Target Indices for Clinical Ablation in Atrial Fibrillation

Insights From Contact Force, Electrogram, and Biophysical Parameter Analysis

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Background—In animal studies of radiofrequency ablation, lesion sizes plateau as the maximum lesion size is reached for an ablation. Lesion parameters are not available in clinical ablations, but preclinical work suggests that these correlate with impedance drop and electrogram attenuation. Characterization of the relationships between catheter contact force, ablation duration, and these surrogate markers of lesion formation may allow us to define targets for effective ablation.

Methods and Results—Fifteen patients undergoing first-time radiofrequency ablation for nonparoxysmal atrial fibrillation were studied. All were in atrial fibrillation at the time of the procedure. Ablations were performed with an irrigated-tip contact force–sensing catheter in temperature-controlled mode (temperature limited to 48°C, power to 30 W). Included were 285 left atrial static ablations, 247 with additional impedance data. The ablation force time integral (FTI) correlated with the attenuation of the electrogram with ablation (Spearman ρ = −0.14; P = 0.02): the relationship plateaueing from 500 g·s, a reduction in the electrogram amplitude of 20%. The FTI also correlated with the impedance drop during ablation (Spearman ρ = 0.79; P < 0.0005): the relationship was logarithmic, the reduction in the impedance with an increasing FTI also plateauing from 500 g·s, an impedance drop of 7.5%. The ablation duration affected the impedance drop at an FTI if the duration was <10 s. Beyond this time point, the FTI achieved rather than the ablation duration or mean contact force applied determined the impedance drop.

Conclusions—During nonparoxysmal atrial fibrillation ablation, an FTI of 500 g·s should be targeted with ablation duration of ≥210 s.


(Circ Arrhythm Electrophysiol. 2014;7:63-68.)

Key Words: atrial electrogram ■ atrial fibrillation with bradyarrhythmia ■ catheter ablation

The aim of ablation for atrial fibrillation (AF) is the generation of a transmural lesion. In animal studies, a plateau is observed between lesion size and delivered ablation energy, with no significant change in lesion size at a fixed ablation power for ablation ≥20 s.1 The relationship between catheter contact force (CF) and lesion depth also plateaus at higher values in studies of temperature-controlled ablation.2 These plateaus therefore represent the maximum lesion size that can be attained for a particular set of ablation parameters. During clinical ablation, one would also expect lesion parameters to plateau as this maximum is reached for an ablation, but in clinical procedures lesion parameters are not known.

Such studies also demonstrate that electrogram amplitude reduction is significantly greater in transmural than in non-transmural lesions.5,6 Therefore, these measures can be used as surrogates of lesion parameters.

Detailed measurements of tissue CF during clinical ablation have now become possible using CF-sensing catheters. We can therefore assess the impact of this controllable factor on indicators of the effect of ablation on tissue: electrogram amplitude and impedance change. In animal studies, the tissue CF has been found to correlate with both lesion depth2,3,7 and impedance drop.2,7 Examination of the inter-relationships between these factors may allow us to optimize our ablations, in particular the identification of a plateau point in man beyond which further ablation has no or minimal effect on the tissue would be especially useful.

The aim of this study was therefore to establish, based on the biophysical and electrogram changes, target indices for radiofrequency ablation.

Received October 2, 2013; accepted December 31, 2013.

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Circ Arrhythm Electrophysiol is available at http://circres.ahajournals.org

DOI: 10.1161/CIRCEP.113.001137
Methods

All participants gave informed consent to participate in the study, which was approved by the UK National Research Ethics Service. Consecutive patients undergoing their first ablation procedure for nonparoxysmal AF (NPAs) were enrolled in the study. All patients were in AF at the start of the procedure, and all procedures were performed with the patients under conscious sedation. A Thermocool SmartTouch catheter (Biosense Webster, Inc, CA) was used to measure tissue CFs, at a sampling rate of 20 Hz. Remote robotic navigation (Sensel Robotic Catheter System, Hansen Medical, Inc, CA) was used in a majority of procedures, although this was at the discretion of the operator. Tissue CF and electrogram characteristics were recorded using the Carto3 electro-anatomic mapping system (Biosense Webster, Inc) and LabSystem Pro electrophysiological recording system (Bard Electrophysiology Division, MA), respectively.

