Atrial fibrillatory rate in the clinical context: natural course and prediction of intervention outcome

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Introduction

Shortening of atrial refractory period during atrial fibrillation (AF) has been considered a hallmark of atrial electrical remodelling since early animal experiments[1] and was subsequently confirmed in patients undergoing interventional electrophysiological examinations and catheter ablation for AF.[2] The atrial fibrillatory cycle length (AFCL), which is intimately related to the atrial fibrillatory rate (AFR), is generally accepted as a surrogate marker for local refractoriness. The value of using AFCL to monitor the progress of atrial ablation therapy has been demonstrated; gradual prolongation of AFCL has consistently been observed to precede arrhythmia termination during paroxysmal or permanent AF ablation.[3]

Since the very first electrocardiographic registrations of AF in patients, such as those made by Sir Thomas Lewis in the early 20th century,[4] atrial electrical activity could be clearly distinguished between QRST complexes as fibrillatory waves, or f-waves, which in some patients with the most visible and high-amplitude f-wave could even be characterized by a certain frequency or rate analogous to ventricular rate.

Advancements in our understanding of AF electrophysiology that occurred during the second half of the 20th century, along with technical development of signal processing techniques, have raised interest in analysis of surface electrocardiogram (ECG) during AF and resulted in methodology for detailed characterization of atrial fibrillatory process.[5,6] The methodology, based on recognizing atrial fibrillatory activity from surface ECG and reviewed in the present paper, has undergone significant modifications over time to improve our ability to non-invasively characterize the AF substrate and explore its potential for monitoring therapeutic interventions for AF and predicting their effect.

Today, AFR is the key characteristic of the fibrillatory process, repeatedly validated against intracardiac recordings and extensively studied in clinical contexts.[5-7] Other measures of AF complexity and organization have been proposed, including measures derived

from frequency analysis, such as the exponential decay, or from non-linear analysis, such as the sample entropy. However, these measures have been shown to be highly correlated to AFR.[8−11]

This paper seeks to provide an overview of clinical data accumulated since the method was introduced in 1998, and to present the current state of knowledge regarding ECG-derived AFR: its time course and dynamics, clinical factors affecting AFR, and available evidence of its value in the clinical context.

Methodology

Lead systems

The standard 12-lead ECG continues to be the preferred lead system for AFR analysis, although the analysis is usually confined to V1 due to its proximity to the right atrium. Since this lead system is focused on ventricular activity, the rarely used posterior leads, i.e. V7, V8, and V9, have been studied and found to better reflect left atrial (LA) events than does the 12-lead ECG.[12] A number of novel lead systems have been proposed which are specially designed to reflect atrial activity (atriocardiography),[13,14] although none of these have been considered in other clinical studies.

Atrial activity extraction

Two main approaches have been pursued for extracting atrial activity—namely, subtracting average heartbeat from the ECG and statistically separating atrial and ventricular activities in the ECG.[15] Both of these approaches involve variants, which extract atrial activity using either single- or multiple-lead recordings.

Average beat subtraction relies on the fact that atrial activity is uncoupled to ventricular activity during AF. This technique has been widely applied in clinical studies, probably due to the ease of implementation as well as interpretation. Since average beat subtraction is a single-lead technique, its performance deteriorates when there are alterations in the electrical axis, causing large QRST-related residuals in the resulting atrial signal. Several efforts have been made to mitigate this problem, spatiotemporal QRST cancellation being the best-known. With this technique, residuals are suppressed through subtracting an average beat computed as a weighted combination of the average beat of the lead subjected to analysis with the average beats of adjacent leads. We note that averaging techniques are unsuitable for atrial activity extraction in very short-duration ECG signals or in signals with sporadic ectopic beats.

The other main approach of extracting atrial activity makes use of the property that atrial and ventricular activities originate from different bioelectrical sources and thus are characterized by different statistical characteristics. With the multi-lead ECG as the starting point, source separation has been accomplished by principal component analysis and independent component analysis. Both of these techniques produce a global atrial signal with contributions from all processed leads, and thus f-wave morphology does not correspond to any of the leads. The separation approach is well-suited for analysis of short-duration recordings, whereas its suitability for analysing long-term ECG recordings remains to be established.

The search for better-performing extraction techniques has continued since the review by Bollmann et al.[16] Several methods have been described which incorporate advanced signal processing techniques to achieve better performance, such as the use of separate averages for the QRS complex and the T-wave,[17] singular value decomposition,[18] constrained independent component analysis,[19] event synchronous adaptive filtering,[20] and an echo state network.[21] It remains to be demonstrated whether the advantages of these techniques foster their use in clinical studies.

Atrial fibrillatory rate determination

Once the atrial signal has been extracted, its power spectrum is computed and the largest peak in the interval 3−12 Hz is determined. The location of this spectral peak (also known as the dominant atrial frequency) is then converted into AFR, which serves as a measure of the average rate for the analysed time interval. Of the various techniques used for computing the power spectrum, the periodogram-based technique is the most common. With this technique, the atrial signal is divided into overlapping segments, each segment is then windowed, and the desired power spectrum is computed by averaging the power spectra of all segments to reduce variance.[22]

It is well-known that atrial frequency can vary quite substantially over time, both when observed spontaneously or when associated with an intervention such as administration of a drug. While a simplistic approach to tracking such variations is to compute the AFR in successive time intervals, it is preferable to consider methods that are specifically designed for characterizing temporal variations in spectral properties of the atrial signal. A review of such methods can be found elsewhere.[22]

Figure 1 shows an example of an ECG signal recorded during a head-up tilt-table test, with the corresponding atrial signal extracted with spatiotemporal QRST cancellation and its power spectrum where a large peak can be identified at ∼5 Hz (the dominant atrial frequency). Finally, the trend of AFR over the whole tilt-up stress test consisting of 10 min of rest and 10 min of tilt is shown: an increase in AFR is observed during tilt.[23]

Most studies on AFR have analysed resting ECG recordings with good signal quality. However, it is of considerable interest to study AFR in patients with paroxysmal or persistent AF over extended time periods, necessitating that ambulatory ECGs are recorded. Since such long-term data often are of poor quality, it is crucial to employ robust signal processing techniques so that reliable results can be produced even in the presence of heavy noise and artefacts. Robust techniques have been proposed as an integral part of time−frequency analysis, either by ensuring that the power spectrum of the atrial signal contains the peaks characteristic of AF[24] or that the trend of the AFR values makes no drastic jumps (most likely caused by noise and/or artefacts).[25] Further research is needed to ensure reliability of long-term analysis.

