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REVIEW

Analysis of surface electrocardiograms in atrial fibrillation: techniques, research, and clinical applications

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Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice. Neither the natural history of AF nor its response to therapy is sufficiently predictable by clinical and echocardiographic parameters. The purpose of this article is to describe technical aspects of novel electrocardiogram (ECG) analysis techniques and to present research and clinical applications of these methods for characterization of both the fibrillatory process and the ventricular response during AF. Atrial fibrillatory frequency (or rate) can reliably be assessed from the surface ECG using digital signal processing (extraction of atrial signals and spectral analysis). This measurement shows large inter-individual variability and correlates well with intra-atrial cycle length, a parameter which appears to have primary importance in AF maintenance and response to therapy. AF with a low fibrillatory rate is more likely to terminate spontaneously and responds better to antiarrhythmic drugs or cardioversion, whereas high-rate AF is more often persistent and refractory to therapy. Ventricular responses during AF can be characterized by a variety of methods, which include analysis of heart rate variability, RR-interval histograms, Lorenz plots, and non-linear dynamics. These methods have all shown a certain degree of usefulness, either in scientific explorations of atrioventricular (AV) nodal function or in selected clinical questions such as predicting response to drugs, cardioversion, or AV nodal modification. The role of the autonomic nervous system for AF sustenance and termination, as well as for ventricular rate responses, can be explored by different ECG analysis methods. In conclusion, non-invasive characterization of atrial fibrillatory activity and ventricular response can be performed from the surface ECG in AF patients. Different signal processing techniques have been suggested for identification of underlying AF pathomechanisms and prediction of therapy efficacy.

Introduction

In recent years, mechanisms leading to atrial fibrillation (AF) induction and maintenance have begun to be explored and rapidly evolving therapies including new antiarrhythmic drugs and catheter ablation techniques have been introduced into clinical practice. Nevertheless, outcome of AF patients is still unsatisfactory, which mainly can be attributed to the progressive nature of this arrhythmia and to only partially effective therapies. Moreover, AF treatment (e.g. rate vs. rhythm control, choice of antiarrhythmic drugs or device therapy, curative ablation) may be viewed as being based on trial and error, because no test is able to predict

the natural history of this arrhythmia or its response to treatment. Consequently, current AF management guidelines[1] provide no treatment recommendations that 'take the various mechanisms and patterns of AF into account'. Thus, it seems desirable to develop tests that quantify AF disease state and guide AF management.[2,3]

Virtually in every patient with AF, standard 12-lead surface electrocardiograms (ECG) and/or Holter recordings are acquired, the main purposes being confirmation of the presence of arrhythmia and the determination of ventricular rate. It is a common observation that fibrillatory waves have various appearances ranging from fine to coarse and from disorganized to organized and that the ventricular rate response varies in a rather unpredictable fashion. Interestingly, the mechanisms behind the fibrillatory process on the ECG as well as the ventricular response

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and, moreover, the possible prognostic information contained within the ECG have just recently begun to be explored.

The purpose of this article is (i) to describe technical aspects of novel ECG analysis techniques and (ii) to present research and clinical applications of these methods for characterization of both the fibrillatory process (Part I, *Table 1*) and the ventricular response (Part II) during AF.

Part I: Characterization of the fibrillatory process

Background

Shortening of atrial refractoriness and maladaptation to rate are hallmarks of atrial electrical remodelling in AF.[4] During AF, re-excitation occurs during the repolarization phase of the preceding electrical wave, implying that local excitation almost always occurs without any obvious latency beyond the refractory period. Consequently, the average atrial fibrillatory rate is likely to reflect averaged refractoriness at any part of the tissue involved. This assumption has been independently verified in both animal[5] and human AF[6,7] by correlating both measures. Therefore, the length of the averaged atrial fibrillatory cycle (which is inversely related to fibrillatory frequency or rate) can be used as an index of the averaged atrial myocardial refractoriness and AF organization.[8]

The importance of shortened refractoriness and its transformation into short atrial cycles or high rates, as assessed by direct intra-atrial measurements for AF progression and response to therapy, has been well established. First, spontaneous arrhythmia behaviour seems to be related to baseline fibrillatory cycle length, with sustained AF having shorter mean cycle lengths compared with non-sustained AF.[9,10] Secondly, response to antiarrhythmic drug therapy has been shown to be associated with both baseline AF cycle length before drug administration and drug-induced cycle length changes. Both longer right atrial cycle length at baseline[11] and greater cycle length prolongation[12] seem to be associated with antiarrhythmic drug-induced AF termination. Finally, there exists a close relation between the degree of electrical abnormalities and AF recurrence following cardioversion, with shorter atrial effective refractoriness and abnormal rate adaptation being predictors of AF relapses.[13–15]

Prompted by the likely usefulness of a non-invasive test that assesses the average fibrillatory rate from the surface ECG for exploration of AF pathophysiology and AF

management, frequency analysis techniques were independently introduced by our groups,[16,17] whereas two earlier studies proposed the use of this technique to subdivide AF and atrial flutter[18] or automatically identify AF among different rhythms.[19]

Techniques for characterization of the fibrillatory process

ECG acquisition

Using digital recording techniques, traditional ECG signals are recorded. In most studies, atrial fibrillatory rate has been obtained by spectral analysis techniques of resting ECG recordings such as standard 12-lead[16,17] or (modified) orthogonal recordings.[20–22] It has been suggested to analyse lead V1 when using a standard 12-lead ECG or, as proposed previously by Waktare *et al.*,[23] a 'bipolar modification of V1' covering the atria (low C1) when applying different ECG recording systems, as the largest fibrillatory waves are usually found in these leads.

The sampling rate of the ECG is commonly determined by the highest frequency of the activity of interest: in our case, the atrial activity whose highest frequency components are well below 50 Hz. Hence, it may be tempting to conclude that the ECG signal can be acquired at a sampling rate of 100 Hz. However, extraction of the atrial signal usually involves signal processing steps which, if to be performed successfully, require a considerably higher sampling rate, i.e. 250 Hz or higher. This observation applies, in particular, to the extraction of atrial activity by QRST subtraction (given subsequently), where a too low sampling rate introduces large residual errors in the atrial signal. Consequently, it may be necessary to increase the original sampling rate to 1 kHz using digital interpolation techniques for QRST subtraction methods.[24]

It is essential to correct for baseline wander, preferably using linear phase filtering,[25] since such noise has serious repercussions on the performance of the atrial signal extraction method. The presence of baseline wander may also influence the lower frequency components of the atrial signal spectrum, though to a lesser extent. Following correction of baseline wander and QRS detection, it is necessary to identify ectopic beats. Although recordings free of ectopy are preferred since they facilitate atrial signal extraction, it is usually possible to handle the presence of ectopic beats within the framework of the selected approach.

Extraction of atrial signals during AF

Since the characterization of the fibrillatory process primarily revolves around the determination of rate, a

Table 1	Methods for analysis of atrial activity		
Method	Objective	Main output	Pathophysiological meaning
Spatiotemporal QRST cancellation, PCA, ICA,	Extraction of atrial (fibrillatory) signal without ventricular activity	Residual ECG with fibrillatory waves	—
Fourier-based spectral analysis	Evaluation of dominant atrial fibrillatory rate	Location of the dominant spectral peak	Atrial refractoriness
Time–frequency analysis	Evaluation of temporal variations in atrial fibrillatory rate	Trends describing variations in the location of the spectral peak and waveform	Atrial refractoriness and dispersion of atrial refractoriness

ICA, independent component analysis; PCA, principal component analysis.

straightforward approach would be to perform spectral analysis on samples in intervals without ventricular activity, i.e. the T–Q intervals.[18] However, such an approach does not fully exploit the on-going nature of the fibrillatory process; samples during the QRST interval can be equally used for determining rate, provided that the ventricular activity has been first removed. The availability of additional samples reflecting atrial activity contributes not only to improved accuracy of the spectral estimate but also circumvents the problem of vanishing T–Q intervals at high heart rates.

