

Left Ventricular Catheter Ablation using Direct, Intramural Ethanol Injection in Swine

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Abstract. *Introduction:* Limitations in lesion volume and particularly lesion depth may negatively effect the efficacy of catheter ablation procedures using radiofrequency energy. This study evaluated the safety and efficacy of myocardial ablation using direct intramural injection of ethanol with a novel injection catheter system.

Methods: Left ventricular lesions were performed in 9 male swine (80–85 pounds); two animals were studied 6 weeks following anterior infarction produced by agarose gel embolization. An 8 Fr deflectable catheter equipped with a 27 gauge adjustable depth, retractable needle was directed to the LV using a retrograde aortic approach. Lesion deployment was guided by fluoroscopy and intracardiac echocardiography (ICE). Lesion characteristics were assessed with ICE imaging and pathologic analysis.

Results: Ethanol lesions were confined to the tissue directly adjacent to the injection port. Lesions were intramural with no evidence of overlying thrombus. Lesions delivered with a single port injection needle in normal myocardium (n=24) averaged $1910 \pm 1066 \text{ mm}^3$ with a depth of $8.9 \pm 3.3 \text{ mm}$. Lesions directed to infarct border zones (n=4) averaged $929 \pm 882 \text{ mm}^3$ with a depth of $4.3 \pm 2.8 \text{ mm}$. Lesions were immediately evident on ICE imaging, and were visualized by increased echo density and tissue swelling. Pathological analysis revealed homogenous lesions with intramural hemorrhage and contraction band necrosis.

Conclusions: Myocardial catheter ablation using direct ethanol injection is feasible, and relatively large and deep intramural lesions can be delivered, even in the infarct border zone. This technique may prove useful in ablation of arrhythmia substrates that are deep to the endocardial surface.

Key Words. catheter ablation, intracardiac echocardiography, ethanol, ventricular tachycardia, electrophysiology

Introduction

Conventional radiofrequency catheter ablation produces lesions of modest volume and shallow depth, particularly in the setting of infarcted myocardium [1,2]. These limitations are thought to

contribute to procedural failure in clinical catheter ablation strategies. Although irrigated radiofrequency energy delivery may obviate some of these problems [3–8], this approach also produces lesions that are limited to the endocardial surface. Arrhythmia substrates that are deep to the endocardium, such as some ventricular tachycardias (both idiopathic and in the setting of structural heart disease) and inappropriate sinus tachycardia, are sometimes difficult to ablate using current techniques. Endocardial thrombus formation, particularly with extensive ablation strategies, also represents a significant limitation of radiofrequency ablation [9].

Absolute ethanol has proven useful for non-surgical ablation of various pathological lesions, particularly hepatic tumors [10,11] and myocardial tissue, both for treatment of arrhythmias [12–16] and septal ablation for hypertrophic cardiomyopathy [17–19]. Transcoronary application of ethanol for the purpose of arrhythmia therapy is conceptually limited as the location of arrhythmia circuits does not necessarily respect the distribution of non-occluded coronary arteries, and lesion size does not correlate well with perfusion field [20]. Limited information is available regarding direct myocardial injection of ethanol for ablation [16,21]. The purpose of the present study was to evaluate the safety and efficacy of myocardial ablation using direct intramural injection of ethanol with a novel injection catheter system.

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Methods

General

Experiments were performed on 80–85 pound male pigs under continuous general anesthesia (inhaled isoflourane and nitrous oxide) using protocols in accordance with the 1996 “Guide for the Care and Use of Laboratory Animals” and approved by the Institutional Animal Care and Use Committee of University of Pennsylvania. In two animals, ethanol ablation was performed 6 weeks following anterior infarction. Our modifications of the closed-chest infarction procedure originally developed by Eldar and coworkers [22], have been previously described [23]. Briefly, an 8-French AL1 or AL2 guide catheter introduced via a femoral artery was positioned in the left anterior descending coronary artery and a 2.5 mm angioplasty balloon was advanced to distal LAD at the site of the second diagonal branch. Following balloon inflation (6 ATM), 300 μ l of agarose gel beads (diameter of 75–150 μ m; Bio-Rad Laboratories, Richmond, CA) diluted in 1.5 ml saline was injected distal to the site of balloon occlusion. The balloon was deflated, and the catheter withdrawn and the animal was allowed to recover.

