ATRIAL FIBRILLATION REVIEW SERIES

The ECG as a tool to determine atrial fibrillation complexity

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ABSTRACT

The use of the ECG for atrial fibrillation (AF) in clinical daily practice is still limited to its diagnosis. Recent research shows however that ECG-derived parameters can also be used to assess the spatiotemporal properties of AF. Specifically, the complexity of the f-waves in the ECG reflects the complexity of the fibrillatory conduction during AF and therefore can be used for quantification of the degree of electrophysiological alterations in the atria. This information might be useful for guiding AF therapy and might form the basis for classification of AF. This review focuses on technical and mathematical aspects of ECG-based atrial complexity assessment and its potential ability to guide treatment strategies.

INTRODUCTION

The ECG is a widely used tool for confirming clinical diagnosis and guiding therapy. For example, the ECG is essential in diagnosing an acute myocardial infarction and guide percutaneous coronary intervention. In case of ventricular tachycardia or ventricular ectopy, the ECG can be used to suggest an exit point in the LV or the RV. In atrial fibrillation (AF) however, the ECG is mainly used to confirm the diagnosis, to monitor the effect of antiarrhythmic drugs (AADs) and to adjust rate-control. Some studies show that during sinus rhythm (SR) the P-wave duration can to some extent predict AF after coronary bypass surgery or new-onset AF.[1 2] Also, atrial ectopy in the recovery phase after normal exercise testing predicts AF in subjects with LV hypertrophy.[3]

Recent research shows more can be learned from ECG potentials on the body surface, particularly from the ECG recorded during AF. This review will focus on recent advances in AF detection, atrial complexity parameters that can be derived from the body surface ECG during AF and their potential to guide different therapy strategies.

ADVANCES IN AF DETECTION

Traditional methods to diagnose AF such as a standard 12-lead ECG or ambulatory Holter monitoring have a limited sensitivity to detect AF, particularly in patients with low frequencies of AF paroxysms and limited symptoms. In patients with symptoms possibly due to AF or patients at risk for AF and a 'virtual' indication for anticoagulation, easy-to-use devices that can be operated in a home environment might result in earlier AF detection and more effective stroke prevention. A recent study used a patient-operated ECG recorder to detect AF in patients without a history of AF but with at least one AF risk factor and found AF in 7 out of the 132 patients.[4] In a validation study, this ECG recorder had a sensitivity of 99% and a specificity of 96% for AF detection.[5] In an ongoing study the recently validated MyDiagnostick, a metal stick recording and analysing an ECG, is used to detect AF during flu vaccination at the general practitioners office among 3000 participants (NCT02006524). The increasing use of smartphones offers another interesting opportunity for early disease detection. A validation study showed the ability of an iPhone to detect AF with a sensitivity of 96% and a specificity of 98% using irregularity of fingertip blood pulsations with the camera.[6] AliveCor, another iPhone application records a single-lead ECG using two electrodes at the back of the iPhone. The validation study of this application showed a high accuracy in diagnosing AF using an automated algorithm determining RR-irregularity and P-wave absence.[7] This application is currently used in a community-based study to identify undiagnosed AF.[8] Implantable loop recorders have the ability to detect symptomatic and non-symptomatic AF during a long time period. In the ongoing REVEAL AF study patients with symptoms and/or at risk for having AF receive an insertable cardiac monitor with a dedicated AF detection algorithm. The purpose is to detect AF episodes ≥6 min during 18 months follow-up.[9] Most of the automated AF algorithms used in the previously discussed recorders are based on the irregularity of the RR-intervals. Shortcomings of these algorithms are limited specificity in the presence of ectopic beats and limited sensitivity for detection of short AF episodes. One study examined the three most commonly used algorithms and found an area under the curve of the receiver-operating characteristics (ROC) of 90.7% in detecting AF episodes of 5 s which increased to 94.0% in episodes of 60 s[10] It seems reasonable that when automated algorithms are used at least 60 s are analysed to detect an AF episode.

