Onset mechanism of paroxysmal atrial fibrillation detected by ambulatory Holter monitoring

Antonio Vincenti[*], Roberta Brambilla, Maria Grazia Fumagalli, Rita Merola, and Stefano Pedretti

Electrophysiology and Cardiac Pacing Unit, Cardiology Department, St Gerardo Hospital, via Donizetti 106, 20052 Monza (MI), Italy

Aims The aim of this study was to evaluate the mechanisms of induction of paroxysmal atrial fibrillation (PAF) by analysis of its onset recorded on Holter monitoring (HM).

Methods and results One hundred and seven HM were evaluated in 90 patients (mean age 67.7, cardiac disease in 31.1%), with one or more self-terminating episodes of PAF, lasting ≥ 30 s. Two hundred and thirty-three episodes of PAF were detected. A triggering premature atrial complex (PAC) was present in 222/233 episodes (95.3%); 118/233 episodes were preceded by a bradyarrhythmic event (BE) or a post-extrasystolic pause (50.6%). According to the polarity of the ectopic P-wave, triggering PACs were left atrial origin in 74.3%, right atrial in 15.3%, not determined in 10.4% of cases. Coupling interval (CI) of triggering PACs was shorter in episodes preceded by BEs; it was shorter than that of non-triggering PACs. Frequency of PACs was significantly higher in the hour preceding the onset of PAF. During the day, three periods of higher frequency of PAF onsets were found from noon to 2 p.m., 6 p.m. to 2 a.m., and 4 a.m. to 6 a.m. Heart rate variability analysis showed a vagal prevalence in the 5 min preceding the onset of arrhythmia, both in the time and in the frequency domain.

Conclusion Paroxysmal atrial fibrillation is generally triggered by a PAC, with left atrial origin in two-thirds of cases: CI and neuroendocrine balance are factors affecting the induction of the arrhythmia.

Introduction

Atrial fibrillation (AF) is the most frequent cardiac arrhythmia, and it is associated with almost all cardiac diseases. Mortality in patients with AF is almost doubled compared with the general population.[1] Morbidity, mainly due to embolic stroke, is also increased.[2]

The mechanism of onset and maintenance of AF is not fully understood, even if many recent studies have allowed an improvement in the comprehension of the pathophysiology of the arrhythmia.[3] Moreover, therapy and prophylaxis of recurrences are not always successful. It is possible that this is due to an 'empirical' use of drugs in the prevention of recurrences, i.e. not based on precise knowledge of triggering mechanisms and arrhythmia substrates. There may be development of structural remodelling of atrial tissue,[3] although it is known that commonly used antiarrhythmic drugs are unable to oppose this process, with only the possible exception of amiodarone.[4]

Any contribution to a better understanding of trigger mechanisms, substrate modifications and the role of the autonomic nervous system may be helpful in achieving the prevention of AF.

The aim of this study was to evaluate the mechanisms of onset of paroxysmal AF (PAF), by observing spontaneous episodes recorded during Holter monitoring (HM).

Materials and methods

Between 1 June 2000 and 31 December 2001, about 6500 ambulatory HM were performed. In 107 of them, one or more episodes of PAF were detected, sustained for ≥ 30 s.

A digital recorder (Syneflash; Ela Medical®, Le Plessis-Robinson, France) was used; digital analysis was performed by the scanner Medical SyneTec from Ela Medical (software 2.00, release 2). The system was provided with an acquisition frequency of 200 Hz and a sensitivity threshold of 10 μV.

Modified V5 and V1 leads were obtained (CM5 and CM1); in the case of a three-channel recording, we chose a modified inferior lead (CMAVF).

Atrial fibrillation was defined according to the International Guidelines[5]; PAF was defined as an arrhythmia lasting for ≥ 30 s with sinus rhythm spontaneously resumed before the end of recording. Persistent and permanent AF, episodes lasting <30 s or present at the beginning of the recording were excluded.

