Better Lesion Creation And Assessment During Catheter Ablation

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Abstract
Permanent destruction of abnormal cardiac tissue responsible for cardiac arrhythmogenesis whilst avoiding collateral tissue injury forms the cornerstone of catheter ablation therapy. As the acceptance and performance of catheter ablation increases worldwide, limitations in current technology are becoming increasingly apparent in the treatment of complex arrhythmias such as atrial fibrillation. This review will discuss the role of new technologies aimed to improve lesion formation with the ultimate goal of improving arrhythmia-free survival of patients undergoing catheter ablation of atrial arrhythmias.

Introduction
Catheter ablation forms an essential part of the management of cardiac arrhythmias including supraventricular tachycardia (SVT), atrial flutter (AFL), atrial fibrillation (AF) and ventricular tachycardia (VT). Catheter ablation has demonstrable superiority over anti-arrhythmic drugs in improving arrhythmia burden and quality of life in patients with atrial arrhythmias and SVT. When the arrhythmia has a well-defined electrophysiologic mechanism and the target region is localized such as in SVT or typical AFL, arrhythmia-free survival approaching 90 to 95% can be achieved. However with more complex arrhythmia mechanisms such as AF, arrhythmia recurrence is observed in 50-70% of patients. This lower efficacy is likely due to limitations in mapping, incomplete understanding of the driving mechanisms of arrhythmia (as is the case in persistent AF), and perhaps most importantly, our inability to create transmural and durable lesions in a linear fashion.

Successful catheter ablation requires not only precise localization of the arrhythmogenic substrate but complete and permanent elimination of that substrate without producing collateral injury. Despite over 30 years of intensive research focusing on novel energy sources, the reliable creation of effective and permanent lesions remains challenging. This review will examine the role of existing and emerging technologies in catheter ablation designed to improve lesion quality during catheter ablation of AF. First, however, it is important to revisit some key concepts in ablation biophysics, which help to define the barriers to better lesion creation, and to explore current methods of assessing an effective lesion.

Ablation Biophysics
Radiofrequency (RF) current is the most common and widely employed source used energy source in catheter-based ablation, mainly due to a well-understood safety profile. RF ablation transfers electromagnetic energy into thermal energy by a process called resistive heating at the surface of tissue. Lethal heating destroys deeper tissue by conduction. The RF current is delivered in unipolar fashion between the catheter tip and the indifferent electrode patch placed on skin. In bipolar RF systems, the current flows between two closely apposed small electrodes.

Some important concepts of RF ablation are worthy of review. First, a rise of tissue temperature to above 50°C is required to produce irreversible thermal injury; with lower tissue temperatures (eg 45-50°C), there may be reversible loss of cellular excitability. Second, lesion size is proportional to the electrode-tissue interface temperature with higher temperature...
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created in which the tissue further from the ablation electrode may not reach its stable maximum (thermal equilibrium) until up to 2 minutes later. Because of this thermal decay, small increases in distance from the ablation target may result in large increases in RF current requirements. Larger current delivery will result in deeper heating of the tissue layers passively through conduction of a hotter surface temperature.

Fifth, lesion size is also directly proportional to the radius of the heat source. Larger electrode diameter (i.e. with larger tip electrodes), length and contact area all result in a larger source radius and larger lesion size for the same current density, which is maintained by increasing power settings when a larger electrode is used. It is important to note that lesion size is proportional to electrode-tissue interface temperature in conventional ablation catheters. With cooled tip catheters it is proportional to power delivered.

Although heat transfer into tissue should be a predictable biophysical phenomenon, in vivo, other factors (including the cooling effect of regional blood flow, and blood flow through the tissue) alter the heat transfer to tissue, making it less predictable. Once tissue temperature reaches or exceeds 70°C, coagulum can form at the electrode tissue interface and a sudden rise in electrical impedance can occur, that limits energy delivery. There is evidence that protein denaturation may start at temperatures around 55°C, which is probably the first step in the cascade that leads to coagulation formation. Reaching temperatures of 100°C also can result in “steam pops”, that may lead to perforation and cardiac tamponade. Convective cooling is a major thermodynamic factor opposing the transfer of thermal energy to deeper tissue layers by limiting surface temperature, however it is exploited because cooling the catheter tip allows greater energy delivery without boiling or coagulum formation at the electrode tip; thus, increasing the amount of current that produces direct resistive heating increases the radius of the effective heat source. For these reasons, greater depth and increased diameter of lesions can be produced with cooled-tip catheters. Electrode tip cooling can be achieved passively with large tip ablation electrode or actively with closed or open-tip irrigated catheters. Electrode tip cooling, however limits the value of temperature monitoring during irrigated catheter ablation, as there is a larger disparity between electrode and tissue temperature.