The extraction of an atrial signal during AF requires non-linear signal processing since atrial and ventricular activities overlap spectrally and therefore cannot be separated by linear filtering. Average beat subtraction is the most widespread technique for atrial signal extraction and relies on the fact that AF is uncoupled to the ventricular activity. Hence, subtraction of the average QRST complex produces a residual signal, which is the atrial fibrillatory signal. This technique was initially developed for identifying P-waves during ventricular tachycardia,[26] but has later been employed for the AF analysis.[16,17,19] Since average beat subtraction is performed in individual leads, it becomes sensitive to alterations in electrical axis, which are manifest as large QRS-related residuals. However, the effect of such alterations can be suppressed by using spatiotemporal QRST cancellation in which the average beats of adjacent leads are mathematically combined with the average beat of the analysed lead in order to produce optimal cancellation (*Figure 1*).[27]

Another approach to atrial signal extraction exploits the property that atrial and ventricular activities arise from different bioelectrical sources. These two sources, exhibiting different statistical properties, can be separated when multi-lead ECG recordings are available. Principal component analysis (PCA)[28] and independent component analysis (ICA)[29] are the two main representatives of the separation approach, which both have found their way into the AF analysis.

Since both approaches have been shown to produce similar performance,[30] the choice of extraction technique may instead be guided by their decidedly different modes of processing the ECG signal. Spatiotemporal QRST cancellation extracts the atrial signal in a specific lead and strives at not modifying the original f-wave morphology. On the other hand, PCA and ICA derive a global atrial signal with contributions from all leads, although dominated by the lead with the largest atrial activity. A recording length of at least 10 s is required for adequate computation of the average beat, whereas the recording length can be shorter when PCA or ICA is used. In addition to these techniques, PCA was recently suggested for QRST cancellation in single leads to account for beat-to-beat changes in morphology.[31] This technique can be viewed as a generalization of average beat subtraction, where more than one component can be used to create a template that best fits each QRST complex.

Fourier-based spectral analysis

Following extraction of the atrial signal, a power spectrum is obtained, which typically exhibits a distinct peak whose location determines the most common fibrillatory rate of nearby endocardial sites.[16,17] Most studies make use of non-parametric, Fourier-based spectral analysis in which the ECG signal is divided into shorter, overlapping segments, each segment subjected to windowing (e.g. Welch's method).[16,17] The desired power spectrum is obtained by averaging the power spectra of the respective segments. It is customary to pad each segment with zeros so that the location of the spectral peak can be determined more precisely (although zero padding *per se* does not improve spectral resolution).

Segment length is the most critical design parameter in non-parametric spectral analysis since it determines the estimation accuracy of fibrillatory rate and restricts spectral resolution. It is advisable that segment length is chosen to be at least a few seconds to produce an acceptable variance of the rate estimate. Concerning spectral resolution, it may seem warranted to use longer segments in order to assure that concurrent, slightly different rates are appropriately resolved; for example, 10 s segments of the atrial signal yield a spectral resolution of ~0.1 Hz. However, no evidence has been put forward, which supports the existence of concurrent fibrillatory rates, but time–frequency analysis of the atrial signal (given subsequently) rather suggests that rate often varies substantially over time. Hence, spectral resolution has secondary importance when choosing the segment length.

Since the frequencies characterizing the atrial signal are mostly confined to the interval well below 50 Hz, a sampling rate much lower than the one suggested earlier for the extraction of the atrial signal may be used to reduce the amount of computations. Although sampling rate decimation is dispensable when non-parametric spectral analysis is performed, it is crucial to perform when parametric spectral estimation techniques are employed in order to avoid the presence of spurious spectral peaks.[32]

Time–frequency analysis

Power spectral analysis reflects the average signal behaviour during the analysed time interval—the location of the dominant spectral peak representing the main information carrier with clinical value. However, power spectral analysis suffers from an inability to characterize temporal variations in fibrillatory rate. The presence of bi- or multimodal spectral peaks, reported in some early studies,[16,33] may be interpreted as spatial variation in fibrillatory rate. When these results are seen in the light of recent studies employing time–frequency analysis,[34,35] such peaks are most likely explained by temporal variation in fibrillatory rate rather than by spatial variation.

Time–frequency analysis is a powerful tool for unveiling the temporal variation of the atrial signal, whether such variation is spontaneous or due to an intervention. In particular, time–frequency analysis can be used to quantify changes in fibrillatory rate, which may be associated with an intervention. Similar to power spectral analysis, a plethora of methods has been developed for time–frequency analysis, and it remains an open issue to select the method that provides the most adequate characterization of the atrial signal.

Recently, a novel approach to time–frequency analysis was presented, in which the time–frequency distribution, defined by local power spectra from successive 1 s segments, is decomposed into a spectral profile and a set of functions that describes the second-to-second variations in fibrillatory rate and f-wave morphology (*Figure 1*).[34,35]
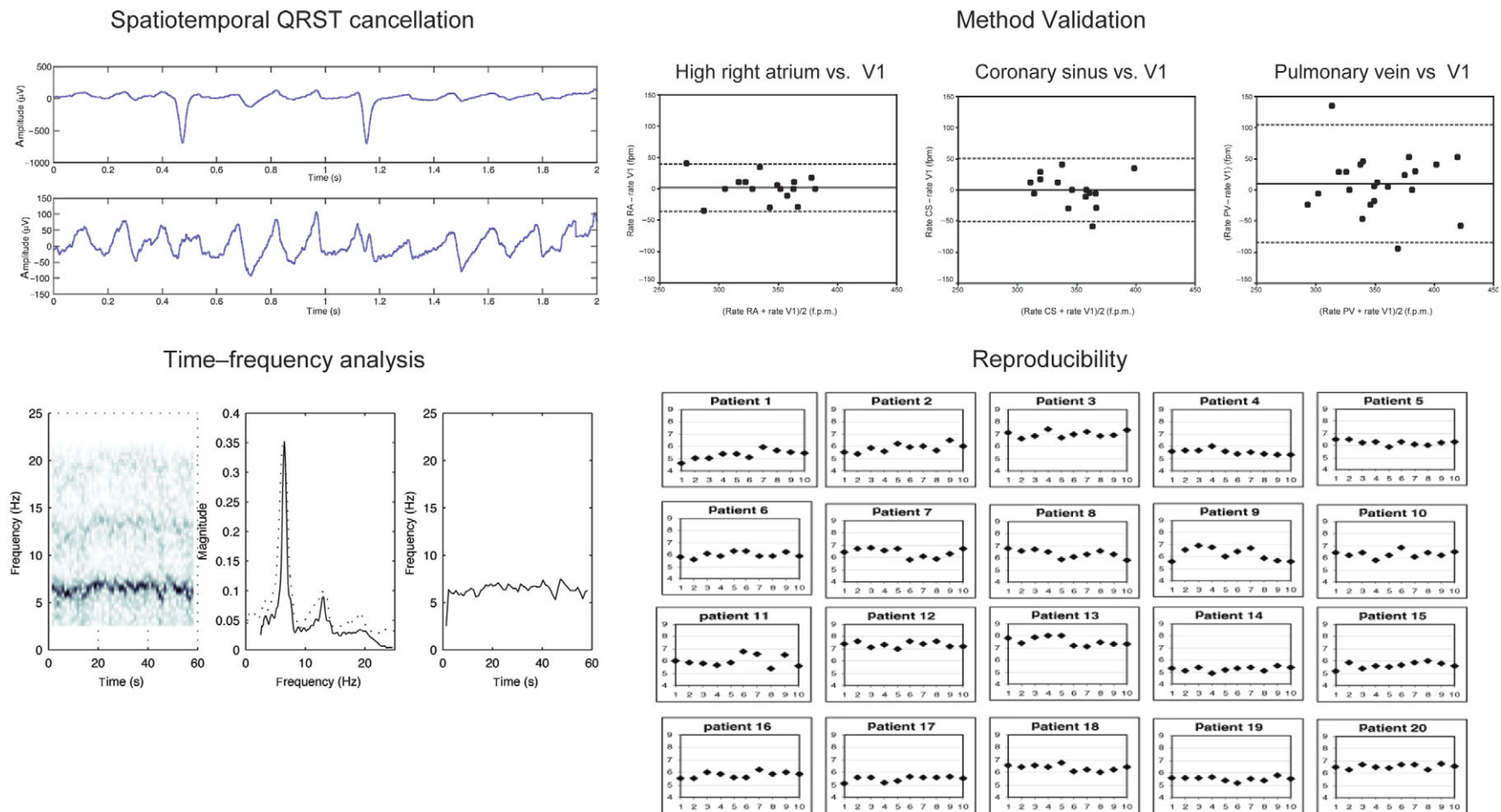
Spatiotemporal QRST cancellation

