Clinical, electrocardiographic and electrophysiological predictors of atrial fibrillation development in different cardiac substrates

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Summary. - We performed a review of the current literature in order to evaluate clinical, electrocardiographic and electrophysiologic parameters predictive of atrial fibrillation development. Clinical parameters were obtained from two large observational studies (the Framingham heart study and the Cardiovascular health study). Different laboratoristic predictors were also reviewed: ECG-derived predictors, among which we separately evaluated those derived from the 12-lead surface ECG and those derived from the signal averaged P-wave, and other electrophysiologic predictors as atrial monophasic action potential analysis. We also evaluated the clinical value of these different parameters in atrial fibrillation in patients with no overt structural heart disease and in the most common clinical conditions known to be related to atrial fibrillation development such as hypertension, heart failure, cardiovascular surgery.

Key words: atrial fibrillation, risk assessment, prediction.


Parole chiave: fibrillazione atriale, analisi del rischio, predizione.

Prediction of atrial fibrillation in the general population

Clinical predictors

Atrial fibrillation (AF) is the most common serious cardiac arrhythmia and it is responsible for substantial morbidity and mortality.

Its prevalence doubles with each advancing decade of age, ranging from 0.5% in the sixth decade to almost 9% in the ninth decade [1-6]. Various clinical conditions may predispose to AF development. The two largest studies evaluating clinical predictors of AF in the general population are the Framingham heart study (FHS) [2] and the Cardiovascular heart study (CHS) [3]. These studies have had a very long follow-up (four decades for FHS) and included transient and chronic AF as outcome of interest.

They showed that patients who develop AF are usually elderly, more likely to have diabetes, left ventricular hypertrophy, echocardiographic abnormalities, CAD, valvular heart disease, heart failure and to have suffered a stroke [1-3]. Male patients are more prone to AF development [1].

About a third of women and 20% of men have valvular heart disease, 28% of men and half of the women have myocardial infarction, and about 25% of both sexes have heart failure [2]. No association is observed with obesity or alcohol consumption in the FHS, while in CHS study high levels of alcohol consumption are associated with a reduced risk [3]. In the CHS high cholesterol, black race, use of beta-blockers and the forced expiratory volume in 1 second are also associated with a reduced risk of AF development [3]. In the same study the use of diuretics, higher levels of systolic blood pressure, height, fasting glucose and a ECG cardiac injury score size are all associated with increased risk of AF [3].
Clinical cardiac risk factors

Various types of heart diseases were associated with AF, including valvular heart disease, acute myocardial infarction, myocarditis, hypertrophic cardiomyopathy, congenital heart disease, pericarditis, hypertensive cardiovascular disease and heart failure [1-4].

In the FHS the most common cardiac precursors of AF were: heart failure, myocardial infarction and valvular heart disease [1-5].

These cardiac conditions accounted for 20% of the AF incidence in men and 31% of its occurrence in women [1]. Among these cardiac conditions, heart failure imposed the greatest risk of AF with a 4.5-fold increased risk in men and a 5.9-fold increased risk in women [1].

Valve disease was associated with a 1.8-fold increase in men and a 3.4-fold increase in women. Myocardial infarction was significantly associated with AF only in men, increasing their risk by 40% [1].

Clinical non cardiac risk factors

Noncardiac conditions related to AF include: thyrotoxicosis, alcohol abuse, severe infections and pulmonary pathology. Cigarette smoking in women, diabetes, hypertension and electrocardiographically demonstrated left-ventricular hypertrophy (ECG-LVH) in both sexes, were significant AF predictors when adjusted for age [1].

Women who smoked were 40% more likely to develop AF; those who were diabetic had a 2-fold increased risk; those with hypertension had a 70% greater risk; and those with ECG-LVH had almost a 4-fold increased risk. In men, diabetes increased risk by 70%, hypertension by 80% and ECG-LVH by 3-fold [1]. After adjusting for other associated conditions, as well as age and sex, diabetes and hypertension remained significant predictors of AF, although with decreased odds ratio (OR) [1].

