Validation of a novel algorithm for quantification of the percentage of signal fractionation in atrial fibrillation

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Aims
Catheter ablation for paroxysmal atrial fibrillation (AF) is rapidly becoming a standard practice. There is literature to support that catheter ablation of persistent AF requires additional ‘substrate modification’. In clinical practice, operators rely on automated fractionation maps created by three-dimensional anatomic mapping systems to rapidly assess complex ‘fractionated’ signals (CFAE). These systems use differing algorithms to automate the process. The agreement between operators and contemporary algorithms has not been examined. We sought to assess the agreement between operators and a novel method of quantification calculating percentage fractionation (PF).

Methods and results
Expert opinion on 80 atrial electrogram 4 s signals of varying levels of activity were gathered and pooled for comparison. Twelve independent experts visually quantified the signal fractionation and offered a threshold level for ablation. We developed an algorithm to find sites with high continuous electrical activity, or high PF. Correlation between experts and PF was 0.78 \[ P < 0.01, \text{ 95\% confidence interval (CI) (0.68–0.86)} \]. Receiver operating characteristics curve sensitivity and specificity for PF were 0.7727 and 0.8103 at the optimal cut-off point of 58.45 PF with area under curve 0.89 CI (0.80–0.99).

Conclusion
The PF statistic represents a more robust and intuitive measure to represent fractionated atrial activity; importantly it demonstrates excellent agreement with expert users and presents a new standard for algorithm assessment. Use of a PF statistic should be considered in automated mapping systems.

Keywords
Fractionation • Complex fractionated atrial electrograms • Atrial fibrillation • Ablation

Introduction
Catheter ablation for persistent atrial fibrillation (AF) following a ‘substrate modification’ approach with or without pulmonary vein isolation (PVI) or left linear ablation has been shown to be effective for slowing or termination of arrhythmia with low recurrence rates.1,2 Nademanee et al. reported high success rates for maintaining post-procedure sinus rhythm in both paroxysmal and persistent AF patients by targeting complex-fractionated atrial electrograms (CFAEs). Complex-fractionated atrial electrogram ablation has since been met with success in subsequent studies, though there are inconsistent published reports as to the benefits of CFAE ablation in addition to PVI.1,3,4

The most widely accepted definition of CFAE is given by the criteria of Nademanee et al., that is:

1) fractionated electrograms composed of two or more deflections and/or a perturbation of the baseline with continuous deflection of a prolonged activation complex; and
2) atrial electrograms with a very short cycle length (≤ 120 ms).1

In practice, these guidelines are limited in application because (i) deflections in the electrogram may be obscured by noise artefact.
What’s new?

- A new metric, percentage fractionation (PF), to quantify fractionation for substrate-based complex fractionated atrial electrogram ablation is introduced.
- Based on clinical results which show that ablation at sites with high continuous electrical activity is associated with positive clinical outcome, PF reflects the percentage (0–100%) of electrogram signal that is continuously fractionated.
- Designed to be robust to spurious artefacts and noise, PF performs favourably in comparison with a contemporary algorithm using the consensus opinion of a panel of experienced electrophysiologists as the gold standard.
- Because PF is designed with the criteria of the expert in mind, and it agrees well with the opinion of the expert user, it presents an intuitive tool for use during substrate ablation, and an important indicator for target areas showing a high degree of continuous fractionation.

We hypothesized that PF, since it rates continuous electrogram activity higher than discrete electrograms and is robust to noise artefact, would correlate well with expert opinion, as (i) substrate ablation of electrograms with ‘continuous’ high-frequency activity results in positive clinical outcome (as opposed to fractionated electrograms separated by an isoelectric segment) and (ii) experienced cardiologists are able to assess CFAE while rejecting spurious electrograms and noise artefact. Use of an electroanatomic mapping system equipped with the PF rating system would shorten procedure times because the algorithm applies the same decision criteria as the expert user.

Methods

Study population

Eighteen consecutive patients (6 persistent, 12 paroxysmal, 2 female) undergoing AF ablation for the first time were asked to participate in the study. Antiarrhythmic drugs were discontinued for at least five half-lives before the mapping and ablation procedure; except for amiodarone which was continued in three patients with persistent AF (see Table 1). In paroxysmal patients, AF was induced by burst pacing as part of an ongoing study, while for the purposes of this study only the initial map was employed and AF allowed to stabilize for not less than 5 min before the acquisition of fractionation points. All patients provided written informed consent. Study methods were approved by the Queen’s University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board, and the study complies with the Declaration of Helsinki.

Using EnSite NavX (St Jude Medical Inc., St Paul, MN, USA) software and previously acquired cardiac computed tomography (CT), left atrial electroanatomic maps were generated. An irrigated, 3.5 mm tip, ablation catheter (St Jude Medical Inc.) with 2 mm interelectrode spacing was used to collect signals during AF. Transseptal puncture was performed and a left atrial geometry was created using a spiral catheter with reference to the prior CT. On completion of the geometry, data were acquired using a point-by-point approach to ensure a dense and even distribution of the LA endocardium. For the purposes of this study, right atrial and coronary sinus data were not collected.

