Non-invasive assessment of atrial fibrillation (AF) cycle length in man: potential application for studying AF

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Summary. - Non-invasive assessment of the fibrillatory frequency of atrial fibrillation (AF) can be performed by frequency domain analysis. The peak frequency in the derived spectrum can be converted to a dominant atrial cycle length (DACL). The DACL can be altered through autonomic modulation or pharmacologic manipulation, but the change in DACL is less marked in those with a short DACL value. In patients with AF, those with a short duration of the arrhythmia have longer DACL values. Finally, patients with paroxysmal AF generally exhibit longer DACL values than patients with permanent AF. Thus non-invasive assessment of the atrial fibrillatory cycle length provides a useful index of atrial refractoriness and has the potential of clinical utility in patient assessment and treatment planning.

Key words: atrial fibrillation, non-invasive, arrhythmia.

Introduction

The mechanisms underlying atrial fibrillation are not been fully investigated, nor fully explained. According to the hypotheses postulated by Moe [1], and later experimentally supported by Allessie et al. [2], the mechanism of self-perpetuation is independent of focal discharge utilising multiple wavelet re-entry. According to this hypothesis multiple wavefronts of depolarisation, termed wavelets, circulate more or less randomly across the atrial myocardium. When a wavefront encounters tissue in the relatively refractory state, it becomes fractionated, creating new daughter wavelets propagating through any excitable tissue they encounter. The wavelets circle around, constantly changing areas of conduction block, re-initiating themselves or each other [1-3].

This now general accepted mechanism of the arrhythmia states that re-excitation of atrial myocardial tissue almost always occurs without significant latency beyond the end of the refractory period (i.e. there is no, or a minimal, excitable gap). Since wavelength is the product of conduction velocity and refractory period [4], it is inherent that the average fibrillatory rate reflects the average refractory state of the tissue, assuming that conduction velocity is relatively fixed. This assumption of a direct relationship between fibrillatory rate and refractoriness has been explored and verified in several studies [5-7], which have consistently found a significant correlation between the atrial fibrillatory cycle length and atrial refractoriness. It can therefore be concluded that the length of the averaged atrial fibrillatory cycle may be used as an index of the average atrial myocardial refractoriness and has the potential of clinical utility in patient assessment and treatment planning.

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sometimes AF. This occurs because the initial stimulation drive train shortens atrial refractory period. Hence, atria exhibiting a short wavelength are more vulnerable to arrhythmia induction and decreases in atrial refractory period favor AF induction. This is in agreement with observations that the ease of initiation, as well as the probability of maintenance of AF, are related to the fibrillatory cycle length [3, 8].

Assessments of atrial fibrillatory electrophysiology from the surface ECG has until recently not been systematically attempted, with earlier studies assessing electrophysiological parameters having been performed through invasive or intraoperative recordings [6, 7, 9-13]. Non-invasive techniques to assess the average fibrillatory cycle length have significant practical advantages however, and would be useful for further exploration of the underlying pathophysiology and treatment of AF in larger population groups or where invasive studies can not be ethically justified. For these reasons a non-invasive methodology capable of assessing the atrial fibrillatory cycle length, was developed by our group. The technique, which is termed “frequency analysis of fibrillatory-ECG” (FAF-ECG), has been validated and its utility tested through diverse studies.

The purpose of this paper is to describe this new method, to briefly summarize and interpret the findings from available studies to date which have explored atrial fibrillatory rate in patients with different types of AF, and to discuss its potential application for further study of AF.