Since few commercial systems offer atrial activity extraction, a straightforward approach is to determine AFR by simply measuring the distance between successive f-waves in the TQ interval. Such measurements can be made manually, although they are associated with poor reproducibility. Another approach is to fill the QT intervals with interpolated samples, and then compute the power spectrum[26]—this approach seems to determine AFR reliably under certain conditions. However, the availability of additional samples during the QRST interval certainly leads to improved spectral estimation and avoids the problem of vanishing TQ intervals at high heart rates.
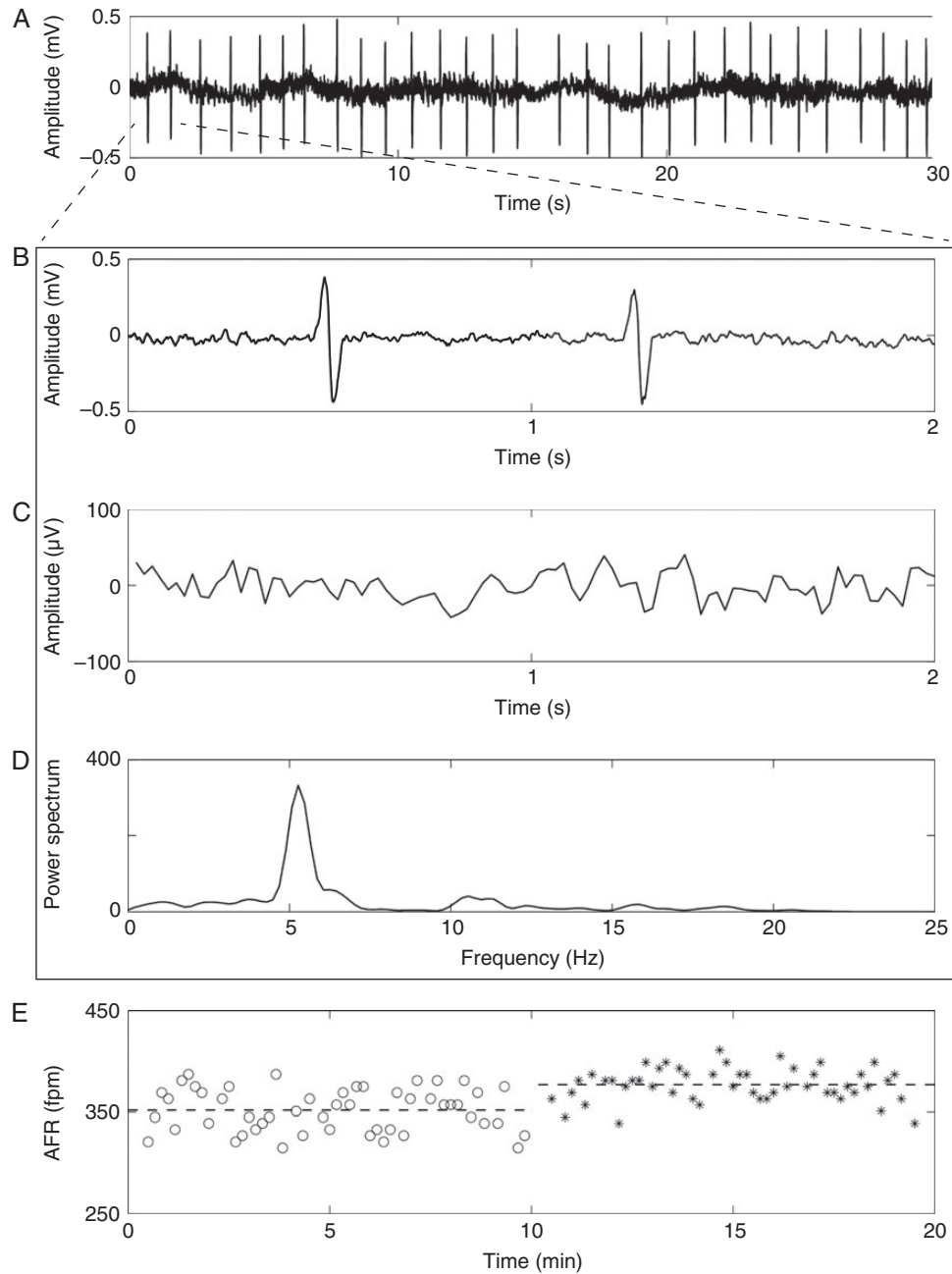
Figure 1 (*A*) Electrocardiogram signal recorded during a tilt-up stress test (only 30 s during rest are shown for sake of clarity); (*B*) 2 s ECG,(*C*) atrial signal extracted with spatiotemporal QRST cancellation from the ECG in (*B*); (*D*) power spectrum where a large peak can be identified at ~5 Hz (the dominant atrial frequency); (*E*) trend of AFR over the whole tilt-up stress test, consisting of 10 min of rest (circles) and 10 min of tilt (stars): an increase in AFR can be noted during tilt (dashed lines represent the mean values of the two phases).

How stable is atrial fibrillatory rate?

Knowledge of a biomarker's stability and temporal variation is essential for interpreting its biological value and applicability for clinical research and practice. Early during the method development and validation, short-term intra-individual variability of AFR was assessed and was shown to be acceptable.[5,6] Repeated daily measurements from patients with persistent or permanent AF (without any changes in the medications) were taken during the same time frame and under similar conditions. These measurements showed insignificant AFR variability,[27] which could be observed in 10 s long ECG segments.[28] In a later study, Holmqvist *et al.*[29] showed that 10 s long snapshot ECG strips contain essentially the same information on AFR as 1 min long recordings most widely used previously, with the mean difference between the two measurements being ~1% of AFR value.

Atrial fibrillatory rate at spontaneous atrial fibrillation onset

It should be emphasized that the mere feasibility of studies on spontaneous AF episodes during the very first beats at AF onset is entirely due to the advancements in ECG processing, since electrophysiological assessment of the spontaneously occurring AF episodes is possible in practice only in patients with implanted devices that have the capability of recording and storing atrial electrograms.