Method Validation

Time–frequency analysis

Reproducibility

Figure 1 Time–frequency analysis of AF (left), validation by comparison of surface ECG lead V1 with intracardiac electrograms (top right), and short-term reproducibility (bottom right). Left: 2 s (out of a 60 s recording) of an ECG signal from a patient with AF (upper panel), and the same interval after QRST cancellation (middle panel, amplitude scale is magnified five times). This fibrillatory signal is then subjected to spectral analysis techniques (lower panel). Time–frequency distribution (left box), power frequency spectrum in which the dominant fibrillatory rate is determined (middle box), and frequency trend (right box).[27,34,35] Top right: agreement of fibrillatory rates from the right atrium (left), coronary sinus (middle), superior pulmonary veins (right) with simultaneously recorded fibrillatory rates from surface ECG lead V1 in patients with persistent AF (Bland–Altman method).[38] Bottom right: repeated determination of fibrillatory rate over 24 h in 20 patients with persistent AF.[42]

The spectral profile differs from the conventional power spectrum in that the local spectra have been frequency-aligned before spectral averaging. As a result, the peaks of the spectral profile become more distinct, implying that determination of the harmonic structure of the atrial signal, i.e. the f-wave morphology, is facilitated.

Method validation and reproducibility

A direct comparison between endocardially recorded electrograms and body surface recordings clearly shows the validity of fibrillatory rate obtained from surface ECG as an index of the average atrial fibrillatory cycle. Although in one preliminary report median right atrial and surface ECG rates exhibited only moderate correlations,[36] dominant fibrillatory rates calculated from lead V1 substituted the right atrial free wall,[16,17,37] and rates from an oesophageal lead reflected atrial septal and left atrial activity.[16] Interestingly, rate differences and variability between ECG and electrograms increase with growing anatomical distance (right atrium—coronary sinus—pulmonary veins) to V1. In a first preliminary report, which assessed the relation between pulmonary venous and ECG fibrillatory rates in 25 patients with persistent AF, correlations were moderate ($R = 0.457$), whereas they were higher for right atrial ($R = 0.885$) and coronary sinus ($R = 0.558$) rates ($P < 0.05$ for all correlations).[38] However, non-standard surface ECG lead positions for characterization of left atrial/pulmonary vein activity or identifying spatial variation have not been studied.

So far, direct comparisons of endocardial and surface signals have only been reported when the surface ECG had been subjected to QRST cancellation (*Figure 1*).[16,17,36–38] This technique has, in addition, been validated by comparing 'pure' AF during brief ventricular asystole with atrial signals obtained with QRST cancellation also showing good agreement of atrial rates.[39] In a comparative study, in which spatiotemporal QRST cancellation, PCA, and ICA algorithms have been applied to the same surface ECG recordings, the dominant rate of the atrial signals extracted by each of the algorithms was within 1 Hz (60 fibrillations per minute), with larger differences due to poorly defined dominant peaks and residual ventricular activity corrupting the frequency response.[30]

Although the gross atrial fibrillatory pattern, studied by multiple simultaneous epicardial recordings, is reproducible already in repeated measurements of only 8 s duration,[40] calculation of fibrillatory rates during steady-state conditions from even longer time intervals discloses a true variability. Thus, increasingly longer recording times of up to 30 min result in a successive decrease in this variability. Prolonging the recording time during steady-state conditions, allowing integration of atrial fibrillatory activity over longer periods, thus enhances the reproducibility of the method. For practical reasons, steady-state recordings may be restricted to 1–5 min, yielding rate variation coefficients of 2.1%.[16] In persistent AF, there is minor short-term rate variability within 30 min,[16,17,39] whereas repeated daily frequency measurements on identical medication at the same time under similar conditions disclose an insignificant fibrillatory rate variability.[41] Very recently, surface ECG atrial fibrillatory wave characteristics have been shown to be highly reproducible over 24 h in clinically stable AF patients even in 10 s ECG segments, as acquired by standard 12-lead ECGs (*Figure 1*).[42]

To date, the dominant spectral peak has been presented as dominating atrial cycle length (in ms), fibrillatory rate [in fibrillations per minute (fpm)], or fibrillatory frequency (in Hz). Since it has become evident that the results of this method are of practical clinical importance, we believe that the results should be expressed in a way which is closest to the nomenclature of other surface ECG rate variables (e.g. sinus, atrial tachycardia, or atrial flutter rate).[43] The expression 'fibrillatory rate', with its unit fpm is therefore appropriate in clinical reports.[21,44]

Moreover, the calculation of cycle length from the frequency power spectrum with its standard unit Hz (cycle length in ms = 1000/frequency in Hz) seems somewhat troublesome.[44] Although this calculation is appropriate for single measurements, its application to multiple simultaneous, or repeated measurements such as pre- and post-drug states may introduce errors. The reason is that the same frequency difference results in larger cycle length differences for low frequencies compared with high frequencies.

Research and clinical applications

Exploring autonomic modulations

Vagal and sympathetic stimulations have been shown to reduce atrial refractory periods and increase their heterogeneity.[45–47] In the human atrium, beta stimulation has been found to predominate over vagal stimulation.[46] Moreover, invasive studies performed in subjects with sinus rhythm have suggested a circadian pattern in atrial refractoriness, with longer refractory periods during night time and refractory period shortening during daytime,[48,49] which supports the role of the autonomic nervous system in modulating atrial electrophysiological properties.

Consequently, atrial fibrillatory rate seems to be ideal for monitoring the effect of autonomic tone changes—either spontaneous (circadian) or by autonomic manoeuvres provoked—on atrial electrophysiology. Indeed, the circadian variability of atrial fibrillatory rate has been explored in independent studies.[50,51] Fibrillatory rate obtained from Holter ECGs with persistent AF showed a significant decrease at night and an increase during the morning hours.[50,51] In six of 30 individuals studied by our group,[50] dominant nocturnal fibrillatory rate increased, however, concomitantly with a decrease in ventricular rate, whereas the opposite change occurred during the morning hours.