ELECTROPHYSIOLOGICAL ATRIAL SUBSTRATE COMPLEXITY

Structural heart diseases, ageing and also AF itself cause a slow but steady process of atrial remodelling involving changes in ion channel function, cellular hypertrophy, interstitial fibrosis, inflammatory changes, amyloidosis and fatty infiltration of the atrial myocardium. This process leads to progressive electrical uncoupling between muscle bundles, conduction disturbances, enhanced dispersion of refractoriness, and an increase in spontaneous electrical

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activity all together increasing the propensity of the atria to AF. These positive feedback mechanisms largely explain the tendency of AF to become more persistent over time. The macroscopic electrophysiological consequence of this process is an increase in conduction block during AF. This increase in conduction block events leading to a higher number of coexisting fibrillation waves has been termed increase in AF complexity.[11 12]

Indeed, the increase in electrophysiological complexity of the AF substrate over time can be demonstrated using invasive direct contact mapping. Several groups showed that patients with persistent AF show a higher number and narrower fibrillation waves compared with patients with acute AF.[11 13] The increase in complexity of the AF substrate has also been demonstrated by non-invasive techniques combining atrial anatomical information with electrograms recorded from the body surface.[12]

Assessment of the atrial electrophysiological substrate, apart from just an anatomical approach, has become more important during ablation of (long-standing) persistent AF.[14] Unfortunately, these mapping procedures can only be applied during an invasive electrophysiological study or open thorax surgery which limits their wide application. In addition, these procedures are costly and time-consuming and need to be validated in more centres. The most important disadvantage relates to the fact that they can only be performed during intervention, while prediction of outcome of therapy is desirable before the intervention. Obviously, compared with an invasive electrophysiological procedure, the surface ECG is much easier to apply. Although it provides a more global presentation of the underlying electrophysiology, AF complexity parameters computed from body surface potentials have been shown to correlate well with invasive electrophysiological complexity. Most research comparing invasive with non-invasive complexity parameters focused on the atrial dominant frequency (DF).[15–19] However, non-invasive sample entropy (SampEn) and F-wave amplitude (FWA) also correlate well with complexity parameters applied on invasive recordings.[19] For example, a good correlation was found between the DF on lead V1 and simultaneously measured right atrial frequency.[15] More recently it has been demonstrated that the left atrial DF is also reflected on the body surface to some extent.[17] Because of the representation of atrial electrograms on the body surface, a non-invasive approach using the ECG or body surface potential mapping (BSPM) could help to assess a patient's AF substrate complexity in a quick and non-invasive manner and might potentially guide therapy.

ECG GUIDING RHYTHM CONTROL STRATEGIES

Table 1 and figure 1 give an overview of various AF complexity parameters studied on a standard 12-lead ECG.[20] These atrial complexity parameters include time and frequency domain parameters. Some of these investigations have been used to predict spontaneous cardioversion of paroxysmal AF. For example, a lower DF predicts spontaneous cardioversion.[21 22] Short AF episodes have a lower DF compared with longer lasting episodes, the DF increases during those episodes and decreases prior to termination.[22] Most studies, however, focused on ECG-based prediction of success of a rhythm control strategy in patients with persistent AF. Several non-invasive atrial complexity parameters have a reasonable predictive value for the maintenance of SR after direct current cardioversion (DCC). Sample entropy is lower in patients that maintain SR 4 weeks after DCC.[23] Furthermore, a higher FWA, a lower harmonic decay and a lower DF predict maintenance of SR.[23–26] Other studies evaluated prediction of the response to AADs. Patients that responded to ibutilide infusion had a significantly lower DF than those who did not.[27] In another study, a lower DF appeared predictive for the response to oral flecainide.[28] Furthermore, surface ECG AF complexity parameters have been used to predict catheter ablation outcome in patients with (long-standing) persistent AF. For example, a higher FWA predicted favourable outcome during the ablation,[29] and at long-term follow-up.[30] Another study showed that a longer AF cycle length on lead V1 was associated with favourable acute and long-term outcome after catheter ablation.[16] Although these results seem promising, some studies using DF or SampleEn showed a lower predictive value for outcome after DCC for persistent AF.[23 31] In another study low DF correlated with successful DCC but not with recurrence of AF during 6 months follow-up.[32] Possible explanations for these conflicting results might be the use of different preprocessing steps, the use of QRST cancellation as opposed to processing the TQ-interval only, or the different techniques to determine AF complexity. In addition, AAD use differed among studies and AADs are known