Methods

Based on the findings that there is a significant correlation between the fibrillatory cycle length and atrial refractoriness [5-7], a non-invasive computer-based technique capable of identifying the dominant atrial cycle length (DAACL) was developed by us [14, 15] and others [16]. In short, a 12-lead ECG with conventional electrode positions is utilized for data acquisition; data with fewer leads from Holter recordings can also be processed. The ECG signal is acquired by a custom-made, optically isolated PC card (Siemens Elema, Solna, Sweden) and stored on hard disk for later off-line analysis. The signal is digitized at a sampling rate of 1 kHz with an amplitude resolution of 0.6 mV using 16 bit A/D conversion. Following linear-phase, highpass filtering for baseline removal (implemented by forward/ backward processing using a sixth order Butterworth filter with cut-off frequency at 0.3 Hz), the ventricular activity is detected, classified and cancelled using a multi-lead approach. The classification of QRST complexes is based on the degree of cross-correlation to different QRST templates: each new QRST complex is either assigned to an existing class or used to create a new class. The basic principle for cancellation of the QRST complexes in the presence of AF is the subtraction of an averaged QRST complexes from the original ECG; the averaged beat contains only ventricular activity since the atrial activity is an unsynchronized activity. Whereas earlier cancellation techniques have been designed for processing of the signal on a lead-by-lead basis, we have developed a new approach to QRST cancellation which takes information from adjacent leads into account in order to improve cancellation performance [17]. Using a least-squares criterion, an average beat is fitted to each QRST complex through the iterative optimization of a set of parameters related to amplitude scaling, interlead dependence and temporal alignment. Since the QRST subtraction process involves both spatial and temporal information, the technique is referred to as a “spatiotemporal QRST cancellation”. The major advantage with this technique is its ability to account for minor variations in the electrical axis which occur during the respiratory cycle. As a result, the large, spurious residuals, relatively often observed when straightforward average beat subtraction is used, are far less common and the resulting signal with atrial fibrillation is more accurate.

The new technique can generate several templates for use in the subtraction process; the maximum number of templates is determined by the cross-correlation based classification procedure. The templates can be dynamically updated to track the slow changes that may occur in QRST morphology, e.g., during pharmacological interventions or autonomic modulation. In an earlier version of our technique, only one template was generated and used in the subtraction process [15]. This approach led to problems when ectopic beats with multiple morphologies were present, and thus the ECG signal was excluded from further analysis.

The resulting residual ECG signal contains atrial fibrillatory activity. This signal is then lowpass filtered and downsampled to 50 Hz. The downsampling is motivated by the fact that the spectral content of interest in the residual ECG is well below 20 Hz and thus the amount of data to be processed is substantially reduced by downsampling. The AF activity is studied in the 3-12 Hz range where the f-wave repetition rate is commonly found whereas the spectral content above 12 Hz is primarily constituted by harmonics reflecting the shape of the f-waves. Power spectral analysis is done with the Welch method using 512 points and a Hanning window length of 128 samples with an overlap of 32 samples. Using these pre-settings a frequency resolution of at least 0.5 Hz is achieved. Using different modes of Fourier-based power spectral analysis, others have developed and applied a similar tool for the calculation of dominant atrial fibrillatory rate [16, 18].

The analysis of the fibrillatory signal exhibits a distinct power maximum that may be described by its frequency value, given in Hz [17-19] or by the correspon-
We have in our clinical publications preferred to describe the power maximum by the use of its corresponding cycle length. The peak frequency \( f \) in the spectrum is therefore converted to a cycle length \( CL = 1/f \), and termed the DACL. Results from other groups presenting the peak values from power frequency analysis of fibrillatory signals have been recalculated and expressed as the corresponding cycle length in the present report. The method is illustrated in Fig. 1.

In our work all spectra are visually inspected and assessed for quality. Spectra without a clear narrow spectral peak in the expected 3-12 Hz range or with a leakage of significant low frequency noise corrupting the spectrum are rejected from further analysis. The peak magnitude must fulfill certain criteria to be regarded as a frequency component in order to avoid local peaks. In cases with two or more peaks present in the spectrum, the peak with the highest amplitude is chosen. A spectrum with one frequency component is labeled “unimodal”, whereas a spectrum two or more frequency component is labeled “multimodal”.