The second area of investigation concerns effects on atrial fibrillatory rate following vagal or sympathetic stimulation during experimental conditions. Carotid sinus massage, mainly supposed to induce vagal stimulation, resulted in a variable effect on fibrillatory rate in 19 patients.[52] A reproducible decrease was noted in nine individuals, whereas a rate increase occurred in eight, and no change was observed in two patients. Interestingly, calcium-channel blocker treatment was the only variable affecting the rate response to carotid sinus massage. Calcium-channel blockers were more frequently used in patients with a decrease in fibrillatory rate compared with patients with a rate increase. The effect of adrenergic stimulation via head-up tilting on fibrillatory rate was studied in 14 patients with long-lasting AF.[53] In 12 patients, head-up tilt increased fibrillatory rate significantly, whereas there was no rate change in the remaining two (*Figure 2*).

Fibrillatory rate response to an antiarrhythmic drug
Flecainide

Fibrillatory rate response to an autonomic manoeuver
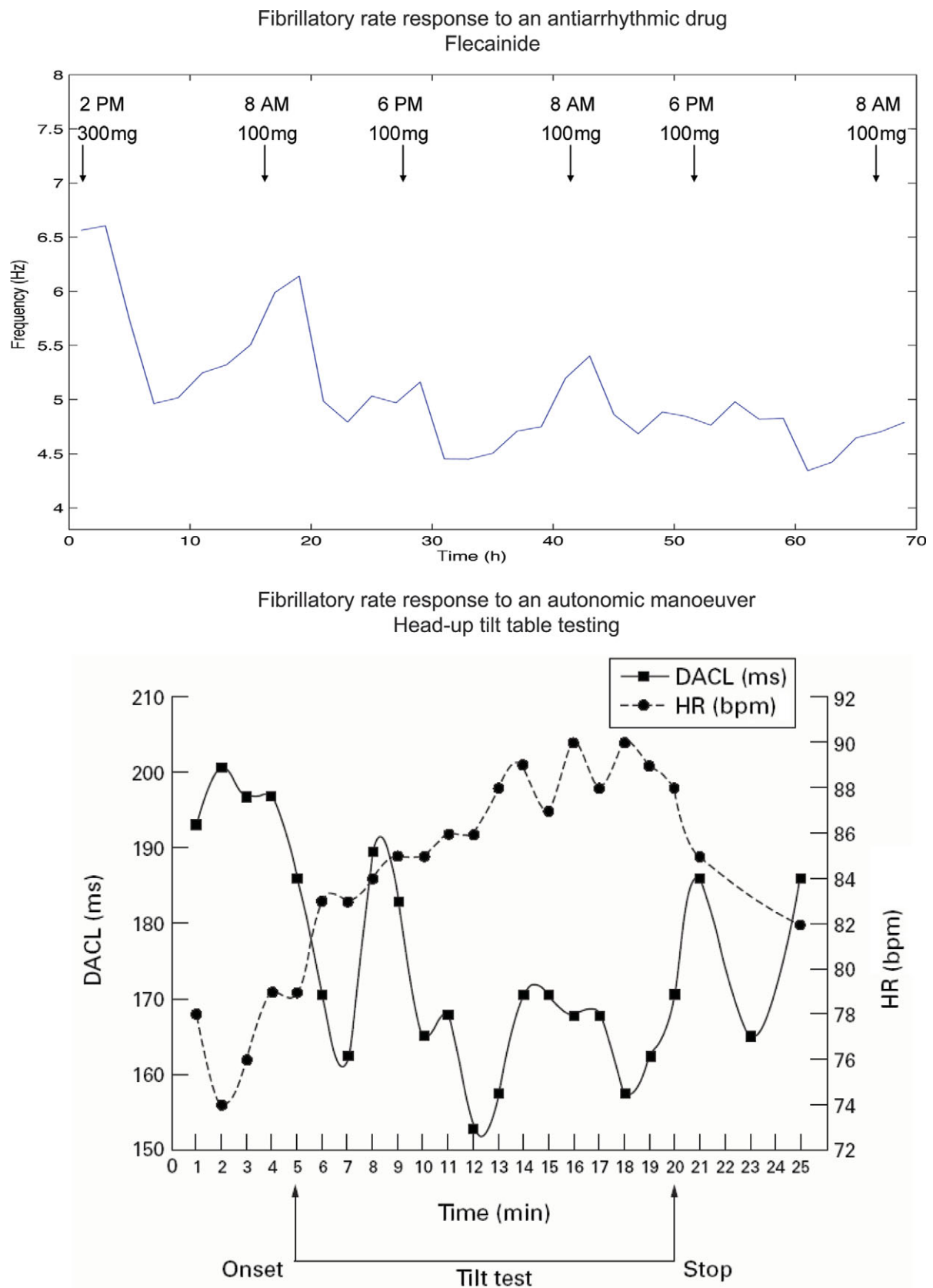Head-up tilt table testing

Figure 2 Monitoring of interventions during AF, such as response to antiarrhythmic drugs (top) or to autonomic manoeuvers (bottom). Top: the solid line indicates the actual fibrillatory rate during oral drug loading with flecainide (300 mg bolus, followed by 100 mg bid) over 72 h. Bottom: typical example illustrating changes in heart rate (HR) and dominant atrial cycle length (DACL, which is inversely related to fibrillatory rate) during head-up tilt testing. An increased sympathetic discharge and withdrawal of vagal activity are known to be the physiological responses to the tilt table test, which is associated with increases in both HR and fibrillatory rate (decrease in DACL).[53]

With the availability of instantaneous fibrillatory rates obtained from time–frequency analysis, their second-to-second variation can be explored by spectral analysis techniques, similar to those used for analysing heart rate variability (HRV). By applying this approach, controlled respiration caused cyclical fluctuations in fibrillatory rate in patients with long-duration AF, which was related to parasympathetic modulations of the atrial refractory period.[54,55]

Predicting spontaneous AF behaviour and therapeutic effects

In contrast to persistent AF, rate variability in paroxysmal AF seems to be related to its natural course, with a rate increase within the first 5 min of an AF episode[56] and a rate decrease prior to termination.[56,57] In fact, fibrillatory rate has been shown to be highly predictive of spontaneous termination of paroxysmal AF. In a study of 30 ECG recordings, a low fibrillatory rate was able to identify patients with spontaneously terminating AF with high accuracy.[58]

Class I and III antiarrhythmic drugs have been shown to increase atrial cycle length (decrease fibrillatory rate), which coincides with increased refractoriness and decreased conduction velocity.[59] A substantial reduction in atrial fibrillatory rates following several different intravenously or orally administered class I and III antiarrhythmic drugs as well as following verapamil or magnesium has been observed when applying Fourier-based spectral analysis and more recently time–frequency analysis[60,61] (*Figure 2, Table 2*). Of special note is the capability of these methods to monitor drug effects serially or continuously, which appear superior to monitoring plasma drug levels.[62]

Interestingly, it is also possible to identify suitable candidates for pharmacological cardioversion. A baseline fibrillatory rate of 360 fpm or lower was highly sensitive and specific for prediction of AF termination following intravenous ibutilide[17] or oral flecainide.[20] In contrast, no baseline fibrillatory rate difference between patients who converted to sinus rhythm and those who did not following oral bepridil administration has been noted. Instead, larger rate increases were associated with AF termination,[63] which has also been found with ibutilide treatment.[64] Although this concept is interesting and well established in experimental AF,[59] it needs to be emphasized that the authors of the former study[63] calculated atrial cycle length from the frequency spectrum, which may have introduced the aforementioned statistical errors.[44]

