

## Clinical Use And Limitations Of Non-Invasive Electrophysiological Tests In Patients With Atrial Fibrillation

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### Abstract

Atrial fibrillation (AF) is a complex arrhythmia, that has been studied non-invasively assessing atrial refractory period, atrioventricular node (AV) node refractory period, and ventricular response. The AV node plays a fundamental role as it filters many of the numerous irregular atrial impulses bombarding the node. Despite its importance, the electrophysiological (EP) characteristics of the AV node are not routinely evaluated since conventional EP techniques for assessment of refractory period or conduction velocity of the AV node are not applicable in AF. Since rate-control drugs control ventricular response through their effect on the AV node, noninvasive assessment of AV node electrophysiology may be useful. The RR series, though being highly irregular, contains information that can be used for risk stratification and prediction of outcome. In particular, RR irregularity measures during AF have been shown to be related to clinical outcome. This paper reviews the attempts done to noninvasively characterize the AV node and the ventricular response, highlighting clinical applications and limitations of the noninvasive techniques.

### Introduction

Atrial fibrillation (AF) is a complex arrhythmia, characterized by irregular atrial depolarization and, consequently, an irregular heart rate that prevents many of the commonly used approaches to evaluate for example autonomic tone or atrioventricular (AV) node properties. However, much effort has been spent on understanding the information that can be extracted in patients with AF.<sup>1,2</sup> In AF, there are three main characteristics of the heart that have been studied non-invasively: i) atrial refractory period ii) AV node refractory period, iii) ventricular response.

It has been shown that shortening of the atrial refractory period is associated with increase risk of AF.<sup>3,4</sup> To non-invasively assess the atrial refractory period, the atrial fibrillatory rate (AFR), being closely related to the atrial fibrillatory cycle length (an indirect estimate of the atrial refractory period), is often studied. AFR has been validated against intracardiac recordings and extensively studied in clinical contexts.<sup>5-7</sup> The interested reader is referred to a recent review<sup>8</sup> for more details on AFR.

### Key Words:

Atrial Fibrillation, Electrophysiological, Arrhythmia.

### Disclosures:

None.

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The AV node plays a fundamental role in AF as a regulator of the ventricular response. Rate-control drugs commonly act on atrial and/or AV node properties to reduce the ventricular rate. During drug development, cardiac electrophysiological (EP) effects of antiarrhythmic drugs are usually assessed invasively in EP studies performed in sinus rhythm. However, an atrial pacing protocol cannot be applied in patients with AF, and thus the EP effects of drugs on the AV node are still not completely understood in AF. When optimizing therapy, non-invasive assessment of the effect of a drug on AV nodal electrophysiology in patients with AF may help in choosing the best therapy. During the early clinical phases of drug development, non-invasive characterization of the AV node may facilitate data collection from large patient cohorts and favor patient-tailored therapy. Various studies have attempted to assess AV nodal refractory period<sup>9-13</sup> as well as to characterize AV nodal function.<sup>14-22</sup>

Even if the ventricular response during AF is highly irregular, it contains information that can be used for risk stratification and prediction of outcome, for example quantified by the RR irregularity measures.<sup>23-28</sup>

FRP: Functional Refractory Period. Mesor represents the average FRP on the 24-hour; Amplitude represents the maximum excursion over the Mesor. \* p < 0.002 CHF vs. No CHF.

This paper reviews the work on noninvasively characterizing AF patients. On one hand, we describe AV node characterization, highlighting clinical applications but also limitations of the noninvasive technique. On the other hand, we describe the

**Table 1: Effect of heart condition on the circadian behavior of FRP**

Study		Mesor (ms)	Amplitude (ms)	Time of peak
Hayano et al. <sup>13</sup>	No CHF	575	63	2:40 a.m.
	CHF	560	35*	2:10 a.m.
Khand et al. <sup>12</sup>	NYHA I-II	532	104	3:30 a.m.
	NYHA III-IV	552	66	3:30 a.m.

