Published in final edited form as:

Heart Rhythm. 2017 August ; 14(8): 1234–1240. doi:10.1016/j.hrthm.2017.04.035.

Evaluation of Ablation Catheter Technology: Comparison between Thigh Preparation Model and an In-Vivo Beating Heart

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Abstract

Background—An *in-vivo* animal thigh model is the standard technique for evaluation of ablation catheter technologies, including efficacy and safety of ablation. However, the biophysics of ablation in a thigh model may not be similar to a beating heart.

Objective—The aim of this study was to compare efficacy and safety of ablation between a thigh preparation model and a beating heart.

Methods—In 7 swine, radiofrequency (RF) ablation using a 3.5mm open irrigated catheter (Thermocool Smart Touch[®]) was performed sequentially in a thigh muscle and in-vivo beating ventricles. Ablation was performed at low (30W for 40Ssec) and high (40W for 60Sec) energy settings and at similar contact force. Ablation lesions were scanned in high-resolution and measured using electronic calipers.

Results—A total of 152 RF ablation lesions were measured (86 thigh and 66 heart). At low-energy, lesion width was greater in the thigh model (12.19±1.8mm vs. 8.99±2.1mm; p<0.001) while lesion depth was similar between the thigh and heart (5.71±0.8mm vs. 5.95±1.3mm, respectively; p=0.18). The planar cross-sectional lesion area was greater in the thigh model (thigh 54.8±10.8mm² vs. heart 43.1±16.1mm²; p<0.001). At high-energy setting, lesion depth, width, and area were all greater in the thigh model (thigh 91.5±16.8mm² vs. heart 56.0±15.5mm²; p<0.001). The incidence of steam pop and char formation was similar between the models.

Conclusion—The thigh preparation model is a reasonable technique for evaluation of ablation catheter technology, however it often results in overestimation of lesion size, especially at higher energy settings.

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Disclosures: EA receives research grants from Biosense Webster and Boston Scientific. CMT receives research grants from Biosense Webster. IZ is an employee of Biosense Webster. EL reports no relevant financial disclosures.

Keywords

Ablation; Thigh muscle; Radiofrequency; Lesion assessment; Ablation biophysics; Animal models

Subject Terms

Electrophysiology; Catheter Ablation

Introduction

Catheter ablation is the mainstay invasive therapy for patients with symptomatic arrhythmias. This field has grown enormously over the past two decades with continuous development of mapping and ablation technologies capable of more accurate mapping and more effective ablation, respectively. Ablation technologies include catheters capable of delivering a variance of energy sources (radiofrequency, cryotherapy, laser, and ultrasound); catheters with progressively larger electrode size capable of bigger ablation lesions; and catheters with more effective cooling of the tissue-electrode interface, resulting in a progressively larger lesion depth. These catheters have distinct biophysical parameters and result in a variance of efficacy and safety profiles.

The standard practice for pre-clinical evaluation and federal safety examination of ablation technologies include testing of the efficacy and safety profiles in an animal thigh muscle preparation model. This novel technique was first described by Hiroshi Nakagawa in canine,¹ and was later applied to other species, including swine and sheep,²⁻⁶ and to other energy sources.⁷⁻⁹ In this technique, ablation energy is delivered in-vivo to an exposed thigh muscle covered with heparinized blood circulated by an external pump at body temperature (Figure 1).

The thigh preparation model has become the mainstay bench test of catheter technologies as it has significant advantaged over a closed-chest beating heart. These include: 1) optimal control over catheter position, electrode orientation, and tissue contact; 2) straightforward identification and measurement of ablation lesions on a homogenous muscle layer compared to the complex cardiac anatomy; 3) larger surface area allowing delivery of higher number of ablation lesions; and 4) simplistic and reproducible technique for evaluation of ablation efficacy (lesion dimensions) and safety (coagulum, char or steam pop within the ablated tissue).^{10, 11}

However, biophysics of ablation in a controlled thigh preparation setup may not mirror ablation in a beating heart. Differences include contractility and motion of the cardiac muscle, complex and articulated cardiac architecture (i.e., trabeculations), differences in the type of muscle,¹² and internal blood supply to the deeper muscular layers can all affect the biophysical properties of ablation.