Previous investigations[65,66] have shown that most AF relapses occur within the first weeks after cardioversion, with decreased but constant recurrence rates thereafter. Early vulnerability to AF re-initiation within this time period is related to electrophysiological abnormalities, whereas structural abnormalities seem to be primarily responsible for later AF recurrences.[67] Consequently, characterization of atrial electrophysiology has been suggested for identification of patients at risk for early AF recurrence.[2]

Previous studies reported higher rates in relapsed patients immediately prior to internal[68] or external cardioversion[22,69] when compared with non-relapsed patients and also close relationships between fibrillatory rate and defibrillation thresholds.[68,70]

So far, one study[22] has investigated the combined predictive value of fibrillatory rate and echocardiographic left atrial parameters for predicting AF recidivism. It could be demonstrated that the combination of fibrillatory rate and systolic left atrial area predicted early AF recurrence after successful cardioversion with high accuracy and was able to provide individual risk estimates. Very recently, fibrillatory rate changes in response to linear left atrial ablation have been monitored non-invasively and the effect on fibrillatory rate of roof and mitral isthmus lines quantified.[71] Even though there was a trend to lower baseline rates with successful ablation, this study was not powered to predict outcome, although an invasive study supports this conclusion.[72]

Taken together, fibrillatory rate seems well suited to describe the individual atrial remodelling and monitor interventions (*Table 3*). The concept of ECG-guided AF therapy may gain even greater importance in the light of two studies showing the same mortality risk for rate- and rhythm-control strategies if adequate anticoagulation is performed.[73,74] This highlights the need to select candidates for cardioversion and other interventional procedures not only based on clinical judgement but also on measures that are able to determine the likelihood of maintaining sinus rhythm, such as rate parameters obtained from the surface ECG.[75]

Part II: Characterization of ventricular response during AF

Background

Given similar outcomes between rhythm and rate control strategies,[73,74] ventricular rate control seems an attractive endpoint for the treatment of AF.[76] AF is accompanied by an irregular ventricular response, mostly with a higher average rate than during sinus rhythm, provided atrioventricular (AV) conduction is patent and unaffected by any drug. It is the result of fast irregular atrial excitations reaching the AV node and its inherent conduction properties.

On the one hand, ease of ventricular rate measurement using ECG recordings with variable length (e.g. standard resting ECG vs. Holter recordings) and under variable circumstances (e.g. exercise ECG) is an obvious attribute. On the other hand, more advanced ECG analysis methods for exploration of autonomic modulation and AV nodal physiology as well as determining outcome of different treatments have been proposed. In particular, this article provides an overview of (i) HRV during AF and before its onset and (ii) analyses of RR-interval histograms, Lorenz plots, and non-linear dynamics (*Table 4*).

Techniques and applications for characterization of ventricular response

HRV during AF

The exploration of autonomic modulation of sinus node impulse activity via HRV analysis is a widely used method. Analysis of ambulatory ECG recordings during sinus rhythm has been proved effective to identify high-risk patients in different cardiovascular diseases. However, during AF, ventricular variability does not purely reflect sinus node modulation but is also dependent on AV nodal refractoriness as well as degree of concealed conduction[77] and left atrial

Table 2 Frequency analysis of AF for monitoring and predicting class I and III antiarrhythmic drug action

Drug(s)	Dosage	Patients (n)	Drug effect (baseline vs. after drug)	AF termination (%)	Converters vs. non-converters
Flecainide[20]	300 mg bolus + 100–200 mg/day p.o.	18	−108 fpm (6.2 ± 0.5 vs. 4.4 ± 0.4 Hz)	50	Baseline fibrillatory rate 354 vs. 384 fpm (5.9 ± 0.4 vs. 6.4± 0.4 Hz)
Cibenzoline Procainamide[57]	1.4 mg/kg i.v. (n = 5) 10 mg/kg i.v. (n = 3)	8	−102 fpm (151 ± 17 vs. 203 ± 21 ms)	100	–
Amiodarone Sotalol Flecainde[56]	600–1200 mg/day p.o. (n = 5) 240–480 mg/day p.o. (n = 3) 200 mg/day (n = 1)	8	−66 fpm (6.9 ± 0.5 vs. 5.8 ± 0.4 Hz)	0	–
Bepidril[63]	200 mg/day p.o.	32	–	69	Fibrillatory rate change 31 ± 10 vs. 17± 5%
Ibutilide[17]	1 mg (+1 mg if required) i.v.	15	−114 ± 42 fpm	60	Baseline fibrillatory rate 338 ± 55 vs. 436 ± 67 fpm
Ibutilide[64]	1 mg (+1 mg if required) i.v.	19	−82 ± 57 fpm	35	Fibrillatory rate change 108 ± 60 vs. 68 ± 52 fpm
Sotalol[16]	80 mg i.v.	5	Fibrillatory rate decrease in all patients (cycle length increased)	0	–
Amiodarone Flecainide Sotalol Metoprolol[28]	7 mg/kg i.v. (n = 5) 1.5 mg/kg i.v. (n = 5) 1.5 mg/kg i.v. (n = 5) 5–15 mg i.v. (n = 5)	20	−55 fpm (5.77 vs. 4.86 Hz) −37 fpm (5.33 vs. 4.72 Hz) −62 fpm (5.94 vs. 4.90 Hz) −14 fpm (5.41 vs. 5.17 Hz)*	0	–
Flecainide Amiodarone [61]	200–400 mg/day p.o. (n = 13) 1200 mg/day (n = 17)		−78 fpm (400 ± 77 vs. 322 ± 52 fpm), more pronounced with flecainide	0	
Flecainide [62]	300 mg bolus +200–400 mg/day p.o.	10	−123 ± 25 fpm, no relation with flecainide dose or plasma level	30	Not reported

Fibrillatory rate (in fibrillations per minute), frequency (in Hz), or cycle length (in ms) have been reported in the original publications. For this review, all variables are expressed as fibrillations per minute, with the original values in brackets. Possible issues pertaining to the report of atrial cycle length based on calculations from frequency power spectra can be found elsewhere.[21,44] All reported differences (except for *) are statistically significant ($P < 0.05$).

Table 3 Frequency analysis of AF for monitoring spontaneous and intervention-induced fibrillatory rate changes

Intervention	Patients (n)	Findings
Spontaneous paroxysmal AF[56]	11	AF paroxyms <15 min (n = 13) with lower initial fibrillatory rate 288 fpm (4.8 ± 0.6 Hz) compared with 318 fpm (5.3 ± 0.7 Hz) in longer episodes (n = 18)
		Constant fibrillatory rate in short AF episodes; rate increase within 5 min and decrease prior termination in longer episodes
Spontaneous circadian variation[50]	30	Increase in nocturnal fibrillatory rate in six patients (20%), decrease in fibrillatory frequency in 24 patients (80%)
		Moderate to strong relation between relative changes in ventricular rate, and fibrillatory rate obtained from two consecutive measurement points
Spontaneous circadian variation[51]	20	Higher fibrillatory rate of 400 fpm (mean 150 ± 17 ms, range 124–179) during the day compared with 382 fpm (mean 157 ± 22 ms, range 125–195) during the night
		Strong relation between mean fibrillatory rate and the magnitude of night–day differences
		Moderate relation between ventricular rate and fibrillatory rate
Head-up tilt table testing[53]	14	Increase in fibrillatory rate from 375 to 400 fpm with change to upright position (160 ± 19 vs. 150 ± 13 ms), decrease in fibrillatory rate from 408 to 389 fpm after returning to supine position (147 ± 16 vs. 154 ± 19 ms)
		Strong relation between changes in ventricular rate and fibrillatory rate (r = 0.71)
Carotid sinus massage[52]	19	Increase in fibrillatory rate in eight patients (42%) from 384 to 408 fpm (6.4 ± 0.5 vs. 6.8 ± 0.5 Hz), decrease in fibrillatory rate in nine patients (47%) from 390 to 366 fpm (6.5 ± 0.8 vs. 6.1 ± 0.8 Hz), no change in fibrillatory rate in two patients (11%)
		Results with carotid sinus massage on the contralateral side reproducible
		Verapamil more frequently used (78 vs. 25%) in patients with rate decrease compared with patients with rate increase
Linear left atrial ablation[71]	26	Fibrillatory rate decreases from 339 to 309 fpm (5.66 vs. 5.15 Hz) after left atrial roof and mitral isthmus ablation (n = 22)
		Greater fibrillatory rate reduction of 19 fpm after left atrial roof ablation compared with 6 fpm after mitral isthmus ablation (0.31 vs. 0.10 Hz)