In both age and risk-factor adjusted analyses, neither obesity nor alcohol intake was a substantial or significant risk factor for AF in the FHS [1].

Echocardiographic predictors

The echocardiographic predictors of AF onset were also investigated in 1924 subjects 50-94 years of age in the FHS [7]. The echocardiographic findings in persons who developed AF were evaluated and the risk of future AF in those who had the abnormalities was investigated. Persons with AF had larger left atrial, left ventricular end-diastolic and end-systolic dimensions; greater ventricular septal and left ventricular posterior wall thickness; more left ventricular mass/height and lower percent fractional shortening and a higher prevalence of mitral annular calcification than persons without AF [7]. Using Cox proportional hazards modelling, the association of these echocardiographic features with subsequent development of AF was quantified after adjustment for age, sex, hypertension, coronary artery disease, heart failure, diabetes and valve disease.

Left atrial size, left ventricular fractional shortening (inverse) and the sum of left ventricular and posterior wall thickness were demonstrated to be independent echocardiographic predictors of AF. For each of these echocardiographic predictors, AF risk increased in a continuous graded fashion. Those with ≥2 of the highest risk-quartile measurements for these features in combination had a 17% risk of AF compared with 3.7% when none was present [7].

Other laboratory predictors of atrial fibrillation

Various ECG derived predictors of AF development were studied in patients with a history of paroxysmal atrial fibrillation (PAF), during sinus rhythm (SR). These predictors can be divided into parameters derived from the simple 12-lead surface ECG and those derived from more complex ECG interpretation techniques, as signal averaged P-wave (P-SAECG). The theoretical basis is that a delay in the interatrial and intra-atrial may be reflected by a P-wave prolongation in the surface ECG, and by filtered P-wave as obtained by signal-averaged ECG which may detect more subtle alterations [8-12].

For the 12-lead surface ECG, various techniques have been used and the most validated are: the computer-assisted or manual P-wave measurements as the maximum P-wave duration (Pmax), the minimum P-wave duration (Pmin), the P-wave dispersion (Pd = Pmax-Pmin) and some other indexes like the P-wave variance (P variance). The results are conflicting and this is likely to be related to the different techniques used and to the different clinical background. In a recent study, evaluating patients with idiopathic PAF, a Pmax value of 106 ms gave an 83% sensitivity, a 72% specificity and a positive predictive accuracy of 79%, whereas a Pd value of 36 ms separated patients from controls with a sensitivity of 77%, a specificity of 82% and a positive predictive accuracy of 85% [13].

For P-SAECG, all the studies agreed to demonstrate that P-wave signal averaged ECG predicts AF. Generally, the negative predictive value of atrial signal-averaged ECG in predicting the risk of AF is relatively high (60-80%), while the positive predictive value is considerably lower [8].

In the most widely used technique, the P-SAECG is recorded from a modified X,Y and Z lead system, with standard lead I used as the X lead, lead aVF used as the Y lead and the precordial lead V1 used as the Z lead. The signal from each lead is amplified, passed through a low bandpass filter and a high bandpass filter and then converted to a digital signal. A specially filtered P-wave derived from the selected dominant sinus P-wave of lead
II or V1 served as a reference signal. After averaging, the filtered signals from X, Y and Z leads were combined into spatial magnitude: \((X^2+Y^2+Z^2)^{1/2}\). The derived parameters generally used were the duration (Ad) and the root-mean-square voltages for the last 10, 20, 30 or 40 ms (RMS10, RMS20, RMS30, RMS40), with an abnormal P-SAECG defined by most authors as Ad > 132 ms and RMS20 < 2.3 µV [14]. Some authors have also studied the frequency content of the P-SAECG, showing that the predictive accuracy of these frequency-domain-derived parameters was comparable with time-domain-derived parameters.

Atrial fibrillation in subjects with structurally normal heart ("lone" atrial fibrillation)

Some case-control studies have attempted to identify risk predictors of AF development in patients without structural heart disease, the so called “lone AF”, with variable results.

