size, and ablation parameters is depicted in Figure 1. No differences in the distribution of ablation site (Table 1) and sex of the animals were noted between cryoenergy and RF lesions. For reasons that remain unclear, 1 dog was unusually thrombogenic, with thrombus formation identified in 10 of 11 ablation sites involving both RF and cryoenergy. Statistical analyses performed with and without these lesions yielded similar results. Therefore, the following data include all lesions.

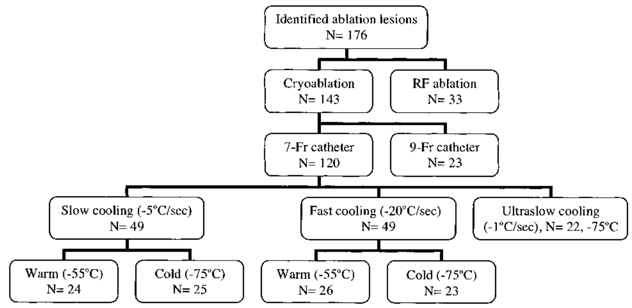

Figure 1. Distribution of ablation lesions.

Presence of Thrombus

The overall incidence of thrombus formation was 75.8% with RF and 30.1% with cryoablation ($P=0.0005$). An example of thrombus at the site of RF ablation is depicted in Figure 2. With the currently available 7F cryocatheter, thrombus was observed in 24.2% of lesions. RF energy remained a strong predictor of thrombus formation in a multivariate analysis controlling for site of ablation, sex, and lesion dimensions (OR, 5.6; 95% CI, 1.7, 18.4; $P=0.0042$). When cryolesions were considered separately, cryocatheter size (7F versus 9F), cooling rate, and target temperature did not predict thrombus formation. Similarly, an analysis of RF lesions found no correlation between RF ablation parameters (ie, power, temperature, and impedance) and thrombus.

In univariate analyses of all ablation lesions, site of ablation and sex were not correlated with thrombus formation. Larger lesion dimensions, however, were associated with a higher incidence of thrombosis. This correlation was found consistently for area ($P=0.0047$), depth ($P=0.0195$), and volume ($P=0.0111$). In multivariate analyses, lesion volume but not area or depth remained an independent predictor of thrombus formation, with an OR of 1.014 and 95% CI of 1.002, 1.025 for a 1-mm^3 increase in volume ($P=0.0218$).

Thrombus Volume

As depicted in Table 1, in multivariate analysis, thrombus volume was significantly greater with RF than with all cryoenergy lesions (mean, 5.4 mm^3 and median, 2.8 mm^3 versus mean, 0.8 mm^3 and median, 0.0 mm^3; $P<0.0001$). Significantly larger thrombi were noted when RF ablation was compared with both 7F (mean, 0.7 mm^3 and median, 0.0 mm^3; $P<0.0001$) and 9F (mean, 1.6 mm^3 and median, 0.5 mm^3; $P=0.0002$) cryolesions (Figure 3).

Independent predictors of thrombus volume for all lesions, RF lesions, and cryolesions are summarized in Table 2. Similar to thrombus formation, lesion dimensions but not site of ablation or sex were associated with thrombus volume. Lesion area ($P<0.0001$), depth ($P<0.0001$), and volume ($P<0.0001$) were significantly positively correlated with thrombus volume. When RF lesions were considered separately, lesion dimensions remained independent predictors of thrombus volume. Moreover, lower average RF ablation

TABLE 1. Characteristics According to Ablation Modality

	RF Ablation (n=33)	Cryoenergy Ablation (n=143)	*P*
Chamber, %			NS
Right atrium	33.3	32.6	
Right ventricle	33.3	34.0	
Left ventricle	33.3	33.3	
Average temperature, °C	66.8±5.5	−60.0±12.1	NA
Presence of thrombus, %	75.8	30.1	0.0005
Thrombus volume, mm^3	2.8 (0.3, 7.2)*	0.0 (0.0, 0.4)*	<0.0001
Lesion volume, mm^3	94.6 (64.2, 229.3)*	43.2 (26.1, 77.7)*	0.0585
Lesion depth, mm	6.0±3.0	4.9±1.7	NS
Lesion area, mm^2	42.0 (28.5, 72.0)*	20.0 (12.0, 25.5)*	0.0018