In agreement with the concept that atrial refractoriness shortens and AF accelerates as a consequence of the AF itself,[1] AFR behaviour at onset of spontaneous AF paroxysms follows that pattern. Atrial fibrillatory rate acceleration during the first few minutes after the onset of an AF paroxysm has been repeatedly reported for spontaneous AF recorded by Holter[30,31] and was also observed in induced AF.[32] Most patients included in those studies had relatively short AF episodes. However, it is unknown to what extent the time course of AFR acceleration reflects the underlying substrate and the propensity for AF to persist. However, in a recent study done on a small group of patients who developed AF with the duration of several hours, i.e. the sort of AF that may prompt patients to contact healthcare facilities, AFR increased over the course of 3–4 h, whereafter it reached a plateau,[33] thus illustrating the importance of knowing the time from AF onset when interpreting AFR values during the first hours of AF.
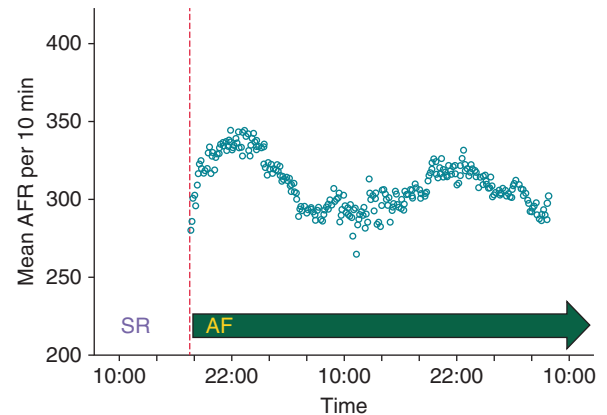
Atrial fibrillatory rate at atrial fibrillation termination

Atrial fibrillatory rate changes at AF termination are likely to be rather sudden, at least when short-lasting AF paroxysms detected by Holter monitoring are concerned. No AFR slowing was observed in a study that assessed AFR using a 10 s time window,[5] but a decrease was detectable just before AF termination when AFR was assessed on a second-by-second basis.[34] It is unknown whether the same can be extrapolated to long-lasting AF episodes. In a study using implantable cardiac monitors (ICM), we observed that AFR decrease prior to spontaneous termination can be seen during a considerably longer 1–2 h long period.[33]

An interesting observation was made by Fujiki et al.,[35] who reported that AFR slowing during 10 min prior to spontaneous AF termination was only observed in patients who converted to sinus rhythm during morning hours, but was not seen in those in whom sinus rhythm was restored in the afternoon or evening. These results suggest that electrophysiological mechanisms of AF termination may be different depending on time of day, and that AF termination in the morning may be caused by a vagolytic autonomic balance.

Circadian dynamics of atrial fibrillatory rate

Distinct circadian dynamics of AFR were observed in patients with long-standing AF using Holter monitoring. Atrial fibrillatory rate demonstrated a significant decrease at night and an increase during the morning hours, reaching its maximum during the afternoon hours.[36] This was reproduced repeatedly.[37,38] These studies, however, have been constrained to 24 h long Holter registrations while longer recordings are likely to provide a better insight in circadian behaviour of atrial electrophysiological characteristics during AF. Finally, circadian variation in AFR may also be observed early in the course of a persistent AF episode, as shown in the *Figure 2* based on data from a patient with ICM.[33]

Figure 2 Circadian oscillations of AFR clearly distinguishable starting from the first hours of spontaneous AF episode lasting over 38 h (AF was still ongoing when registration was ended). Atrial fibrillatory rate was derived from long-term ECG monitoring on a minute-by-minute basis and averaged by 10 min.[32] AF, atrial fibrillation; AFR, atrial fibrillatory rate in fpm (fibrillations per minute); SR, sinus rhythm.

Impact of the autonomic nervous system

The autonomic nervous system affects atrial electrical properties, and, as shown in several studies reviewed below, it may have a significant impact on AFR. Carotid sinus massage that is supposed to induce a vagal stimulation resulted in variable response among 19 patients included in a study by Bollmann et al.,[39] although most of the patients demonstrated reproducible decrease in AFR values. Parasympathetic modulation of atrial refractory period caused cyclical fluctuations in AFR as reported by studies on patients with permanent AF using controlled respiration.[40,41]

Reproducible AFR increase during head-up tilt-test has been reported earlier[23,42] and was recently reproduced by our group in a study that included the head-down phase in the tilt-test protocol. As expected, AFR decreased significantly during the head-down phase.[43]

Exercise-induced adrenergic activation and reduced parasympathetic modulation reveal significant inter-individual variability in AFR response, varying from no response at all to significant increase—or decrease—in AFR as a result of exercise.[44] Notably, patients with high baseline AFR were less likely to demonstrate AFR modification during stress testing. Based on the limited data available, the authors hypothesized that AFR's unresponsiveness to exercise may be predictive of AF recurrences after sinus rhythm restoration.

Long-term evolution of atrial fibrillatory rate

Atrial fibrillation progression is associated with atrial remodelling that leads to progressive AFCL shortening and AF acceleration. Invasive data in patients with AF consistently demonstrate shorter AFCL in patients with paroxysmal AF as compared with patients with persistent or long-standing AF,[3,45] which was in agreement with AFR determined non-invasively.[5]

Sasaki et al. suggested the existence of a 'nadir' AFCL value, i.e. the shortest AFCL that atrial remodelling can lead to in a patient with

persistent AF. The time lapse required to reach this point likely depends on a variety of clinical factors. However, it is likely to be within the time frame of 1.5–2 years when AFCL reaches a plateau at the level of 120–130 ms (500 fpm) as suggested by Haissaguerre et al.[3] Once the AFR plateau is reached, AFR may remain stable for several years, as we have observed by analysing ECG recordings taken at our clinic during annual visits from patients with permanent AF (Figure 3).

Clinical factors affecting atrial fibrillatory rate

Apart from being a marker of electrical remodelling and a surrogate measure of atrial refractoriness, a number of clinical factors may significantly affect AFR in patients with AF.

The association between gender and AFR has not been observed in initial small-cohort studies, although more recent larger studies have reported significant association between female gender and lower AFR.[46,47] Whether this association can be partly related to differences in heart size between men and women is not known; however, gender-related differences in AFR reported by these two studies were independent from LA diameter as an index of LA size.

Available data consistently demonstrate a highly significant negative correlation between age and AFR, which has been documented in patients with paroxysmal[8,47] and persistent AF.[46] In a recent study, our group observed the same phenomenon in patients with persistent AF and mild-to-moderate congestive heart failure.[48] This association may be explained by age-related increase in atrial fibrosis, which may lead to extension of boundaries in atrial myocardium, thus hampering the propagation of excitation waves and slowing down the

atrial fibrillatory process. This hypothesis is supported by anecdotal cases of spontaneous arrhythmia termination after several years of permanent AF occasionally observed in clinical practice.