During wide area circumferential ablation of the ipsilateral pulmonary veins in pairs and complex fractionated atrial electrogram ablation, 30-s static study ablations were performed, with the ablation catheter in a stable position ±2.5 s before the onset of ablation, and for 28 s after ablation. In all cases, ablations were performed in temperature-controlled mode with temperature limited to 48°C, and power to 30 W. The irrigation flow rate was set to 2 mL/min during mapping and 17 mL/min during ablation. All ablations were performed at a CF of between 5g and 40g. During ablation, the pulmonary vein catheter was kept in either a pulmonary vein or the left atrial appendage. Ablations where there was visually evident macro-displacement of the ablation catheter were excluded from the analysis. All study ablations were nonoverlapping and, once they were completed within a lesion set, further ablation was at the operator’s discretion and generally performed as continuous drag ablations.

Preablation electrograms were collected on the electrophysiological recording system for 2.5 to 8 s: the former for points in the wide area circumferential ablation and the latter for the complex fractionated atrial electrogram ablation points. The longer period for the complex fractionated atrial electrogram points was used because of the potential greater complexity of the electrogram at these locations. Postablation electrograms were collected for 8 s and the first 0.5 s discarded to reduce the effects of postablation noise. Synchronicity between the mapping and electrogram recording system was ensured by either manually acquiring points simultaneously or, in the last 8 patients, through the use of the LabLink data interface (Bard Electrophysiology Division). In a subset of 10 patients, impedance during ablation was also recorded. This was measured between the tip of the ablation catheter and the ground patch (positioned on the patient’s left thigh) using a 50-kHz current and sampled at 10 Hz. The ablation power was also recorded at this sampling rate.

The electrogram data were exported from LabSystem Pro, whereas the CF, location, and ablation biophysics data were exported from Carto3. The data were processed and analyzed using custom written Matlab (MathWorks, MA) scripts; an expanded Methods with detailed descriptions has been provided in the Data Supplement.

Drift of the catheter between the pre- and postablation points of >3.5 mm (the length of the ablation element) relative to the pulmonary vein catheter was counted as displacement and excluded that ablation from the analysis.

The force time integral (FTI) was determined by the area under the force-time curve as established by trapezoidal integration. To examine the dynamic relationship between the FTI and impedance drop, all of the ablations were divided into consecutive, cumulative, 10-g-s FTI intervals. The maximum impedance drop was then compared with the initial impedance at the start of ablation. So, for example, a 500-g s ablation would yield 50 measurements, with the maximum impedance drop assessed from 0 to 10, 0 to 20, 0 to 30, and so on up to 0 to 500 g/s.

The electrogram data collected at a point were subjected to automated analysis to identify complexes in the bipolar signal recorded from the ablation catheter. The complex amplitude was defined as the difference between the largest peak and trough in a single complex.
was used for the subsequent analysis. Figure 1 presents the relationship between the percentage impedance drop and the incremental FTI. There was an initial plateau until 20 g·s, and then after this there was an increase in the impedance drop with an increasing FTI until a plateau starting from 500 g·s, corresponding to a mean impedance drop of \( \approx 7.5\% \).

To determine quantitatively, the FTI at which the rate of change in the impedance drop engendered by an increasing FTI becomes significantly reduced, a logarithmic curve of best fit was fitted to the data set \( y = 2.57x \ln(x) - 8.89 \), adjusted \( R^2 = 0.56 \): from this curve, the relative plateau was found to develop from an FTI of 514 g·s. At this point, the impedance drop determined from the formula of the fitted curve was 7.2%.

The FTI is a function of tissue CF during ablation and the duration of the ablation. We sought to determine the relative importance of mean tissue CF and ablation duration on lesion formation as assessed by impedance drop.