We tried to detect a triggering premature atrial complex (PAC) at the beginning of each episode, and its presence was confirmed

* Corresponding author. Tel: +39 039 2333032; fax: +39 039 2333065.
 E-mail address: antvince@tin.it

if a clear ectopic P-wave was the last beat just before the onset. In this case, the coupling interval (CI) of the triggering PAC was measured, both as an absolute value and as a ratio of the previous cycle (PC) length (prematurity index = CI/PC). Polarity (positive, negative, or diphasic) of triggering ectopic beats was recorded in both CM5 and CM1 leads, to apply the criteria of Tang et al.[6] for the localization of origin of ectopic beats. Heart rate was measured before the arrhythmia started and within the first 8 s of AF. Time of day and duration of the episode were recorded. Polarity of triggering PACs P-wave (positive, negative, biphasic, or not defined) was evaluated in CM5 and CM1 leads; on the basis of these polarities, the origin of each ectopic beat was determined.[6]

When present, also CI of non-triggering PACs was measured, randomly selecting the premature beats at different times of the day.

Premature atrial complex frequency was measured in the hour preceding the AF onset, as well as in the remaining part of the recording, after exclusion of the AF period(s) and of the hour(s) preceding it (them).

The presence of a bradyarrhythmic event (BE) before onset was also noted; a BE was defined when a pause of 1 s or more or bradycardia (60 bpm or less) for more than 2 beats, or a post-extrasystolic pause (PEP) was present just before the arrhythmia onset.

All manual evaluations were performed by two independent experts on surface ECG interpretation.

According to the time of onset, episodes were assigned to one of the 12 2-h periods in which the 24 h were divided; in this way the circadian distribution of PAF onset could be obtained. Each period was arbitrarily considered relevant if it contained more than 10% of onsets. Moreover, in consideration of the importance of the duration of the episodes on circadian distribution, the presence of AF was also evaluated in 96 periods of 15 min each.

Heart rate variability (HRV) before the onset of arrhythmia was calculated, by means of custom made software HRV for Elatec (Ela Medical). Time domain and frequency domain HRV were evaluated in six 5 min periods before the arrhythmia onset and in a control 5 min period. The control period was chosen at a distance of at least 60 min from any PAF onset, with an average heart rate similar (±10 bpm) to the 5 min period just before the start (5–0 min). According to the current International Guidelines,[7] mean heart rate (RR) and standard deviation (SDNN) of normal RR cycles were evaluated in the time domain; for the frequency domain, we obtained low frequency (LF), high frequency (HF) powers in normalized units, and the LF/HF ratio. Heart rate variability was considered in a subgroup of patients from the general population, whose characteristics are summarized in Table 1.

Episodes in which none of the 5 min periods could be analysed for HF of PACs were excluded from the analysis.

Statistical analysis

All measures are indicated as mean $\pm$ SD. Mean values were compared using Student's t-test for paired or unpaired data, with similar or different variance, when appropriate. Variances were compared using the F-test. Frequencies were compared with χ^2 distribution. Trends of circadian distribution of daytime of onset were determined using six-degrees regression functions, obtained according to the least square method. For the comparison of multiple series data, analysis of variance was used, employing the Bonferroni correction.

For all comparisons, a significance level $\alpha = 0.05$ was considered.

Results

Characteristics of patients

Episodes of PAF were recorded in 90 patients, with a mean age of 67.7 (range 34–93), 58 of whom were males (64.4%); in 28/90 patients (31.1%), organic heart disease was present. The characteristics of the population are summarized in Table 1. This table also shows the patient groups in which the time domain and the frequency domain analyses of HRV were performed.

Type of onset

Two hundred and thirty-three episodes of PAF were detected (mean 2.18 for every recording, range 1–15).

On the basis of the presence of a triggering PAC and of the presence of BE/PEP before the arrhythmia started, each episode was classified as Type 1 (no triggering PAC, BE/PEP detectable before the AF start), Type 2 (no triggering PAC, no BE/PEP detectable), Type 3 (presence of triggering PAC, BE/PEP present), and Type 4 (presence of triggering PAC, BE/PEP absent).

A triggering ectopic beat was detected in 222/233 episodes (95.27%); 118/233 episodes were preceded by a BE or PEP (50.64%) (Table 2).