Table 1 Commonly used ECG parameters for AF complexity

Atrial complexity parameter	Analysis method	Description
Dominant atrial frequency/ AF rate	Frequency domain	Atrial frequency with the highest power. The atrial frequency is typically between 3 Hz and 12 Hz. In general, a lower frequency corresponds to a more organised signal.
Spectral organisation index	Frequency domain	Ratio of the area under the five largest peaks in the power spectrum to the area of the total power spectrum. An organised signal has a higher ratio.
Spectral entropy	Frequency domain	Spectral entropy can be considered a measure of uniformity of the spectral content. Lower entropy values mean a larger uniformity within the signal.
Sample entropy	Time domain	Sample entropy is an estimate of the regularity within the signal. Larger values correspond to a larger irregularity of the signal.
F-wave amplitude	Time domain	Amplitude of the F-wave between their maxima and minima in mV. A larger amplitude reflects a low AF complexity.
F-wave power	Time domain	The power of the F-waves within a time interval.
Harmonic decay	Frequency domain	Harmonic decay reflects the slope of the line connecting the dominant frequency with its first harmonic. A low decay corresponds to a high amplitude of the first harmonic and a more organised signal.
Number of principal components	Time domain	A lower number of principal components represents a more organised atrial signal.
Spatiotemporal organisation	Frequency domain	Measurement that quantifies spectral homogeneity between different leads. Higher values mean a higher degree of organisation.

AF, Atrial fibrillation.

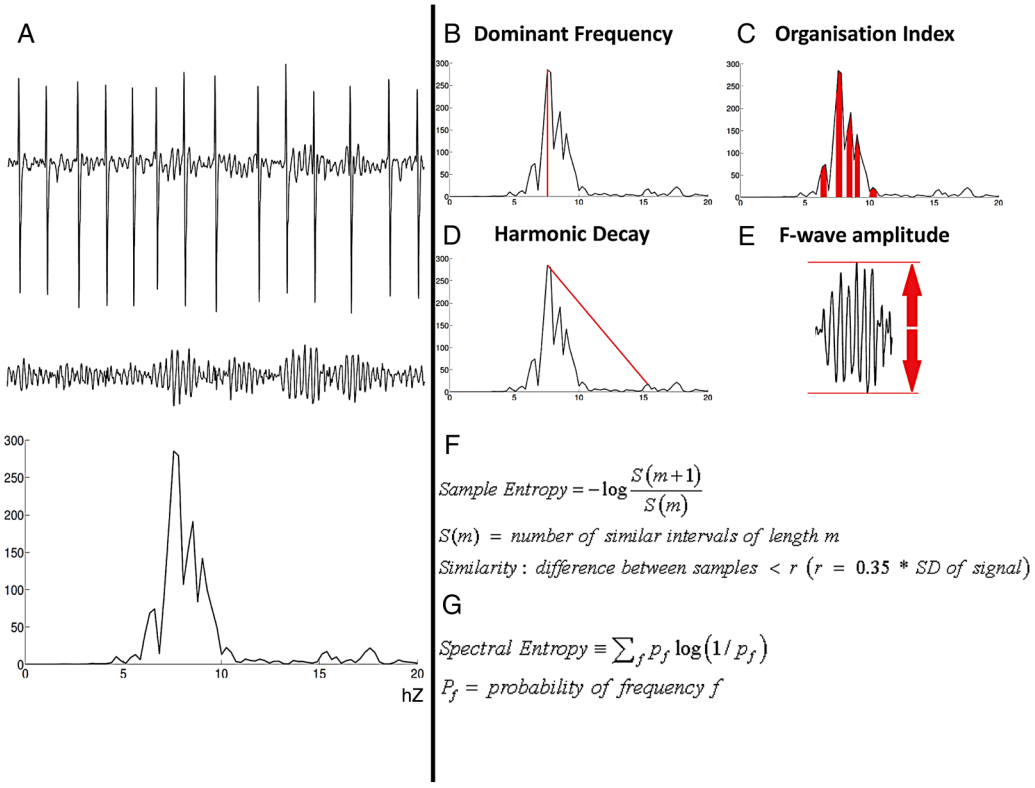

Figure 1 (A) Upper panel shows the original ECG signal lead V1, middle panel the atrial signal after QRST cancellation and the bottom left panel shows the frequency spectrum. Right panel shows visualisation of complexity parameters computed on a single lead. (B) The red line indicates the highest peak in the power spectrum that is, the dominant frequency. (C) The red bars schematically show the areas under the five highest peaks in the power spectrum. The ratio of the total red area divided by the area under the entire power spectrum gives the organisation index. (D) The harmonic decay reflects the slope of the line (here indicated in red) connecting the dominant frequency with its first harmonic. (E) The F-wave amplitude is the amplitude between the minima and the maxima of a F-wave. Usually, the mean amplitude during a time-interval is measured. (F) Sample entropy examines similarities within time series. Sample entropy is calculated by the negative logarithm of the probability that two sequences which are similar for *m* points remain similar for *m*+1 points. (G) The spectral entropy is the application of Shannon's entropy on a normalised power spectrum.