FRP: functional refractory period. Mesor represents the average FRP on the 24-hour; Amplitude represents the maximum excursion over the Mesor. \*  $p < 0.002$  CHF vs. No CHF.

ventricular response, highlighting the association between reduced RR irregularity and clinical outcome as well as the effect of commonly used drugs on irregularity.

## Av Node Electrophysiological Measures

### Classical Invasive Measures

To evaluate AV node characteristics during an EP study, various pacing protocols can be applied. The S1S2 protocol is commonly used: a basic cycle length is chosen and a fixed number of S1S1 cycles is given, followed by a premature S2 stimulus, creating a shorter S1S2 interval. Being the driving stimuli applied at one or several atrial sites (A) while simultaneously recording the His (H) electrogram, A1A2 is shortened until A2 is not followed by His activation (H2). Shortening of A1A2 results in prolongation of A2H2. Two important quantities can be defined: the effective refractory period (ERP), equal to the longest A1A2, resulting in AV nodal block, and the functional refractory period (FRP), equal to the shortest achievable H1H2 interval. Finally, during an EP study, the existence of dual AV nodal pathway can be easily identified by the so-called jump that can be observed in the A2H2 value.

### Non-Invasive Measures

Noninvasive estimation of AV characteristics can rely on the analysis of surface ECG: from this signal the RR intervals can be derived and used as a surrogate of the H1H2 interval. The estimation of the functional refractory period of the AV node in AF has been attempted in different phenomenological studies. The FRP, defined as the shortest H1H2 interval, was estimated as the shortest RR interval in some phenomenological studies.<sup>9-11</sup> Talajic et al. showed in dogs that the shortest RR interval in AF correlated well with the FRP estimated invasively during an EP study in sinus rhythm, and therefore used the shortest RR interval as a surrogate measurement of the FRP. A disadvantage with this method is, however, its sensitivity to outlier RR intervals due to falsely detected or missed beats. A more robust FRP estimation was later obtained by using the 5th percentile of the RR series.<sup>12</sup>

Hayano et al.<sup>13</sup> used the 1.0-s intercept of the lower envelope of the Poincaré plot and the degree of scatter above the envelope as surrogate measurements of AV node refractoriness and concealed AV conduction, respectively. The method is based on the Poincaré plot, where each RR interval is plotted against the previous one. Briefly, the scattergram plane is divided vertically into eight consecutive bins in the preceding RR interval; in each bin, the minimum value of the subsequent RR interval is determined, and the eight minimum values thus obtained are linearly regressed on the average preceding RR interval for each bin. With this method the possible dependence between consecutive RR intervals is taken into account. However, the measurements produced by this approach depend of RR interval bin size, and therefore a comparison of results needs to be made with caution.

**Table 2: Results from the studies assessing prognostic value of ventricular response**

Study	N	Mean age (years)	Follow-up (years)	End point	Clinical characteristics	Prognostic measure
Cygankiewicz et al. <sup>25</sup>	155	69 ± 10	4.1	total mortality (cardiac, non cardiac)	heart failure in NYHA class II and III	ApEn < 1.68 SE < 6.44
Frey et al. <sup>26</sup>	35		1		advanced heart failure	SDANN < 100ms
Platonov et al. <sup>23</sup>	68	69 ± 8	2	total mortality	congestive heart failure	pNN20 < 87
Stein et al. <sup>27</sup>	21		9.1	mortality and progression to mitral valve surgery	chronic nonischemic mitral regurgitation	SDANN
Yamada et al. <sup>28</sup>	107	64 ± 9	2.75	death (cardiac, fatal stroke, all-cause)	chronic AF	ApEn < 1.83