Figure 2 is a plot demonstrating the influence of the components of the FTI on the impedance drop where each line is an FTI target and each point on the line is the (grouped) mean CF to get to that target FTI. As the mean CF during an ablation increased, the time taken to reach the target FTI reduced. Looking first at the 100 g·s curve, the longer it took to reach the FTI target, and so the lower the mean CF, the greater the impedance drop. In fact, for each curve until the 400 g·s curve, there was a significant heterogeneity in the impedance drop based on the CF group \( P < 0.025 \). Beyond ablation durations of 10 s, the curves relatively flattened, suggesting that the influence of the ablation duration (and so mean CF) on the impedance drop at an FTI was no longer evident. If ablations <10-s long were excluded, there were no longer any significant differences in the impedance drop at each FTI secondary to the mean CF group.

**Electrogram and Ablation**

There was a significant difference between the pre- and post-ablation mean complex sizes \( P < 0.0005 \); preablation median, 0.12 mV [range, 0.05–0.59 mV], postablation 0.09 mV [range, 0–0.43 mV], median decrease of 21% [range, 100% decrease to 72% increase]).

There was a significant correlation between both the FTI and mean CF and the change in the electrogram complex size (Spearman \( \rho = -0.14, P = 0.02 \) for both).

There was a linear increase in the amount of electrogram attenuation with an increasing FTI until \( \approx 500 \) g·s after which a plateau occurred, at around a 20% reduction in the complex size (Figure 3).

A quantitative assessment of the plateau was not performed as the fitted logarithmic curve was only weakly predictive of the decrease in the complex size (adjusted \( R^2 = 0.03 \)). This was reflective of the high degree of variability in the attenuation of the electrogram observed. To allow for a quantitative comparison, the electrogram attenuation above and below the point from which there was a qualitative plateau suggested by the data was compared. The percentage reduction in the complex size was significantly lower for FTIs <490 g·s than equal to or
above this value (P=0.03: <490 g·s; median, –18% [-70% to 72%] and ≥490 g·s; median, –23% [-100% to 31%]).

Discussion
This study prospectively assessed the relationship between catheter CF and biophysical and electrogaram parameters in patients undergoing NPAF ablation. An increasing FTI was associated with a greater impedance drop with this relationship plateauing from 500 g·s. There was also a relationship between the FTI and the attenuation of the fibrillating electrogram, with a relative plateau again from ≈500 g·s. The amplitude of the fibrillating electrogram had a more variable response to ablation than the impedance drop and so may not be as useful as a surrogate for lesion formation as the percentage impedance drop, particularly at the level of the individual ablation. The ablation duration affected the impedance drop at an FTI if the duration was <10 s. Beyond this time point, the FTI achieved rather than the ablation duration or mean CF applied determined the impedance drop.

During temperature-controlled radiofrequency ablation, the maximum temperature reached within the tissue correlates linearly with lesion volume. Catheter tip temperature is less reflective of this maximum temperature with irrigation as this cools the catheter tip. The maximal tissue temperatures can therefore reach higher levels in irrigated than in nonirrigated temperature-controlled radiofrequency ablation, although in both types of ablation a plateau occurs in the tissue temperature during the course of the ablation. A linearly increasing fall in impedance with an increasing catheter tip temperature has been described for nonirrigated ablation. This has been suggested to be because of increased conductivity of cardiac tissue with heating. Therefore, during irrigated radiofrequency ablation, the occurrence of a plateau in the impedance drop can be assumed to reflect a plateau in the size of the lesion.

In this study, the CF during ablation correlated with impedance drop. This has been described previously in animal studies (using nonirrigated ablation) and recently during clinical ablation in paroxysmal AF and atrial flutter patients, and in another study of almost exclusively paroxysmal AF patients, with both clinical studies using temperature-controlled, power-limited irrigated ablation. The current study and previous work have demonstrated that for a given ablation duration, the CF during ablation significantly affects the impedance drop. This is not unexpected as greater contact for the same ablation duration would result in more efficient energy delivery to the myocardium, an increase in the tissue temperature and therefore a greater impedance drop. The FTI is a measure that incorporates both ablation duration and mean CF and therefore includes 2 important factors affecting impedance drop.