NA indicates not applicable. Continuous normally distributed variables are expressed as mean±SD.
*Nonnormally distributed variables are expressed as median value and interquartile range (25th, 75th percentile).

temperatures were associated with larger thrombi ($P=0.0008$), in part explained by the strong relationship between higher average delivered power and lower temperature ($P<0.0001$).[8] In contrast, a subgroup analysis of all cryolesions revealed no association between lesion dimensions and thrombus volumes. The 9F compared with 7F cryocatheter was associated with thrombi that were, on average, 1.25 mm^3 larger ($P=0.0413$). Cryoenergy cooling rates and temperatures did not correlate with thrombus size.

Ablation Lesion Characteristics

Histologically, on qualitative analysis, cryolesions were well-circumscribed discrete lesions with sharp borders, dense areas of fibrotic tissue, and contraction band necrosis (see Figure 2). In contrast, RF lesions were characterized by intralesional hemorrhage and ragged edges less clearly demarcated from underlying normal myocardium. Moreover, replacement fibrosis confined to the outer margin of RF lesions but not cryolesions suggests a slower postablation healing response to RF energy. Interestingly, lesions free of thrombus formation exhibited intact endothelial cell layers.

RF ablation resulted in lesions of greater area ($P=0.0018$) and nearly significantly larger volume ($P=0.0585$) but not depth compared with cryolesions. Cryolesion dimensions were of equal depth but of greater area ($P=0.0305$) and volume ($P=0.0454$) with 9F compared with 7F cryocatheters. Moreover, colder temperatures were associated with deeper lesions. For example, achieving a peak temperature 10°C colder resulted in an average lesion 0.38 mm deeper (95% CI, 0.19, 0.57; $P=0.0001$). Not unexpectedly, ventricular ablation lesions were deeper than their atrial counterparts ($P<0.0001$), with all atrial lesions being transmural. Lesion area and volume were not significantly associated with cooling rate, temperature, or ablation site.

Discussion

Since its first clinical use in 1986,[9] RF ablation has evolved as an effective nonpharmacological therapy for a wide array of tachyarrhythmias. Although the procedure carries a low risk of cardiovascular complications, thromboembolism is of concern. Although rare in otherwise healthy patients, thromboemboli may have devastating long-term consequences.[10]

Incidence of Thromboembolic Complications

The incidence of thrombus formation at the ablation site had not been well defined previously. Using DC energy ranging from 100 to 360 J, Moro et al[11] reported a 20% incidence of thrombosis in mongrel dogs 7 days after ablation. In the present study, thrombus was detected histologically in 75.8% of RF ablation sites. This high incidence reflects, in part, the enhanced detection capabilities of a sensitive morphometric analysis. Although detected thrombi may indicate potential for systemic emboli, smaller lesions are probably not clinically significant, because symptomatic events are manifestly less common. In a study by Goli et al,[12] 2 thrombi were identified in 95 patients with routine transesophageal echocardiography after ablation, both of which were at sites remote from ablation lesions.

Several cases involving neurological,[2,10,13–15] pulmonary,[14,16] coronary,[17] and peripheral artery[14,18] thromboembolic complications after RF ablation have been reported. The incidence of such complications was reviewed recently.[1] In the Multicenter European Radiofrequency Survey,[14] thromboembolic complications were reported in 33 of 4398 patients (0.8%). Patients with ventricular tachycardia ablation had a 2.8% incidence of thromboemboli. In exclusively left-sided ablations, Thakur et al[15] and Epstein et al[2] reported 2% and 1.8% embolic rates, respectively. The lower incidence in right-sided ablations has been attributed to the clinically silent nature of most small to moderate-size pulmonary emboli.[1] Consistent with this hypothesis, the present study reports an equal incidence of thrombus formation with right- and left-sided ablations.