Direct evidence of negative correlation between the extent of fibrosis and AFR was recently reported in a study by Swartz et al.,[49] who assessed AFR from the surface ECG in patients with AF undergoing open-heart surgery; they also examined the histology of atrial appendage biopsies. This concept is further supported by studies showing that lower AFR has been consistently associated with the presence of structural heart diseases[3,47] and has correlated with indices of congestive heart failure severity.[48]

Left atrial enlargement was reported as being another factor possibly leading to AFR slowing;[46] however, this association is likely to be observed in patients with moderate LA enlargement. The association was not found in either patients with short-duration paroxysmal AF and normal-size LA[47] or in patients with severe LA dilatation AF associated with congestive heart failure.[48]

Finally, genetic variants affecting the function of ion channels present in atrial myocardium may affect AFR. In a small-size study, an association between a common variant in a potassium channel KCNE1 and a higher AFR in patients with persistent AF was reported.[50] These findings, however, were not reproduced in another study on patients with lone AF in whom no association was reported between AFR and the presence of eight common single-nucleotide polymorphisms discovered in earlier genome-wide association studies.[51]

Effects of antiarrhythmic drugs
Monitoring of drug effect

Class I and III drugs used for rhythm control have been shown to increase atrial cycle length that corresponds to increased refractoriness of the atrial myocardium.[52] Non-invasive AFR assessment may offer a way to monitor antiarrhythmic drug effects, which may be particularly useful in drug development, as it avoids the complexity of invasive electrophysiological testing and offers a valuable complement to pharmacokinetic studies. Feasibility of non-invasive monitoring of drug effects during AF has been shown previously.[35,53] Figure 4 illustrates dynamic changes occurring to the residual atrial signal and AFR derived from surface ECG (lead V1) during intravenous (i.v.) infusion of vernakalant for conversion of persistent AF.

Recently, the same methodology was used in a Phase II study of an antiarrhythmic compound aimed at AF conversion. The study showed significant inter-individual differences in AFR response to drug administration closely linked to the drug's propensity for
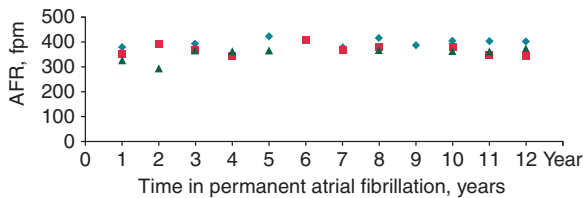
Figure 3 Long-term AFR dynamics in three patients with permanent AF derived from standard 12-lead ECG. Atrial fibrillatory rate assessment was based on 10 s long ECG recordings recorded at yearly visits to an outpatient clinic and stored in a digital ECG database.
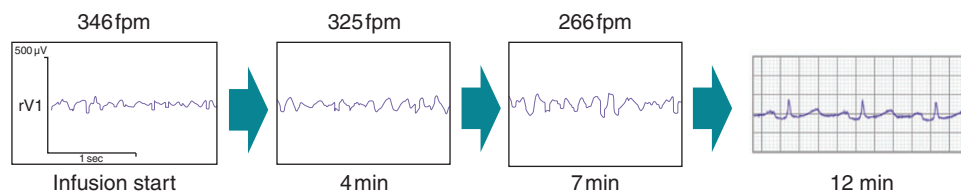
Figure 4 Subsequent changes in residual atrial signal observed during i.v. infusion of vernakalant for conversion of persistent AF. Observe gradual decrease in AFR (values in fpm above ECG tracings) and increased amplitude/organization of atrial activity prior to termination of the arrhythmia at the 12th minute of infusion.

converting AF.[54,55] A comparative study of the effects of dronedarone and amiodarone on AFR patients with persistent AF revealed significant differences in the magnitude of AFR reduction in favour of amiodarone, which may explain amiodarone's superiority in preventing recurring AF.[56]

Apart from traditional Class I and III drugs used for rhythm control, AFR reduction (although not associated with restoration of sinus rhythm) was observed after administering other cardioactive drugs, such as beta-blockers,[57,58] verapamil,[27] A1-receptor agonist tecadenoson,[57] and angiotensin-receptor blockade with candesartan.[46]

Atrial fibrillatory rate in prediction of intervention effect

Spontaneous conversion
In clinical practice, the ability to predict spontaneous conversion of AF to sinus rhythm, particularly in patients with recent-onset AF with tolerable symptoms, would be useful for planning cardioversion, and help to avoid interventions in patients prone to regaining sinus rhythm within a reasonable time frame. The proper stratification tool, however, is lacking at the moment.

Possible use of AFR for predicting spontaneous conversion of AF was suggested by initial observations of lower AFR in patients with short duration, rather than sustained AF episodes, either induced[5] or spontaneous.[34] Similar findings were reported in patients with new-onset AF,[8] and were further confirmed in an unselected cohort of patients with recent-onset AF (<48 h).[47] Both the latter clinical studies demonstrated surprisingly similar AFR cut-off values predictive of spontaneous conversion being <355 and <350 fpm, respectively.

Electrical cardioversion
Following initial small-cohort studies indicating a significant association between low AFR and higher likelihood of sinus rhythm maintenance after electrical cardioversion,[59,60] though not confirmed by other studies,[61] a larger-scale study was performed by Holmqvist *et al.*[29] which provided the first indicator of how AF episode duration may affect the significance of AFR as an interventional efficacy predictor. Although lower AFR appeared to be the strongest predictor of sinus rhythm maintenance after cardioversion in the entire cohort of 175 patients, the overlap in AFR values between those who relapsed in AF and those remaining in sinus rhythm at the end of follow-up was significant, and did not allow identification of any clinically useful cutoff. However, when only patients with AF duration shorter than 30 days were analysed, the separation between the groups became more distinct, and AFR > 384 fpm showed sensitivity of 79% and specificity of 80% when predicting AF relapse after electrical cardioversion (Table 1).

The importance of AF duration for interpreting the predictive value of AFR was further supported in more recent studies where AFR showed no association with sinus rhythm maintenance after cardioversion in patients with long-standing AF enrolled in the CAPRAF study.[46] A similar observation was made using invasively assessed AFCL in patients with long-lasting AF undergoing internal cardioversion.[62] A prospective evaluation of AFR as a non-invasive predictor of cardioversion effect is currently under way in the CASAF study (Cardioversion of Short-duration Atrial Fibrillation, ClinTrials.gov identifier NCT02112318).

Pharmacological conversion
Given the feasibility of drug effect monitoring using AFR decrease as a surrogate measure of antiarrhythmic effect, it has been tempting to assess AFR value for selecting candidates suitable for pharmacological, rather than electrical, cardioversion of AF. In this context, patient selection may be especially valuable since pharmaceutical cardioversion is much less efficient than electrical cardioversion, although pharmaceutical cardioversion is less demanding technically and requires no general anaesthesia. Early identification of patients, likely or unlikely to respond to an antiarrhythmic drug, is therefore expected to increase the success rate of pharmacological cardioversion in a properly selected population. However, published studies that would provide useful information are scarce (Table 2).

