Towards Standardization of Non-invasive Atrial Fibrillation Substrate Complexity Quantification: Effect of Choice of ECG-leads and Complexity Measure on Prediction of Pharmacological Cardioversion

Stef Zeemering, Theo Lankveld, Harry Crijns, Ulrich Schotten

Maastricht University, Maastricht, The Netherlands

Abstract

A large variety of parameters have been proposed for quantification of atrial fibrillation substrate complexity computed on a standard 12-lead ECG. A direct comparison of the predictive performance of these complexity parameters using a single dataset has not been performed. We retrospectively studied 221 patients undergoing pharmacological cardioversion (CV) with flecainide to compare the predictive performance of dominant atrial frequency (DF), spectral organization index (OI), spectral entropy (SE), sample entropy (SampEn) and fibrillation wave amplitude (FWA).

Prediction of successful CV using a single parameter computed on a single lead was poor for all parameters with a maximum AUC of 0.67 (OI on lead II). Performance improved by incorporating multiple leads, with maximum AUC of 0.75 (SampEn on I, II, aVR and V_6), and by combining parameters and leads with a maximum AUC of 0.83, using DF (I), OI (II), SE (I), SampEn (I, II and V_6) and FWA (aVF and V_1).

The approach taken in this study to compare the performance of different non-invasive AF complexity parameters can be seen as a first step towards a standardization of AF substrate complexity quantification.

1. Introduction

Current studies on ECG-based non-invasive outcome predictors in patients with atrial fibrillation (AF) vary widely in choice of ECG lead, the extracted features used to estimate AF complexity and the dataset on which prediction performance was assessed. Consequently, the predictive power of different techniques cannot be compared based on current literature [1]. We performed a retrospective analysis of ECGs of patients undergoing pharmacological cardioversion (CV) with IV flecainide to compare the ability of several non-invasive AF substrate complexity parameters to predict CV success and to study the effect of the number and choice of ECG leads used in the prediction model on outcome prediction performance. In this way we aim to provide a standardized approach to evaluate the added value of non-invasive AF substrate complexity quantification methods when it comes to the prediction of therapeutic outcome.

2. Methods

2.1. Patient database

Patients were selected from our institutional database of patients with recent onset (< 48 hours) AF that underwent CV with intravenous flecainide between January 2008 and December 2012. Inclusion criteria were no chronic treatment with anti-arrhythmic drugs, no treatment with extra medication during the procedure and no previous CV attempt. CV success was defined as restoration of sinus rhythm within one hour from the start of flecainide administration. Furthermore, only patients were selected that had a 12-lead ECG recorded prior to treatment. Each recording was examined visually to exclude low quality data (defined as more than one lead with missing data and/or a poor signal to noise ratio). In this way, out of a total of 721 records (including multiple visits from one patient), a subset of 221 patient records was selected for analysis. Patient characteristics are listed in Table 1.

2.2. ECG preprocessing

ECG recordings of 10 seconds were available for each selected patient. ECGs were recorded at a sampling frequency of 500Hz. Signals were filtered by applying a zero-phase band-pass filter between 1 and 100 Hz to

Table 1. Patient characteristics.

	Success (157)	**Failure (64)**	**p-value**
Male/Female	93/64	52/12	0.002
Age	61±13	57±15	0.08
Hypertension	47%	47%	1
Left atrial diameter (mm)	40±5	43±6	0.003
Time since first episode (days)	654±108	691±176	0.823

Table 2. Complexity parameter details.

Parameter	Description	Computation settings	Example of application
Dominant atrial frequency	Frequency with highest power between 3 and 12 Hz	Welch PSD estimate, 1024 points, 50% overlap	Predicting spontaneous cardioversion of paroxysmal AF [3]
Spectral organization index	Relative power of N frequency peaks	Number of peaks: 2 Peak width: 1Hz	Discrimination between persistent and long-standing persistent AF using a multi-scale version of OI and SE [4]
Spectral entropy	Shannon entropy of signal spectrum		
Sample entropy	Regularity estimate of a signal	Number of samples: 2 Tolerance: 0.35 * SD	Predicting spontaneous cardioversion of paroxysmal AF [5]; Classification of paroxysmal / persistent AF [7]
Fibrillation wave amplitude	F-wave amplitude based on peak and valley detection	Minimum distance between peaks: 100ms	Prediction of AF termination by ablation [6,8]

remove baseline wander and to suppress high-frequency noise. Power line interference, if present, was removed using a 50Hz notch filter. The atrial signal was extracted in all 12 leads by cancelling the ventricular signal using a modified version of the adaptive singular value QRST cancellation [2], wherein QRST windows were grouped prior to QRST template computation using hierarchical clustering based on window correlation. During QRST cancellation, the signals were temporarily up-sampled to 2kHz to improve the temporal alignment of the QRST templates.