Mechanism of Thromboembolism After RF Ablation

Although some authors believe that thromboembolic complications occur as a result of catheter manipulation and not ablation,[2,19,20] a study by Manolis et al[21] found that D-dimer levels doubled after catheter manipulation but increased 6-fold after ablation. A recent report described a lobulated

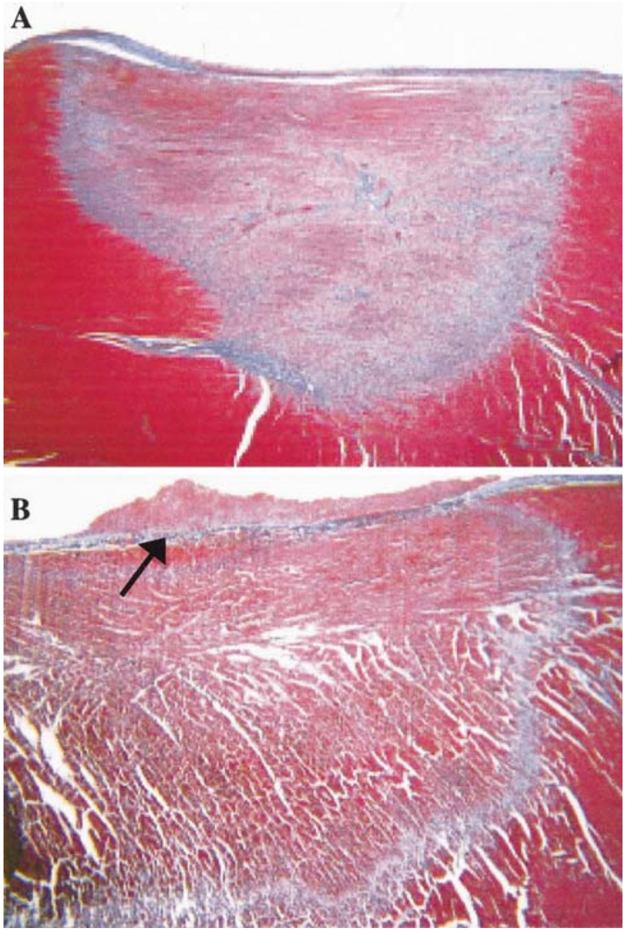

Figure 2. Histology of cryoenergy and RF lesions. Typical histological characteristics 1 week after cryoenergy (A) and RF (B) ablation when stained with Masson's trichrome and magnified 16-fold. Note more homogeneous nature of cryolesion, with a smoother, sharper demarcation from intact myocardium (A). In contrast, RF lesion is less well circumscribed, with serrated edges (B). Arrow indicates endocardial thrombus formation at ablation site.

1-cm thrombus identified by transesophageal echocardiography attached to the right atrial septum at the ablation site.[22]

With RF ablation, events leading to thrombus formation are thought to be initiated by endothelial cell injury.[1] Endothelial cells are highly sensitive to injury and are damaged or destroyed by RF energy, despite selective applications.[23] When continuity of the endothelium is interrupted, anticoagulant properties are lost. Subendothelial components such as collagen, tissue factor, and von Willebrand's factor become exposed to circulating blood.[24] Consequently, platelet adhesion and activation and thrombin production ensue. Given this proposed pathophysiological mechanism, it may be expected that thrombus size would be directly related to extent of RF tissue injury. Indeed, in the present study, when RF ablation lesions were analyzed separately, larger lesion dimensions were associated with more voluminous thrombi. A direct relationship between thrombus volume and embolic complications, although seemingly intuitive, remains to be demonstrated.