Previous work has demonstrated a weaker relationship between the impedance drop and FTI than the current study. The current study was conducted in a different patient cohort (NPAF rather than paroxysmal AF or atrial flutter patients). Also, in the current study, the impedance data were sampled at a higher frequency (10 Hz rather than 0.2 Hz during ablation) and the resulting waveform filtered, which would have contributed to the stronger relationship, as well as the use of the percentage rather than absolute impedance drop. Regardless of the improved strength of the relationship observed in the current study, we would concur with previous work that impedance drop cannot be used reliably in place of real-time CF measurement to judge contact during ablation because of the point-by-point variability. This was even more so the case for electrogram attenuation. The focus of the current study, however, was the dynamics of the relationships between the CF and these surrogates of lesion dimension to establish targets for ablation, rather than using these surrogates as an alternative to measuring the CF during ablation.

Another recent study has investigated the dynamics of the relationship between the impedance and the overall ablation mean CF rather than FTI. The sampling rate of the impedance in that study was every 10 s. For ablations at a mean CF of ≤5 g, there was no real impedance drop after the initial 10-s measurement during ablation and the group therefore recommended a minimum of 5 g of contact for ablation. The lower CF cut off in the current study was 5 g and so we have not studied the dynamics of the relationships below this level.

This study is the first to correlate catheter CF with electrogram attenuation and impedance parameters during NPAF ablation. In this case, there was a plateau in the degree of electrogram attenuation related to the FTI at around a 20% reduction. This is less than the 62% reduction secondary to the production of transmural lesions seen in a pacing-induced AF sheep model and the 48% to 65% reduction seen in sinus rhythm patients.

![Figure 3. Force time integral vs percentage change in electrogram complex size. Black squares are mean value. Error bars, 1 SD.](image-url)

Discussion This study prospectively assessed the relationship between catheter CF and biophysical and electrogaram parameters in patients undergoing NPAF ablation. An increasing FTI was associated with a greater impedance drop with this relationship plateauing from 500 g·s. There was also a relationship between the FTI and the attenuation of the fibrillating electrogram, with a relative plateau again from ≈500 g·s. The amplitude of the fibrillating electrogram had a more variable response to ablation than the impedance drop and so may not be as useful as a surrogate for lesion formation as the percentage impedance drop, particularly at the level of the individual ablation. The ablation duration affected the impedance drop at an FTI if the duration was <10 s. Beyond this time point, the FTI achieved rather than the ablation duration or mean CF applied determined the impedance drop.

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undergoing ablation. With regard to the paced sheep model, it may be that there is greater ablation sensitivity to CF in that model than in man. The chaotic nature of AF makes changes in the electrogram amplitude less consistent. This would suggest that electrogram attenuation is an unreliable surrogate for lesion size at the individual ablation level in AF.

The relationship between the FTI and electrogram attenuation plateaued at around 500 g·s⁻¹: this was consistent with the impedance data, although the relationship was stronger in the latter case. The identification of a plateau in the relationships among the FTI, electrogram attenuation, and impedance drop is the key finding of this study as it represents the lesion approaching the maximum possible size at those ablation settings. The observation that these 2 surrogates of lesion size, despite the variability in their response to ablation at a single lesion level, are in agreement on the existence of this plateau and where this occurs provides internal validation for this finding. Beyond this 500 g·s⁻¹ plateau, continued ablation is likely to yield minimal further gains. Such diminishing returns need to be weighed against the potential for complications from continued application of radiofrequency energy at a point such as perforation, steam pops, and damage to extracardiac structures such as the esophagus.