Ablation Procedure

Left ventricular ablation was performed using a retrograde aortic approach after femoral artery

catheterization. Ethanol injection (0.5 ml, absolute ethanol) was performed with an 8 Fr deflectable catheter equipped with a 27-gauge extendable/retractable needle (MyoStar™, Biosense-Webster, Diamond Bar, CA). Needle depth was adjustable, but was set at 4–6 mm for the current study, with the intent of producing mid-myocardial lesions. Two needle designs were evaluated: single port, in which the needle had a single, terminal exit site and multiport, in which the needle had a series of 4 laser etched holes evenly distributed along its course (Fig. 1). The needle was deployed only after satisfactory catheter positioning was verified at the ablation target site; deployment was marked by induction of a single premature ventricular complex and a decrease in catheter movement throughout the cardiac cycle. Catheter positioning and stability during lesion deployment was guided by fluoroscopy, intracardiac echocardiography (ICE, see below) and electroanatomic mapping. Ablation target sites were chosen with reference to anatomic sites (apex, papillary muscles, infarct border zone) to facilitate identification after animal sacrifice, as lesions were intramural and not easily detected at the endocardial surface. In two animals, a modification of the needle to allow unipolar pacing was used to assess pacing threshold pre and post ethanol injection.

At the conclusion of the ablation procedure, the animal was euthanized and the heart resected

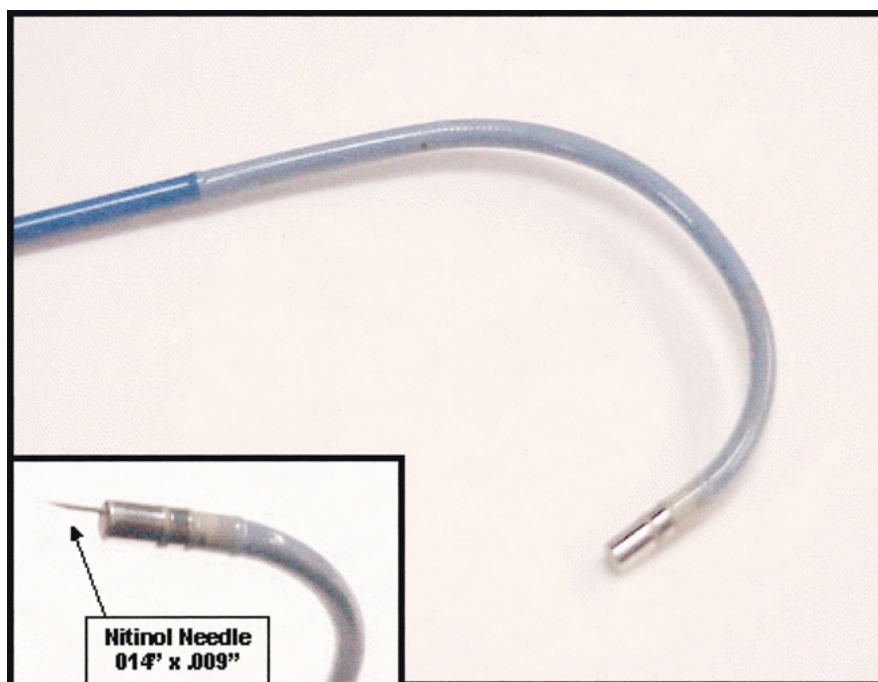


Fig. 1. The Biosense-Webster “Myostar” injection catheter. The inset shows the extended 27 gauge nitinol needle.

immediately. Lesion morphology was measured with hand calipers on fresh tissue specimens after sectioning to identify intramural lesions. Lesion depth (endocardial to epicardial dimension), length (apex to base dimension) and width were measured to calculate lesion volume, using an assumed ellipsoid lesion geometry (volume = $4/3 \pi * \text{depth} * \text{length} * \text{width}$). The distance from the most superficial extent of the lesion to the endocardium ("depth from endocardium") was also measured. The tissue was placed in 10% neutral buffered formalin, and selected sections were embedded in paraffin. Blocks were sectioned at $4 \mu\text{m}$ thickness and stained with hematoxylin and eosin.