To date, the thigh preparation model has not been validated in the in-vivo beating heart. The purpose of this study was to prospectively compare the biophysical properties of ablations between a thigh preparation model and a closed-chest beating heart. We aimed to compare

ablation efficacy (lesion dimensions) and safety using two different energy settings between the thigh model and the beating heart.

Methods

Study protocol

Seven Yorkshire swine weighing 55.6 ± 6 kg were anesthetized with inhaled isoflurane and mechanically ventilated, after premedication with oral Amiodarone 800mg b.i.d for 2 full days. Animals were placed in the supine position. Femoral venous and arterial access was achieved using ultrasound guidance. Continuous IV Lidocaine drip was infused throughout the heart mapping and ablation procedure.

Ablation in the beating heart—The left ventricle (LV) was accessed using the retrograde transaortic approach. The chamber geometry including the its apex, mitral and aortic valves were mapped with Carto 3™, (Biosense Webster, Diamond Bar, CA) using a 3.5mm open irrigated catheter (Thermocool Smart Touch®; Biosense Webster, Diamond Bar, CA). Ablation applications were delivered in two energy settings: low (30W for 40Sec) and high (40W for 60Sec), with a target contact force of 10gr and an irrigation rate of 30ml/min and tag on the Carto map. Ablation applications were limited to 10 and separated by 15mm to avoid overlap between ablation lesions, and to allow clear identification of each ablation application. Following mapping and ablation in the LV, the right ventricle (RV) was similarly mapped and ablated with high energy lesions limited to the intraventricular septum. For each ablation application, continuous temperature and impedance data were recorded at a sampling rate of every 33msec. Ventricular arrhythmias arising from beating heart ablations were treated by DC shocks of 200J, and ablations continued in that chamber only if no map shift was noted.

Ablations in the thigh muscle—After completion of the heart lesions, the swine was positioned in a left decubitus posture. A 20cm incision was made over the right thigh muscle, skin dissected free of connective tissue and raised to form a chamber overlying the thigh muscle.¹ The thin superficial muscle was dissected to expose the deeper and thicker *biceps femoris* muscle. The fascia was gently removed to expose the muscle. A 400ml of arterial blood were extracted from the femoral artery, stirred with 5,000 units of unfractionated heparin at 37°C, circulated through an external pump and placed over the *biceps femoris* muscle. The ablation catheter was positioned perpendicular to the tissue at a pressure of 10gr against the muscle. Ablation was performed in the filled chamber with heparinized blood circulating at an exchange flow rate of 200 mL/min. After each ablation application, the chamber was evacuated from blood, catheter was moved to a new position, and the chamber was refilled with heated heparinized blood. After each ablation application the catheter tip and lesion surface were examined for char and coagulum. The institutional animal care and use committee approved this research protocol.

Data analysis

Lesion dimension measurement—Following completion of both heart and thigh ablations and 15 minutes prior to euthanasia, 10ml of triphenyl tetrazolium chloride (TTC)