In a large recent study of 90 idiopathic PAF patients and 70 healthy subjects the Pmax and the Pd dispersion were found to be significantly higher in patients than in controls, with reported high positive predictive accuracy [13].

Dilaveris et al. assessed the Pmax and the Pd from the 12-lead surface ECG in 60 patients with an idiopathic PAF history and 40 age-matched healthy control subjects. They showed that a Pmax value of 110 ms and a Pd value of 40 ms separated patients from controls with a sensitivity of 88% and 83% and a specificity of 75% and 85% respectively [15].

Andrikopoulos et al. evaluated the increased prognostic value of the P variance as compared to Pmax and Pd dispersion in 60 patients with “lone” paroxysmal AF and 50 healthy controls. The Pmax, the Pd and the P variance from 12-lead ECG were all significantly higher in patients than in controls and a P variance value of 120 ms separated patients from controls with comparable sensitivity and specificity than other parameters; however, the reproducibility of P variance was higher [16].

Ishimoto et al. measured the P-wave triggered SAECG derived parameters (filtered P-wave duration, Ad, and root mean square voltages for the last 20 ms of the vector magnitude, RMS20) and atrial volumes calculated by cine-magnetic resonance imaging in 38 patients with “lone” AF and in 34 controls. In this study, Ad was longer (131.7 ± 10.9 ms vs 120.8 ± 8.6 ms, p < 0.0001) and RMS20 was lower (2.89 ± 1.29 µV vs 3.62 ± 1.48 µV, p < 0.05) in the PAF group than in controls. However, the atrial volumes were similar in the 2 groups and no correlation was found between Ad and atrial volumes in PAF patients [17].

In conclusion, the available data suggest that 12-lead ECG derived and P-wave triggered SAECG parameters are useful to predict AF development even in patients without structural heart disease. Largest sample size and more experience, however, are required to propose a large-scale use of these simple and inexpensive markers.

Atrial fibrillation in hypertension

A large number of studies have been performed to investigate predictive parameters of AF development in hypertensive patients.

In the most recent study by Ciaroni et al., 97 consecutive patients with hypertension who attended a cardiology outpatient clinic were followed for a mean of 25 months and 19 patients subsequently developed AF. In the multivariate analysis, age (OR = 3.28), diurnal systolic blood pressure (OR = 1.16), maximum duration of the P-wave (OR = 2.09), dispersion of the P-wave (OR = 2.52), echocardiographic left ventricular mass (OR = 1.43), left atrial dimension (OR = 2.81) and velocity of the A-wave (OR = 2.24) were independent predictors for the onset of AF. The ECG parameters and the A-wave velocity remained significant predictors of AF even when corrected for age [18].

Other studies investigate the simple 12-lead ECG predictive parameters for PAF development in hypertensive patients during SR.

The background for using P-wave-related parameters is that atrial myocardial fibrosis, a well-known responsible of depressed intra-atrial conduction, which may play a major role in the initiation of atrial re-entry, can manifest as a lengthening of the P-wave duration, even in the simple 12-lead surface ECG.

Various parameters have been studied and compared: Dulhoste et al. studied P-wave-related indexes on the signal averaged ECG (P-SAECG) in 12 control patients (group I), 12 hypertensive patients (group II) and 7 patients with history of PAF in absence of organic heart disease (group III). In this study the filtered P-wave duration (Ad), the duration of P-wave in lead II (P II), and the root mean square voltage of the last 20 ms (RMS20) were significantly different in the group II than in group I, but not in group II vs group III; noteworthy, the linear regression test do not show correlation between Ad and P II nor between RMS20 and P II [19].

Ozer et al. measured the maximum P-wave duration (Pmax), the minimum P-wave duration (Pmin) and the P-wave dispersion (Pd = Pmax – Pmin). These data were calculated from a 12-lead surface ECG in 44 hypertensive patients with history of PAF (group I) and in 50 hypertensive patients without history of AF (group II) [20].