Fibrillatory rate (in fibrillations per minute), frequency (in Hz), or cycle length (in ms) have been reported in the original publications, all variables are expressed as fibrillations per minute, with the original values in brackets. Possible issues pertaining to the report of atrial cycle length based on calculations from frequency power spectra can be found elsewhere.[21,44] All reported differences are statistically significant ($p < 0.05$).

size.[78] The typical RR-interval irregularity of ventricular response during AF has been considered a factor that might prevent an appropriate application of HRV analysis in these patients. Indeed, although time domain parameters can be easily computed also in AF patients, frequency domain analysis has been rarely performed as a consequence of the difficulty in interpreting the huge number of spectral peaks of the variability signal. Spectral analysis of tachograms of AF patients is commonly used to represent a white noise signal. However, in one study published a few years ago, a respiration-related component in addition to a predominant very low-frequency component has been recognized by subjecting patients with chronic AF to sequential autonomic blockade.[79]

These considerations of complex determinants of ventricular rate during AF may explain why HRV analysis has mostly been applied to evaluate autonomic modulation of the sinus node during sinus rhythm before AF onset and after cardioversion rather than on ventricular response during the arrhythmia.

Signs of enhanced parasympathetic activity or of sympathetic activation have been reported by different authors[80–85] who analysed short-term HRV before paroxysmal AF onset. One common finding was the detection of transient alterations of neural modulatory activities before the arrhythmic event. Timing of arrhythmias onset, age, and clinical characteristics of subjects enrolled in the studies are some of the factors that have been advocated to explain the difference in autonomic parameters before AF onset. In more detail, Bettoni and Zimmerman[84] suggested that an early increase in adrenergic tone was followed by late parasympathetic activation buffering the adrenergic predominance. More recently, Lombardi et al.[85] reported that signs of a predominant sympathetic and reduced vagal modulation of the sinus node were detectable in most paroxysmal AF episodes that started during the daytime and were characterized by the presence of atrial ectopies, whereas a more physiological autonomic modulation of the sinus node was associated with spontaneous recovery of sinus rhythm. Vagal predominance was detectable in ~30% of cases mainly occurring during night-time.

The prognostic value of HRV for predicting arrhythmia recurrence after successful cardioversion has also been analysed. Signs of increased sympathetic and reduced vagal modulation (LF/HF ratio >2) at the time of discharge after successful cardioversion were associated with early but not late AF recurrence.[66] In contrast, persistently higher values of 24 h time domain parameters reflecting vagal modulation have been reported in patients with AF recurrences after internal cardioversion performed under general anaesthesia.[86] Differences in patient population, pharmacological treatment, recording conditions, and/or type of analysis may explain why either sympathetic activation or enhanced vagal modulation may be associated with AF recurrences. It seems, therefore, that similar to what has been described to occur before paroxysmal AF

Table 4 Methods for analysis of ventricular response

Method	Objective	Main output	Pathophysiological meaning
HRV	Evaluation of autonomic tone	Selected time domain parameters (SDNN, rMSSD, pNN50)	Autonomic modulation of sinus node
		Selected frequency domain parameters (TP, VLF, LF, HF, LF/HF)	
RR-interval histogram analysis (heart-rate stratified)	Evaluation of AV node physiology	Morphology of RR distribution (uni-, bi-, or multimodal)	Presence of dual AV nodal physiology
		PV: location of dominant RR-interval for fast (f) and slow (s) RR population	Refractoriness of fast [PV(f)] and slow [PV(s)] AV pathway
Lorenz plots	Evaluation of AV node physiology and concealed conduction	LE slope: slope of the regression line on the lower envelope	Cycle-length-dependent function of AV node refractoriness
		LE1.0: 1.0 s intercept of the regression line on the lower envelope	
		Scattering index: degree of scatter above the lower envelope	Concealed conduction
		Mesor, amplitude, acrophase, significance of rhythm for circadian variation of LE slope, LE1.0, scattering index	Autonomic modulation of AV node physiology and concealed conduction
		Presence of RR-interval clustering	Organization of atrial fibrillatory activity
Non-linear dynamics	Evaluation of ventricular response dynamics	ApEN Regularity index	Short-term cardiac regulation, predictability (recurrences) of short sequences of RR intervals
		$1/f$ power law behaviour	Long-term regulatory mechanism and modulation of VR

onset, transient alteration of autonomic modulation rather than a specific autonomic change seems to favour both arrhythmia onset and recurrence.

As to the changes in RR intervals during AF, it must be recalled that in the electrophysiology laboratory, slowing or pseudo-regularization of atrial activity often precedes spontaneous termination of induced AF episodes. To evaluate whether such a phenomenon could also occur in the clinical setting, Lombardi *et al.*[85] analysed RR intervals during the initial, central, and final part of paroxysmal AF episodes, with the assumption that a less disorganized atrial activity could be reflected by a pseudo-regularization of ventricular response. No changes in mean RR intervals, variance, and coefficient of variation of RR intervals were observed in the 5 min preceding spontaneous recovery of sinus rhythm in comparison with the initial and central parts of the arrhythmic episode.

However, using different techniques for expressing HRV during AF, this method has been found useful for providing information about risk in patients with AF and severe mitral regurgitation[87] as well as in the setting of advanced heart failure,[77,88] but may also reflect a general risk during AF.[89] As with reduced HRV in sinus rhythm, reduced ventricular response irregularity during AF has been found to be associated with increased cardiac mortality in chronic AF patients.[89]

RR-interval histogram analysis
When constructing RR-interval histograms obtained from Holter recordings with persistent AF, uni-, bi-, or multimodal RR distribution patterns can be found.[90–93] In up to 55% of patients, the ventricular response during AF shows two separate populations of RR intervals already at naked eye inspection of the ECG.[94] A special technique for displaying and analysing RR-interval histograms is the so-called heart rate stratified histogram analysis (HRSH). RR-interval histograms are reconstructed on the basis of mean heart rate of the analysed ECG segment that contains 20[95]–64[90,91] beats (*Figure 3*). Using this technique, a bimodal RR-interval distribution was found in 26 of 32 individuals (81%) with persistent AF.[91] Prerequisites for this demonstration are the clustering of RR-interval distributions by average ventricular rate and enough observations over a span of ventricular rates reaching at least 120 b.p.m.[90] The advantage of this technique over simple RR-interval histogram analysis is first of all that the RR distribution is equally well visualized at all heart rate levels and comparable between them. Secondly, the identification of multiple RR populations is markedly improved by this technique.