was administrated systemically. TTC was used to differentiate metabolically active from inactive tissue, in order to accurately identify the extent of tissue necrosis surrounding each ablation lesion. The heart and thigh muscles were harvested and tissue fixed in formalin for 7 days. The hearts were sectioned at 1–2mm slices perpendicular to the intraventricular groove from apex to the base (Figure 2A). Each ablation application was identified on the 3D electro-anatomical Carto map. The medial plane of each cardiac ablation lesion was identified by the maximal catheter tip impression (dimple) within the lesion, and measurements were performed at that plane in attempt to ensure accurate and reproducible measurements (Figure 2B). The ablation on the thigh muscle were examined and identified on the lesion index map created at the time of ablation (Figure 2C). Each ablation lesion was cut through its center perpendicular to the surface. Measurements were performed at the border between necrotic cell tissue and live tissue as determined by H&E and Mason trichrome staining (Figure 3). All ablation lesions were scanned in high-resolution (Epson GT-1500 scanned at 3200dpi resolution) and measured using electronic calipers. Maximal depth, width and planar cross-sectional lesion area were measured for each lesion. We intentionally avoided measurement of ablation volume as ablation in a curved and trabeculated endocardium often results in an irregular lesion shape.¹³ All measurements were sequentially performed by two investigators blinded to the ablation parameters. After separate measurements, each lesion measurement was discussed and included in the data set following agreement between the 2 investigators.

Biophysical parameters and safety measurements—Temperature and impedance data for each ablation application, including maximal temperature, initial and final and impedance were recorded for each heart and thigh ablation applications. Safety outcomes (steam-pops and char formation in both specimen types; coagulum formation in the thigh lesions) were examined after each lesion. Results were recorded simultaneously using an electronic data spreadsheet.

Statistical Analysis

Descriptive statistics are reported as mean $\pm$ standard deviation and 25–75% interquartile range (IQR) for continuous variables. Comparison between thigh and heart ablation lesions was performed using the Wilcoxon sum rank test. Linear regression with bivariate correlation was performed using the Pearson r correlation coefficient. Difference in result variance was examined using the F test. A p value <0.05 was considered statistically significant. Statistical analyses were performed with Stata/MP version 13 (StataCorp, College Station, TX).

Results

In 7 swine, a total of 152 RF ablation lesions, 86 in thigh muscle and 66 in the heart (maximum 10 in a single ventricle) were included in the analysis. We excluded 19 heart lesions: 10 due to geometrical overlap between lesions precluding accurate measurement and additional 9 due to tissue contact force outside the accepted range (6–14 grams). Ventricular arrhythmias were encountered in 3 cases; two treated with DC shock without

map shift and one case requiring 3 DC shocks resulting in a decision to abort additional lesions in that chamber.

Lesion Dimensions

At low-energy setting (43 thigh muscle and 35 heart ablation applications), lesion depth was similar between the thigh muscle and the beating heart ($5.71 \pm 0.8 \text{ mm}$ [IQR 4.68–6.89mm] vs. $5.95 \pm 1.3 \text{ mm}$ [IQR 3.95–7.63mm], respectively; $p=0.18$). Transmurality was observed in 12 low-energy setting lesions on the RV free-wall, and although the external rim of the lesion was seen in 10/12 lesions, the depth in low-energy cardiac ablations maybe slightly underestimated. The width of the lesions was greater in the thigh muscle ($12.19 \pm 1.8 \text{ mm}$ [IQR 9.32–14.9mm] vs. $8.99 \pm 2.1 \text{ mm}$ [IQR 6.97–11.56mm]; $p<0.001$). The maximal planar cross-sectional area was also greater in the thigh muscle ($54.8 \pm 10.8 \text{ mm}^2$ [IQR 39.7–69.3mm²] vs. $43.1 \pm 16.1 \text{ mm}^2$ [IQR 26.9–61.8mm²]; $p<0.001$; Figure 4; Panel A).

At high-energy setting (43 thigh and 31 heart ablation applications), lesion depth, width and cross-sectional area, were all significantly greater in the thigh muscle compared to the beating heart. Depth (thigh $7.54 \pm 1.0 \text{ mm}$ [IQR 6.18–9.01mm] vs. heart $6.76 \pm 1.1 \text{ mm}$ [IQR 5.31–8.17mm]; $p=0.002$); Width (thigh $15.41 \pm 1.5 \text{ mm}$ [IQR 13.51–17.55mm] vs. heart $10.41 \pm 1.9 \text{ mm}$ [IQR 8.21–12.9mm]; $p<0.001$); Maximal planar cross-sectional area (thigh $91.5 \pm 16.8 \text{ mm}^2$ [IQR 68.2–112.2mm²] vs. heart $56.0 \pm 15.5 \text{ mm}^2$ [IQR 36.3–76.1mm²]; $p<0.001$; Figure 4; Panel B).