The above-mentioned studies do not account for the dual pathways of the AV node. Recently, statistical model-based analysis, combining ventricular response and information on atrial activity derived from the surface ECG (Figure 1), was proposed for evaluating essential AV nodal characteristics in AF. The method estimates five parameters which characterize the AV node in patients with AF, with emphasis put on the refractory periods of the two AV nodal pathways, and the probability of an impulse to not pass through the fast pathway, i.e. to pass through the slow pathway.<sup>16-18</sup> The AV node is treated as a lumped structure that accounts for both temporal and spatial summation of the electrical activity of the cells. Atrial impulses are treated as if they arrive randomly to the AV node, with a mean arrival rate proportional to atrial fibrillatory rate (AFR), determined from the f-wave pattern.<sup>29</sup> Impulses arriving to the AV node are assumed to produce ventricular activations unless blocked by a refractory AV node. The slow and the fast AV nodal pathways are characterized by their absolute refractory period (aRP) and relative refractory period (rRP); slow or fast pathway is indicated by appending the letter s or f. All atrial impulses arriving to the AV node before the end of the aRP are blocked, whereas no impulses arriving after the end of the maximally prolonged refractory period (aRP+rRP) are blocked. The definition of aRP defines the shortest possible time between conducted impulses and hence may serve as an indirect estimate of the functional refractory. The rRP accounts not only for relative refractoriness but also for concealed conduction. The probability of an impulse to pass through the slow pathway provides global information on the impulse pattern, but not on the pathway selected by each individual impulse. A detailed description of the method and the technique for estimating the parameters can be found in.<sup>16-18</sup>

## Non-Invasive Ep Tests On Av Node For Circadian Rhythm Assessment

Circadian rhythm assessment can be accomplished through the use of cosinor analysis in which a single-component cosinor with a 24-h period is fitted to the RR series to determine whether a circadian variation exists. The following variables are studied: the midline estimating statistics of rhythm (mesor); the amplitude, i.e., a measure of half the extent of predictable variation within a cycle and the time of peak estimated rhythm.

Khand<sup>12</sup> investigated the circadian rhythm of FRP as an index of autonomic function in patients with chronic AF and varying severity of heart failure. They found that the diurnal change in hourly 5th

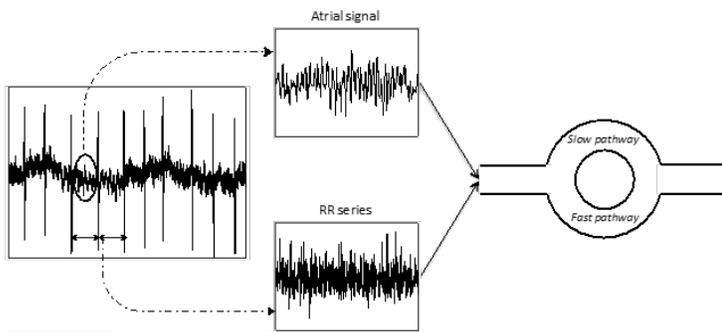


Figure 1:

**Scheme of the method for assessing AV node characteristics: the ECG is processed to produce the RR series and the atrial signal that form together the basis for estimation of the AV node parameters**

percentile of the RR intervals was correlated to the NYHA class of heart failure (classes III and IV heart failure vs. classes I and II). Hayano<sup>13</sup> assessed the circadian changes in AV nodal properties in AF patients with or without congestive heart failure. The results showed that both AV node refractoriness and the degree of concealed AV conduction in AF are associated with circadian rhythms, attenuated in patients with congestive heart failure. In both studies a smaller circadian variation of the FRP was observed in patients with severe heart failure<sup>12</sup> or in patients with CHF,<sup>13</sup> even if not statistically significant.