PAF characteristics

Mean duration of episodes was 115 $\pm$ 220 min (median value 10 min). Mean ventricular rate at the onset was

Table 1 Characteristics of the whole population and of subgroups in which time domain or frequency domain analysis of HRV was performed

Characteristic	General population	Time domain	Frequency domain
Patients	90	45	34
Number of episodes	233	52	41
Mean age (years)	67	67	65
Range (years)	34–93	46–93	46–89
Males (%)	58 (64)	31 (69)	23 (68)
Organic heart disease (%)	28 (31)	16 (36)	11 (32)
Ischaemic heart disease	13		
Dilated cardiomyopathy	10		
Hypertensive cardiopathy	3		
Sick sinus syndrome	1		
Permanent pacing	1		
Pharmacological prophylaxis (%)	46 (51)	30 (67)	22 (65)
Amiodarone	19	12	10
Propafenone	7	2	
Flecainide	6	4	10
Digitalis	3	1	1
Verapamil	3	3	3
Quinidine	2		
Sotalol	2	1	1
Other β-blocker	4	6	4

Table 2 Distribution of AF episodes according to the presence of triggering PACs and preceding bradyarrhythmic episodes

	Presence of bradyarrhythmia (%)	Absence of bradyarrhythmia (%)	Overall (%)
Sudden onset	7 (3.0)	4 (1.7)	11 (4.7)
Triggering PAC detected	111 (47.6)	111 (47.6)	222 (95.3)
Overall	118 (50.6)	115 (49.4)	233 (100)

104 $\pm$ 26 bpm. These values were not statistically different in subgroups of patients, except for starting heart rate that was lower in episodes preceded by BE/PEP (95 $\pm$ 23 vs. 113 $\pm$ 26 bpm, $P < 0.0001$).

Characteristics of triggering PACs

All 222 triggering PACs were classified according to their polarities in CM5 and CM1 leads. Using the criteria of Tang *et al.*,[6] a left atrial origin was recognized for 165/222 PACs (74.32%), a right atrial origin in 34/222 (15.32%) cases, whereas in 23/222 (10.36%) the site of origin remained unclear (*Table 3*).

Mean triggering PACs' CI was 468 $\pm$ 74 ms; the PC was 979 $\pm$ 245 ms [*Table 4(B)*]. Coupling interval of triggering PACs in absolute value was significantly shorter when AF was not preceded by BE/PEP [Type 4; *Table 4(A)*]; however, the prematurity index (CI/PC) was greater in these episodes.

Characteristics of non-triggering PACs

Coupling interval of non-triggering PACs was significantly longer than CI of triggering PACs (494 $\pm$ 109 vs. 468 $\pm$ 74 ms, $P < 0.001$). Even dispersion of CI was higher for non-triggering PACs ($P = 0.002$) [*Table 4(B)*].

In 33 patients with one (28 patients) or two episodes (5 patients) in the recording, it was possible to evaluate the density of supraventricular ectopic beats in the hour before the beginning of arrhythmia, compared with the remaining period of the day (after exclusion of the arrhythmia and pre-arrhythmia periods): mean number of ectopic beats in the hours preceding the arrhythmia onset was 162 $\pm$ 301, whereas in the remaining parts of the recording, it was 79 $\pm$ 110.7 ($P = 0.04$) (*Figure 1*).

Circadian variability of onset and presence of PAF

Results of circadian variability are shown in *Figure 2*. Three high incidence periods can be observed from noon to 2 p.m., 6 p.m. to 2 a.m., and 4 to 6 a.m.

The analysis of the presence of AF showed that during the night the arrhythmia is more frequently present, suggesting that episodes starting in the evening were more sustained (*Figure 3*). The durations of episodes according to the time of onset are reported in *Table 5*: episodes starting from noon to 6 p.m. and 6 p.m. to midnight were significantly longer compared with episodes beginning in other periods of the day.
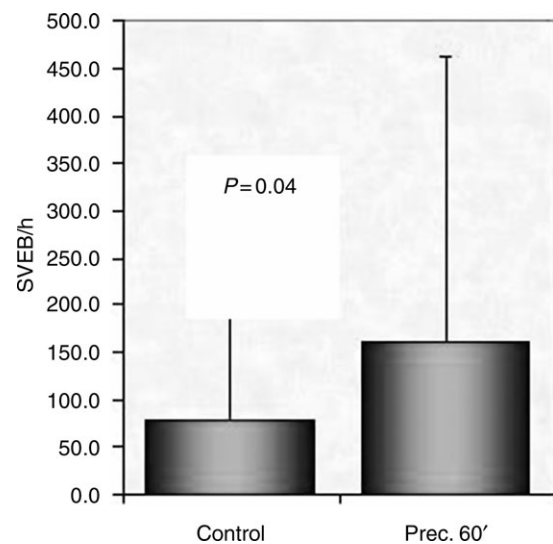
Table 3 Classification of triggering PAC according the criteria of Tang *et al.*[6]