to lower the DF.[33–35] On the other hand, with increasing duration of the AF episode AF complexity increases.[34] Also, the underlying structural heart disease might have an effect in itself on the AF ECG characteristics. The latter point appears to be particularly important. A lower DF usually means favourable outcome regarding rhythm control therapy. However, in a study on patients with mild to moderate heart failure (HF) a lower DF was associated with increased mortality, mainly due to death from progressing HF.[35] In patients in whom the AF cycle length was measured invasively during catheter ablation structural heart disease was associated with a low DF.[34] In an animal study, AF was slower and more organised (ie, lower DF, higher organisation index (OI) and lower SampEn) in pacing-induced HF as compared with AF induced by vagal stimulation.[36] Furthermore, an increased amount of fibrosis correlated with a higher OI and lower DF.[36] Another recent study using delayed enhancement on MRI to quantify atrial fibrosis in patients with (long-standing) persistent AF undergoing catheter ablation also found slower and more organised atrial electrograms at the site of atrial fibrosis.[37] However, the baseline cycle length measured in the left atrial appendage was shorter in patients with more pronounced fibrosis. Because the ECG provides a more global representation of the electrical complexity the exact effect of atrial fibrosis on the surface ECG still needs to be thoroughly investigated. Also ageing by itself has an effect on atrial complexity parameters.[32 35 38 39] All these studies found a lower DF in older patients. These changes might be due to increased amount of fibrosis with increasing age.

Additionally, most studies conducted on this topic were relatively small and there is a need to validate the results in larger uniform patient cohorts with, if possible, well characterised underlying pathology. An overview of research already conducted on the prediction of rhythm control therapy using a 10 s 12-lead ECG is provided in table 2.

LEAD PLACEMENT

Most of the above mentioned research focused on lead V1 because of the high amplitude of the atrial signal compared with other leads (see figure 2). Lead V1 is known to reflect right atrial electrical activity more than left atrial activity.[42] Recent research, however, showed that the leads positioned more leftward on the thorax (V3–V6) have a higher predictive value for maintenance of SR after ablation than lead V1.[41] This is remarkable because of the smaller FWA resulting in a smaller signal-to-noise ratio. Obviously, information on left atrial electrical activity is particularly important for prediction of AF recurrences after AF ablation.

In the conventional 12-lead ECG the precordial leads are positioned to follow the global depolarisation and repolarisation of the ventricles. In contrast, to assess (left) atrial signals at the body surface, an alternative lead placement may appear more suitable. One research group developed a lead configuration

Table 2 Examples of studies on ECG parameters for AF complexity for prediction of rhythm control therapy outcome

Author	Year	n	Population	Complexity parameters	Main findings
Alcaraz[23]	2011	63	Persistent AF	Dominant atrial frequency, F-wave power, F-wave amplitude, sample entropy	Lower F-wave amplitude, F-wave power and higher sample entropy predicts recurrence of AF 4 weeks after cardioversion.
Bollmann[27]	1998	15	Persistent AF	Fibrillatory rate	A lower fibrillatory rate predicts success of cardioversion after ibutilide infusion.
Bollmann[28]	2002	18	Persistent AF Paroxysmal AF	Fibrillatory rate	A lower fibrillatory rate predicts SR restoration using oral flecainide.
Bollmann[26]	2003	44	Persistent AF	Fibrillatory rate	A higher fibrillatory rate is an independent predictor of AF recurrence within 4 weeks after successful DCC.
Bollmann[32]	2008	124	Persistent AF	Fibrillatory rate	Lower fibrillatory rates are associated with successful cardioversion but not with recurrence of AF.
Cheng[30]	2013	54	Persistent AF	F-wave amplitude	Low F-wave amplitude could predict recurrence after catheter ablation during 9 months of follow-up.
Choudhary[21]	2013	105	Paroxysmal AF	Fibrillatory rate	Fibrillatory rates below 350 fpm predict spontaneous conversion within 18 h.
Holmqvist[24]	2006	54	Persistent AF	Harmonic decay	Patients with a relapse of AF within 4 weeks after successful DCC have a higher harmonic decay.
Holmqvist[25]	2006	175	Persistent AF	Fibrillatory rate	AF recurrence within 1 month is predicted by a higher fibrillatory rate in patients undergoing cardioversion.
Matsuo[16]	2009	90	Persistent AF	AF cycle length	Patients with a longer AFCL have a favourable procedural and clinical outcome during long-term follow-up.
Meo[40]	2011	18	Persistent AF	Principal component analysis, F-wave amplitude	Multilead based complexity is superior to single-lead complexity in predicting termination of AF during catheter ablation.
Meo[41]	2013	54	Persistent AF	F-wave amplitude, spatiotemporal variability	Using a multilead approach improves prediction of termination of AF during catheter ablation. Especially leftward orientated leads seem important.
Nault[29]	2009	90	Persistent AF	F-wave amplitude	A higher F-wave amplitude predicts termination of AF during catheter ablation.
Petersson[31]	2011	66	Persistent AF	Sample entropy	Sample entropy was lower in patients who remained in SR 4 weeks after cardioversion. However, there was a large overlap between patients who did and did not remain in SR.