2.3. Substrate complexity parameters

AF substrate complexity parameters were computed on all 12 leads of the ECG recorded before the flecainide administration. These parameters were chosen to cover both frequency-domain and time-domain based measures that have been shown to be instrumental in describing AF complexity. They are dominant atrial frequency (DF) [3], spectral organization index (OI) [4], spectral entropy (SE) [4], sample entropy (SampEn) [5] and fibrillation wave amplitude (FWA) [6]. More details on these parameters and their computation are listed in Table 2.

2.4. Statistical analysis

Significant differences between CV success and failure were computed for each parameter-lead combination using a 2-tailed Student t-test. Differences with a p-value less than 0.05 were considered significant.

To assess the predictive value of the substrate complexity parameters, a broad range of possible prediction model configurations was investigated. For each parameter, logistic regression models were estimated to predict CV outcome, containing single lead or multiple lead information. Models consisting of multiple leads and combinations of complexity parameters were selected using a stepwise approach and elastic net logistic regression [9]. In the stepwise approach, a logistic regression model is built by starting from an empty model and adding the best prediction parameter until no significant improvement can be made, also known as forward selection. Although used often, stepwise logistic regression has the disadvantage that it does not always produce the best model when there are redundant predictors. Elastic net logistic regression is a shrinkage estimator that identifies the important predictors by optimizing the model fit while at the same time penalizing both the L_2 and the L_1 norm of predictor coefficients. It is especially suitable if there are correlated predictors, a situation that is likely to occur when computing the same parameter on all 12 ECG leads.

Prediction models were estimated using 10-fold cross validation and predictive performance was expressed as

Table 3. Significant univariate parameter differences.

Parameter	Lead	Success	Failure	p-value
DF	II	5.5Hz	6.0Hz	0.005
	V_6	5.1Hz	4.6Hz	0.004
OI	II	71%	65%	< 0.001
	aVF	70%	66%	0.013
	V_5	73%	69%	0.039
	V_6	74%	70%	0.031
SE	II	3.0	3.1	0.009
	III	3.0	3.1	0.040
	aVF	3.0	3.1	0.015
SampEn	II	0.24	0.27	0.003
	aVF	0.25	0.28	0.012
	V_5	0.22	0.20	0.033
	V_6	0.22	0.19	0.003
FWA	II	7.6μV	6.7μV	0.002
	III	7.4μV	6.6μV	0.007
	aVF	6.8μV	5.9μV	< 0.001

the area under the curve (AUC) of the receiver operating characteristics (ROC) curve of the prediction model.

3. Results

Univariate analysis shows several significant differences for all complexity parameters between patients with a successful and an unsuccessful CV attempt, as listed in Table 3.

The results for the models estimated using the stepwise logistic regression are summarized in Table 4 and Figure 1. Prediction of CV success using a single complexity parameter on a single lead was best using OI on lead II, but performance was poor, with an 82% sensitivity, 41% specificity and an AUC of 0.67. Exploiting multi-lead information enhanced performance of all parameters, with again SampEn performing best, using information from 4 leads (I, II, aVR, V_6) with an 83% sensitivity, 70% specificity and an AUC of 0.75, followed closely by DF on the same leads with 79% sensitivity, 70% specificity and an AUC of 0.75. Combining parameters and leads further improved prediction to an 80% sensitivity, 70% specificity and an AUC of 0.83.

Elastic net logistic regression tends to estimate somewhat smaller models that include fewer parameters and fewer leads (see Table 5). Again, DF and SampEn were the best performing parameters with an AUC of 0.72 and 0.71 respectively, while the models containing OI and SE were reduced to constant models, indicating that their applicability in this prediction task is limited. The model combining parameters and leads was slightly smaller than in the stepwise approach, but with a comparable performance (78% sensitivity, 73% specificity and an AUC of 0.81).

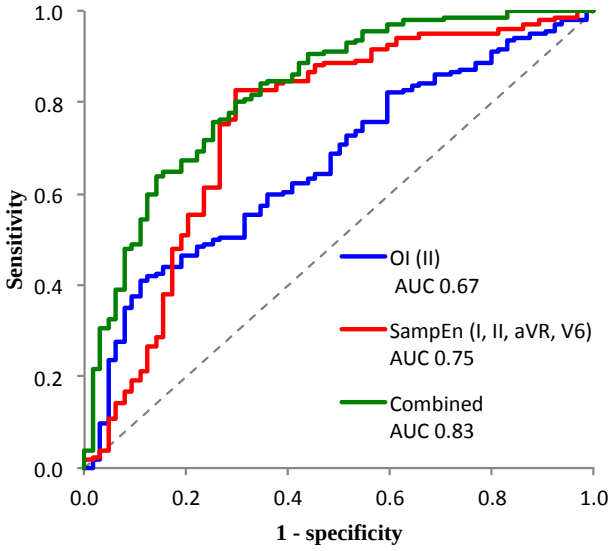

Figure 1. ROC curves for best single parameter/lead predictor (blue, OI on lead II), best multi-lead predictor (red, SampEn on I, II, aVR and V_6, and the optimal combination of leads and parameters (green) using stepwise logistic regression.