Class	CM1	CM5	Number of PACs	Anatomical origin
1	+	+	81	LA
2	+	−	6	LA
3	+	±	47	LA
4	+	ND	29	LA
5	±	−	1	LA
6	ND	−	1	LA
7	−	+	5	RA
8	−	−	1	RA
9	±	+	21	RA
10	ND	+	7	RA
11	±	±	10	ND
12	ND	±	2	ND
13	ND	ND	11	ND

ND, not definite.

Figure 1 Density of PACs in the hour preceding the onset of AF, compared with the remaining part of the day, after exclusion of other periods of AF and the hours preceding it.

Table 4 (A) Coupling interval, preceding cycle, and prematurity index according to BE presence before the AF onset and (B) coupling interval and preceding cycle for triggering and non-triggering PACs

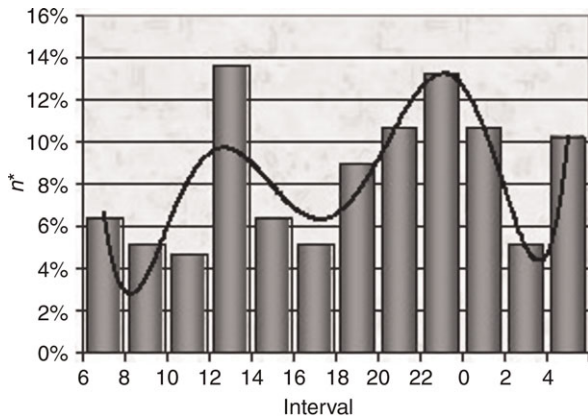|	Type 3	Type 4	*P* (mean values)	*P* (variance)
(A)				
CI (ms)	490 $\pm$ 76	445 $\pm$ 65	<0.00001	NS
PC (ms)	1133 $\pm$ 232	825 $\pm$ 137	<0.0000001	<0.0000001
Prematurity index	44.42 $\pm$ 8.59	54.83 $\pm$ 8.53	<0.0000001	NS
(B)				
	Triggering PACs	Non-triggering PACs	*P* (mean values)	*P* (variance)
CI (ms)	468 $\pm$ 74	494 $\pm$ 109	0.002	<0.0000001
PC (ms)	979 $\pm$ 245	957 $\pm$ 233	NS	NS
Prematurity index	49.62 $\pm$ 10.00	53.35 $\pm$ 12.07	0.001	0.0007

Figure 2 Circadian distribution in 12 2-h periods of the onsets of PAF episodes.
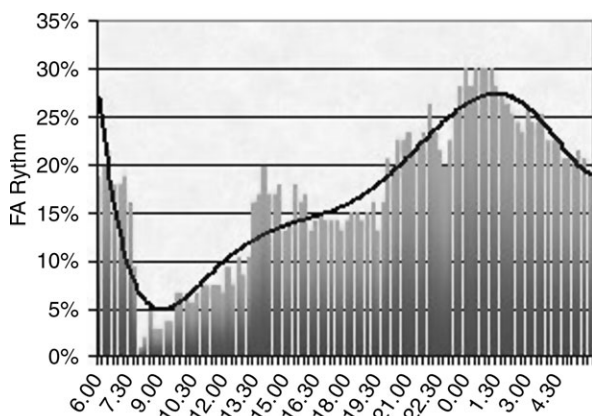

Figure 3 Circadian distribution of presence of AF in 96 periods of 15 min.