Data acquisition

With the ablation catheter in stable position, 4 s data segments (n = 265.6 ± 116.4 per patient—paroxysmal and persistent AF cases combined, or 204.5 ± 98.8 for paroxysmal and 341.9 ± 91.7 for persistent patients) were collected at 1200 Hz and analogue filtered from 0.5–250 Hz by the EnSite NavX preprocessing system, with 60 Hz power-line interference removal.

<table>
<thead>
<tr>
<th>Table 1 Baseline characteristics of patients</th>
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<tr>
<td>Number of patients</td>
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<tr>
<td>Age</td>
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<tr>
<td>AF history (years)</td>
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<td>LA diameter (mm)</td>
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Expert annotation
The data from the patient cohort were examined and each sample was inspected in a manner previously described. A total of 3481 samples were available for inspection by the PF algorithm (see Algorithms) and ranked according to PF statistic. A random number generator was then employed to choose indices following an approximately normal distribution. Eighty 4 s samples were obtained and 20 repeated to evaluate intraobserver consistency. A panel of 12 experts in catheter ablation of AF from six Canadian centres were asked to evaluate the electrogram samples blinded to case details and outcome. We created a questionnaire displaying each atrial electrogram, each accompanied by a continuous visual analogue scale from 0 to 100 ‘degrees fractionated’. In order to assess whether PF or CFE-mean algorithms were good predictors of experts’ opinion on highly fractionated signal suitable for ablation, receiver operating characteristics (ROC) curves were calculated. Experts agreed (unanimously) that they would ablate at electrogram sites where scores exceeded 70 degrees fractionated.

Algorithms
A novel algorithm designed to assess the amount of continuous electrical activity, or PF, scored each signal from 0 to 100%, where 0% is nowhere fractionated and 100% is continuously fractionated, was developed on previously stored data and generated signals. The algorithm implemented modified ‘Nademanee criteria’ to determine the percentage of time the signal was fractionated, that is, the percentage of time deflections above baseline occurred <120 ms apart (Figure 1). Deflections were detected in the electrograms by way of a five-step preprocessing algorithm consisting of (i) Baseline wander removal: using an expansion in band-limited (discrete prolate spheriodal sequences) tapers. (ii) Signal rectification: using the Hilbert transform method. (iii) Filtering: lowpass filtering from 0 to 100 Hz using an order 4 infinite impulse response filter design. (iv) Deflection detection: instead of using a threshold, the data were divided into segments of 30 ms width to avoid over detection. Maximum voltage for each segment was identified and in order to eliminate detections occurring at the boundary, the data were re-segmented with an offset of 15 ms, and the maximal voltages were reassessed. Peaks common to both segments were used for the analysis. (v) Percentage fractionation was calculated by summation of all peak-to-peak lengths (cycle lengths in other literature) <120 ms in length and divided by the total signal length to give a percentage (Figure 1).

In addition, each signal was analysed online using the automated algorithm contained in the NavX System. The algorithm employed, ‘CFE-mean’, which delivers the average time between deflections in the electrogram and is dependent upon three user-defined parameters: the deflection must (i) exceed an adaptive peak-to-peak sensitivity (typically 0.03–0.05 mV), (ii) possess a down stroke and exceed a (iii) refractory period (a blanking period to avoid over detection nominally set at 30 ms). Parameters were set following guidelines consistent with previous studies.

Statistical analysis
Data are presented as mean ± standard deviation unless stated otherwise. Interobserver variability was assessed quantitatively using Pearson correlation and visually using ranked boxplots. Pearson or Spearman correlation, when appropriate, was used to assess agreement between expert and algorithm, and ROC curves were created to find optimal cut-off values for CFAE. Data were analysed using MATLAB (MathWorks, Natick, MA, USA) and R (R Development Core team, Vienna, Austria).

Results
Expert characteristics
Of 20 Canadian experts approached from six centres, 12 completed the assessment; the respondents had 5.5 ± 2.8 years
experience as primary operators with 5.4 ± 1.9 ablation procedures per month, of which 26 ± 11% were for persistent AF.

**Intraobserver consistency**

On the 20 repeated electrogams, the 12 experts displayed a high level of reproducibility (Pearson correlation between the first and second sighting of each signal was 0.85 ± 0.067, *P* < 0.01).

**Interobserver agreement**

Median annotation vs. signal dispersion (interquartile range) for each of the 80 non-repeated signals was shown using side-by-side boxplots (Figure 2), ordered in increasing median degree of fractionation. The boxplots showed that near the extremes of degree of fractionation the agreement tends to be better (shorter box length) while the moderately fractionated signals tend to demonstrate less agreement.