Intracardiac Echocardiography

Intracardiac echocardiography (ICE) was performed using a 10 Fr catheter based ultrasound (5.5–10 MHz) system (AcuNav™, Acuson, Mountain View CA). The ICE catheter tip contains a 64-element vector phased array transducer scanning in the longitudinal monoplane. It provides a 90° sector 2D and M-mode images with Doppler and color flow imaging. ICE catheter was positioned in the right atrium or right ventricle using a femoral venous approach. ICE imaging was used to guide catheter positioning, to ensure optimal catheter contact prior to and following needle deployment, and to assess the characteristics of intramural lesion development.

Statistical Analysis

Data are presented as mean value \pm standard deviation, unless otherwise stated. Student's *t* test with adjustment for unequal variances was used to compare lesion characteristics achieved with the two needle conformations. A *p* value of ≤ 0.05 was considered statistically significant.

Results

Alcohol injection was confined to the tissue directly adjacent to the needle. Lesions were intramural and there was no evidence of overlying thrombus. Myocardial perforation or ventricular arrhythmias were not observed with needle deployment or lesion creation; single ventricular premature beats were observed with needle deployment and were used to identify satisfactory position within the myocardium. Although no objective measurements were made, needle deployment subjectively appeared to improve catheter tip stability with the myocardium, as assessed by fluoroscopic and ICE imaging. Lesions were observed immediately using ICE imaging, and were characterized by increased echo density and tissue swelling (Fig. 2).

A total of 35 lesions were delivered in areas of normal myocardium, 24 with the single port, and 9 with the multiport injection catheter. Lesions created with the single port needle were significantly larger in volume ($1910 \pm 1066 \text{ mm}^3$

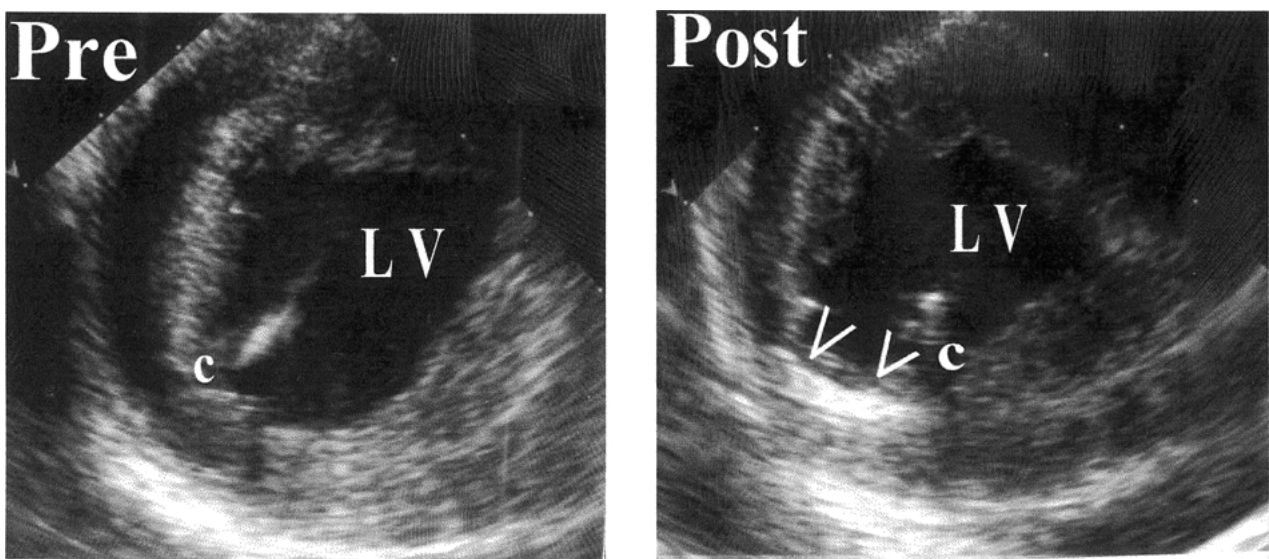


Fig. 2. Intracardiac echocardiographic images of the LV showing needle application and ablation. The left panel shows the catheter (c) positioned prior to ablation. In the right panel, the catheter has been withdrawn slightly after lesion deployment. The lesion (arrowheads) is marked by tissue swelling and increased echo density.