AF, atrial fibrillation; DCC, direct current cardioversion; SR, sinus rhythm.

based on the independent information derived from leads of simulated and measured BSPMs.[43] Important to note is the use of one lead on the patient's back which may provide additional electrical information from the left atrium.[17] Another group also looked at an alternative lead placement with electrodes placed on the right anterior and posterior sides of the thorax.[44] They showed gradients in fibrillatory rates from anterior to posterior in patients with persistent AF. ECG signals from the left atrium can be detected on the posterior or left anterior side of the thorax,[17] and also in the oesophagus.[45] Future research should address the validity of (left) atrial complexity assessment using conventional leads other than lead V1 in monitoring rhythm control strategies and predicting rhythm control outcomes. In addition, alternative lead placements, either at the anterior or the posterior chest or in the oesophagus, should be evaluated and compared with the conventional ECG.

ECG-IMAGING GUIDING ABLATION STRATEGY

Another potentially useful application of surface ECG is to guide AF ablation. The cornerstone of catheter ablation for patients with paroxysmal AF is isolating the pulmonary veins. In patients with persistent AF different ablation strategies and methods have been recommended with varying results. In these patients, non-invasive ECG analysis could be useful to determine whether advanced ablation strategies should be applied. In 2004 the first human applications of ECG imaging (ECGI) was reported.[46] In ECGI, the spatial ECG information obtained from a BSPM is combined with anatomical information of the atria using CT. First, the epicardial propagation of the atrial activation during SR and a typical counterclockwise atrial flutter was demonstrated. In 2010 the same group reported the first data of patients with AF using ECGI.[12] They showed more pronounced AF complexity in patients with long-standing persistent AF compared with persistent or paroxysmal AF. Furthermore, they suggested that ECGI can distinguish various pathophysiological arrhythmogenic mechanisms, mostly in patients with persistent AF. They found simultaneous wavelets in 92% of the patients, a single-wave macro re-entry in 8%, rotors in 15%, and focal activity from the pulmonary veins in 69% and non-pulmonary vein regions in 62% of cases. Identifying different AF mechanisms in different patients could lead to a patient-tailored ablation strategy. A feasibility study in two patients based on this principle showed that ablating active sources identified by ECGI terminated AF during catheter ablation.[47] Further research in a larger patient cohort with follow-up is needed to explore the potential of this approach.

The clinical application of ECGI is limited by its need for image modalities such as CT or MRI. The first study to use BSPMs during AF did not use an image modality. Nevertheless, the authors were able to demonstrate large variability in the activation patterns between individual patients.[48] A limitation of this study was that no correlation with invasive measurements was investigated. More recent studies investigated the ability of BSPM to identify invasively measured high-frequency sources non-invasively during AF without an image modality.[17] High-frequency sources are reflected on the surface electrode closest to the atrium of interest: right atrial signals are projected on the right-anterior part of the body surface. Left atrial signals are projected mainly on the posterior and the left-anterior part.[17] Earlier research showed that the use of BSPMs may help to identify the location of focal triggers for AF using premature atrial activations during SR.[49] Whether identifying