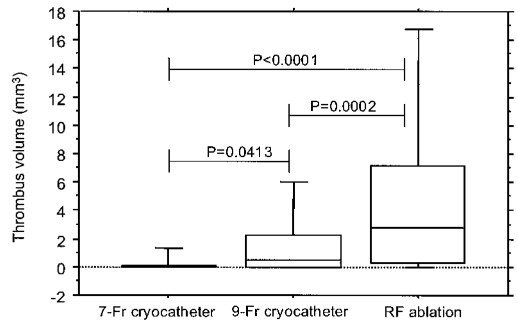

Figure 3. Thrombus volume with RF ablation and 7F and 9F cryoablation.

Cryoenergy Ablation and Thromboembolic Complications

The thromboembolic risk associated with RF ablation elicits the question of whether an alternative energy source may provide a safer profile. Like RF, both microwave and laser energy achieve endocardial ablation through heating and are therefore subject to the same inherent risks of thrombus formation.[1] In contrast, cryoenergy may be advantageous in that the tissue damage produced spares the endothelial lining.

The mechanism of cryoenergy tissue injury is highly complex and involves freeze/thaw effects, hemorrhage, inflammation, and replacement fibrosis.[6,25–27] The net result is tissue destruction with sharply delineated lesions that preserve underlying tissue and extracellular matrix architecture. Whether the theoretical advantage of maintaining intact endocardium translates into a lower incidence of thrombus formation had not been determined previously. In a multivariate analysis, the present study quantified a highly significant 5.6-fold lower risk of thrombus formation with cryoenergy compared with RF ablation. In contrast to RF ablation, no correlation between lesion dimensions and thrombus volume was noted with cryolesions. This provocative observation is consistent with different mechanisms of lesion formation, with a less clear relationship between cryoablation lesion size and extent of endothelial cell injury. A plausible clinically relevant corollary to this finding is that interventions requiring more extensive tissue destruction, such as procedures for

TABLE 2. Independent Predictors of Thrombus Volume

Variable	β-Coefficient±SE	*P*
All ablation lesions		
Radiofrequency vs cryoablation	3.36±0.62	<0.0001
Lesion depth	0.69±0.12	<0.0001
Lesion area	0.03±0.01	<0.0001
Lesion volume	0.01±0.001	<0.0001
Radiofrequency ablation lesions		
Lesion depth	2.57±0.01	<0.0001
Lesion area	0.03±0.01	0.0097
Lesion volume	0.01±0.001	<0.0001
Average RF ablation temperature	−0.47±0.14	0.0008
Cryoablation lesions		
9F vs 7F cryocatheter	1.25±0.61	0.0413

atrial fibrillation and ventricular arrhythmias, may benefit most from the lower thrombogenic nature of cryoablation. A review of the literature on surgical cryoablation suggests a very low risk of thromboembolic complications.[28–32] In 118 patients undergoing surgical ablation of reentrant supraventricular arrhythmias[30] and 82 patients with ectopic atrial tachycardia,[31] no thromboembolic complications were reported. In a series of 14 patients undergoing the maze procedure for atrial fibrillation, 1 patient with Yamagushi disease had a small pulmonary embolus.[32] No thromboembolic complications were noted in Ferguson and Cox's[28] series of 100 consecutive patients undergoing the cryosurgical maze procedure.

The larger thrombi resulting from 9F compared with 7F cryoablation could not be explained by the predictably larger lesion dimensions resulting from greater contact area and double freeze/thaw cycles.[33] Catheter-induced mechanical trauma sufficient to alter electrical properties and damage accessory pathways has been described previously.[34,35] It is theoretically possible, although not histologically quantified by this analysis, that larger cryocatheters produced a greater extent of mechanical trauma with endothelial disruption, resulting in larger thrombi.