Table 1. Ethanol lesion characteristics

Needle type	Lesion volume (mm ³)	Lesion depth (mm)	Depth from endocardium (mm)
Single port	1910 ± 1066*	8.9 ± 3.3*	1.8 ± 1.2 [†]
Multiport	825 ± 753	4.9 ± 2.5	0.3 ± 0.7

*p < 0.005, single port versus multiport.

[†]p < 0.001, single port versus multiport.

versus 825 ± 753 mm³; p < 0.005), had a greater depth dimension (endocardial to epicardial dimension), and were farther from the endocardium than lesions created with the multiport needle (Table 1). Analysis of fresh pathologic specimens demonstrated intramural, brownish homogenous lesions (Fig. 3). Microscopic analysis demonstrated that myocytes in the area of the lesions were hypereosinophilic; some exhibited contraction band necrosis. Congested capillaries and interstitial hemorrhage were also observed (Figs. 4–5).

Unipolar pacing thresholds were determined at 0.5 msec pulse width from the needle tip pre and post lesion deployment in two animals (7 lesions). Ethanol ablation significantly increased pacing threshold (3.3 ± 2.5 V versus 8.1 ± 8.9 V; p < 0.005). Unipolar pacing at an output of 10 V did not result in capture after ablation in 4 of 7 lesions.

On a single occasion, incomplete deployment of the multiport needle resulted in leakage of ethanol into the left ventricular chamber. ICE imaging demonstrated hyperechoic bubbles exiting the lesion site and immediate endocardial thrombus formation.

A limited number of lesions (n = 4, 2 single port, 2 multiport) were deployed to the infarct border zone in 2 animals with healed anterior infarction. These lesions measured 929 ± 882 mm³ in volume and 4.3 ± 2.8 mm in depth; again, lesions delivered with the single port needle were larger than those delivered with the multiport needle.

Discussion

The major finding of the present study is the feasibility of direct ethanol injection for creation of relatively large, deep, intramural lesions in normal porcine myocardium. Two needle configurations were tested, and the single port needle produced larger and deeper lesions. In addition, the single port configuration appears safer, as ethanol reflux was observed with the multiport needle on one occasion, presumably due to relatively close position of the proximal port to the

endocardial surface. Although not tested formally in this study, the adjustable depth of the needle would allow for lesion design at various depths from the endocardial surface depending on the desired arrhythmia target. Although the number of lesions delivered was limited, ethanol ablation also appears feasible in the infarct border zone.

Several clinical catheter ablation procedures are limited by the small size and shallow depth of conventional radiofrequency lesions. Ventricular tachycardia circuits may exist within the intraventricular septum or deep to the endocardium, either in idiopathic VT or in the setting of structural heart disease. Radiofrequency ablation is particularly limited in this latter setting, as lesions delivered in infarcted tissue are smaller and more shallow than those in normal myocardium [3–8]. Because of the epicardial location of the sinus node, ablation for inappropriate sinus tachycardia is also difficult with radiofrequency energy delivery [24]; multiple lesions at the endocardial surface are required to “summate” and produce effect at the actual epicardial target location. The ability to deliver relatively large lesions at specific tissue depths may be helpful in improving procedural efficacy in these syndromes.

Ethanol is thought to produce tissue damage by its direct cytotoxic action; in trans-arterial delivery strategies, additional injury is produced from acute ischemia as well. Very limited information exists about the cellular effects of direct ethanol injection. Qi and coworkers commented that ethanol acute lesions were marked by focal and diffuse myocardial necrosis, with intense inflammatory reaction and secondary intravascular thrombosis [16]. In their study, ethanol was delivered by both epicardial injection and transarterial administration of ethanol, and no distinction between methods was mentioned regarding pathologic results. In the present study, it was documented that acute ethanol lesions are hypereosinophilic and marked by contraction band necrosis, interstitial hemorrhage and intravascular thrombosis.

Inadvertent release of ethanol into the circulation is potentially dangerous, and is certainly a limitation of this strategy presently. Additional safeguards against ethanol reflux need to be established before clinical application of injection catheter methods. Reflux of ethanol causes immediate endocardial thrombus formation; larger amounts of ethanol may cause coronary or peripheral embolus with resultant tissue death. Precise ICE visualization may prove helpful in this regard. As seen in Fig. 2, careful imaging can distinguish the intramural location of the needle tip.