The two different RR populations are suggested to correspond to conduction along two different atrio-nodal conduction routes.[90] Interestingly, in individuals with AF, in whom the HRSH method was performed before and following surgical incision in the right atrium, this intervention constantly changed the pattern of RR distribution during AF, including the transformation from a unimodal to a bimodal pattern.[96] A tempting interpretation of this finding is that the timing between the fibrillatory signals reaching the different atrio-nodal inputs has been changed by the

Determination of AV-nodal conduction properties using heart rate-stratified RR histogram analysis
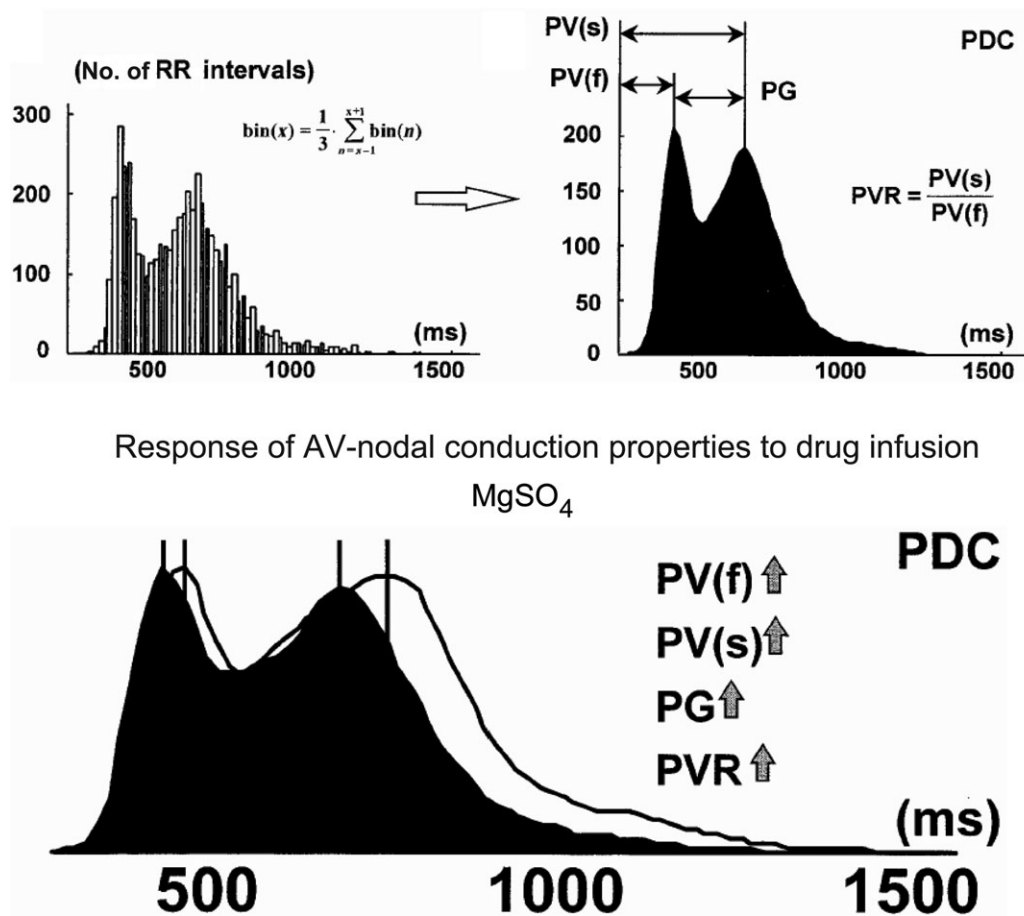

Response of AV-nodal conduction properties to drug infusion

Figure 3 Illustration of the HRSH method (top) and its application for monitoring drug effects (bottom).[95] Top: each QRS complex is identified, and all RR intervals in the recording are calculated. The entire series of RR is then divided into sequences of 20 individual RR intervals, and one-step movements (i.e. 1–21, 2–22) create the sequences in which the average heart rate is calculated. All individual RR intervals within sequences are then pooled into histograms at different heart-rate levels, calculated from the average of 20 consecutive RR intervals. Thus, RR intervals with the same average heart rate are pooled into the same histogram. At lower heart-rate levels, the peak corresponding to the longer RR-interval population is dominant. As the heart rate increases, the peak of the shorter RR-interval population will increase and become dominant. The heart-rate level at which a change in peak dominance (PDC) occurs is used for further analysis (left). By applying the formula shown (left), the original histogram smoothes and the position of the two RR-interval populations [PV(s) and PV(f)] and derived variables (PG, PVR) can be estimated (right). Bottom: the two superimposed histograms obtained at PDC exhibit changes in both RR populations induced by MgSO$_4$ infusion. However, conduction delay in the longer RR population was more pronounced than in the shorter RR population, indicating that the two RR populations were differently affected by the drug. PDC, peak dominance change; PV(s), peak value of the longer RR-interval population; PV(f), peak value of the shorter RR-interval population; PG, peak gap (difference between the two RR populations); PVR, peak value ratio (quotient of the longer and shorter RR-interval populations.

incision. In fact, later pacing and conduction studies in atrio-nodal tissue preparations speak in favour of this interpretation.[97] RR-interval distribution had a sensitivity of 88% and a specificity of 80% for identifying dual AV node physiology, provided dual pathways could be independently confirmed.[92]

Some investigators,[94,98] moreover, analysed the correlation between RR-interval distribution pattern and efficacy of radiofrequency modification of the AV node in patients with chronic AF. These authors observed that this procedure was more effective in controlling ventricular response in patients with bimodal distribution of RR-interval pattern. Interference with posterior atrio-nodal input is considered

to be the prevailing mechanism of rate control in these patients.

Finally, the HRSH analysis has been applied to analyse the effects of magnesium on AV nodal conduction. In this study, magnesium at high concentrations caused a delay in both the shorter and longer RR intervals, with a more pronounced conduction delay in the longer RR population, indicating a different effect on the two corresponding AV nodal pathways (*Figure 3*).[95]

Rarely, RR-interval histograms disclose more than two different and well-defined RR populations,[93] which may be due to nodal escape rhythms[91] and/or to any additional atrio-nodal inputs, for example from the left atrium.[99]