### Non-Invasive Ep Tests On Av Node For Drug Effect Evaluation

The evaluation of drug effect on AV nodal electrophysiology in AF, without the need for cardiac catheterization, may be useful during drug development or when optimizing the therapy. We used our recently proposed method<sup>16,17</sup> on data from patients with AF taking different drugs. The results showed that the parameter estimates reflect the expected changes in AV nodal properties for the investigated drugs. To illustrate the use of the method, Figure 2 shows the response of six patients to two different antiarrhythmic drugs: a beta blocker (metoprolol) and calcium channel blocker (verapamil) in a controlled setting, i.e., data from the “RATE control in Atrial Fibrillation” (RATAF) study.<sup>30</sup> It can be noted that in patients (a) and (b) both drugs act in the same way: the RR fitted models with both drugs are right-shifted and broader when compared to baseline, and the FRP is prolonged. In patients (c) and (d), as well as in patients (e) and (f), there is one drug acting more on the AV node, making the RR fitted model right-shifted, thus prolonging the FRP. The method provides an estimate of the probability of an atrial impulse passing through the slow pathway—an estimate which provides information on whether a drug changes the pathway in which the impulses pass through. The availability of a noninvasive and rapid test of different drugs on patients can help in defining the therapy.

Figure 3 shows the percentage of prolongation with respect to the baseline value of the refractory period of the slow (a) and fast (b) pathway in different cohorts of patients with AF. It can be observed that the effect of all drugs is similar on both pathways. All of the estimated FRP prolongations were in agreement with the results previously reported in invasive studies performed in sinus rhythm. In particular, in EP studies tecadenoson was found to prolong the ERP of the AV node and to slow down its conduction.<sup>31</sup> Esmolol was found to prolong refractoriness and conduction time in both pathways during AV nodal reentrant tachycardia.<sup>32</sup> In<sup>19</sup> the

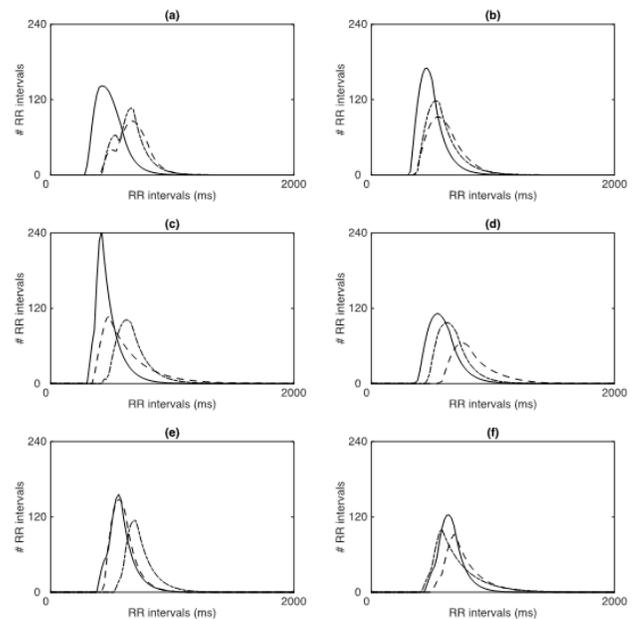


Figure 2:

**Response of six patients to two different rate-control drugs: a beta blocker (metoprolol, dotted line) and a calcium channel blocker (verapamil, dashed line) response are compared to baseline behavior (solid line). (a)-(b) both drugs act in the same way, right-shifting the RR fitted model; (c)-(e) verapamil seems to affect the RR fitted model more than metoprolol; (d)-(f) metoprolol seems to affect the RR fitted model more than verapamil (see text for details)**