Factors that influence passive cooling at the electrode-tissue interface include the magnitude of regional blood flow and stability of the electrode catheter on the tissue surface. The tricuspid and mitral valve annuli have high volume of regional blood flow. When endocardium is smooth, catheter stability may be difficult. Both of these factors can decrease lesion size. In contrast, ablation in trabeculated myocardium or under valve leaflets can result in highly efficient heat transfer and risk of excessive tissue heating. Other factors such as electrode-tissue contact force (CF) can directly affects lesion size, depth and volume and this will be reviewed in detail in subsequent sections. Because of the variability of these factors in vivo, applied energy, power and current are poor indicators of the extent of lesion formation during RF ablation. However, as tissue is heated, there is a temperature-dependent fall in tissue impedance. that is a useful surrogate for lesion formation. The availability of contact force measurements has also improved the ability to create reliable lesion size.

In summary there are multiple factors that effect RF ablation lesion size including power, ablation electrode temperature, duration of energy delivery, ablation circuit impedance, catheter-tissue CF, electrode size and myocardial blood flow. It is important to note that although larger RF ablation lesions can increase the success of ablation, they can also increase the risk of collateral tissue injury, for example, to the esophagus during pulmonary vein isolation (PVI). It is thus critical to revisit our motivation for attempting to create larger, more permanent RF lesions.

The Need For Better Lesion Creation
It is now well accepted that the pulmonary veins (PVs) play...
a critical role in the initiation and maintenance of AF,\textsuperscript{37} and that complete electrical disconnection of the PVs from the left atrium (LA) is an important electrophysiological endpoint.\textsuperscript{28-30} Although electrical disconnection can be achieved almost universally by the end of the procedure, long term efficacy of catheter ablation remains soberingly modest, with single and multiple procedure success rates of 54% and 79% recently reported for paroxysmal AF over long term follow up (≥ 3 years).\textsuperscript{14} The time-dependent inevitability of PV reconnection and its relationship to future AF recurrence has been demonstrated in many studies showing that, prior to the use of contact force for guiding ablation lesions, up to 50-64% of PVs reconnect during an intra-procedural waiting period of up to 60 minutes post acute PV isolation.\textsuperscript{31-33} It is well appreciated that AF recurrence post catheter ablation is usually associated with resumption of PV-LA conduction.\textsuperscript{28,29,34} Gaps in lines that allow PV to LA reconnection allow PV triggers to also serve as triggers for other macro-reentrant atrial arrhythmias and as the substrate for some macroreentrant atrial tachycardias after circumferential antral PVI.\textsuperscript{28,29,31,34,35} In a histopathologic study in patients undergoing MAZE for recurrent AF after initially successful catheter ablation for AF, Kowalski et al performed intraoperative assessment of PV-LA junction conduction during the procedure and took biopsies from the PV antrum at sites of endocardial scar. They found that PVs showing electrical reconnection after catheter-based RF ablation frequently exhibited either anatomic gaps or non-transmural lesions at sites of ablation. However, non-transmural lesions in some PVs had evidence of persistent PV-LA block suggesting that fact that lesion geometry may influence PV conduction.\textsuperscript{36} Indeed, gap geometry plays a critical influence on conduction through discontinuities in RF lesions such that bifurcated (“Y” shaped) or angled gaps (containing two right angles within the conduction path) were less likely to produce bidirectional conduction block but were more likely to produce unidirectional or rate dependent conduction block compared with straight gaps.\textsuperscript{37}
blood compared to myocardium and greater interface area between the electrode and blood. However, impedance varies at different sites in the heart, and the baseline impedance does not appear to be a reliable indicator of RF ablation lesion formation. With RF application, tissue heating results in reduced myocardial resistivity and a fall in tissue impedance. Animal studies have shown that the magnitude of impedance fall early after the onset of RF ablation strongly correlates with lesion depth (correlation coefficient squared, R² = 0.68) and volume (R = 0.72). Furthermore, CF influences the rate and duration of impedance decrease with “poor” contact lesions resulting in earlier plateau (≤13 seconds) compared to “good” contact during which a continuous fall in impedance may reach a later plateau (e.g., plateau at 40 seconds).