The FAF-ECG method generates additional parameters with a possible, pathophysiologic basis (Fig. 2). The spectral width represents the difference of cycle lengths enclosed by the spectral peak at 75% of its maximum height in a unimodal power spectrum. The DACL difference is the difference between DACL measured in the oesophagus and that measured in lead V1. These parameters are hypothesized to represent indices of the dispersion of duration’s in the fibrillatory cycles within a single atrium and between the atria respectively, and thus represent measures of the dispersion of atrial refractoriness [20].

A limitation with the above approach to spectral analysis is its inability to resolve the temporal variability of the fibrillatory repetition rate which may be present during the analysis interval of interest. In fact, a broad unimodal or multimodal spectrum does not necessarily have to reflect spatial variability but can as well reflect the temporal variability of “single-component” atrial fibrillation. Consequently, the above-mentioned spectral technique has been further developed to include time-frequency analysis with which short- and long-term variations in DACL can be investigated and quantified [19]. Different time-frequency representations have been developed for short- and long-term analysis, in order to reliably detect subtle long-term changes in DACL, e.g., related to pharmacological interventions, which otherwise would have been obscured by the “spontaneous” variations in DACL. The cross Wigner-Ville distribution is particularly useful for short-term analysis due to its ability to track rapid changes in the
fibrillatory rate. The value of time-frequency analysis is illustrated by a one-minute recording from leads V1, V2 and V3 from a patient with chronic atrial fibrillation for which a substantial short-term variation in DACL exists (Fig. 3). In terms of frequency, the variation is as large as 2.5 Hz during an interval of just a few seconds. Although the time-frequency analysis is performed independently in each lead, short-term variations often exhibit a similar pattern in the three precordial leads.

Method validation

Direct comparison between simultaneously recorded signals using intracardiac electrodes, a unipolar esophagus electrode and conventional surface ECG electrode positions have been used to validate the use of DACL as an index of the average fibrillation cycle. Lead V1 was shown to correlate well to the spatial mean of intracardiac recordings from the right atrial free wall [15, 16], whereas the unipolar esophageal electrode correlated best to intracardiac signals of posterior parts of interatrial septum and are also likely to arise from posterior parts of both the left and the right atria [15, 20].

There was no significant difference in the mean DACL values extracted from precordial V1, V2 and the esophageal lead. However, individual differences were seen between lead V1 and those of the simultaneously recorded esophageal lead in individual patients, ranging between -15 to +30 ms. The mean absolute difference in DACL between these two leads was 10 ± 8 ms [21]. The clinical consequence of this demonstrated sign of increased dispersion of atrial refractoriness remains to be further explored.

The variability of DACL with a seemingly stochastically pattern is well noticed using short-term analysis of the AF frequency as illustrated in Fig. 3 [19]. The studies utilizing the FAF-ECG method clearly demonstrate that there is a spontaneous variability of fibrillatory cycle length, which can be attenuated successively with longer recordings. The reproducibility of the method is thus enhanced by prolonging the recording time, allowing integration of atrial fibrillatory activity over longer periods [15]. For practical reasons, we believe that steady state recordings may be restricted to 5 minutes, yielding a DACL variation coefficient of 2,1 % [15]. Repeated daily recordings of DACL at identical medication and at the same time of the day revealed minor variability with a mean intraindividual variation of only 3 ± 3 ms, with a range of 2 to 11 ms [21].

![Fig. 3. - Short-term analysis of the AF frequency from a patient with chronic AF illustrating the variability of DACL over one minute in precordial leads V1, V2 and V3. Modified from [19].](image-url)
Results and discussion

Effects of the autonomic nervous system

Although vagal stimulation has been shown to decrease the action potential duration and the atrial refractory period during normal physiological conditions [4, 22-24], the effect on fibrillating human atrial tissue is not fully explored. There are some reports indicating that vagal stimulation reduces atrial conduction velocity on rabbit [25], but other studies have not been able to demonstrate any effect on dogs following administration of acetylcholine [4]. The effect on conduction velocity in human fibrillating atria has not been explored to our knowledge. Consequently, unless increased vagal tone has the opposite effect during AF than during sinus rhythm, the expected effect of enhanced vagal tone would be to shorten cycle lengths in the fibrillatory wavelets leading to an increased fibrillatory frequency.