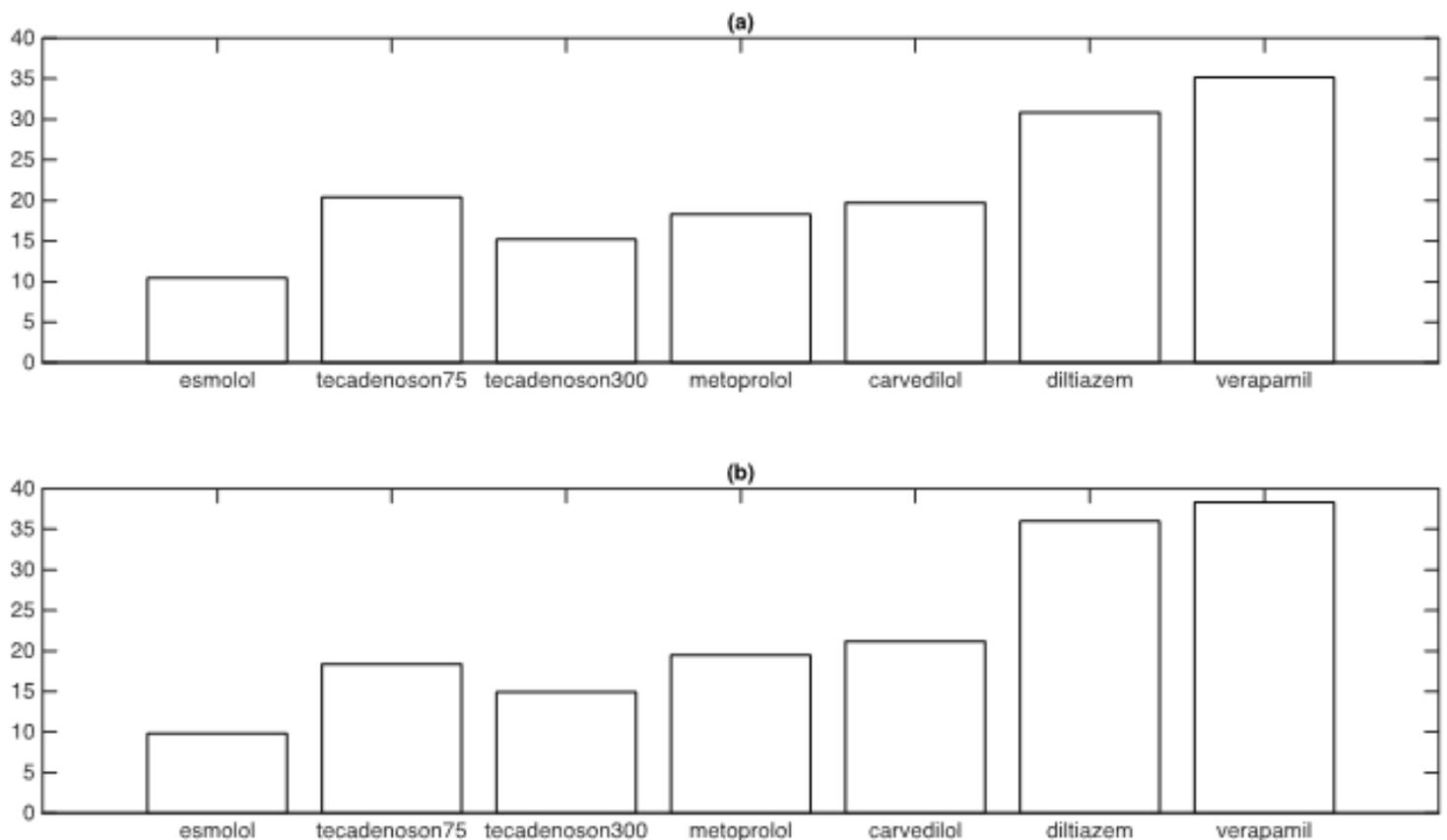
noninvasive estimate of FRP was prolonged during tecadenoson and esmolol administration. Both pathways were equally influenced, suggesting either prolonged effective refractory period or prolonged AV conduction, or both. In addition, tecadenoson reduced heart rate without significantly changing atrial rate, suggesting that this drug mainly affects the AV node properties. In previous invasive studies, calcium channel blockers and beta blockers were found to prolong the FRP, the prolongation in calcium channel blockers being greater than in beta blockers (metoprolol<sup>33</sup> and carvedilol<sup>34</sup> vs. verapamil<sup>35</sup> and diltiazem<sup>36</sup>); this result was observed also in.<sup>21</sup>

### Ventricular response

Variability measures and irregularity entropy-based measures have been successfully applied. Variability measures are related to the dispersion of data, providing an estimate of overall heart rate variability, as well as long-term and short-term components of heart rate variability.<sup>37</sup> Irregularity measures are related to the degree of unpredictability of the data fluctuations, reflecting the likelihood that a certain pattern is repeated. Approximate entropy (ApEn)<sup>38</sup> and sample entropy (SampEn)<sup>39</sup> are the most commonly used measures.