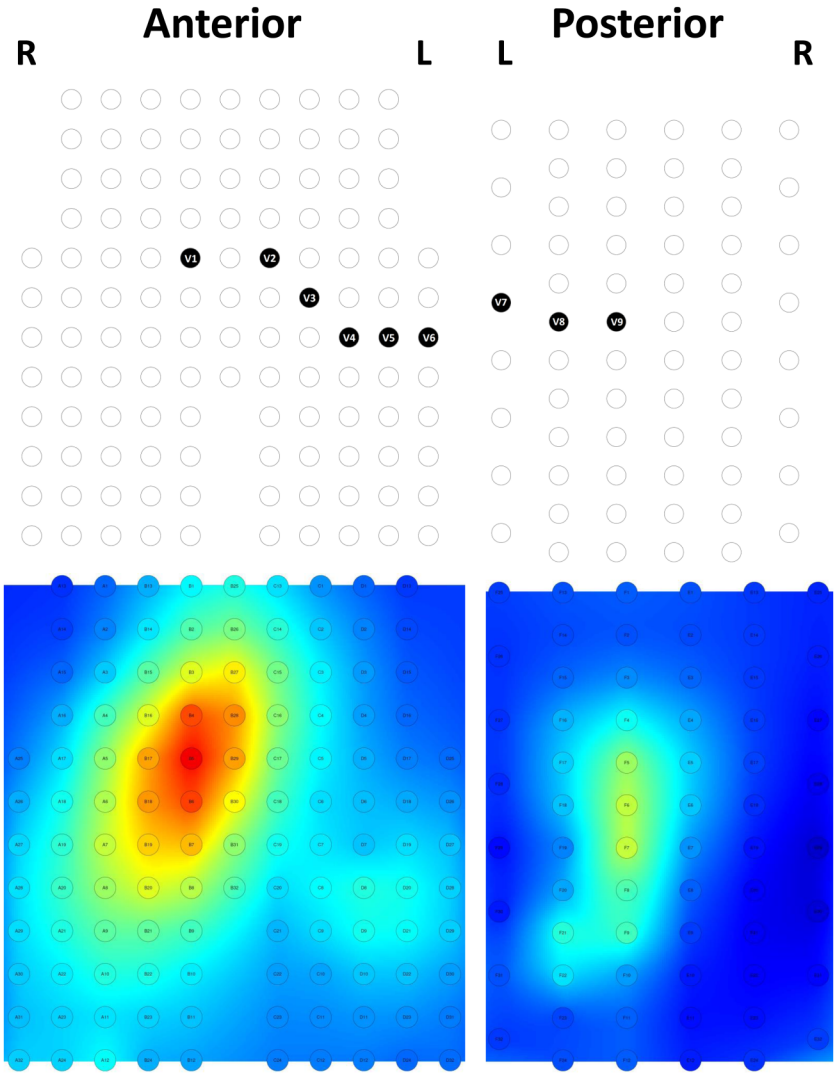

Figure 2 Upper panel shows the distribution of the body surface potential electrodes on the anterior (left) and posterior (right) thorax. The standard 12-lead ECG and additional leads V7–V9 are given as a reference. The lower panel shows the F-wave amplitude of all the electrodes, red means a high and blue a low F-wave amplitude. The F-wave amplitude on the electrodes positioned near lead V1 are larger than at leads positioned on other parts of the thorax. Note the higher amplitudes near lead V9.

high-frequency sources or focal triggers before arrival at the electrophysiology laboratory can guide ablation and improve long-term success certainly warrants further investigation.

ECG BASED CLASSIFICATION

The ultimate goal of research on AF complexity measures based on the ECG is to develop an AF classification allowing patient-tailored AF treatment as advocated by recent guidelines and consensus conferences.[50 51] The current classification of AF, divided in paroxysmal, persistent or long-standing persistent AF, is purely based on the duration of the AF episodes and whether or not AF terminates by itself. Assessing the duration of AF can be challenging due to high variability of symptoms. The ECG derived atrial complexity parameters mentioned in this review might serve as a basis to determine the relative degree of electrophysiological changes occurring over time, because some of these parameters are able to distinguish between patients from the different groups.[38 52 53] Patients with paroxysmal AF have a lower DF and lower SampEn than patients with persistent AF.[38 52] Patients with persistent AF have a higher degree of spatiotemporal organisation compared with patients with long-standing persistent AF.[53] Figure 3 shows an example of V1 and the frequency spectrum from a patient with paroxysmal AF and a patient with persistent AF. The patient with paroxysmal AF shows a lower DF, higher OI and lower SE than the patient with persistent AF. In figure 4 an example of a BSPM from a patient with paroxysmal and persistent AF is given. While the DF is higher in the patient with persistent AF (upper panel) the organisation is lower. The degree of these changes certainly partly reflects the duration of AF episodes but also might reflect the presence of predisposing structural alterations due to HF or ageing. These structural alterations—besides duration of AF—have also been shown to be significant determinants of successful rhythm control therapy.[54] For this reason, ECG-based atrial substrate complexity parameters might be more accurate to classify patients than the clinical history.