Table 5 Mean duration of episodes of PAF according to the onset time

Period n	Onset time	Number of episodes	Mean duration (min)	SD
1	0.00–6.00 a.m.	61	60.3	103.15
2	6.01–12.00 a.m.	38	48.4	65.71
3	0.01–6.00 p.m.	58	154.7	289.4
4	6.01–12.00 p.m.	75	161.8	260.5

Period 3, $P = 0.01$ vs. Period 1, $P = 0.02$ vs. Period 2; Period 4, $P = 0.004$ vs. Period 1, $P = 0.009$ vs. Period 2; other comparisons were not significantly different.

HRV before PAF onset

We observed higher SDNN values in 5–0 min, compared with all other intervals and the control period (*Figure 4*); the differences reached statistical significance were indicated in *Table 6*.

In the frequency domain, a significant lowering of LF [normalized unit (nu)] value in the 5–0 min interval was noted, whereas HF was similar in all intervals (*Table 7*); as a consequence, also LF/HF ratio was significantly lower in 5–0 min interval (*Table 7* and *Figure 5*).
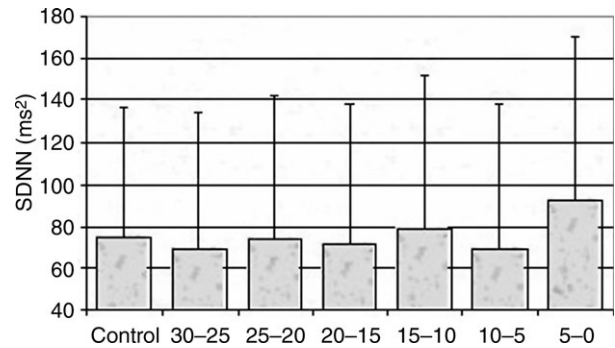

Figure 4 Time domain HRV: standard deviation of normal RR intervals (SDNN) in six periods of 5 min each, in the half hour preceding the AF onset and in a 5 min control period at least 60 min from PAF onset, and with heart rate similar (± 10 bpm) to the 5–0 min interval.

Analysis of HRV in the frequency domain (LF/HF) in subgroups showed a substantially similar pattern, in patients younger or older than 65 years, and for episodes occurring during day or night. Moreover, no significative difference was noted between patients with and without heart disease.

Discussion

The main findings of this non-randomized, retrospective, observational study are the following:

- the great majority of episodes of self-terminating PAF is induced by supraventricular ectopic beats; in more than half of the cases, a BE or PEP is present just before the arrhythmia starts;
- about two-thirds of triggering ectopic beats originate from the left atrium;
- coupling interval of triggering PACs is shorter in the absence of BE/PEP, whereas the prematurity index is higher; in brief, when bradycardia is present, AF may be induced with a longer CI;
- triggering PACs have a shorter CI compared with non-triggering PACs;
- in the hour preceding the start of arrhythmia, an increase in number of PACs is noted;
- paroxysmal atrial fibrillation onset is more frequent in the evening, during the night, and after lunch;
- a substantial increase in vagal tone is present in the minutes before the arrhythmia starts, even if a BE is not present.

The initiation of PAF by a PAC is well known,[8] as well as the more frequent left atrial origin of triggering PACs. In this report, we confirm that triggering of PAF by PACs is a general rule, including when the arrhythmia occurs in patients with organic heart disease.

The role of BEs or PEPs in facilitating the induction of PAF has been poorly studied, other than in the context of sick sinus syndrome (SSS)[9,10]; in our series, only one patient was affected by overt SSS, but about 50% of episodes were preceded by a BE or PEP; thus it is possible that bradycardia is simply the effect of increased vagal tone, which seems to be the hallmark of the autonomic balance before the onset of PAF.

Table 6 HRV analysis in time domain in six periods of 5 min each, before PAF onset

	Mean 24 h	Control	30–25	25–20	20–15	15–10	10–5	5–0
RR (ms)	812.8	902.5	901.9	899.9	904.8	890.4	900.9	875.6
SD′ ($\pm$)	180.7	166.6	159.5	168.8	161.5	164.6	166.6	154.1
SDNN (ms^2)	182.5	75.3	69.6	74.2	71.6	79.1	69.4	92.7
SD ($\pm$)	66.6	61.2	65.0	67.9	67.2	72.5	69.2	77.4
P-value*		**0.0591**	**0.0042**	**0.0584**	**0.015**	**0.1284**	**0.006**	

Alpha-level for statistical significance: $P < 0.0083$. RR: time between contiguous R-waves; SDNN: standard deviation of normal RR intervals.
*Difference with 5–0 min. Bold indicates a statistically significant value.