### Long-term prognosis based on RR series

Reduced RR variability/irregularity in AF has been associated to poor clinical outcome or death. The first two studies that addressed this issue analyzed patients with AF and advanced heart failure<sup>26</sup> and chronic non-ischemic mitral regurgitation,<sup>27</sup> respectively. Both these studies showed that lower RR variability was associated with poor outcome; in particular, the standard deviation of the mean RR intervals during 5-min periods (SDANN) was identified as the parameter linked to outcome. Another study<sup>28</sup> involving 107 consecutive patients with chronic AF followed up for 2.5 years (in mean) did not confirm the independent prognostic value of SDANN,



**Figure 3:** Percentage of prolongation in respect to baseline of FRP of the slow (a) and fast (b) pathway estimated using the method in 16, 17 in patients with AF, taking different drugs

whereas a reduced RR irregularity measured as ApEn was predictive of cardiac mortality after adjustment for clinical covariables.

Recently, the association between RR irregularity during AF and clinical outcome was assessed in the patients enrolled in the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II) study, presenting AF at baseline. RR variability was assessed using pNN<sub>x</sub>, i.e., the percentage of interval differences of successive NN intervals greater than x ms, with x varying from 10 to 50 ms in steps of 10 ms. At the end of the 2-year follow-up, 19 patients died (28%). In univariate analysis, pNN<sub>10-30</sub> were lower in patients who died during follow-up. pNN<sub>20</sub> was an independent predictor of all cause mortality after adjustment for significant clinical covariates in multivariate Cox analysis.<sup>23</sup> ApEn was not confirmed as predictive of clinical outcome: this may be due to the worse clinical characteristics of the patients enrolled in the MADIT-II study, all having congestive heart failure.

The association between variability and irregularity measures to clinical outcome was assessed in the patients enrolled in the MUSIC (Muerte SUBita en Insuficiencia Cardiaca) study, presenting AF at baseline. None of the variability measures was significantly different between survivors and non-survivors. On the contrary, the irregularity parameters were significantly lower in non-survivors than in survivors across all-mortality outcome parameters, i.e., total mortality as well as cardiac, sudden and congestive heart failure related mortality. ApEn was found to be a significant predictor of total mortality, sudden death and heart failure death in the univariate analysis as well as after adjustment for significant clinical covariates, including rate-control drugs, in a multivariate model.<sup>25</sup>

As noted from Table 2, summarizing the results of the above-mentioned studies, there is no uniform finding regarding the specific variability or irregularity measure linked to clinical outcome. However, these results suggest that reduced variability or irregularity is correlated with poor outcome in patients with AF.

### Unanswered questions and future directions

We are still far from a clear understanding of mechanisms underlying variability and irregularity of ventricular response during AF and its relationship to clinical outcome. Noninvasive assessment of AV nodal characteristics may improve our understanding of AV node function during AF and the effects of antiarrhythmic drugs on AV conduction. Different methodologies for assessing the properties of the RR series have been proposed over the years. Some methods are sensitive to the influence of outliers in the RR series,<sup>9</sup> or require that a bin size is defined.<sup>13</sup> Still the main limitation of all these studies<sup>9,13,18,19,21</sup> is that direct validation of non-invasive estimates of AV node properties in clinical settings during AF remains to be done. Testing the methodology<sup>16,17</sup> in different groups of patients confirmed the hypothesis that the estimates of AV nodal refractory periods reflect overall changes in AV nodal properties previously reported on in studies accomplished invasively during sinus rhythm. Non-invasive assessment of AV node properties during AF appears to have potential for assessment of drug effects during AF and bringing our understanding of electrophysiological processes occurring in the AV node during AF on a new level.

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