Low baseline AFR (<360 fpm) was associated with higher conversion rates following administration of oral flecainide[63] or i.v. ibutilide,[5] but could not be reproduced in another ibutilide study.[64] Furthermore, no association between baseline AFR and response to antiarrhythmic drug was observed in recent studies in patients with AF < 48 h using vernakalant[67] or in patients with several weeks-long AF who received combined potassium and sodium channel blocker AZD7009.[55] No association between baseline AFR and conversion rate was seen in bepridil-treated patients with long-standing AF.[65,66]

The value of AFR as a predictor of cardioversion effect is likely drug-specific, and may depend on the mechanism of action, interindividual variations in drug metabolism, and rate dependency of drug action. Some drugs express their maximal ion channel inhibitory effect at higher rate, such as vernakalant,[68] which can cause the drugs to be more effective in patients with faster AFR, i.e. those patients who are otherwise less likely to restore sinus rhythm.

Even though a 'snapshot' AFR at baseline does not seem to be a powerful predictor of antiarrhythmic drug effect, the magnitude and steepness of AFR decrease as an effect of drug administration was associated with AF conversion in some studies[55,64] although not in all,[5] thus illustrating the need for drug- and context-specific approaches to the use of AFR as a stratification marker. Clearly, more studies are needed, but non-invasive AFR estimation technology available today facilitates analysis on data coming from large-scale studies that can give answers to the questions we have today.

Catheter ablation
The value of AFR for predicting the effect of catheter ablation has not been widely studied. While there have been reports of association between AFCL and the effect of ablation,[3] the non-invasive approach to estimating AFCL was, to the best of our knowledge, only used in one study.[7] Together with long-standing AF duration, AFCL > 142 ms (corresponding to AFR < 422 fpm) has been an independent predictor of intraprocedural restoration of sinus rhythm as well as a predictor of freedom from AF during follow-up (hazard ratio = 6.0, 95% confidence interval: 2.0–18.5, $P = 0.001$).

Clinical summary and unresolved issues

The experience of using AFR in the clinical context provides important information on factors affecting AFR values in different

Table 1 Clinical studies, in which AFR was evaluated for prediction of sinus rhythm maintenance after electrical cardioversion

Study	n	Mean age (years)	AF duration	Lone AF (%)	LA diameter (mm)	AAD class I or III (%)	Mean AFR at baseline (fpm)	AFR threshold (fpm)	Comment
Bollmann et al.[59]	19	58	10 ± 2 months	31	45 ± 6	0	396 ± 66	420	Internal cardioversion: AFR ≥ 420 fpm is 64% sensitive and 88% specific for prediction of AF recurrence
Bollmann et al.[60]	44	62	18 ± 27 months	22	45 ± 5	100	393 ± 38	ND	All patients on AAD Class Ic or III; area under ROC curve for AFR 0.805; increased AFR predicts AF recurrence (β 0.029, $P = 0.021$)
Meurling et al. 2006[61]	37	69	5 [1−21] months[a]	71	44 ± 7	0	$392 - 378$[b]	NS	AFR alone not predictive
Holmqvist et al.[29]	175	68	94 [2−1044] days[a]	37	48 ± 7	9	383 ± 60	384	AFR > 384: OR = 3.2, CI 95%: 1.7−6.1, $P < 0.0001$ for AF relapse
Holmqvist et al.[29]	29	65	<30 dagar	55	46 ± 7	14	384 ± 70	384	AFR > 384: OR = 15, CI 95%: 2.4−89, $P = 0.003$ for AF relapse
Bollmann et al.[46]	124	65 vs. 63[c]	ND	51 − 44	46 ± 5	0	399 ± 48 to 402 ± 58	NS	No separation between survival curves in Kaplan−Meier analysis depending on AFR
Efremidis et al.[62]	99	63	22 ± 45 months	18	42 ± 6	43	330[b]	NS	Internal cardioversion

AAD, antiarrhythmic drugs; AF, atrial fibrillation; AFR, atrial fibrillatory rate; CI, confidence interval; fpm, fibrillations per minute; LA, left atrium; ND, no data; NS, not significant; OR, odds ration; ROC, receiver-operator characteristics curve.
[a]Median [range].
[b]Converted from AFCL (ms) to AFR (fpm).
[c]No value for the total study cohort, data presented on a per group basis.

Table 2 Clinical studies, in which AFR was evaluated for prediction of efficacy of pharmacological cardioversion

Study	AAD	N	Mean age (years)	AF duration	Lone AF	LA diameter (mm)	Mean AFR at baseline, fpm	AFR threshold, fpm	AFR drop rate or magnitude	Comment
Bollmann et al.[63]	Flecainide	18	64 ± 13	>24 h	38%	44 ± 5	372 ± 30	360	ND	AFR < 360 fpm predicted conversion to sinus rhythm with Se 89% and Sp 78%
Bollmann et al.[5]	Ibutilide	15	ND	11 vs. 14 days[a]	45%	46 ± 5	338 ± 55 to 436 ± 67[b]	360	−	AFR < 360: 100% conversion vs. >360 fpm: 29% conversion. No difference in magnitude of slowing between responders and non-responders
Schwartz and Langberg[64]	Ibutilide	19	56 ± 16	8 patients <24 h, 3 patients <1 month, 8 patients >1 month	ND	ND	350 ± 62	NS	+	NS difference between baseline AFR in responders vs. non-responders, but the rate of AFR decrease was faster in responders
Fujiki et al.[65]	Bepridil	32	61 ± 8	49 months 69% >3 months	ND	ND	405 − 384[b,c]	NS	+	NS difference between baseline AFR in responders vs. non-responders. The magnitude of AFR decrease was greater in responders
Fujiki et al.[66]	Bepridil	23	59 ± 10	49 months, all >1 month	26%	44 ± 6 to 46 ± 5[a]	394−422−431[a,c]	NS	+	NS difference between baseline AFR in responders vs. non-responders. The rate of AFR decrease was faster in responders
Aunes-Jansson et al.[54]	AZD7009	70	63 ± 11	33 vs. 44 days[a]	ND	LA area: 22 ± 6 vs. 27 ± 6 cm^2[a]	393 ± 59 to 400 ± 56[b]	NS	+	NS difference between baseline AFR in responders vs. non-responders. The rate of AFR decrease was faster in responders
Mochalina et al., 2014[67]	Vernakalant	72	63 [23−87][d]	<48 h	66%	>50 mm in 45%	350 ± 60	NS	ND	

AAD, antiarrhythmic drugs; AF, atrial fibrillation; AFR, atrial fibrillatory rate; fpm, fibrillations per minute; ND, no data; NS, not significant.