Temperature

The temperature profile at the catheter-tissue interface during ablation was different between the thigh muscle preparation and the beating heart, with higher temperature recorded in the heart compared with the thigh muscle preparation. The most significant difference was in the maximal temperature parameter. Maximal temperature was higher in both low-energy setting (heart $39.7 \pm 3.9^\circ \text{C}$ vs. thigh $35.9 \pm 2.4^\circ \text{C}$) and high-energy setting (heart $41.4 \pm 3.6^\circ \text{C}$ vs. thigh $36.3 \pm 2.6^\circ \text{C}$; $P<0.001$ for both comparisons; Figure 5A).

Impedance

Impedance decrease during ablation was greater in the thigh muscle as compared with the beating heart (low-energy: $30.5 \pm 11 \Omega$ vs $19.8 \pm 9.9 \Omega$; high-energy ablations $40.1 \pm 12.3 \Omega$ vs. $25.9 \pm 11.7 \Omega$; $P<0.001$ for both comparisons; Figure 5B). The greater decrease in impedance in the thigh muscle preparation is consistent with the greater lesion dimensions described above.

Biophysical differences between energy settings within each model

The biophysical parameters between the low and high-energy settings were compared within each model. Decrease in impedance was greater at the high-energy setting (thigh $p<0.001$; heart $p=0.014$). Maximal temperature was higher at high-energy setting in the heart ($p=0.023$) but similar at the thigh muscle ($p=0.42$).

Performance and Safety

The variability of lesion dimensions was compared between the thigh muscle preparation model and the beating heart. At low-energy settings, the variance between ablation lesions was smaller in the thigh model, thus resulting in greater reproducibility ($F=2.2$; $p=0.016$). However, at high-energy settings, the variance of ablation dimensions was higher compared with low-energy setting and similar between the models ($F=0.85$; $p=0.65$)(Figure 6).

We next examined whether the relationship between inter-lesion dimensions (depth, width, and cross-sectional area) are similar between the models. The thigh model demonstrated a similar correlation between lesion depth and width compared to the beating heart ($r=0.58$ vs $r=0.53$, respectively). There was also a similar correlation between inter-lesion dimensions and the cross-sectional area (Appendix Figure 1). No difference was found in the incidence of steam pops, with only 1 occurrence in the thigh model and none in the beating heart. Char and coagulum formation were not observed during the study.

Discussion

In this study, we compared between the thigh preparation model and the beating heart for assessment of radiofrequency ablation lesion size and for ablation safety parameters. Major findings include:

1. Lesion dimensions: at low-energy settings, ablation lesion dimensions were similar between the models. However, at higher energy settings, the thigh preparation model resulted in overestimation of lesion size, including width, depth, and cross-sectional area.
2. Reproducibility: At low-energy setting, ablation in the thigh model resulted in highly reproducible lesion dimensions and reduced lesion-to-lesion variability as compared to the beating heart. However, at high-energy setting, the lesion variability in size was higher in the thigh and similar between both models.
3. Safety profile: the frequency of adverse effect, including steam pop, char, and coagulum was similar between the models. In particular, the thigh model did not underestimate the frequency of ablation-related complications of the beating heart, providing an adequate platform to assess safety.