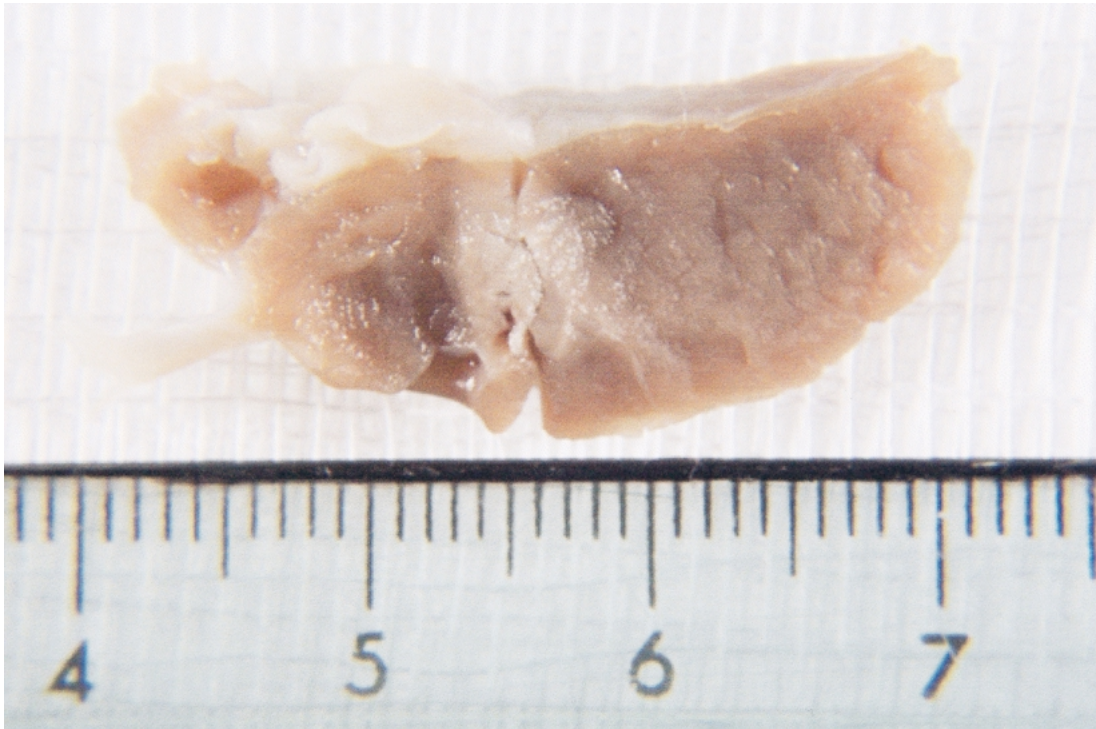


Fig. 3. Gross pathology (cross section) of an alcohol lesion. The lesion is marked by a homogenous brownish color and is entirely intramural. The endocardial surface is oriented above and the epicardial surface below.