Pd was significantly greater in group I than in group II (50 ± 12 vs 38 ± 8 ms, p = 0.001). The value of Pmin and the echocardiography-measured LVEF were also significantly lower in group I than in group II. In multivariate analysis, however, only P-wave dispersion remained a significant predictor or PAF development [20].
In partial contrast to these data, however, another study by Dilaveris et al. of 110 patients showed that Pmin, Pd, LVEF and other calculated ECG parameters were all significant univariate predictors of AF development, but in multivariate analysis only Pmin was a significant independent predictor [21].

The observed difference may be related to the different methods used (manual vs authomatized measurements) or to drug administration; however the data proved that a risk stratification using only simple and widely available methods is feasible.

These studies, however, do not addressed the possible therapeutic implications, i.e. if a more aggressive blood pressure control may achieve a reduction in AF episodes. For this reason, longer follow-up studies are warranted in larger populations.

Atrial fibrillation in congestive heart failure

Structural cardiac disease underlie AF in 80% to 97% of patients and chronic congestive heart failure (CHF) is one of its most common precursors. On the other side AF is believed to be associated with impaired hemodynamics, clinical deterioration and increased risk of thromboembolic events in CHF patients, although a causative role for AF to increase the CHF morbidity and mortality is uncertain.

Two large prospective studies have attempted to identify the clinical and laboratory predictors of AF development in CHF patients.

Pozzoli et al. [22] prospectively studied 344 patients with severe CHF while in SR, referred for evaluation for heart transplantation. The development of chronic AF was the primary end point of this study. During a follow-up period of 19 ± 12 months AF developed in 28 patients. AF persisted despite cardioversion in 9 patients, whereas SR was restored by pharmacological or electrical cardioversion in 19. AF reoccurred in 9 of these patients and SR could not be restored. Thus, 18 patients (5%) overall developed chronic AF.

The study failed to identify baseline predictors of AF development as clinical, ergometric, neurohormonal, electrocardiographic, hemodynamic and echocardiographic variables were not different between the two groups.

When only the variables measured in the two groups at the last evaluation were considered, the maximal late diastolic velocity of mitral flow (the A-wave at the Doppler measurement of the mitral inflow) was significantly lower in patients who subsequently experienced AF than in patients with stable SR, whereas maximal early diastolic velocity (the E-wave) was higher in the former than in the latter. Within the clinical variables, only previous reversible AF was significantly associated (p = 0.0001) with late AF development [22]. Surprisingly, neither left atrial dimension nor pulmonary artery wedge pressure were associated with the risk of AF development. Thus the authors hypothesize that an “atrial myopathy” not entirely dependent on mechanical overload may precede the onset of AF [22].

Yamada et al. [14] attempted to determine prospectively whether new variables, like the P-wave SAECG or the plasma concentration of atrial natriuretic peptide (ANP) would be useful to assess the risk of PAF attacks in 75 patients with stable mild-to-moderate CHF. At the study entry, 29 patients had an abnormal P-SAECG (group I), whereas the others 46 patients did not (group II).

In the follow-up period of 21 ± 9 months, 9 (31%) of the group I patients developed PAF, whereas only 1 patient (2%) in group II experienced PAF attacks (p < 0.0002). The Ad was significantly longer (p < 0.005) and the LP20 was lower (p = 0.02) in the PAF group than in the non-PAF group; in conclusion the incidence of an abnormal P-SAECG was significantly greater (p < 0.001) in the PAF group. Furthermore, ANP concentration was significantly higher (p = 0.01) in the PAF group than in non-PAF group. By multivariate analysis, an abnormal P-SAECG and an elevated ANP level were independently related to PAF development: the combination of abnormal P-SAECG and an elevated ANP level gave a sensitivity of 70%, specificity of 94%, positive predictive value of 64% and negative predictive value of 94% for the identification of patients at risk of PAF development. Specifically, by combining these two parameters, the positive predictive value increased from 30% of each single indicator to 64% [14].