The thigh muscle preparation model was introduced by Hiroshi Nakagawa over two decades ago,¹ and is an attractive research tool to evaluate the efficacy and safety of ablation biophysical properties. This technique allows control over key variables such as catheter stability, catheter orientation, and tissue contact. In addition, the thigh model allows for measurements to be obtained within the tissue during the ablation session, such as tissue temperature at different tissue depth.¹ Although utilized as an evaluation tool for ablation technologies and required by federal boards for technology approval, the precautions and limitations of extrapolating conclusions from the thigh muscle ablation model to the beating heart have not been highlighted. Our study validates the utility of this technique for evaluation of low-energy RF ablation parameters, including for the assessment of ablation-related local adverse effects. However, we found that at high-energy settings (power >30W; duration>40s), ablation in a thigh model preparation results in overestimation of lesion size.

These differences in ablation lesion size between the models occurred despite controlling for energy strength and tissue contact force. The increased ablation lesion size in the thigh model was consistent with the higher degree of impedance drop during energy application. The differences in ablation lesion dimensions can potentially be explained by the following variables: 1) cardiac motion: contraction of the chamber results in continuous changes in the contact between the catheter tip and the underlying the tissue, in contrast to the continuous and stable contact applied in the thigh model ; 2) The catheter position in the heart is influenced by curves and trabeculations that can result in reduced catheter-tissue interface surface area; 3) catheter measured temperature: ablation in the beating heart was associated with increased temperature despite similar temperature of the circulating blood (37°C in the thigh and heart ablations). This can potentially be explained by reduced convective blood cooling and irrigation in the beating heart at areas of trabeculations further resulting in lower penetration of energy into the tissue, and lastly; 4) potential differences in muscle properties between the striated thigh muscle and the heart muscle. Some factors listed above may also explain differences encountered by others when trying to compare epicardial ablation lesions to endocardial ones.^{14, 15} Irrespective of these reasons, differences exist between the thigh preparation model and the beating heart that may become more important as ablation energies delivered are more powerful. A combination of factors accentuate the difference between the models in the high-energy setting, including longer time to produce stable contact in the beating heart, influence of on-going differences in convective blood cooling and higher energy delivery emphasizing the intrinsic differences between the models.

Despite the inherent differences between the methods reflected in the results presented here, the thigh model serves as the gold standard for incorporating new ablation technologies (although not all technologies are appropriate for thigh model evaluation, such as balloon based energy delivery), due to the ablation lesion reproducibility and additional merits discussed above. While the thigh model imperfectly represents real-life cardiac ablations, its use over the years as an assessment tool for incoming technologies has provided reliable and consistent efficacy and safety results.

Accuracy of lesion measurement

Previous publications on ablation in thigh model preparation did not report a uniform method for lesion size measurement, particularly in respect to histology and/or electrical excitability.^{2, 16, 17} Evaluation of radiofrequency ablation in the thigh model with histopathological correlation was performed in a rabbit model for evaluation of solid tumor RF treatment.^{18–20} In order to accurately measure ablation lesion dimensions in the thigh preparation and in the heart, we performed histological analysis to identify the border between healthy and dead cells (Figure 3) and correlated the result to the gross pathology.

Limitations

This study was performed in swine and discrepancies between thigh and heart muscle cannot be generalized across animal species, but evaluated for each model. Likewise, we evaluated the effect of radiofrequency energy in the two models, therefore this data should not be generalized to other ablation energy sources, and the applicability of the comparison between the two methods is limited to the parameters and technologies used. While the

study was powered to compare the efficacy of ablation between models, during the assessment of safety endpoints in both models we only observed a single safety event (steam pop in the thigh preparation model). However, ablation in the thigh preparation model did not underestimate the amount of safety endpoint observed in the beating heart. Cardiac RV lesions were susceptible to transmuralities that may have resulted in underestimation of lesion depth in the low-energy setting. In addition, 19 cardiac lesions were excluded from the analysis due to lesion overlap preventing delineation of lesion borders required for accurate measurement (n=10/19) and when the target contact force was not achieved during ablation application (n=9). Exclusion of this data, while necessary, is a source of potential selection bias into our results.