The current study demonstrates that for a given FTI, the efficacy of ablation as judged by the impedance drop is affected by the former’s constituents: the mean CF and the ablation time. Ablation for <10 s seems suboptimal regardless of the CF applied or FTI, whereas >10 s the FTI (rather than its constituents) becomes the overriding determinant of the impedance drop. This time dependence may be secondary to the progressive ramping up of the power in the temperature-controlled, power-limited ablations performed in this study: on average, it took around this time frame for the ablation power to first reach the maximum power cut off. This finding is clinically important, as, if one uses an FTI target for ablation without accounting for the ablation duration, suboptimal lesions could be delivered if the duration is <10 s, regardless of the FTI achieved. This is especially important with the advent of newer iterations of 3-dimensional mapping systems (for example, the Carto3 Visitag module, Biosense Webster, Inc), which are able to place lesion markers in an automated manner based solely on reaching an FTI threshold at a point.

Previous work to establish CF targets for ablation has focused on comparing CF parameters retrospectively based on reconnections in the pulmonary vein isolation lines. A mean segment CF during ablation of ≥19.6 g was less frequently observed to be associated with acute reconnection,15 and at 3-month follow up, segments within a wide area circumferential ablation ablated with a minimum FTI <400 g·s⁻¹ had a greater chance of being reconnected.16 These previous studies subdivided the ipsilateral pulmonary vein isolation lines into 7/8th or 8/8th segments and judged the adequacy of the multiple ablations in these segments based on whether the whole segment reconnected. The current study differs in approach as we investigated at the level of the individual lesion, using biophysical and electrogram parameters, rather than against the wider segment outcome. In so doing, we were able to explore the parameters for the successful creation of an ablation lesion. Based on segment reconnection data, a recommendation has been made that the optimal mean CF during ablation should be 20 g16; the current study suggests that the duration of ablation and FTI reached are more important determinants of the efficacy of ablation. Within the limits of the CF and duration parameters investigated, radiofrequency energy applied for a longer period with CF <20 g seems to have the same impact in terms of lesion formation as long as the same FTI is attained and 10 s of ablation exceeded. This study therefore suggests that it is more clinically relevant to focus on FTI and ablation duration targets to generate adequate lesions.

Limitations
The gold standard for establishing the effectiveness of an ablation is the histological assessment of the lesion produced. This is not available in humans and therefore the current study used parameters previously shown to correlate with histological lesion parameters. Conclusions are therefore necessarily based on these surrogate markers of lesion formation. Electrode orientation is known to affect lesion size.17,18 In this study, the catheter orientation was not included in the analysis and may have contributed to some of the variance observed. The majority of patients in this study had ablations performed using remote robotic navigation. This may also have influenced the results of this study. All of the ablations were performed with the same power setting, and the irrigation flow rates were those recommended by the ablation catheter’s manufacturer for the power setting used in the study. In preclinical studies, irrigation flow rates have been demonstrated to affect the size of lesions produced.19,20 It is likely that the use of different power or irrigation settings would alter the energy delivered during ablation and affect lesion formation.

Conclusions
The results of this study suggest that during NPAF ablation, impedance drop may be a more accurate surrogate of adequate lesion formation than fibrillatory electrogram attenuation. End points in terms of biophysical parameters for optimal lesion formation include an impedance drop of 7.5% and electrogram attenuation of 20%. However, there was considerable variation in these biophysical parameters on a point-by-point basis. A more pragmatic primary target for ablation lesions is therefore an FTI of 500 g·s⁻¹, beyond which there seems to be minimal incremental benefit from further ablation. In addition, ablations should ≥20 l s in duration, regardless of CF or FTI. The clinical impact of adopting such targets for ablation requires further prospective evaluation.

Acknowledgments
The research was supported by the National Institute for Health Cardiovascular Biomedical Research Unit at Barts.

Sources of Funding
The study was funded through an Investigator Initiated Study funding agreement (IIS-146) with Biosense Webster, Inc.