Experimental studies have shown that sympathetic discharge shortens the atrial refractory period both in sinus rhythm and during AF [22-24]. Other animal studies have demonstrated that atrial refractoriness during sinus rhythm shortens following isoproterenol [4]. Adrenergic stimulation appears to have a negligible effect on atrial conduction velocity, with no significant increase having been observed following isoproterenol [4, 26] or epinephrine [27] and with only a slight increase noted following sympathetic stimulation [24]. Like studies concerning the effects of vagal tone on human atrial fibrillatory properties, studies on adrenergic manipulation are sparse. The evidence that does exist points to the expected effect of enhanced adrenergic tone, with a decrease in atrial fibrillatory cycle length, and leading to a increased fibrillatory frequency.

Sympathetic stimulation, caused by head-up tilt test decreased the DACL by 10 ms compared to the value observed during supine rest [28]. In one patient a rapid sudden decline of heart rate associated with syncope was seen. This clinical compatible strong vagal stimulation induced a further shortening of DACL in the order of 15 ms [28].

From unpublished data, isoproterenol-infusion was associated with a significant shortening of the DACL in patients with chronic AF by 9 ms [29]. In the same group of patients atropine-injection caused a transitory but significant prolongation of DACL by 3 ms [29].

Diurnal fluctuations in atrial refractoriness have been demonstrated during sinus rhythm [30, 31]. The diurnal variability in the fibrillatory cycle length has been studied non-invasively utilizing power-spectrum analysis in several independent patient groups [32-34]. In one study, hourly estimations irrespective of body position and physical activity demonstrated a significant mean prolongation of the DACL of 7 ms during night. However the magnitude of DACL change was markedly individual and ranged between 0 and 23 ms [32]. The magnitude of the variability was significantly and positively correlated to the mean DACL value. Observations from the other studies also demonstrate a slight but significant and individual nocturnal DACL prolongation [33, 34].

Permanent AF

Non-invasive assessment of the atrial fibrillatory cycle length can be accurately detected from precordial leads in the vast majority of patients with AF, provided that the ventricular rate is not excessively high [14, 15]. The range in DACL values during rest in our entire material (including unpublished data) varied between 105 and 195 ms in lead V1. Some of these patients were on digitalis, but patients on other cardioactive drugs which could affect atrial repolarization or impulse conduction velocity were excluded from our reports. Patients that were referred to cardioversion (i.e persistent AF) had a mean DACL of 154 ± 16 ms (range 120 to 175 ms) [20] compared to a mean DACL of 145 ± 12 ms (range 122 to 162 ms) in another group of patient that was considered beyond any possible benefit of a new cardioversion attempt [21]. These findings are at least partly in agreement with the progressive shortening of the refractory period with time demonstrated in the atrial myocardium during AF [35]. Bollmann et al. reported in their studies corresponding DACL values of a range of 132 to 204 ms in patients with chronic AF [16] and of a range of 130 to 156 ms in patients with a duration of AF more than 3 months [18].

Paroxysmal AF START

In patients with recent onset AF in our material the DACL ranged between 140 and 180 ms [15]. In Bollmann material, values corresponding to a DACL ranged between 111 to 262 ms immediately after pacing-induced AF [16] and between 145 to 256 ms measured shortly after a spontaneous start of a AF attack [18]. In the latter study, the DACL-value decreased further during the following 15 minutes in those the arrhythmia was sustained. However, in cases with spontaneous termination of AF, the DACL was prolonged. This observation is consistent with the theory first postulated from Moe [1] and later experimentally supported by Allessie et al. [2], that AF could only be sustained by the existence of a critical number of circulating electrical wavelets. Hence, an increase of the cycle length in a constant atrial area would lead to a decrease in the maximum number of wavelets.