In human studies, the extent of fall in impedance has been shown to correlate with the CF. Kumar et al. showed that there was modest linear relationship between CF during ablation and the impedance fall (r = 0.32, P < 0.001). Similarly, de Bortoli et al. found a stronger association between contact force and maximum impedance fall (r = 0.54, P < 0.01). An impedance fall of 10 ohms at 10 seconds was shown to correspond to a contact force > 20 g. However there was a large degree of overlap between different ranges of CF and impedance fall was only able to roughly differentiate low, intermediate and high CF beyond 15 seconds of RF.

These findings were confirmed by an independent study by Reichlin and colleagues. In that study, the impedance decrease in the first 20 seconds was larger with increasing average category of CF over the same time. CF < 5 g, 5–10 g, 10–20 g, and >20 g was associated with a median fall in impedance at 20 seconds of 5 ohm (interquartile range [IQR]. 3–7-8 ohm. 4–10 10 ohm. 7–16 and 14 ohm. 10–19 with one commercially available CF sensing catheter (SmartTouch, Biosense-Webster, Diamond Bar, CA, USA). Similar findings have been noted with another type of CF-sensing catheter (Tacticath, St. Jude Medical, St. Paul, MN, USA) (Figure 2).

The effectiveness of a lesion also may be assessed from a change in electrogram (EGM) amplitude or morphology or increase in pacing threshold at the site. EGM changes have been described as a surrogate for lesion transmurality. A reduction in EGM amplitude of >80% is thought to indicate a transmural lesion. Changes in unipolar and bipolar EGM morphology post versus pre-ablation may also detect lesion transmurality. Elimination of the negative deflection on the unipolar EGM identified a transmural lesion with 100% sensitivity and specificity in an animal study. Indeed, continuing RF application until the creation of a completely positive unipolar signal at a particular site was associated with improved AF-free survival compared to empirc 30 seconds of RF at each site alone during PVI in one non-randomized study. It is important to note that unipolar distal EGM amplitude changes are likely to provide more useful information than bipolar recordings as the signal from the ring electrode may dominate the EGM bipolar amplitude and wavefront of activation is less important.

Although changes in EGM properties have been used to guide lesion effectiveness, the magnitude of change in pacing threshold with RF ablation has been shown to be substantially greater than the magnitude of decrease in bipolar or unipolar EGM. In the atrium, loss of bipolar capture post ablation predicts formation of a uniform transmural lesion, and is superior to EGM-based detection of gaps within ablation lines. In the ventricle, change in pacing threshold correlates with and is a better marker of lesion size than change in unipolar or bipolar EGM amplitude. In human studies, RF ablation with the endpoint of electrical inexcitability along a circumferential line during a PVI has been shown to markedly enhance single procedure success of AF ablation compared with the aim of achieving bidirectional PV-LA conduction block alone. It may also reduce acute PV reconnection rates and dormant conduction.

Real-time MRI, and MRI thermography, although not readily available, are promising methods for intra-procedural assessment of lesion completeness. Cardiac MR imaging appears capable of delineating areas of permanent tissue damage caused by ablation, and of identifying gaps in atrial ablation lesion lines in animal studies. Important limitations exist when using methods to define a “better lesion”. The gold standard of transmural tissue necrosis by histopathology is highly relevant for animal models, but is not applicable clinically. Thus the effectiveness of any new technology in human studies is primarily assessed by acute and long term clinical outcomes, which are clearly the most clinically relevant goals. Further work is thus needed to validate simple intra-procedural parameters for assessing acute lesion efficacy that reliably translate to long-term procedural success.

Technologies For Better Lesion Creation
There has been a rapid expansion of research aimed at improving the efficacy, simplicity and speed of catheter ablation. A number of “single shot” devices such as endoscopic ablation systems, multielectrode catheters, and balloons seek to provide a simpler and quicker approach to PVI. Whether these technologies will be more effective than traditional point-by-point RF ablation has not been established, and has been reviewed elsewhere. In this review we will discuss: (i) improvement in our ability to assess real-time catheter tissue contact with force sensing; (ii) variation of existing systems that allow creation of deep intramural lesions (bipolar ablation); (iii) catheters that allow extensive and deep myocardial lesions without significant damage to collateral structures (electroporation).