There was a significant positive correlation between PF and the median value of degree of fractionation as assessed by the experts. Pearson correlation for PF against consensus expert opinion was 0.78 (*P* < 0.01, 95% confidence interval (CI) (0.68–0.86)). Receiver operating characteristics curve sensitivity and specificity for PF were 0.77 and 0.81 at the optimal cut-off point of 58.45 PF with ROC curve area under curve (AUC) = 0.89, CI (0.80–0.99), with respect to the operator-defined cut-off of 70 degrees fractionated.

There was no significant correlation between the CFE-mean value and the degree of fractionation assessed by the experts. Spearman correlation (with CFE ranked backwards so that positive correlation indicates agreement) was 0.27 (*P* = 0.016, 95% CI (0.045–0.49)). Receiver operating characteristics curve area (AUC) was not significant (*P* = 0.602, AUC = 0.602, 95% CI (0.456–0.747)). Figure 3 shows CFE-mean and PF electroanatomic maps for comparison. Note that the two metrics work differently: CFE-mean indicates increasing fractionation by shorter cycle length, while PF indicates increasing fractionation by higher percentage. The colours have been reversed in the right-side (CFE-mean) diagram for direct comparison and scaled to centre near the optimal cut-off determined in the ROC analysis. It is clear that the two metrics prioritize different sites for therapy.

**Discussion**

Substrate ablation for persistent AF is accepted by most as necessary to achieve an optimal outcome after catheter ablation. However, the nature and targeting of CFAE remains debated with poor understanding of the role of CFAE as functional or truly anatomic substrate. The studies suggesting CFAE is important for maintenance of AF used operator definitions and interpretation. To date, no study has rigorously compared an automated assessment algorithm with operator interpretation. We examined the most consistently reported important feature of CFAE—the percentage of time a signal is continuously fractionated—and designed an automated real-time assessment tool to quantify this feature. In order to validate this algorithm, we compared it with consensus expert operator-defined values.

Alternative approaches to quantification of atrial electrograms in both the time and frequency domain are being pursued. For example, dominant frequency (the highest peak in a power spectrum estimate of the signal) has been implemented in new releases of electroanatomic systems, despite conflicting clinical reports which may be due to differences in implementation. Dominant frequency assumes that a single frequency, or ‘cycle length’, is adequate to describe the driving force of the fibrillation, while rejecting secondary contributions to signal power (even if they are significant), and without concern for non-stationarities (changes in the average or variance of the signal over time). Rigorous assessment of automated algorithms is important when studying the physiopathology of AF and assumptions made must reflect clinician understanding of the process.
The main finding of this study was that the percentage of continuous activity in an atrial electrogram, as assessed by an automated algorithm, agrees with consensus expert identification of CFAE. The PF correlated with experts’ opinion with a sensitivity of 77% and specificity of 81%. Furthermore, with expert opinion as the gold standard, PF prioritized CFAE over non-CFAE in 89% of the signals under study. CFE-mean, which evaluates the mean time between electrogram deflections did not compare significantly with expert opinion, as hypothesized, (CFE-mean output ignores variability in peak-to-peak length.) Notably, studies using CFE-mean-guided ablation have reported significant positive clinical outcome.7

Algorithmic determination of PF differs from ‘CFE-mean’ in that the PF statistic itself is robust (not-sensitive to outlying data points) to anomalously long or short peak-to-peak distances, whereas an assessment of the mean is unstable in this respect. Percentage fractionation reflects the overall percentage of continuous electrical activity, whereas CFAE-mean reflects only the average behaviour of the cycle lengths over the recording (though it includes standard deviations of these cycle lengths). An algorithm for substrate ablation that is (i) based on the same decision criteria that are used by operators and (ii) has been associated with positive clinical outcome is required for implementation in intuitive software systems that guide ablation. Percentage fractionation not only satisfies these two criteria, but is the only metric for CFAE that does. Subsequent studies are now required to assess the efficiency of PF-guided ablation with respect to clinical outcome.

## Limitations

There is no gold standard for quantification of fractionation, though we have used experienced expert opinion as a proxy. There was a modest degree of interobserver variability as the signals were derived from real cases and thus contained a practical amount of noise artefact. Some experts remarked that this had affected their judgement. Also, signals were presented to experts context-free, i.e. there was no information given about the location of the catheter during signal collection.

## Conclusion

Catheter ablation for paroxysmal AFs is rapidly becoming standard practice. There is concern that catheter ablation of persistent AF requires additional ‘substrate modification’. Clinical studies have confirmed that signals with high continuous fractionation represent sites with positive clinical outcome after substrate ablation. The PF statistic is designed to determine the percentage of the signal that represents fractionated atrial activity. Importantly, PF demonstrates excellent agreement with expert users and, as such, presents a new standard for algorithm assessment. Use of a PF statistic should be considered in future prospective studies of automated mapping systems.

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## Conflict of interest

none declared.

## References