Table 7 HRV analysis in the frequency domain in six periods of 5 min each, before PAF onset.

	Control	30–25	25–20	20–15	15–10	10–5	5–0
LF (nu)	24.1	30.4	26.4	25.8	27.4	23.1	15.0
SD′ ($\pm$)	18.9	19.1	18.2	17.3	18.8	12.3	11.0
Difference from 5–0 min: *P*-value	*0.00121*	*0.00004*	*0.00010*	*0.00014*	*0.00052*	*0.00208*	
Difference from contiguous: *P*-value	*0.03057*	*0.20180*	*0.82090*	*0.61030*	*0.12018*		
HF (nu)	14.3	16.7	17.4	15.0	21.1	17.2	15.2
SD ($\pm$)	17.0	19.6	19.3	18.1	21.0	19.4	11.7
Difference from 5–0 min: *P*-value	*0.74685*	*0.59515*	*0.43583*	*0.95845*	*0.06506*	*0.48208*	
Difference from contiguous: *P*-value	*0.27926*	*0.68801*	*0.1862*	*0.01871*	*0.09758*		
LF/HF	4.5	6.3	6.4	6.0	4.9	6.2	1.5
SD ($\pm$)	4.6	8.2	10.6	6.9	9.1	8.5	1.5
Difference from 5–0 min: *P*-value	*0.00010*	*0.00061*	*0.00553*	*0.00012*	*0.01925*	*0.0053*	
Difference from contiguous: *P*-value	*0.09413*	*0.90853*	*0.67097*	*0.17555*	*0.09929*		

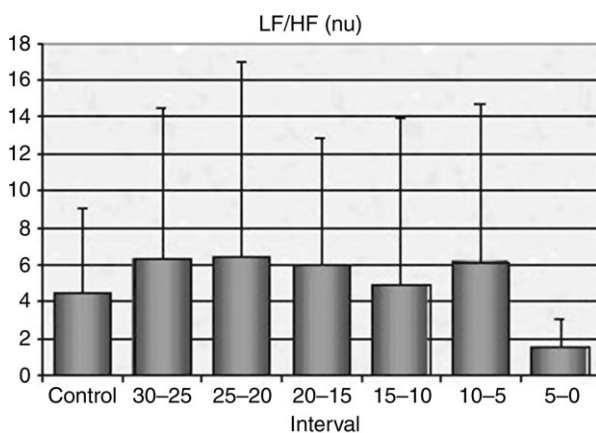Alpha-level for statistical significance: $P < 0.0045$.

Figure 5 Frequency domain HRV: values of LF/HF ratio in six periods of 5 min each, in the half hour preceding the AF onset and in a 5 min control period at least 60 min from PAF onset, and with heart rate similar (± 10 b.p.m.) to the 5–0 min interval.

Triggering PACs show a shorter CI than non-triggering PACs, and the frequency of PACs increases in the 60 min before the arrhythmia starts: we may affirm that the induction of the arrhythmia is a probabilistic matter and that induction is more probable when ectopic beats are more frequent and more premature, as affirmed in a previous report.[11]

Circadian distribution of episodes shows a prevalence of PAF onsets in periods of the day when generally vagal tone is predominant. This pattern confirms many previous reports[12–14]; another peak of frequency is noted during lunchtime and could be possibly related to gastric distension giving a mechanical stimulus to the atrial wall.

Finally, the vagal prevalence in the minutes before the onset of arrhythmia is confirmed in our series[12–20]; interestingly, the vagal predominance is also present if no BE or PEP is recorded before the PAF induction. The role of increased vagal tone is thus not only manifest by bradycardia (that increases *per se* the dispersion of refractoriness and slows conduction velocity) but it is possibly related to the pure effect of acetylcholine on K^+ channels, with dispersion of refractoriness and facilitation of spiral waves.[21]

A very similar analysis to ours was published by Dimmer *et al.*[22]: in a smaller number of episodes of PAF, they identified 21% of cases in which HR decelerates before AF and 37% of cases in which HR accelerates. This method of classification of HR variation before AF induction is different from ours, and this can explain the differences between the two series (21% of decelerators for Dimmer *et al.* vs. 50.6% of BE/PEP in our group); however, in both series, an increase of SD before AF was observed (also normalized for HR in Dimmer's series) as well as an increase in PACs before the arrhythmia onset. The spectral analysis showed no variation of LF/HF ratio, although we could demonstrate its reduction, possibly because of a larger sample size.