Prevention of Thromboembolic Complications

There is a disheartening lack of scientific evidence supporting strategies to prevent thromboembolic complications in patients undergoing catheter ablation. The fact that cryoablation is significantly less thrombogenic than RF ablation is a noteworthy finding in this regard. Neither procedure duration, number of RF applications, nor anticoagulation protocols have been associated with thromboembolic events.[22] In an initial study by Manolis et al,[36] combination therapy with aspirin and ticlopidine reduced D-dimer levels after ablation. However, when 59 patients undergoing RF ablation were randomized to pretreatment with aspirin or ticlopidine, neither agent prevented the rise in D-dimer levels.[37] Intraprocedural heparin has likewise not been proved to reduce thromboembolic events, although its use seems reasonable, particularly in patients undergoing ablation in left-sided chambers.[1] At present, there is no consensus on anticoagulation protocols for catheter ablation.

In a multicenter study comparing RF temperature with power-controlled ablation modes,[3] catheter coagulum was lower with temperature monitoring. A reduction in thromboembolic events, however, has not been demonstrated. In a series by Epstein et al,[2] a temperature-controlled mode was used in 75% of patients in whom thromboembolic complications occurred. Irrigated catheter technology may prove advantageous over temperature-controlled RF ablation by maintaining a cooler electrode-tissue interface, but its salutary effects remain to be demonstrated. Evidently, further studies are necessary to assess strategies aimed at reducing thromboembolic events.

Limitations

A large proportion (71.4%) of the 21 nonidentified lesions were created by 7F cryocatheters. These lesions were more likely to be smaller and free of thrombus formation. Therefore, a selection bias was introduced at the time of analysis comparing cryolesions with RF ablation lesions and 7F with 9F cryolesions. However, the direction of bias is toward the null hypothesis, leading to underestimation of the true risk associated with RF versus cryoablation and 9F versus 7F cryocatheters. Second, initial recommendations for cryoablation involved double rather than single freeze/thaw cycles.[33] Single freeze/thaw cycles with 7F catheters are emerging as the procedure of choice and were therefore compared with the original 9F double freeze/thaw cycles.[38,39] The number of freeze/thaw cycles may potentially confound the relationship between catheter size and dimension of ablation lesions as well as thrombus volume. The study design does not permit dissociating the effects of catheter size from number of freeze/thaw cycles. Nevertheless, conclusions regarding comparisons between 9F and 7F cryolesions remain valid, with the caveat that original versus newer protocols were used.

All dogs were killed at 7 days. As such, histological analyses were performed at 1 predetermined point in time. Potentially different latency periods between RF and cryoablation and thrombus formation were not considered. Given that tissue destruction, hemorrhage, and inflammation occur within the first 48 hours,[6] there was no a priori reason to suspect that cryoablation would result in a higher incidence of late (ie, >7 days) thrombus formation. Finally, caution must be exerted in extrapolating animal studies to humans. Although such research may provide useful information and define priorities for clinical studies, reliable quantitative estimates of human risk cannot be inferred.

Conclusions

For endocardial ablation lesions of equal size in equivalent cardiac chambers, ablation using RF energy confers a >5-fold increased risk of thrombus formation, with larger thrombus volumes, compared with cryoenergy. Whereas the extent of RF tissue injury is positively correlated with thrombus bulk, cryoenergy lesion size does not predict thrombus volume. This probably reflects the histological observation that cryoablation results in well-delineated, discrete lesions with preservation of tissue ultrastructure, including the endothelial cell layer. In contrast, RF lesions have serrated edges with more extensive endothelial cell destruction.

Acknowledgments

This work was supported in part by a fellowship award (Dr Khairy) from the Canadian Institutes of Health Research. We thank Emma De Blasio, Christine Villemaire, Dominique Lauzier, and Véronique Philibert for their expert technical support.