[a]No value for the total study cohort, data presented on a per group basis

[b]Responders vs. non-responders.

[c]Converted from AFCL (ms) to AFR (fpm); ' + '—significant association between steepness or magnitude of AFR decrease and propensity to restoration of sinus rhythm; ' − '—no association between the steepness or magnitude of AFR decrease and propensity to restoration of sinus rhythm.

[d]Median [interquartile range].

populations, and forms realistic expectations concerning this non-invasive ECG-derived characteristic of the atrial fibrillatory process:

- Atrial fibrillatory rate demonstrates that short-time dynamics during the first hours of AF episodes are affected by autonomic stimulation and a number of medications, including medications that are not traditional Class I and III antiarrhythmic drugs, for which AFR decrease would be an expected sign of therapeutic effect.
- Progression of atrial structural remodelling and fibrosis due to ageing, progression of underlying structural heart disease or to AF itself,[69] is likely to slow down AFR over time; however, there are currently no longitudinal studies that would prove this hypothesis.
- Using AFR as a marker to predict the intervention effect is likely to be most valuable for patients with shorter AF duration and minimal structural remodelling, because in this patient group AFR is presumably affected by the degree of atrial electrical remodelling, and, to a lesser extent, affected by structural changes in the atrial myocardium, which are likely to reduce AFR due to increased atrial fibrosis.
- Atrial fibrillatory rate reference values are therefore likely to be clinical context-specific, which needs to be considered in planning prospective follow-up clinical studies that are increasingly needed to introduce this AF complexity measure in clinical decision-making.

Conclusion

In conclusion, AFR is a promising, easily available AF characteristic that can be derived from the conventional surface ECG. It is clearly a useful tool for monitoring drug effects. Reference values for predicting intervention effect are likely to be population- and context-specific and related to age, clinical types of AF, as well as to the presence and advancement of underlying structural heart disease. Prospective studies in homogeneous patient populations are needed to establish the clinical value of AFR.

Conflict of interest: none declared.

References

1. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. *Circulation* 1995;**92**: 1954–68.
2. Asano Y, Saito J, Matsumoto K, Kaneko K, Yamamoto T, Uchida M. On the mechanism of termination and perpetuation of atrial fibrillation. *Am J Cardiol* 1992;**69**: 1033–8.
3. Haissaguerre M, Lim KT, Jacquemet V, Rotter M, Dang L, Hocini M *et al.* Atrial fibrillatory cycle length: computer simulation and potential clinical importance. *Europace* 2007;**9**(Suppl 6):vi64–70.
4. Lewis T. Auricular fibrillation: a common clinical condition. *BMJ* 1909;**42**:1528.
5. Bollmann A, Kanuru NK, McTeague KK, Walter PF, DeLurgio DB, Langberg JJ. Frequency analysis of human atrial fibrillation using the surface electrocardiogram and its response to ibutilide. *Am J Cardiol* 1998;**81**:1439–45.
6. Holm M, Pehrson S, Ingemansson M, Sornmo L, Johansson R, Sandhall L *et al.* Noninvasive assessment of the atrial cycle length during atrial fibrillation in man: introducing, validating and illustrating a new ECG method. *Cardiovasc Res* 1998;**38**:69–81.
7. Matsuo S, Lellouche N, Wright M, Bevilacqua M, Knecht S, Nault I *et al.* Clinical predictors of termination and clinical outcome of catheter ablation for persistent atrial fibrillation. *J Am Coll Cardiol* 2009;**54**:788–95.
8. Husser D, Cannom DS, Bhandari AK, Stridh M, Sornmo L, Olsson SB *et al.* Electrocardiographic characteristics of fibrillatory waves in new-onset atrial fibrillation. *Europace* 2007;**9**:638–42.
9. Holmqvist F, Stridh M, Waktare JE, Roijer A, Sornmo L, Platonov PG *et al.* Atrial fibrillation signal organization predicts sinus rhythm maintenance in patients undergoing cardioversion of atrial fibrillation. *Europace* 2006;**8**:559–65.
10. Petersson R, Sandberg F, Platonov PG, Holmqvist F. Noninvasive estimation of organization in atrial fibrillation as a predictor of sinus rhythm maintenance. *J Electrocardiol* 2011;**44**:171–5.
11. Alcaraz R, Sandberg F, Sornmo L, Rieta JJ. Classification of paroxysmal and persistent atrial fibrillation in ambulatory ECG recordings. *IEEE Trans Biomed Eng* 2011;**58**: 1441–9.
12. Petrutiu S, Sahakian AV, Fisher W, Swiryn S. Manifestation of left atrial events and interatrial frequency gradients in the surface electrocardiogram during atrial fibrillation: contributions from posterior leads. *J Cardiovasc Electrophysiol* 2009;**20**: 1231–6.
13. Husser D, Stridh M, Sornmo L, Toepffer I, Klein HU, Bertil Olsson S *et al.* Electroatriography—time-frequency analysis of atrial fibrillation from modified 12-lead ECG configurations for improved diagnosis and therapy. *Med Hypotheses* 2007;**68**: 568–73.
14. Ihara Z, van Oosterom A, Jacquemet V, Hoekema R. Adaptation of the standard 12-lead electrocardiogram system dedicated to the analysis of atrial fibrillation. *J Electrocardiol* 2007;**40**:68 e1–8.
15. Sörnmo L, Stridh M, Rieta JJ. Atrial activity extraction from the ECG. In Mainardi LT, Sörnmo L, Cerutti S (eds). *Understanding Atrial Fibrillation: The Signal Processing Contribution.* San Francisco, USA: Morgan & Claypool Publishers; 2008. p53–80.
16. Bollmann A, Husser D, Mainardi L, Lombardi F, Langley P, Murray A *et al.* Analysis of surface electrocardiograms in atrial fibrillation: techniques, research, and clinical applications. *Europace* 2006;**8**:911–26.
17. Lemay M, Vesin JM, van Oosterom A, Jacquemet V, Kappenberger L. Cancellation of ventricular activity in the ECG: evaluation of novel and existing methods. *IEEE Trans Biomed Eng* 2007;**54**:542–6.
18. Alcaraz R, Rieta JJ. Adaptive singular value cancelation of ventricular activity in single-lead atrial fibrillation electrocardiograms. *Physiol Meas* 2008;**29**:1351–69.
19. Llinares R, Igual J. Application of constrained independent component analysis algorithms in electrocardiogram arrhythmias. *Artif Intell Med* 2009;**47**:121–33.
20. Lee J, Song MH, Shin DG, Lee KJ. Event synchronous adaptive filter based atrial activity estimation in single-lead atrial fibrillation electrocardiograms. *Med Biol Eng Comput* 2012;**50**:801–11.
21. Petrenas A, Marozas V, Sornmo L, Lukosevicius A. An echo state neural network for QRST cancellation during atrial fibrillation. *IEEE Trans Biomed Eng* 2012;**59**:2950–7.
22. Sandberg F, Sörnmo L, Stridh M. Time–frequency analysis of atrial fibrillation. In Mainardi LT, Sörnmo L, Cerutti S (eds). *Understanding Atrial Fibrillation: The Signal Processing Contribution.* San Francisco, USA: Morgan & Claypool Publishers; 2008. p81–102.
23. Corino VD, Sandberg F, Lombardi F, Mainardi LT, Sörnmo L. Atrioventricular nodal function during atrial fibrillation: model building and robust estimation. Biomed Signal Process Control 2013;**8**:1017–25.
24. Corino VD, Mainardi LT, Stridh M, Sornmo L. Improved time–frequency analysis of atrial fibrillation signals using spectral modeling. *IEEE Trans Biomed Eng* 2008;**55**: 2723–30.
25. Sandberg F, Stridh M, Sornmo L. Frequency tracking of atrial fibrillation using hidden Markov models. *IEEE Trans Biomed Eng* 2008;**55**:502–11.
26. Sassi R, Corino VD, Mainardi LT. Analysis of surface atrial signals: time series with missing data?. *Ann Biomed Eng* 2009;**37**:2082–92.
27. Meurling CJ, Ingemansson MP, Roijer A, Carlson J, Lindholm CJ, Smideberg B *et al.* Attenuation of electrical remodelling in chronic atrial fibrillation following oral treatment with verapamil. *Europace* 1999;**1**:234–41.
28. Xi Q, Sahakian AV, Ng J, Swiryn S. Atrial fibrillatory wave characteristics on surface electrogram: ECG to ECG repeatability over twenty-four hours in clinically stable patients. *J Cardiovasc Electrophysiol* 2004;**15**:911–7.
29. Holmqvist F, Stridh M, Waktare JE, Sornmo L, Olsson SB, Meurling CJ. Atrial fibrillatory rate and sinus rhythm maintenance in patients undergoing cardioversion of persistent atrial fibrillation. *Eur Heart J* 2006;**27**:2201–7.
30. Bollmann A, Sonne K, Esperer HD, Toepffer I, Langberg JJ, Klein HU. Non-invasive assessment of fibrillatory activity in patients with paroxysmal and persistent atrial fibrillation using the Holter ECG. *Cardiovasc Res* 1999;**44**:60–6.
31. Petrutiu S, Sahakian AV, Swiryn S. Short-term dynamics in fibrillatory wave characteristics at the onset of paroxysmal atrial fibrillation in humans. *J Electrocardiol* 2007;**40**:155–60.
32. Ravelli F, Mase M, Del Greco M, Faes L, Disertori M. Deterioration of organization in the first minutes of atrial fibrillation: a beat-to-beat analysis of cycle length and wave similarity. *J Cardiovasc Electrophysiol* 2007;**18**:60–5.

