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

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Shortening of atrial refractory period during atrial fibrillation has been considered a hallmark of atrial electrical remodelling. The atrial fibrillatory cycle length, which is intimately related to the atrial fibrillatory rate (AFR), is generally accepted as a surrogate marker for local refractoriness. The value of using AFR to monitor the progress of atrial ablation therapy has been demonstrated and gradual slowing of AFR has consistently been observed to precede arrhythmia termination during paroxysmal or permanent atrial fibrillation ablation. Today, AFR is the key characteristic of the fibrillatory process, repeatedly validated against intracardiac recordings and extensively studied in clinical contexts. This paper provides 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. We conclude that 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, however, are likely to be population- and context-specific and related to age, clinical types of atrial fibrillation, as well as to presence and advancement of underlying structural heart disease. Prospective studies in homogeneous patient populations are still needed to establish the clinical value of AFR.

Keywords
Atrial  ●  Atrial fibrillation

Introduction

Shortening of atrial refractory period during atrial fibrillation (AF) has been considered a hallmark of atrial electrical remodelling since early animal experiments¹ 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.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 AF24 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 QT 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 spectrum26—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 QT intervals at high heart rates.
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. 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, which could be observed in 10 s long ECG segments. In a later study, Holmqvist et al. 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.

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).
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, AF 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 and was also observed in induced AF. Most patients included in those studies had relatively short AF episodes. However, it is unknown to what extent the time course of AF 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, AF increased over the course of 3–4 h, whereafter it reached a plateau, 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, but a decrease was detectable just before AF termination when AFR was assessed on a second-by-second basis. 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 period.

An interesting observation was made by Fujiki et al. 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. This was reproduced repeatedly. 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.

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., 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.

Reproducible AFR increase during head-up tilt-test has been reported earlier 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.

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. Notably, patients with high baseline AFR were less likely to demonstrate AF 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, which was in agreement with AFR determined non-invasively.

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.8 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 dif-
fences 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 nega-
tive correlation between age and AFR, which has been documented
in patients with paroxysmal8,47 and persistent AF.46 In a recent study,
our group observed the same phenomenon in patients with persist-
ent AF and mild-to-moderate congestive heart failure.48

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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 in-
crease atrial cycle length that corresponds to increased refractori-
ness of the atrial myocardium.52 Non-invasive AFR assessment may
offer a way to monitor antiarrhythmic drug effects, which may be par-
sicularly useful in drug development, as it avoids the complexity of in-
vasive electrophysiological testing and offers a valuable comple-
ment to pharmacokinetic studies. Feasibility of non-invasive monitoring of
drug effects during AF has been shown previously.35,53 Figure 4 illus-
trates 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
AFR in the clinical context

**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 or i.v. ibutilide, but could not be reproduced in another ibutilide study. Furthermore, no association between baseline AFR and response to antiarrhythmic drug was observed in recent studies in patients with AF <48 h using vernakalant or in patients with several weeks-long AF who received combined potassium and sodium channel blocker AZD7009. No association between baseline AFR and conversion rate was seen in bepridil-treated patients with long-standing AF.

The value of AFR as a predictor of cardioversion effect is likely drug-specific, and may depend on the mechanism of action, inter-individual 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, 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, although not in all, 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, the non-invasive approach to estimating AFCL was, to the best of our knowledge, only used in one study. 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

**AFR in the clinical context**

**Afrofibrillatory 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 or spontaneous. Similar findings were reported in patients with new-onset AF, and were further confirmed in an unselected cohort of patients with recent-onset AF (<48 h). 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, though not confirmed by other studies, a larger-scale study was performed by Holmqvist et al. 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. A similar observation was made using invasively assessed AFCL in patients with long-lasting AF undergoing internal cardioversion. 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).

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

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Mean age (years)</th>
<th>AF duration</th>
<th>Lone AF (%)</th>
<th>LA diameter (mm)</th>
<th>AAD class I or III (%)</th>
<th>Mean AFR at baseline (fpm)</th>
<th>AFR threshold (fpm)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bollmann et al. 59</td>
<td>19</td>
<td>58</td>
<td>10 ± 2 months</td>
<td>31</td>
<td>45 ± 6</td>
<td>0</td>
<td>396 ± 66</td>
<td>420</td>
<td>Internal cardioversion: AFR ≥ 420 fpm is 64% sensitive and 88% specific for prediction of AF recurrence</td>
</tr>
<tr>
<td>Bollmann et al. 60</td>
<td>44</td>
<td>62</td>
<td>18 ± 27 months</td>
<td>22</td>
<td>45 ± 5</td>
<td>100</td>
<td>393 ± 38</td>
<td>ND</td>
<td>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)</td>
</tr>
<tr>
<td>Meurling et al. 2006</td>
<td>37</td>
<td>69</td>
<td>5 [1–21] months</td>
<td>71</td>
<td>44 ± 7</td>
<td>0</td>
<td>392 – 378&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NS</td>
<td>AFR alone not predictive</td>
</tr>
<tr>
<td>Holmqvist et al. 29</td>
<td>175</td>
<td>68</td>
<td>94 [2–104] days</td>
<td>37</td>
<td>48 ± 7</td>
<td>9</td>
<td>383 ± 60</td>
<td>384</td>
<td>AFR &gt; 384; OR = 3.1; CI 95%; 1.8–6.1, P &lt; 0.0001 for AF relapse</td>
</tr>
<tr>
<td>Holmqvist et al. 29</td>
<td>29</td>
<td>65</td>
<td>&lt;30 dagar</td>
<td>55</td>
<td>46 ± 7</td>
<td>14</td>
<td>384 ± 70</td>
<td>384</td>
<td>AFR &gt; 384; OR = 15; CI 95%; 2.4–89, P = 0.003 for AF relapse</td>
</tr>
<tr>
<td>Bollmann et al. 46</td>
<td>124</td>
<td>65 vs. 63&lt;sup&gt;c&lt;/sup&gt;</td>
<td>ND</td>
<td>51 – 44</td>
<td>46 ± 5</td>
<td>0</td>
<td>399 ± 48 to 402 ± 58</td>
<td>NS</td>
<td>No separation between survival curves in Kaplan–Meier analysis depending on AFR</td>
</tr>
<tr>
<td>Efremidis et al. 62</td>
<td>99</td>
<td>63</td>
<td>22 ± 45 months</td>
<td>18</td>
<td>42 ± 6</td>
<td>43</td>
<td>330&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NS</td>
<td>Internal cardioversion</td>
</tr>
</tbody>
</table>

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.

<sup>a</sup>Median [range].

<sup>b</sup>Converted from AFCL (ms) to AFR (fpm).

<sup>c</sup>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

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

AAD, antiarrhythmic drugs; AF, atrial fibrillation; AFR, atrial fibrillatory rate; fpm, fibrillations per minute; ND, no data; NS, not significant.
<sup>a</sup>No value for the total study cohort, data presented on a per group basis
<sup>b</sup>Responders vs. non-responders.
<sup>c</sup>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.
<sup>d</sup>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, 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 homogenous patient populations are needed to establish the clinical value of AFR.

Conflict of interest: none declared.

References

AFR in the clinical context