4. Conclusion

Successful CV with flecainide may be predicted from

Table 4. Stepwise logistic regression results.

			Selected leads											
Parameter	**Leads**	**AUC**	I	II	III	aVR	aVL	aVF	V_1	V_2	V_3	V_4	V_5	V_6
DF	Single	0.63												•
	Multi	0.75	•	•		•								•
OI	Single	0.67		•										
	Multi	0.69		•	•		•							
SE	Single	0.63		•										
	Multi	0.70	•	•								•	•	
SampEn	Single	0.63												•
	Multi	0.75	•	•		•								•
FWA	Single	0.64						•						
	Multi	0.71			•	•	•		•					
Combined*		0.83	•	•				•	•					•

*Combined model parameters: DF (I), OI (aVR), SE (I), SampEn (I, II and V_6) and FWA (aVF and V_1)

Table 5. Elastic net logistic regression results.

			Selected leads											
Parameter	**Leads**	**AUC**	I	II	III	aVR	aVL	aVF	V_1	V_2	V_3	V_4	V_5	V_6
DF	Multi	0.72	•	•										•
OI	Multi	N/A	Constant model											
SE	Multi	N/A	Constant model											
SampEn	Multi	0.71		•										•
FWA	Multi	0.64						•						
Combined*		0.81	•	•				•						•

*Combined model parameters: DF (I and V_6), OI (II), SE (I), SampEn (II and V_6) and FWA (aVF)

the surface ECG during AF using a combination of AF complexity parameters computed on several ECG leads. Outcome prediction is poor using a single lead and a single parameter, but prediction is notably improved by combining information derived from multiple ECG-leads and multiple AF complexity parameters.

Best performing ECG-derived AF substrate complexity parameters are sample entropy and dominant atrial frequency. Useful information is predominantly located in the (augmented) limb leads and precordial lead V_6.

The approach described here illustrates a way to evaluate the performance of a parameter that quantifies AF substrate complexity within a standardized framework. Future research will also incorporate clinical parameters into the analysis and will evaluate the added value of non-invasive AF substrate complexity parameters in predicting other therapeutic outcomes, such as AF recurrence after electrical cardioversion or ablation.

Acknowledgements

This study was supported by a grant from the European Union (FP7 Collaborative project EUTRAF, 261057) and by a grant from the Center of Translational Molecular Medicine (CTMM – COHFAR).

References

[1] Schotten U, Maesen B, Zeemering S. The need for standardization of time- and frequency-domain analysis of body surface electrocardiograms for assessment of the atrial fibrillation substrate. Europace 2012; 25:4(8): 1072–5.

[2] Alcaraz R, Rieta J. Adaptive singular value QRST cancellation for the analysis of short single lead atrial fibrillation electrocardiograms. Computers in Cardiology 2007 :513–6.

[3] Chiarugi F, Varanini M, Cantini F, Conforti F, Vrouchos G. Noninvasive ECG as a tool for predicting termination of paroxysmal atrial fibrillation. IEEE Trans . Biomed . Eng 2007;54(8):1399–406.

[4] Uldry L, Van Zaen J, Prudat Y, Kappenberger L, Vesin JM. Measures of spatiotemporal organization differentiate persistent from long-standing atrial fibrillation. Europace 2012; 25;14(8):1125–31.

[5] Alcaraz R, Rieta JJ. The application of nonlinear metrics to assess organization differences in short recordings of paroxysmal and persistent atrial fibrillation. Physiol Meas 2009;31(1):115–30.

[6] Nault I, Lellouche N, Matsuo S, Knecht S, Wright M, Lim K-T, et al. Clinical value of fibrillatory wave amplitude on surface ECG in patients with persistent atrial fibrillation. J Interv Card Electrophysiol 2009; 30;26(1):11–9.

[7] Alcaraz R, Sandberg F, Sörnmo L, Rieta JJ. Classification of paroxysmal and persistent atrial fibrillation in ambulatory ECG recordings. IEEE Trans Biomed Eng 2011;58(5):1441–9.

[8] Meo M, Zarzoso V, Meste O, Latcu DG, Saoudi N. Spatial variability of the 12-lead surface ECG as a tool for noninvasive prediction of catheter ablation outcome in persistent atrial fibrillation. IEEE Trans Biomed Eng 2013;60(1):20–7.

[9] Zou H, Hastie T. Regularization and variable selection via the elastic net. J Royal Statistical Soc B 2005; 67(2):301–20.

Address for correspondence.

Stef Zeemering, Maastricht University, Dept. of Physiology.
P.O. Box 616, 6200 MD Maastricht, The Netherlands.
s.zeemering@maastrichtuniversity.nl