33. Platonov PG, Stridh M, de Melis M, Urban L, Carlson J, Corbucci G et al. Analysis of atrial fibrillatory rate during spontaneous episodes of atrial fibrillation in humans using implantable loop recorder electrocardiogram. *J Electrocardiol* 2012;**45**:723−6.

34. Petrutiu S, Sahakian AV, Swiryn S. Abrupt changes in fibrillatory wave characteristics at the termination of paroxysmal atrial fibrillation in humans. *Europace* 2007;**9**:466−70.

35. Fujiki A, Sakabe M, Nishida K, Mizumaki K, Inoue H. Role of fibrillation cycle length in spontaneous and drug-induced termination of human atrial fibrillation. *Circ J* 2003;**67**:391−5.

36. Bollmann A, Sonne K, Esperer HD, Toepffer I, Klein HU. Circadian variations in atrial fibrillatory frequency in persistent human atrial fibrillation. *Pacing Clin Electrophysiol* 2000;**23**:1867−71.

37. Meurling CJ, Waktare JE, Holmqvist F, Hedman A, Camm AJ, Olsson SB et al. Diurnal variations of the dominant cycle length of chronic atrial fibrillation. *Am J Physiol Heart Circ Physiol* 2001;**280**:H401−6.

38. Sandberg F, Bollmann A, Husser D, Stridh M, Sornmo L. Circadian variation in dominant atrial fibrillation frequency in persistent atrial fibrillation. *Physiol Meas* 2010;**31**:531−42.

39. Bollmann A, Wodarz K, Esperer HD, Toepffer I, Klein HU. Response of atrial fibrillatory activity to carotid sinus massage in patients with atrial fibrillation. *Pacing Clin Electrophysiol* 2001;**24**:1363−8.

40. Holmqvist F, Stridh M, Waktare JE, Brandt J, Sornmo L, Roijer A et al. Rapid fluctuations in atrial fibrillatory electrophysiology detected during controlled respiration. *Am J Physiol Heart Circ Physiol* 2005;**289**:H754−60.

41. Stridh M, Meurling C, Olsson B, Sornmo L. Detection of autonomic modulation in permanent atrial fibrillation. *Med Biol Eng Comput* 2003;**41**:625−9.

42. Ingemansson MP, Holm M, Olsson SB. Autonomic modulation of the atrial cycle length by the head up tilt test: non-invasive evaluation in patients with chronic atrial fibrillation. *Heart* 1998;**80**:71−6.

43. Östensson SE, Platonov PG. Modulation of atrial fibrillatory rate during head-up and head-down tilt test in patients with persistent atrial fibrillation. Heart Rhythm Society's 35th Annual Scientific Sessions. 2014. [Abstract].

44. Husser O, Husser D, Stridh M, Sornmo L, Corino VD, Mainardi LT et al. Exercise testing for non-invasive assessment of atrial electrophysiological properties in patients with persistent atrial fibrillation. *Europace* 2007;**9**:627−32.

45. Sanders P, Nalliah CJ, Dubois R, Takahashi Y, Hocini M, Rotter M et al. Frequency mapping of the pulmonary veins in paroxysmal versus permanent atrial fibrillation. *J Cardiovasc Electrophysiol* 2006;**17**:965−72.