Disclosures
Dr Schilling has received research funding and research fellow support from Biosense Webster, Inc, and Drs Spotton, M.J. Earley, and W. Ullah have received lecturing honoraria from Biosense Webster, Inc.
References

CLINICAL PERSPECTIVE
Preclinical studies have demonstrated that lesion size plateaus as the maximum size is reached for a particular radiofrequency application. We investigated whether such a plateau is evident during clinical persistent atrial fibrillation ablation using impedance drop and atrial fibrillation electrogram attenuation as surrogates for lesion parameters and comparing these with the ablation force time integral (FTI). We studied 30-s static left atrial ablations, assessing impedance drop during ablation and comparing the electrogram pre- and post ablation. For both surrogates, the relationships were observed to plateau, and this occurred from ≈500 g·s FTI. This suggests that beyond this FTI there is only minimal further lesion growth. There was greater variability observed in the electrogram attenuation compared with the impedance drop per FTI, suggesting that the former is a less useful measure in judging individual radiofrequency applications. Our second goal was to investigate the components of the FTI (mean contact force and ablation duration) to determine their relative importance compared with the attained FTI. Our data suggest that for ablations <10-s duration, the mean contact force and ablation duration significantly affect the impedance drop achieved at an FTI. Beyond this time point, the actual FTI reached during ablation determines the impedance drop without significant influence from the mean contact force and ablation duration. This study highlights the importance of the FTI and duration of ablation in generating adequate lesions, with an FTI of 500 g·s and ablation duration of ≥10 s suggested by the data.
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*Circ Arrhythm Electrophysiol.* 2014;7:63-68; originally published online January 18, 2014; doi: 10.1161/CIRCEP.113.001137
*Circulation: Arrhythmia and Electrophysiology* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3149. Online ISSN: 1941-3084

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http://circep.ahajournals.org/content/7/1/63

Data Supplement (unedited) at:
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SUPPLEMENTAL MATERIAL

Expanded Methods

Stability during RF ablation was assessed by comparing the average position of the RF catheter tip relative to the averaged location of the poles of the pulmonary vein catheter in three dimensional space over 2.5 seconds (location data recorded at 60Hz). The pulmonary vein catheter was chosen as a reference to allow for movement secondary to respiration to be taken into account. If the average distance between the ablation catheter and pulmonary vein catheter changed by more than 3.5mm (the length of the ablation electrode) between the pre- and post-ablation points taken on Carto3, the catheter was deemed to have been excessively unstable and the ablation excluded from the analysis.

The electrograms analysed in this study were bipolar electrograms (set up between the distal adjacent electrodes on the ablation catheter). Signals in the electrogram recording system were recorded at a low cut-off of 30Hz and a high cut-off of 250Hz. Electrograms which on inspection suffered from excess noise were discarded. After export, the signals were filtered with a 10th order 100Hz Butterworth low pass filter. The peaks and troughs in the signal were identified using a 70ms cut off as used previously by our group to prevent double counting of complexes1. Complexes less than 0.05mV (peak to trough) were assigned as noise2, and a 1mV upper cut-off for the atrial electrogram size adopted based on review of the signals and previous work3. The angles of the rising and falling signal were determined for the dominant peak or trough in a complex, from a point at one-third of the complex size from the peak or trough of the signal. A correction factor of 1000 (500 if the electrogram was sampled at 2Khz) for angle measurements was used to make the signal equivalent to that displayed on LabSystem Pro at a sweep speed of 100mm/s and a 32x scale.
A rising or falling angle of over 45˚ meant the complex was discarded as farfield\(^1\). The complex size was measured from the dominant peak to trough of a complex.

If a pre-ablation electrogram had less than 2 complexes identified or a post-ablation electrogram had only 1 complex identified, it was not included in the analysis (as an isolated complex could be spurious). In a previous study of ablation in paroxysmal AF patients, an increase in the electrogram with ablation was taken to represent micromovement\(^4\): in the case of patients in AF, the inherent variability of the electrogram was felt to renders this criterion less reliable and therefore in the current study, the electrogram more than doubling in size with ablation was felt to be a reasonable indicator of micro-displacement.

**References**