Contact Force Sensing

Two new contact force (CF) sensing catheters are now available for clinical use in the USA: the TactiCath (St Jude Medical, St Paul, MN, USA) and SmartTouch Thermocool (Biosense Webster, Diamond Bar, CA, USA) catheters. These allow real-time measurement of the catheter tip-to-tissue CF during catheter ablation. TactiCath is a 7 French (Fr) open irrigation catheter (6 holes at the distal tip) with a 3.5-mm tip electrode, and a force sensor incorporated into the distal part of the catheter between the second and third electrode. The force sensor has a deformable body (elastic polymer) and 3 optical fibers that measure micro-deformations correlating with force applied to the catheter tip. Infrared laser light is emitted through the proximal end of the 3 optical fibers. The light is reflected by fiber Bragg gratings on the deformable body at the distal end of the optical fibers, near the tip of the catheter. Applying CF to the tip of the catheter produces a microdeformation, causing the fiber Bragg gratings to either stretch or compress, thereby changing the wavelength of the reflected light. The change of wavelength is proportional to the CF applied to the tip. The system is able to calculate and display the vector of the CF (magnitude and angle) at a sampling rate of 100 milliseconds (ms). It has a resolution and sensitivity of about 1 gram in bench testing. During RF delivery, the force-time integral (FTI; measured in grams x seconds, g*s) is displayed (Figure 3).

The SmartTouch Thermocool catheter is a steerable, 3.5-mm six-hole open-irrigated tip ablation catheter. The catheter tip electrode is mounted on a precision spring that permits a small amount of electrode deflection. A transmitter coil that is coupled to the tip electrode, distal to the spring, emits a location reference signal. Location sensor coils placed at the proximal end of the spring detect micromovement of the catheter tip. Adapters and optical fibers incorporated into the distal part of the catheter between the second and third electrode. The force sensor has a deformable body (elastic polymer) and 3 optical fibers that measure micro-deformations correlating with force applied to the catheter tip. Infrared laser light is emitted through the proximal end of the 3 optical fibers. The light is reflected by fiber Bragg gratings on the deformable body at the distal end of the optical fibers, near the tip of the catheter. Applying CF to the tip of the catheter produces a microdeformation, causing the fiber Bragg gratings to either stretch or compress, thereby changing the wavelength of the reflected light. The change of wavelength is proportional to the CF applied to the tip. The system is able to calculate and display the vector of the CF (magnitude and angle) at a sampling rate of 100 milliseconds (ms). It has a resolution and sensitivity of about 1 gram in bench testing. During RF delivery, the force-time integral (FTI; measured in grams x seconds, g*s) is displayed (Figure 3).

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of creating large myocardial lesions and interestingly, there seems to be a greater safety margin for achieving large myocardial lesions without damage to surrounding structures such as the epicardial coronary arteries. The impetus for this interest is derived from the fact that RF ablation near coronary arteries can lead to acute vessel injury, and also progressive vessel stenosis from tunica intima and media thickening.117-120 Tissue cooling by arterial flow can also lead ineffective lesion formation and unsuccessful ablation at sites adjacent to an arterial branch.121

In pre-clinical work IRE catheters (7 French).115, 122-127 have been developed in varying shapes (circular, linear) and varying number of electrodes.8-10 Energy is applied between the electrodes and a remote indifferent electrode using a monophasic external defibrillator charged to delivery energy in a range of 50 and 360 J.122 In animal work, greater applied current through IRE resulted in a linear increase in median lesion depth. No signs of thermal damage to the electrode or ablation site (when examined histologically) were seen, suggesting that the putative mechanism of injury is likely non-thermal,115 though tissue temperature was not examined specifically in those studies. Furthermore the region of IRE-induced injury did not have a sharp “cut off” as is usually seen grossly with RF lesions, but often irregular borders were observed.115