Figure 5 shows a possible flow chart for the management of patients with AF based on a combination of the patient's symptoms with an ECG-based classification of AF. In patients with a low AF complexity, a rhythm control strategy using either AADs or catheter ablation with pulmonary vein isolation only could be the preferred treatment option. In patients with a highly complex AF substrate rate control might be the best treatment option. Should rhythm control still be pursued, catheter ablation with extensive substrate modification rather than cardioversion and prophylactic AADs could be the most successful treatment. To assess the true value of a model containing different atrial complexity parameters to guide treatment a prospective clinical trial should be undertaken using the ECG as a guide for treatment.

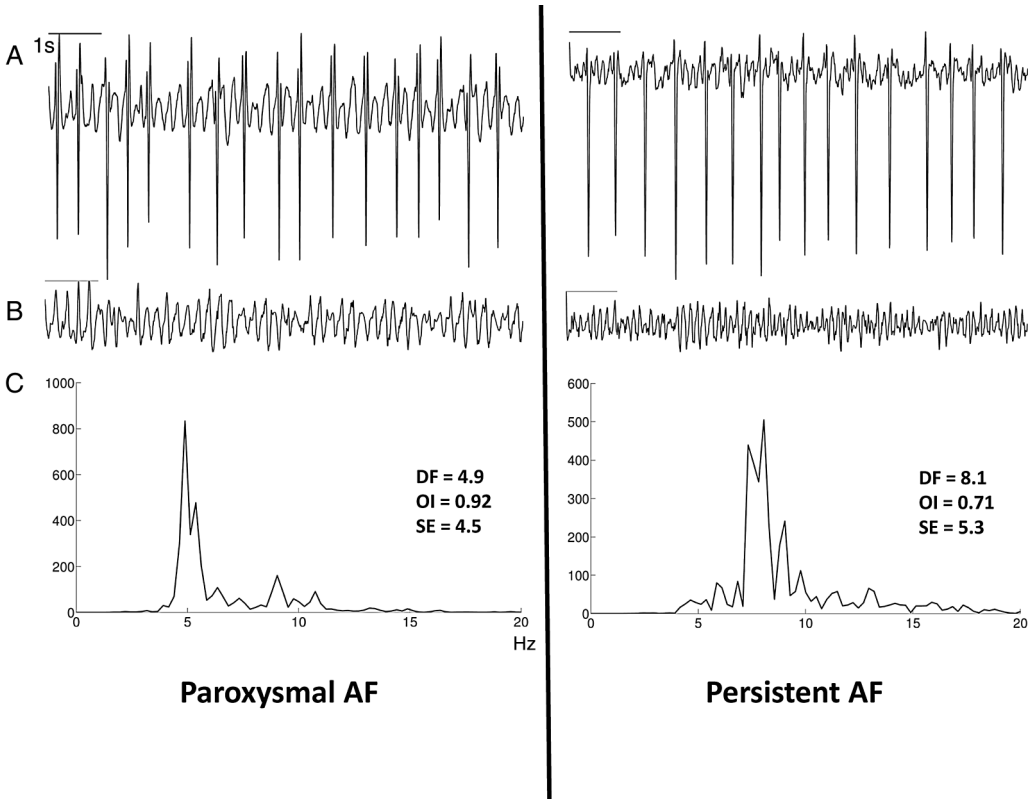

Figure 3 The left panel shows lead V1 from a patient with paroxysmal atrial fibrillation (AF) and the right panel shows lead V1 from a patient with persistent AF. (A) Shows lead V1, (B) shows the atrial signal after QRST cancellation and (C) shows the corresponding frequency spectrum. Note the lower dominant frequency (DF) and spectral entropy and higher organisation index in the patient with paroxysmal AF compared with the patient with persistent AF.