Most information that can be drawn from our observational study on a non-invasive diagnostic tool may be

useful to plan and perform interventional procedures in patients with PAF. The knowledge, for example, of a trigger predominantly originating from the right atrium, may avoid long and potentially harmful procedures in the left atrium; the evidence of a vagal predominance before the start of arrhythmia may indicate performance of not only isolation of the pulmonary vein but also vagal denervation of the zone around pulmonary vein orifices.[23]

At the same time, it is possible to detect those cases where pacing therapy can be useful to prevent recurrences of AF. Hoffmann et al.[24] described the onset scenario of AF using telemetric data of an implanted pacemaker: an atrial based pacing device may avoid BEs before the arrhythmia onset and reduce the number of ectopic beats with specific algorithms.

The third major factor affecting the arrhythmia induction, besides triggering and autonomic balance is the substrate: in this field, little information can be drawn from our episodes of PAF recorded with ambulatory monitoring. Modifications of substrate due to structural remodelling are more frequently associated with the persistent and permanent forms of AF, and as shortening of the refractory period is the hallmark of atrial remodelling, the remodelling process is poorly disclosed by ambulatory ECG recordings.

Limitations of the study

Our results refer to PAF episodes lasting from 30 s to <24 h: this is due to the method that was used (24 h HM); however, all the considerations that have been made have excluded episodes of PAF lasting up to 7 days, that is the limit considered for the paroxysmal form of AF in the ACC/AHA/ESC guidelines.[5]

Even though a triggering PAC was recognized in almost all cases, we cannot exclude the presence of a triggering PAC even in 'sudden onset' episodes, as an early ectopic P-wave can occur during ventricular repolarization and, thus, be masked by the T-wave. Furthermore, atrial ectopic depolarization can generate a P-wave with an axis perpendicular to the recording dipolar yield a flat and potentially undetectable P-wave. Also artefacts can influence the accuracy of triggering PAC detection. Unfortunately, little information is available regarding symptomatic or asymptomatic episodes.

Exclusion of episodes with an excess of PACs from HRV analysis in the frequency domain, caused by the impossibility to calculate the power spectrum of the period, can actually represent a critical point, because it is possible that we excluded a significant population. Even if time domain results, obtained without this exclusion, are coherent demonstrating a higher value of SDNN in the 5 min before the onset, we cannot definitively exclude that the frequency domain analysis is applicable to the population with few ectopic beats in the 30 min before the onset of the arrhythmia.

Conclusions

Difficulties in preventing PAF require improvement in understanding the physiopathological aspects of its onset. This is particularly complex, because PAF onset results from interactions of three complex systems, which are substrate, triggers, and the autonomic nervous system.

Our results suggest that a careful evaluation of the relative predominance of each of these aspects permits a more appropriate therapeutic decision.

Is noteworthy that much information on the mechanism of onset can be obtained easily and at low cost with ambulatory monitoring.

In particular, we recommend evaluation of the time of onset for the choice of type and time of administration of antiarrhythmic drugs; evaluation of frequency and origin of PACs and to guide the decision on drugs or ablation; evaluation of CI of triggering PACs may imply use of a Class III antiarrhythmic drug to prolong refractory period; last, but not least, the evaluation of autonomic balance, as many of the available drugs for the prevention of PAF themselves modulate this balance.