The methodologic difference between these studies may explain the different outcomes, but there are some clear points. First of all heart failure is a high risk situation for AF, either paroxysmal or chronic, and the occurrence of this serious rhythm disturbance, even if more specific data are needed, is likely to play a pathogenetic role in the clinical deterioration of the patient. Secondly the use of some simple echocardiographic, electrocardiographic and laboratory markers might identify an higher risk subset for AF development which is likely to require a more intensive approach.

Atrial fibrillation after cardiovascular surgery

AF is the most common arrhythmia occurring after cardiac surgery with a prevalence as high as 40% after coronary artery bypass grafting and 60% after valvular surgery. It results in increased morbidity and prolonged hospital stay [23].

The pathophysiology of postoperative AF is probably related to pre-existing age-related degenerative cardiac changes coupled with perioperative abnormalities in several electrophysiologic parameters such as dispersion.
of atrial refactoriness, atrial conduction velocity and atrial transmembrane potential. These electrophysiologic abnormalities could be due to many perioperative factors such as pericarditis, atrial injury from surgical handling or from cannulation, acute atrial pressure or volume overload, atrial ischemia, hyperadrenergic state, hypoxia.

Many clinical characteristics and laboratory parameters have been described for risk stratification of AF after cardiac surgery.

The most important clinical predictors are listed in Table 1.

In the past few years some investigators have reported different rates of incidence of AF according to different methods of revascularization: AF has been reported to be uncommon following minimally invasive direct coronary bypass surgery (MIDCAB), occurring in 0% to 24% of patients [24-26].

This very low incidence of AF was attributed to the lower extent of atrial manipulation, lack of cardiopulmonary bypass and atriotomy related to this method of revascularization. However subsequent randomized studies have not confirmed these results showing similar incidence rate of AF in MIDCAB and in classic CABG [27-28].

**Laboratory predictors**

Signal-averaged P-wave duration (SAPWD) is one of the most largely tested predictors of AF after cardiovascular surgery. Existing data suggest that the longer the duration of filtered P-wave the higher the risk to develop AF after cardiac surgery [29-32].

However even combining signal-averaged P-wave duration with other clinical predictors (es. age) the positive and negative predictive accuracy remain quite low (57% and 82%), making SAPWD of limited clinical usefulness [33].

Recently Pichlmaier et al. [34] and our group [35] have evaluated the possibility to predict the onset of AF using the monophasic action potential. The underlying hypothesis of our work was that the electrical alterations that culminate in the occurrence of postoperative atrial arrhythmias are reflected by gradual changes in the cellular action potentials and therefore in the atrial MAP. The MAP signal was recorded for 72 hours after the procedure using an epicardial MAP bipolar fractal electrode (Biotronik, Berlin). Before AF, specific and significant alteration of the MAP were observed. In the work by Pichlmaier et al. work, specific alterations of the MAP morphology were reproducibly detected: the MAP developed a triangular shape (nMAPd90 - nMAPd25: -4%); MAPd90 shortened independently of the cardiac rhythm (nMAPd90: -25 ± 4%); the plateau amplitude decreased from 5 ± 1 mV to 2 ± 0.2 mV. The administration of sotalol and a combination of verapamil, digoxin and quinidine successfully treated AF in all cases. After treatment, MAP morphology reverted to normal. However these preliminary data need to be demonstrated in larger studies.

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### Table 1. - Clinical predictors of development of postoperative atrial fibrillation

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<th>Predictor</th>
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<td>Advanced age</td>
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<td>Valvular heart disease (mitral valvular disease, stenosis)</td>
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<td>Increased left atrial size</td>
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<td>Long bypass times</td>
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<td>Absence of beta-blocker treatment (or withdrawal of previous treatment)</td>
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<tr>
<td>Electrolyte disturbances (hypokalemia, hypomagnesemia)</td>
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<td>Previous atrial arrhythmias</td>
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<td>Chronic renal failure</td>
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<td>Pericarditis</td>
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<td>Right coronary artery grafting</td>
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<td>Previous cardiac surgery</td>
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<td>Methods of cardioprotection and hypothermia during bypass</td>
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<td>Elevated postoperative adrenergic tone</td>
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### REFERENCES