CONCLUSIONS

Atrial complexity parameters derived from a standard 12-lead ECG may be used to identify patients likely to respond to rhythm control therapy, at least during short-term follow-up. There is still only limited evidence for the predictive value for long-term outcome. BSPMs with or without the use of anatomical imaging techniques seem promising in guiding catheter ablation. Expanding the spatial information of a standard 12-lead ECG by applying different or additional lead positioning may help to improve assessment of the (left) atrial electrical signals, which may thereby improve the predictive value of non-invasive atrial AF substrate complexity parameters. The ultimate goal would be to guide AF therapy based on the complexity of the AF substrate of the individual patient.

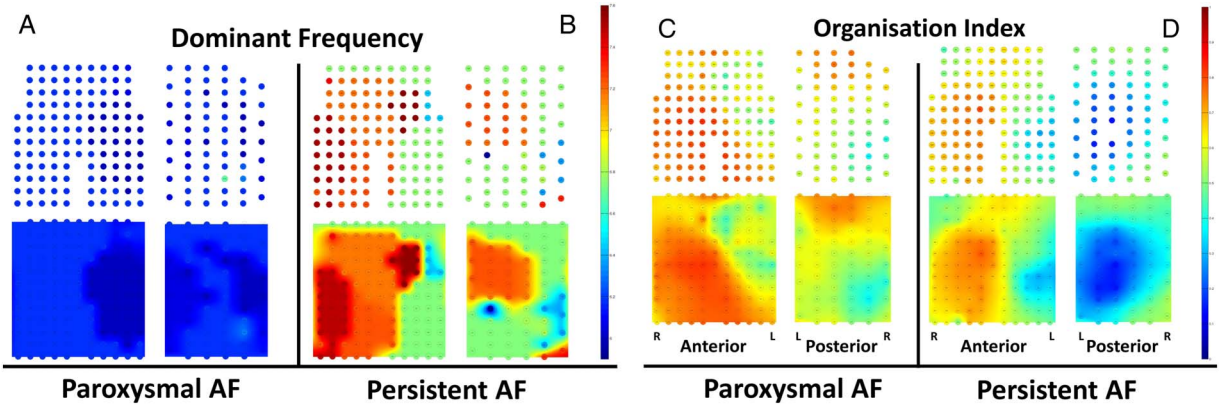

Figure 4 (A) Shows the dominant frequency on a body surface potential map of a patient in paroxysmal atrial fibrillation (AF) with first the dominant frequency of every single electrode and below the interpolated signals. (B) Shows the dominant frequency of a patient in persistent AF. (C and D) show the organisation index of the same patients. Blue means a low value whereas the red colour means a higher value. The dominant frequency in the patient with paroxysmal AF is lower and more evenly distributed on the body surface compared with the patient with persistent AF. Furthermore, the organisation index is higher in the patient with paroxysmal AF.

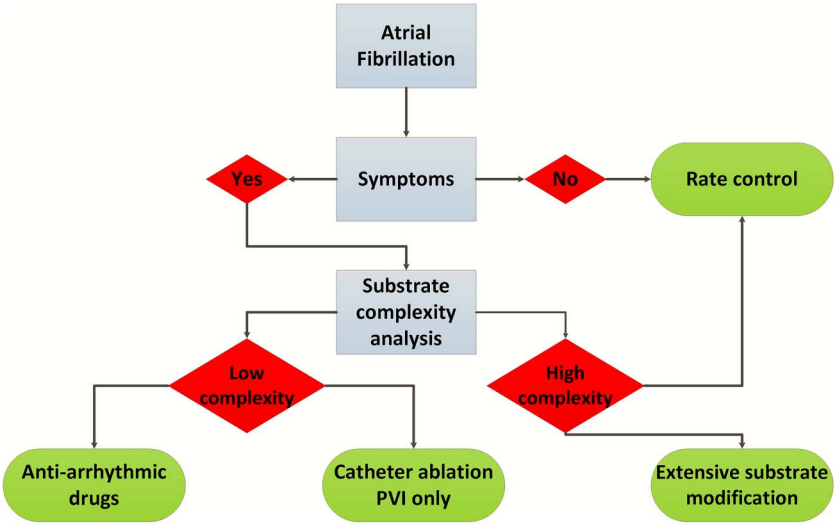

Figure 5 Possible flow chart for the management of patients with atrial fibrillation (AF) based on a combination of the patient's symptoms with an ECG-based classification of AF.

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