References

1. Kannel WB, Wolf PA, Benjamin EJ et al. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. Am J Cardiol 1998;82:2N–9N.
2. Lévy S, Maarek M, Coumel P et al. Characterization of different subsets of atrial fibrillation in general practice in France. The ALFA study. Circulation 1999;99:3028–35.
3. Allessie MA, Boyden PA, Camm J et al. Pathophysiology and prevention of atrial fibrillation. Circulation 2001;103:769–77.
4. Shinagawa K, Shiroshita-Takeshita A, Schram G, Nattel S. Effects of antiarrhythmic drugs on fibrillation in the remodeled atrium: insights into the mechanism of the superior efficacy of amiodarone. Circulation 2003; 107:1440–6.
5. Task Force report: ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation. Eur Heart J 2001;22:1852–923.
6. Tang CW, Scheinman MM, Van Hare GF et al. Use of P wave configuration during atrial tachycardia to predict site of origin. J Am Coll Cardiol 1995;26:1315–24.
7. Task Force of the European Society of Cardiology, and the North American Society of Pacing and Electrophysiology: heart rate variability: standards of measurement, physiological interpretation and clinical use. Circulation 1996;93:1043–65.
8. Haïssaguerre M, Jaïs P, Shah DC et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med 1998;10:659–66.
9. Saksena S, Delfaut P, Prakash A, Kaushik RR, Krol RB. Multisite electrode pacing for prevention of atrial fibrillation. J Cardiovasc Electrophysiol 1998;9(Suppl.):S155–62.
10. Saksena S, Prakash A, Hill M et al. Prevention of recurrent atrial fibrillation with chronic dual-site right atrial pacing. J Am Coll Cardiol 1996;28:687–94.
11. Capucci A, Santarelli A, Boriani G, Magnani B. Atrial premature beats coupling interval determines lone paroxysmal atrial fibrillation onset. Int J Cardiol 1992;36:87–93.
12. Herweg B, Dalal P, Nagy B, Schweitzer P. Power spectral analysis of heart period variability of preceding sinus rhythm before initiation of paroxysmal atrial fibrillation. Am J Cardiol 1998;82:869–74.
13. Fioranelli M, Piccoli M, Mileto GM et al. Analysis of heart rate variability five minutes before the onset of paroxysmal atrial fibrillation. Pacing Clin Electrophysiol 1999;22:743–9.
14. Bettoni M, Zimmermann M. Autonomic tone variations before the onset of paroxysmal atrial fibrillation. Circulation 2002;105:2753–9.
15. Coumel P, Attuel P, Leclerque JF et al. Arythmies auriculaires d'origine vagale ou catècholaminergique. Arch Mal Couer 1982;4:373–81.
16. Zimmermann M, Kalushe D. Fluctuation in autonomic tone is a major determinant of sustained atrial arrhythmias in patients with focal ectopy originating from pulmonary veins. J Cardiovasc Electrophysiol 2001;12:285–91.
17. Dimmer C, Tavernier R, Gjorgov N et al. Variation of autonomic tone preceding onset of atrial fibrillation after coronary artery bypass grafting. Am J Cardiol 1998;82:22–5.

18. Klingenheben T, Gronefeld G, Li YG *et al*. Heart rate variability to assess changes in cardiac vagal modulation before the onset of paroxysmal atrial fibrillation in patients with and without structural heart disease. *Ann Noninvas Electrocardiol* 1999;**4**:19–26.

19. Coumel P. Autonomic influence in atrial arrhythmias. *J Cardiovasc Electrophysiol* 1996;**7**:999–1007.

20. Huang JL, Wen ZC, Lee WL *et al*. Changes in autonomic tone before the onset of paroxysmal atrial fibrillation. *Int J Cardiol* 1998;**66**:275–83.

21. Kneller J, Zou R, Vigmond EJ *et al*. Cholinergic atrial fibrillation in a computer model of a two-dimensional sheet of canine atrial cells with realistic ionic properties. *Circ Res* 2002;**90**:E73–87.

22. Dimmer C, Szili-Torok T, Tavernier R, Verstraten T, Jordaens J. Initiating mechanisms of paroxysmal atrial fibrillation. *Europace* 2003;**5**:1–9.

23. Pappone C, Santinelli V, Manguso F *et al*. Pulmonary vein denervation enhances long-term benefit after circumferential ablation for paroxysmal atrial fibrillation. *Circulation* 2004;**109**:327–34.

24. Hoffmann E, Janko S, Stenbeck G, Edvardsson N, Camm J. Onset scenario of paroxysmal atrial fibrillation using new diagnostic pacemaker functions. *Pacing Clin Electrophysiol* 2000;**23**:656–69.