References

1. Zhou L, Keane D, Reed G, et al. Thromboembolic complications of cardiac radiofrequency catheter ablation. *J Cardiovasc Electrophysiol*. 1999;10:611–620.
2. Epstein MR, Knapp LD, Martindill M, et al. Embolic complications associated with radiofrequency catheter ablation. *Am J Cardiol*. 1996;77:655–658.
3. Calkins H, Prystowsky E, Carlson M, et al. Temperature monitoring during radiofrequency catheter ablation procedures using closed loop control. *Circulation*. 1994;90:1279–1286.
4. Dubuc M, Khairy P, Rodriguez-Santiago A, et al. Catheter cryoablation of the atrioventricular node in patients with atrial fibrillation. *J Cardiovasc Electrophysiol*. 2001;12:439–444.

5. Skanes AC, Dubuc M, Klein GJ, et al. Cryothermal ablation of the slow pathway for the elimination of atrioventricular nodal reentrant tachycardia. *Circulation*. 2000;102:2856–2860.
6. Khairy P, Dubuc M. Transcatheter cryoablation. In: Liem LM, Downar E, eds. *Progress in Catheter Ablation: Clinical Application of New Mapping and Ablation Technology*. Dordrecht, Netherlands: Kluwer Academic Publishers; 2002:389–408.
7. Dubuc M, Talajic M, Roy D, et al. Feasibility of cardiac cryoablation using a transvenous steerable electrode catheter. *J Interv Card Electrophysiol*. 1998;2:285–292.
8. Wittkampf FH, Hauer RN, Robles de Medina EO. Control of radiofrequency lesion size by power regulation. *Circulation*. 1989;80:962–968.
9. Borggrefe M, Budde T, Podczeck A, et al. High frequency alternating current ablation of an accessory pathway in humans. *J Am Coll Cardiol*. 1987;10:576–582.
10. Cannon BC, Kertesz NJ, Friedman RA, et al. Use of tissue plasminogen activator in a stroke after radiofrequency ablation of a left-sided accessory pathway. *J Cardiovasc Electrophysiol*. 2001;12:723–725.
11. Moro C, Aragoncillo P, Jorge P. Thrombus apposition on catheter ablation injuries. *Eur Heart J*. 1989;10:833–837.
12. Goli VD, Prasad R, Hamilton K, et al. Transesophageal echocardiographic evaluation for mural thrombus following radiofrequency catheter ablation of accessory pathways. *Pacing Clin Electrophysiol.* 1991;14: 1992–1997.
13. Chen SA, Chiang CE, Tai CT, et al. Complications of diagnostic electrophysiologic studies and radiofrequency catheter ablation in patients with tachyarrhythmias. *Am J Cardiol*. 1996;77:41–46.
14. Hindricks G. The Multicentre European Radiofrequency Survey (MERFS): complications of radiofrequency catheter ablation of arrhythmias. *Eur Heart J*. 1993;14:1644–1653.
15. Thakur RK, Klein GJ, Yee R, et al. Embolic complications after radiofrequency catheter ablation. *Am J Cardiol*. 1994;74:278–279.
16. Hockstad E, Gornick CC. Mildly symptomatic pulmonary emboli associated with electrophysiologic procedures. *Chest*. 1994;106:1908–1911.
17. Hope EJ, Haigney MC, Calkins H, et al. Left main coronary thrombosis after radiofrequency ablation. *Am Heart J*. 1995;129:1217–1219.
18. Kuck KH, Schluter M, Geiger M, et al. Radiofrequency current catheter ablation of accessory atrioventricular pathways. *Lancet*. 1991;337: 1557–1561.
19. Raitt MH, Schwaegler B, Pearlman AS, et al. Development of an aortic valve mass after radiofrequency catheter ablation. *Pacing Clin Electrophysiol.* 1993;16:2064–2066.