Remodeling

The “multiple wavelet hypothesis” has become the general accepted theory for the electrophysiological mechanism maintaining AF [1-3]. The refractory period
of the atrial myocardium decreases progressively during AF [35], providing a mechanism whereby the arrhythmia can predispose to its own perpetuation. This phenomenon has been called electrical remodeling. The shorter DACL observed in patients with AF of longer duration described above, is in agreement with this phenomenon. These electrophysiological changes are (at least in part) reversible, and improve after termination of the arrhythmia. Moreover it seems that inducibility and probability of AF relapse are correlated to the length of the atrial refractory period during the recovery period [35-38]. Because electrical remodeling can be attenuated by medications that lower intracellular calcium, it has been suggested that these electrophysiological changes are, at least in part, mediated by intracellular calcium overload [36, 37, 39].

Although the time course of electrical remodeling has not been fully explored in humans, the possible reversibility of the phenomenon by oral verapamil has been explored in a group of patients with permanent and longstanding AF in whom repeated cardioversion attempts had failed [21]. The primary prolongation in DACL was demonstrated within the first day of treatment, but further elongation continued for at least 4 more days with continued treatment. The mean increase of DACL was 17 ms and it remained at that level for at least 6 weeks of continued verapamil treatment. Although administration of intracellular calcium-lowering medication during chronic AF seems to reverse already established electrical remodeling, it remains to be seen whether the success rate of cardioversion and subsequent maintenance of sinus rhythm can be improved by this treatment.

Interestingly, the prolongation of DACL following verapamil treatment was proportionate to its initial value (i.e. those with a longer initial DACL increased more than those with a shorter initial value). A comparable finding was observed during isoproterenol-infusion, with those who had a short initial DACL exhibiting minimal further decrease [29]. Finally, in our study on the diurnal variability of DACL, those who had a short DACL exhibited minimal diurnal variation [32]. Consequently it seems that atria with shorter DACL values, typically below approximately 125 ms, are unaffected by both verapamil treatment or autonomic influences. The underlying mechanism of this observation is unclear at the present time, but data from a more recent study suggests that persisting morphological and ultrastructural changes besides electrical remodelling may be involved [40]. If these observations are dependent on arrhythmia duration, it could obviously have clinical implications. In such a scenario a diminished response to other pharmacological, physiological and pathophysiological stimuli and consequently “a remodeling beyond the point of no return” (SB Olsson) may have occurred in patients with long standing AF.

Antiarrhythmic drugs

Since a critical number of reentry wavelets must be present for AF to self-perpetuate, and since a lengthening of wavelength will lead to a decreased number of reentry wavelets, any such change would also, in theory, lead to a lower probability for the arrhythmia being sustained [4, 8]. This hypothesis is in agreement with observation that the ability of antiarrhythmic drugs to terminate experimentally induced AF is dependent on prolongation of the wavelength [41].

As expected, Class III antiarrhythmic drugs such as ibutilide [16] and amiodarone [18], prolong the DACL markedly. Our group has shown that sotalol, which is well recognized to exhibit inverse use-dependence at high stimulation frequencies, also prolongs the DACL significantly [15]. In one of these previous mentioned studies, Bollman et al. observed that, patients who were referred to cardioversion and who had a DACL value exceeding 167 ms converted to sinus rhythm following i.v. ibutilide [16]. This observation illustrates a possible clinical use of the FAF-ECG method. However, the patients in whom therapeutic success could be predicted in this study had a mean fibrillatory cycle length close to the range identified in patients with PAF, underlining that the degree of electrical remodeling may not have been very pronounced. From a theoretical point of view, the degree of electrical remodeling and consequently the value of DACL should be related to arrhythmia duration. According to such a hypothesis, patients successfully cardioverted by pharmacological means are probably less electrically remodeled. This is consistent with the clinical observation that pharmacological cardioversion of AF is generally is highly successful in terminating AF of short duration, but is usually ineffective in AF that has been present more than a few days.