Catheter stability and orientation (perpendicular vs parallel) in the beating heart cannot be controlled to a degree of a stationary thigh model. While, this may contribute to discrepancies in lesion dimensions between the models, catheter motion is a real life phenomenon, and should be accounted in the predication of lesion size. Lastly, fixation in formalin may result in tissue shrinkage and effect lesion measurements. However, since both the thigh and the heart tissues underwent a similar fixation treatment, we assumed a minimal contribution of the shrinkage for the comparative analysis.

Conclusions

The thigh muscle preparation model is a reasonable research tool for assessment of ablation lesion size, and tissue adverse effects including: steam pop, char, and coagulum formation. It provides an accurate predication of ablation lesion dimensions in the heart at low radiofrequency energy settings, however may overestimate ablation lesion dimensions at high-energy settings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: Partly supported by an investigator-initiated grant from Biosense Webster and a National Institutes of Health grant 1R21HL127650-01. EL is a recipient of an NIH training grant 5T32HL007374-37

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Figure 1. Schematic presentation of the thigh muscle preparation model

The skin over the thigh muscle was incised and raised to form a cradle. The cradle was filled with heparinized blood from the same animal at 37°C to 38°C. Adopted with permission from Nakagawa et al, *Circulation* 1995;91:2264–2273. ****Permission will be obtained following manuscript acceptance****

Figure 2. Thigh and heart ablation lesion analysis

Panel A: following formalin fixation, the heart was sliced into 1–2mm thick slabs oriented perpendicular to the intraventricular groove. The whole ventricle is then reconstructed in an anatomical perspective and orientation. The left anterior descending artery and anterior intraventricular groove are used to accurately align the slabs (between the dashed lines). Panel B: the heart slabs are scanned from both sides and lesion dimensions are measured at the level of maximal catheter tip impression using electronic calipers. In this example, asterisks mark the same ablation lesion at different slabs (heights within the left ventricle). Lesion dimensions were measured at the location of maximal catheter tip impression (arrow). Panel C: ablation in the thigh muscle preparation were marked using a picture index map. The thigh muscle underwent a similar fixation process in formalin. The lesions were sliced perpendicular to the tissue surface at 1–2mm thick sections, and similarly scanned and measured using electronic calipers.

Figure 3. Determination of ablation lesion size

In order to accurately measure the size of the ablation lesion, the border between necrotic cell and live tissue in both the heart and thigh muscle tissue was evaluated with histology (H&E staining). In this representative example, the histological specimen (left) shows a central area of coagulative myocytolysis, while the peripheral border shows early liquefactive necrosis (asterisk in both the gross pathology and histology panels; highlighted window bottom left). A thin rim (<1 mm) of granulation tissue and red blood cell serves as a sharp transition to healthy tissue and correlated with the external rim observed in gross pathological section (arrows, right).

Figure 4. Comparison of ablation lesion dimensions

Panel A: at the low-energy settings (30W for 40seconds), lesion depth was similar between the thigh and heart ($5.71 \pm 0.8\text{mm}$ vs. $5.95 \pm 1.3\text{mm}$, respectively; $p=0.18$). However, lesion width and cross-sectional area were larger in the thigh lesions ($p<0.001$ for both comparison). Panel B: at high-energy settings (40W for 60seconds), all measurements including depth, width, and cross-sectional area were larger in the thigh muscle preparation ($p<0.001$).

Figure 5. Changes in temperature and impedance between the models

Panel A: The maximal temperature measured by the catheter was higher in the beating heart compared to the thigh lesions in both energy settings ($p < 0.001$). Panel B: Ablation in the thigh muscle preparation resulted in a larger impedance drop in both low and high-energy settings ($p < 0.001$).

Figure 6. Distribution of ablation lesion cross-sectional area measurements

At low-energy setting (30W/40sec), the thigh model demonstrated narrower distribution of ablation cross-sectional area ($F=2.2$; $p=0.016$). At high-energy setting (40W/60sec), the distribution and variance of ablation lesion dimension was similar between the models ($F=0.85$; $p=0.65$).