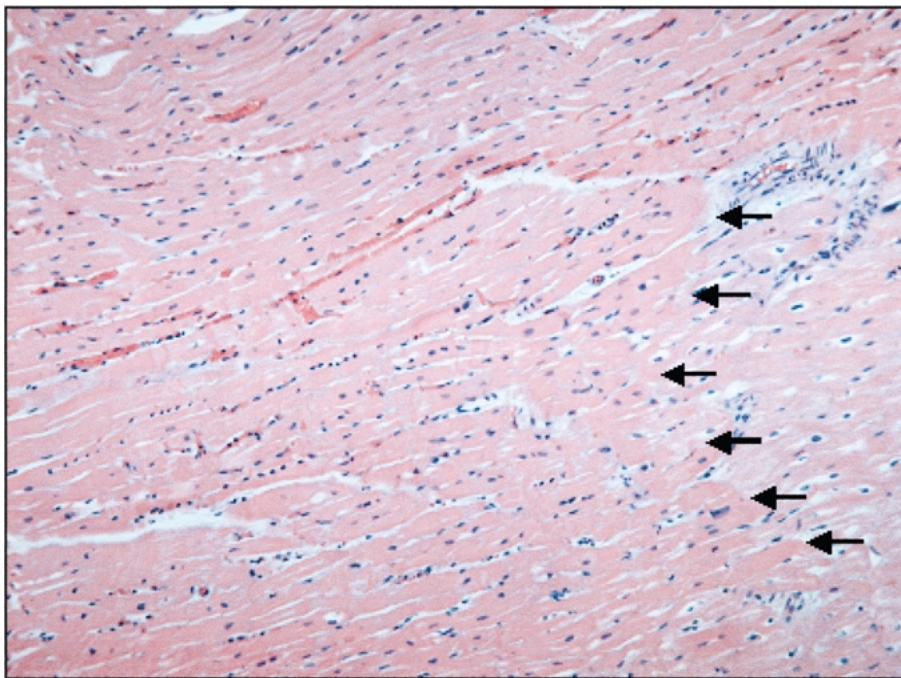


Fig. 4. Microscopic pathology of the alcohol lesion (10× magnification). The myocytes in the region of the alcoholic ablation are hypereosinophilic with congested capillaries and interstitial hemorrhage. The arrows point to the junction of effected myocytes (left) and the normal myocytes (right) following alcohol ablation.

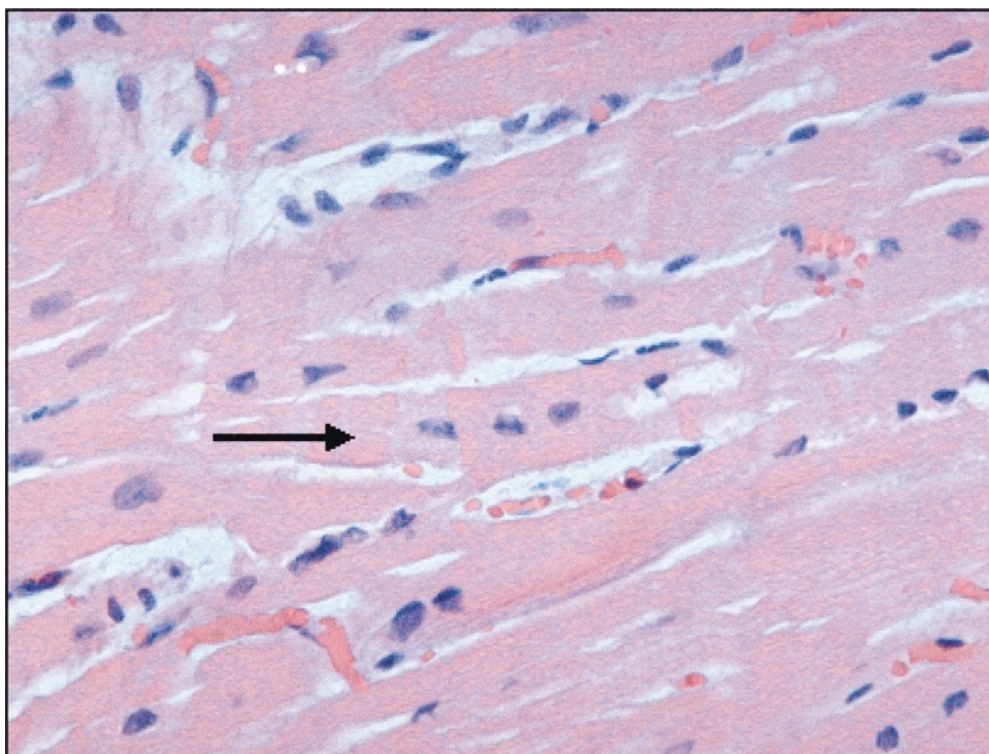


Fig. 5. A higher magnification (40 \times) of the myocytes in the area of alcohol ablation shows the congested capillaries, interstitial hemorrhage, and contraction band necrosis in the myocytes (arrow).

Conclusion

In summary, myocardial ablation using direct, intramural catheter injection of absolute ethanol is feasible. Relatively large homogenous lesions can be delivered deep to the endocardial surface with this method. Ethanol injection may prove helpful in selected catheter ablation procedures where deeper lesions are essential for procedural success.

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