The electrophysiological effect of magnesium (Mg) is mainly believed to be related to blockade of calcium channels [42] and of the inward rectifier current [43]. Our group could show that Mg-infusion causes a slight but significant prolongation of DACL in patients with longstanding AF [44]. This effect was even more pronounced following infusion of glucose, insulin and potassium [44].

Prediction of sinus rhythm maintenance following cardioversion

Since the refractory period shortens following high rate depolarisation’s, patients with a short atrial refractory period presumably have a higher degree of electrical remodelling than the others. Previous work has demonstrated that a short right monophasic action potential is predictive of relapse after conversion of atrial fibrillation [38]. However, the length of the refractory period and hence the DACL may only be used as a predictor before maximal shortening of the refractory
period has occurred. Electrical remodelling develops quickly in animals [39], but the time course over which electrical remodelling occurs in humans is largely unknown. Moreover, estimation of the degree of remodelling is not possible during atrial fibrillation because the patient’s initial refractory period, when they first developed AF, is not known. The hypothesis on which using DACL as a predictor following cardioversion is based on that a lesser shortening of the refractory period would be more resistant to re-induction of atrial fibrillation. Furthermore, the time of electrical recovery until the patients regain their normal length of the refractory period as well as normal rate adaptation would theoretically be shorter.

In one study from the group of Langberg et al., the DACL was lower in those patients who remained in sinus rhythm compared with those who relapsed into AF within three months [45].

In an unpublished study from our group, DACL was shorter in those who relapsed into AF, but this trend failed to reach statistical significance [46]. However, the duration of AF was longer in the patients in our study, consistent with the hypothesis that patients with long standing AF, electrically remodeling are already nearly fully developed. Therefore, the DACL may only be a good sole predictor within the first weeks of AF onset or alternatively in detecting patients with a genetically determined ability to develop a higher and more severe degree of electrical remodeling.

In our study the ratio of DACL to left atrial size, combining electrical and anatomical parameters, proved to be a significant predictor of maintenance of sinus rhythm for six weeks after DC-cardioversion. However, the ability to identify those who will relapse into AF remained modest in both studies [45, 46]. Therefore other etiological factors must be involved not dependent of degree of electrical remodelling (i.e. the length of the refractory period). As pointed out previously, data from a more recent study suggests that vulnerability to AF recurrence after cardioversion is more dependent on persisting morphological and ultrastructural changes than on electrical remodeling [40].

Detection of rapidly firing atrial foci?

An alternative mechanism of AF is a local rapid firing focus capable of both initiating and maintaining AF. It has been reported that some of these patients may exhibit

Fig. 4. - Short-term analysis of the AF frequency illustrating a sudden change in the fibrillation frequency to a more stable pattern, which lasts for 10 seconds and then reverts back to the typical more irregular AF pattern that is illustrated in Fig. 3. One plausible explanation of this different type of atrial activity could be that it represents an underlying local rapid firing focus or small reentry circuit.
distinct clinical profile and ECG characteristics, suggestive of the diagnosis. Using short-term analysis of the AF frequency in a patient with persistent AF, we have detected a sudden change in the typical time-varying fibrillation pattern to a more stable frequency not consistent with traditional AF, which lasted for 10 seconds. This regular pattern then reverted to the previously seen more irregular AF-pattern. What this regular pattern represents is undetermined but it is reasonable to speculate that it may represent an underlying local rapid firing focus. Alternatively it may be due to temporary organization of the AF into a single reentry circuit. The recording is shown in Fig. 4.

Submitted on invitation. Accepted on 29 March 2001.

REFERENCES


46. Meurling CJ, Rosier A, Waktare JE. The role of atrial fibrillatory rate in prediction of sinus rhythm maintenance following DC-cardioversion of persistent atrial fibrillation. (Submitted).