Determination of AV-nodal conduction properties
using Lorenz plots

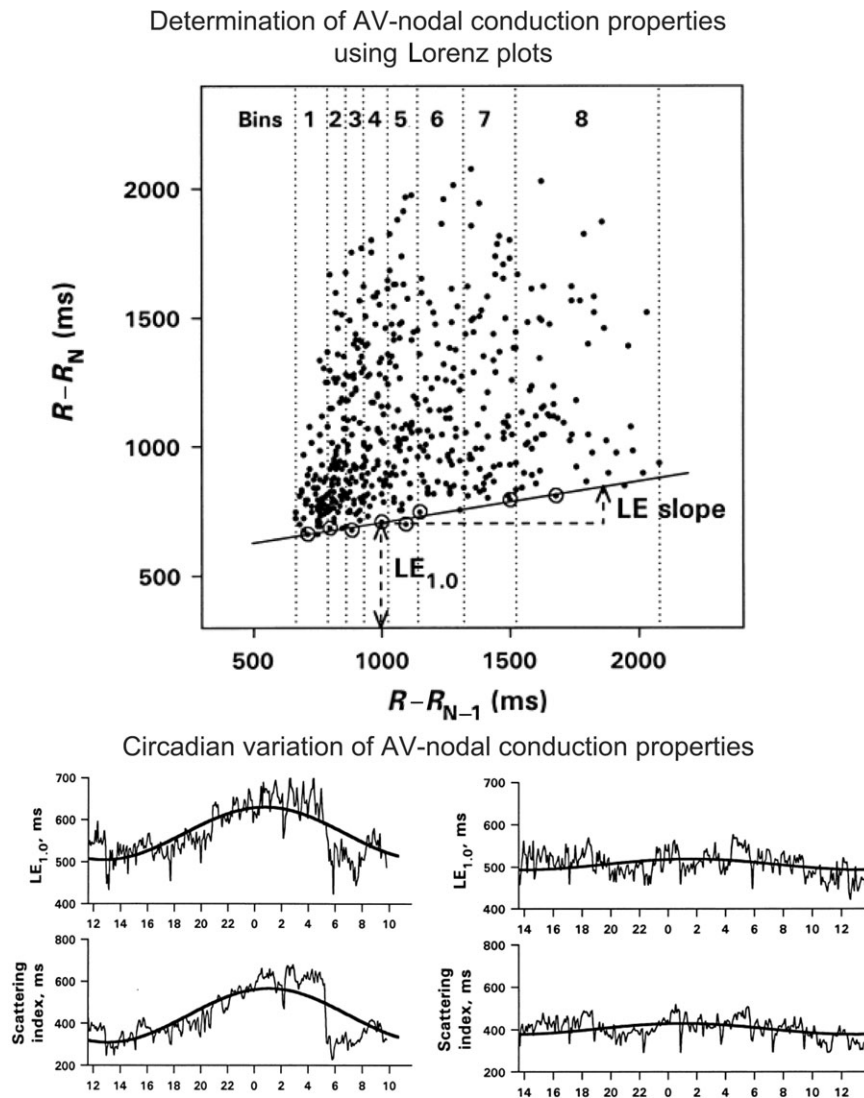Circadian variation of AV-nodal conduction properties

Figure 4 Illustration of Lorenz plot analysis (top) and its application for monitoring circadian rhythms (bottom).[77] Top: Lorenz plots of 512 successive RR intervals in AF and linear regression of the lower envelope of the plots. Dotted vertical lines indicate the separations between bins, each of which includes 64 points of the plots. Circled points indicate the minimal values for individual bins. The solid line indicates the regression line on the minimal values. The following variables can be obtained: (i) slope of the regression line on the lower envelope (LE slope); (ii) 1.0 s intercept of the regression line on the lower envelope ($LE_{1.0}$); and (iii) the degree of scatter above the lower envelope calculated as the root mean square difference of RR intervals from the regression line on the lower envelope (scattering index). Bottom: circadian variations in variables obtained from the Lorenz plot analysis, with a time resolution of 5 min in a patient with chronic AF without heart failure (left) and with heart failure (right). Thick solid lines indicate the least square cosine curves fitted to the circadian variation of individual variables.

Lorenz plots

In Lorenz plots, individual RR intervals are plotted against the corresponding preceding RR interval. In this way, it is possible to identify (i) the lower envelope of the Lorenz plot as a measure of the cycle-length-dependent function of the functional refractory period of the AV node[100] and (ii) the degree of scatter as a measure of concealed conduction (*Figure 4*).

By applying Lorenz plot analysis to 24 h Holter recordings of 48 patients with chronic AF, it was suggested that both AV node refractoriness and the degree of concealed AV conduction during AF may show a circadian rhythm, but that these circadian rhythms may be attenuated in patients with heart failure (*Figure 4*).[77] In a similar vein, sleep apnoea has very recently been shown to entrain the ventricular response to

AF by inducing rhythmic oscillations in AV node refractoriness and the degree of concealed conduction.[101] These findings point to the possibility of obtaining information concerning altered autonomic control of the RR intervals in patients with AF (and heart failure or other disease) with this simple technique.

Lorenz plots of RR intervals from 24 h recordings sometimes exhibited two separate sectors of RR intervals.[102] When this occurred, the RR-interval histogram disclosed a bimodal distribution in ~40% of patients. It should be noted, however, that these RR-interval histograms were not stratified for different average heart rates, a method which, as pointed out before, markedly increases the identification of more than one RR population.[91] It has been suggested that Lorenz plots with two sectors hold

information of the functional refractory periods of each of the two conduction routes.[102] Interestingly, the circadian variability of the fast pathway functional refractoriness was more pronounced than that of the slow pathway.

By adding the number of occurrences of RR-interval pairs, a three-dimensional Lorenz plot can be constructed, in which clusters of RR intervals can be identified. Moreover, in AF patients whose RR intervals were clustered (47% of 66 patients), electrical cardioversion was more effective in restoring sinus rhythm, and also, those patients had a higher likelihood of remaining in sinus rhythm than their counterparts without well-defined clusters.[103] It is speculated that RR-interval clustering represents a relatively high degree of organization of atrial fibrillatory activity.

Non-linear dynamics

New insights into the inner dynamics of ventricular response during AF have recently been obtained using non-linear analysis methods. Even if ventricular responses during AF have been widely described as a non-harmonic, totally random process,[104] glimpses of underlying order have been recently documented in both long-term (hours)[105] and short-term (few beats) dynamics of RR series.[106] These findings support pioneering and sporadic observations of non-randomness in animals[107] and humans[108] during AF.

The spectral characteristics of 24 h RR-interval series in patients with chronic AF revealed the presence of two correlation ranges[105]: a flat spectrum was observed at higher frequencies (>0.005 Hz), whereas the long-term spectral components (long-range correlation) were characterized by a $1/f$ power law behaviour. The long-range correlation was similar to that observed in normal sinus rhythm, suggesting that during AF, long-term regulatory mechanisms are still effective in modulating ventricular responses. These findings are in agreement with the observation of circadian rhythms in patients with chronic AF.[109]

Non-random features appear also when ventricular response dynamics are explored on a short-term basis. Stein et al.[106] developed a non-linear forecasting algorithm to search for short-term predictability in the ventricular responses during AF. The authors observed a weak predictability (lasting for a few beats), which was explained as the evidence of autonomic modulation of the AV node buried by a random sequence of impulses due to multiple circulating wavefronts. Patterns of predictability were also assessed using approximate entropy (ApEn) and regularity measurements in non-terminating and terminating AF episodes, with a decreased regularity index and increased ApEn in self-terminating episodes.[110]

Altered complexity and correlation properties of ventricular activation were investigated before the onset of AF episodes. A reduction of ApEn was observed prior the onset of AF, and the values were significantly lower than in healthy controls.[111] More recently, analysis of heart rate turbulence (i.e. the short-term oscillation of heart rate after a premature beat) revealed different patterns before AF onset. In particular, the turbulence onset was significantly less negative during the 1 h preceding AF than during non-AF hours.[112]

Taken together, the different methods used for exploring and quantifying the ventricular response during AF have all shown a certain degree of usefulness, either in scientific explorations of AV nodal function or in selected clinical questions. Several additional issues remain to be further clarified. Most importantly, the RR distribution pattern is not only a likely sign of conduction via different AV nodal routes, but primarily affected by the atrial fibrillatory input to the AV node. Hence, further exploration of how these factors may be individually mirrored within different methods is needed.

Conclusions

Non-invasive characterization of atrial fibrillatory activity and ventricular response can be performed from the surface ECG in AF patients using different signal processing techniques. ECG analysis of AF has been suggested for identification of underlying AF pathomechanisms and prediction of therapy efficacy (drug-induced conversion, maintenance of sinus rhythm, selecting antiarrhythmic drugs, identifying candidates for non-pharmacological AF therapy). However, further larger studies are necessary to determine the role of these techniques in different AF management strategies in order to select and time the appropriate therapy for the individual patient.

Acknowledgements

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