IRE, when used to deliver a single pulse, non-arching 200J application between the catheter and an indifferent electrode patch at the PV ostia of swine (maximum 4 pulses/pig), resulted in acute PV EGM attenuation, increased PV stimulation threshold, and no PV stenosis with a 3.5 mm-deep lesions histologically at 3 weeks follow up.127 In a follow up study in pigs, IRE to PVs resulted in acute PV stenosis that reversed at 3 months; in comparison, RF application at equivalent sites resulted in acute PV stenosis that persisted at 3 months.126 Epicardial IRE in pigs, caused extensive myocardial lesions whilst preserving coronary artery patency and wall integrity.122 Lesion depth and width increased with energy of electroporation applications in swine epicardium with reproducible transmurality observed and, critically, no evidence of intimal hyperplasia of the coronary arteries located within the regions of myocardial damage.123,124 Further studies in pigs have shown epicardial IRE delivered intentionally overlying major epicardial coronaries resulted in short-lasting (<30 minutes) luminal narrowing in the targeted area with subsequent normalization, suggesting coronary spasm.125 No injury to organs adjacent to the pericardium was noted.123 Importantly, there was myocardial injury to tissue surrounding the arteries, as the presumed mechanism of injury was not related to tissue heating. This finding is of particular interest as myocardial sparing around an artery is not uncommon in RF or cryoablation as a result of tissue cooling (or warming) by arterial flow.128, 129 Overall, the findings from the intriguing animal work suggests that the myocardium may be more sensitive to electroporation injury than the coronary arteries, a property that could be potentially exploited in the future in epicardial ablation. However, important issues such as controlling lesion size (wide ranges of lesion depths were noted in some studies), effect on phrenic nerve injury, the prevention of acute coronary artery vasospasm, and long term effects on the coronary lumen are important issues that need to be addressed.116 The catheter has not been tested in humans and is not available for use in the USA. It is likely to have important clinical applications if safety and efficacy can be demonstrated.
Other Technologies For Assessing RF Lesion Creation

A number of other technologies have been tested that will be mentioned briefly. None are available for clinical use at this stage. Direct endocardial visualization (IRISTM Ablation Catheter, Voyage Medical, Redwood City, CA, USA) are catheters that allow direct visualization of tissue characteristics (for example dense scar versus border zone in infarcted ventricles), to monitor catheter location and stability, lesion development and lesion contiguity. In one study, this catheter created wider lesions at lower power compared to irrigated tip ablation but with comparable pacing and sensing efficacy. In an animal model, visually-guided RF ablation in the ventricle resulted in more reliable lesion creation as assessed on histopathology compared with standard open irrigated catheter guided by “traditional” markers of contact where only 78% of lesions delivered were identifiable histologically. This technology appears promising in improving the efficacy of ablation using currently available RF-methods.

Investigators have previously demonstrated that variable catheter tip sliding can lead to poor tissue contact, compromise lesion efficacy and create unpredictable lesion dimensions. Electrogram-gated pulsed RF ablation is a variation of currently available RF technology that aims to deliver the same average power as a conventional ablation but for a shorter duration based on the onset of the local electrogram. This method aims to counteracts the effects of sliding catheter movement that results in degradation of ablation efficiency. This system was shown to create consistently deeper lesions irrespective of the degree of catheter movement as well as reaching target lesion depths significantly faster than conventional ablation in one study carried out on a thermochromic gel myocardial phantom. Further work is needed to validate this technology in vivo.

Acoustic radiation force impulse (ARFI) imaging is an ultrasound-based technique that allows quantification of tissue stiffness based on mechanical displacement of tissue in response to ultrasonic impulses and monitors the tissue response using conventional ultrasound methods. The technology can be utilized with intracardiac echo (ICE) and can visualize the relative elasticity difference between ablated and unablated myocardium and can accurately assess focal RFA lesion morphology in vitro. This technology has the potential for guiding lesion transmurality in the future.

Conclusions

A number of important developments have been made in catheter ablation aiming to improve lesion creation whilst minimizing collateral injury and improving long term arrhythmia free survival. With each new development, one must be wary of potential for harm not uncovered from small pre-clinical or clinical studies. Randomized controlled data is valuable in validating and accepting the superiority of new technology compared to traditional methods of catheter ablation, but the safety and efficacy of each technology must be tested in a systematic fashion. Rigorous surveillance of safety is important to prevent avoidable harm to patients. Progress has been made, but further work is needed on intra-procedural methods of identifying lesion completeness that reliably predict arrhythmia-free survival in long term follow up.

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