46. Bollmann A, Tveit A, Husser D, Stridh M, Sornmo L, Smith P et al. Fibrillatory rate response to candesartan in persistent atrial fibrillation. *Europace* 2008;**10**:1138−44.

47. Choudhary MB, Holmqvist F, Carlson J, Nilsson HJ, Roijer A, Platonov PG. Low atrial fibrillatory rate is associated with spontaneous conversion of recent-onset atrial fibrillation. *Europace* 2013;**15**:1445−52.

48. Platonov PG, Cygankiewicz I, Stridh M, Holmqvist F, Vazquez R, Bayes-Genis A et al. Low atrial fibrillatory rate is associated with poor outcome in patients with mild to moderate heart failure. *Circ Arrhythm Electrophysiol* 2012;**5**:77−83.

49. Swartz MF, Fink GW, Lutz CJ, Taffet SM, Berenfeld O, Vikstrom KL et al. Left versus right atrial difference in dominant frequency, K(+) channel transcripts, and fibrosis in patients developing atrial fibrillation after cardiac surgery. *Heart Rhythm* 2009;**6**:1415−22.

50. Husser D, Stridh M, Sornmo L, Roden DM, Darbar D, Bollmann A. A genotype-dependent intermediate ECG phenotype in patients with persistent lone atrial fibrillation genotype ECG-phenotype correlation in atrial fibrillation. *Circulation Arrhythm Electrophysiol* 2009;**2**:24−8.

51. Seifert MB, Olesen MS, Christophersen IE, Nielsen JB, Carlson J, Tveit A et al. The lack of association between genomic predictors of atrioventricular conduction and atrial electrocal remodeling in patients with lone atrial fibrillation. Heart Rhythm Society's 35th Annual Scientific Sessions. 2014. [Abstract].

52. Wijffels MC, Dorland R, Mast F, Allessie MA. Widening of the excitable gap during pharmacological cardioversion of atrial fibrillation in the goat: effects of cibenzoline, hydroquinidine, flecainide, and d-sotalol. *Circulation* 2000;**102**:260−7.

53. Husser D, Stridh M, Sornmo L, Geller C, Klein HU, Olsson SB et al. Time-frequency analysis of the surface electrocardiogram for monitoring antiarrhythmic drug effects in atrial fibrillation. *Am J Cardiol* 2005;**95**:526−8.

54. Aunes-Jansson M, Edvardsson N, Stridh M, Sornmo L, Frison L, Berggren A. Decrease of the atrial fibrillatory rate, increased organization of the atrial rhythm and termination of atrial fibrillation by AZD7009. *J Electrocardiol* 2013;**46**:29−35.

55. Aunes M, Egstrup K, Frison L, Berggren A, Stridh M, Sornmo L et al. Rapid slowing of the atrial fibrillatory rate after administration of AZD7009 predicts conversion of atrial fibrillation. *J Electrocardiol* 2013.

56. John S, Salmas J, Kornej J, Lobe S, Stridh M, Sornmo L et al. Effects of dronedarone and amiodarone on atrial fibrillatory rate in patients with persistent atrial fibrillation. *Int J Cardiol* 2013;**167**:2354−6.

57. Corino VD, Holmqvist F, Mainardi LT, Platonov PG. Beta-blockade and A1-adenosine receptor agonist effects on atrial fibrillatory rate and atrioventricular conduction in patients with atrial fibrillation. *Europace* 2014;**16**:587−94.

58. Raine D, Langley P, Murray A, Dunuwille A, Bourke JP. Surface atrial frequency analysis in patients with atrial fibrillation: a tool for evaluating the effects of intervention. *J Cardiovasc Electrophysiol* 2004;**15**:1021−6.

59. Bollmann A, Mende M, Neugebauer A, Pfeiffer D. Atrial fibrillatory frequency predicts atrial defibrillation threshold and early arrhythmia recurrence in patients undergoing internal cardioversion of persistent atrial fibrillation. Pacing Clin Electrophysiol, 2002;**25**:1179−84.

60. Bollmann A, Husser D, Steinert R, Stridh M, Soernmo L, Olsson SB et al. Echocardiographic and electrocardiographic predictors for atrial fibrillation recurrence following cardioversion. *J Cardiovasc Electrophysiol* 2003;**14**:S162−5.

61. Meurling CJ, Roijer A, Waktare JE, Holmqvist F, Lindholm CJ, Ingemansson MP et al. Prediction of sinus rhythm maintenance following DC-cardioversion of persistent atrial fibrillation—the role of atrial cycle length. *BMC Cardiovasc Disord* 2006;**6**:11.

62. Efremidis M, Alexanian IP, Oikonomou D, Manolatos D, Letsas KP, Pappas LK et al. Predictors of atrial fibrillation recurrence in patients with long-lasting atrial fibrillation. *Can J Cardiol* 2009;**25**:e119−24.

63. Bollmann A, Binias KH, Toepffer I, Molling J, Geller C, Klein HU. Importance of left atrial diameter and atrial fibrillatory frequency for conversion of persistent atrial fibrillation with oral flecainide. *Am J Cardiol* 2002;**90**:1011−4.

64. Schwartz RA, Langberg JJ. Atrial electrophysiological effects of ibutilide infusion in humans. *Pacing Clin Electrophysiol* 2000;**23**:832−6.

65. Fujiki A, Tsuneda T, Sugao M, Mizumaki K, Inoue H. Usefulness and safety of bepridil in converting persistent atrial fibrillation to sinus rhythm. *Am J Cardiol* 2003;**92**:472−5.

66. Fujiki A, Sakabe M, Nishida K, Sugao M, Tsuneda T, Iwamoto J et al. Drug-induced changes in fibrillation cycle length and organization index can predict chemical cardioversion of long-lasting atrial fibrillation with bepridil alone or in combination with aprindine. *Circ J* 2004;**68**:1139−45.

67. Mochalina N, Juhlin T, Öhlin B, Carlson J, Holmqvist F, Platonov PG. Predictors of successful cardioversion with vernakalant in patients with recent-onset atrial fibrillation. *Ann Noninvasive Electrocardiol* 2014. Jul 9. doi: 10.1111/anec.12178. [Epub ahead of print].

68. Fedida D, Orth PM, Chen JY, Lin S, Plouvier B, Jung G et al. The mechanism of atrial antiarrhythmic action of RSD1235. *J Cardiovasc Electrophysiol* 2005;**16**:1227−38.

69. Platonov PG, Mitrofanova LB, Orshanskaya V, Ho SY. Structural abnormalities in atrial walls are associated with presence and persistency of atrial fibrillation but not with age. *J Am Coll Cardiol* 2011;**58**:2225−32.