20. Greene TO, Huang SK, Wagshal AB, et al. Cardiovascular complications after radiofrequency catheter ablation of supraventricular tachyarrhythmias. *Am J Cardiol*. 1994;74:615–617.
21. Manolis AS, Melita-Manolis H, Vassilikos V, et al. Thrombogenicity of radiofrequency lesions. *J Am Coll Cardiol*. 1996;28:1257–1261.
22. Farah A, Khan F, Machado C. Thrombus formation at the site of radiofrequency catheter ablation. *Pacing Clin Electrophysiol*. 2000;23: 538–540.
23. Kongsgaard E, Foerster A, Aass H, et al. Power and temperature guided radiofrequency catheter ablation of the right atrium in pigs. *Pacing Clin Electrophysiol*. 1994;17:1610–1620.
24. Lijnen HR, Collen D. Endothelium in hemostasis and thrombosis. *Prog Cardiovasc Dis*. 1997;39:343–350.
25. Holman WL, Ikeshita M, Douglas JM Jr, et al. Cardiac cryosurgery: effects of myocardial temperature on cryolesion size. *Surgery*. 1983;93: 268–272.
26. Lustgarten DL, Keane D, Ruskin J. Cryothermal ablation: mechanism of tissue injury and current experience in the treatment of tachyarrhythmias. *Prog Cardiovasc Dis*. 1999;41:481–498.
27. Mazur P. Cryobiology: the freezing of biological systems. *Science*. 1970; 168:939–949.
28. Ferguson TB, Cox JL. Surgery for supraventricular arrhythmias. In: Baue AE, Geha AS, Hammond GL, eds. *Gleen's Thoracic and Cardiovascular Surgery*. Stanford, Conn: Appleton and Lange; 1996:2141–2149.
29. Cox JL, Holman WL, Cain ME. Cryosurgical treatment of atrioventricular node reentrant tachycardia. *Circulation*. 1987;76:1329–1336.
30. Cox JL, Gallagher JJ, Cain ME. Experience with 118 consecutive patients undergoing operation for the Wolff-Parkinson-White syndrome. *J Thorac Cardiovasc Surg*. 1985;90:490–501.
31. Bredikis J, Lekas R, Benetis R, et al. Diagnosis and surgical treatment of ectopic atrial tachycardia. *Eur J Cardiothorac Surg*. 1991;5:199–204.
32. McCarthy PM, Castle LW, Maloney JD, et al. Initial experience with the maze procedure for atrial fibrillation. *J Thorac Cardiovasc Surg*. 1993; 105:1077–1087.
33. Dubuc M, Roy D, Thibault B, et al. Transvenous catheter ice mapping and cryoablation of the atrioventricular node in dogs. *Pacing Clin Electrophysiol.* 1999;22:1488–1498.
34. Chiang CE, Chen SA, Wu TJ, et al. Incidence, significance, and pharmacological responses of catheter-induced mechanical trauma in patients receiving radiofrequency ablation for supraventricular tachycardia. *Circulation*. 1994;90:1847–1854.
35. Belhassen B, Viskin S, Fish R, et al. Catheter-induced mechanical trauma to accessory pathways during radiofrequency ablation. *J Am Coll Cardiol*. 1999;33:767–774.
36. Manolis AS, Vassilikos V, Maounis TN, et al. Pretreatment with aspirin and ticlopidine confers lower thrombogenic potential of radiofrequency catheter ablation. *Am J Cardiol*. 1997;79:494–497.
37. Manolis AS, Maounis T, Vassilikos V, et al. Pretreatment with antithrombotic agents during radiofrequency catheter ablation. *J Cardiovasc Electrophysiol*. 1998;9:1144–1151.
38. Rewcastle JC, Sandison GA, Muldrew K, et al. A model for the time dependent three-dimensional thermal distribution within iceballs surrounding multiple cryoprobes. *Med Phys*. 2001;28:1125–1137.
39. Weber SM, Lee FT Jr, Chinn DO, et al. Perivascular and intralesional tissue necrosis after hepatic cryoablation: results in a porcine model. *Surgery*. 1997;122:742–747.