

Review Article

Circadian Distribution and Autonomic Tone Modulation in Paroxysmal Atrial Fibrillation

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Understanding the role played by autonomic tone changes in the initiation of paroxysmal atrial fibrillation (PAF) may be helpful in preventing the occurrence of the arrhythmia. The purpose of this review article is to discuss the relationship between sympathovagal imbalance and the initiation of PAF from past literature and our data regarding circadian distribution and heart rate variability (HRV) analysis in PAF. PAF in non-structural heart disease (NHD) frequently occurs during evening and night hours with a longer duration of each episode, and its initiation is directly associated with an increase in vagal tone. According to our data of HRV analysis in NHD, HF power (indicator of vagal tone) showed a reduction 15 to 30 minutes before PAF, followed by a sharp increase immediately before the onset, suggesting a primary increase in sympathetic tone followed by a marked changes toward vagal predominance. Very few studies have been reported on PAF onset or the modulation of autonomic tone in structural heart disease (SHD). Some studies showed no significant differences in the circadian variation of the onset between NHD and SHD. However, we demonstrated a triphasic circadian pattern with maximum peaks in early morning, late afternoon, and night in SHD, suggesting an association with not only a vagally induced origin but also a sympathetically induced or stress triggered origin in PAF onset in SHD. The occurrence of PAF greatly depends on modulation of autonomic tone and is extremely complicated. Further studies are required to clarify the relationship between the occurrence of PAF and autonomic modulation.

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Key words: PAF, Circadian variation, Autonomic changes, Structural heart disease, Non-structural heart disease

Introduction

Circadian distribution has been reported in some cardiovascular disorders such as acute myocardial infarction,¹⁻³⁾ sudden cardiac death,^{4,5)} transient myocardial ischemia^{6,7)} and stroke,⁸⁾ with a predominance of incidents occurring in the early morning.

One reason for this is considered to be related to an abrupt change from a predominantly vagal tone to a dependent sympathetic tone in the early morning. Ventricular premature contractions and supraventricular premature contractions have been known to demonstrate circadian fluctuation patterns with high reproducibility in each patient; daytime, nighttime and both day- and nighttime onset, and irregular

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occurrence.⁹⁻¹¹⁾ There are also many reports regarding the circadian distribution of the occurrence of episodes of paroxysmal supraventricular tachycardia (PSVT).¹²⁻¹⁹⁾

In recent years, heart rate variability (HRV) analysis has enabled us to provide a quantitative evaluation of sympathovagal interaction in patients with cardiac disorders. Reduced vagal and augmented sympathetic activities have been increasingly linked to life-threatening ventricular arrhythmias, sudden cardiac death, total mortality after myocardial infarction, and congestive heart failure.²⁰⁻²³⁾ Alterations in sympathovagal balance with reduced vagal and increased sympathetic outflow to the heart are also reported in patients with advanced hypertrophic and dilated cardiomyopathy.²⁴⁾

Atrial fibrillation is a common arrhythmia with or without structural heart disease.²⁵⁾ Especially, initiation of paroxysmal atrial fibrillation (PAF) in patients with non-structural heart disease (NHD) is reportedly associated with specific circadian distribution^{13,15-18,26-30)} and with changes of sympathetic or vagal tone seen clinically³¹⁻³³⁾ or with HRV analysis.^{28,34-38)}

In this article we reviewed the circadian distribu-

tion of PAF and the effect of autonomic tone modification on PAF initiation.

Holter monitoring and atrial fibrillation

Holter monitoring is an indispensable tool for detection, diagnosis, or management of arrhythmia. In order to learn which clinical and basic uses of Holter monitoring have been favored by cardiologists around the world, a search for ‘Holter monitoring’ was done from literature included in PUBMED/MEDLINE.³⁹⁾ The 10 most prevalent topics from a search for ‘Holter monitoring’ for literature published between January 2002 and March 2007 are shown in **Figure 1**. The most frequently observed subject was ‘heart rate variability (HRV),’ which was found in 182 out of 1,885 articles followed by ‘atrial fibrillation’ in 99 articles. Thus, Holter monitoring is frequently used to investigate HRV and atrial fibrillation.

Figure 2 shows the 10 most prevalent topics obtained from a search for ‘Holter monitoring and atrial fibrillation’ between January 2000 and March 2007 in articles included in PUBMED/MEDLINE.³⁹⁾ Among them, the seventh most prevalent topic was ‘autonomic nervous system’.

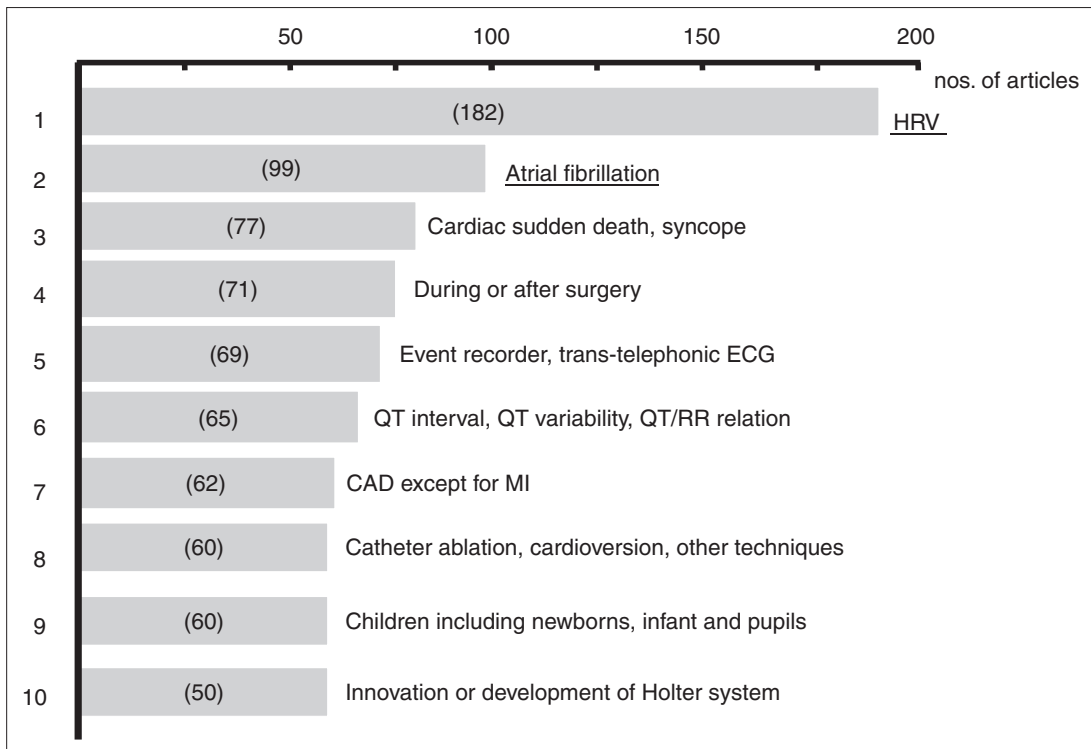


Figure 1 Top 10 topics among 1885 articles from a PUB/MED search for ‘Holter monitoring’ between Jan 1, 2002 and March 31, 2007.

HRV: heart rate variability, CAD: coronary artery disease, MI: myocardial infarction

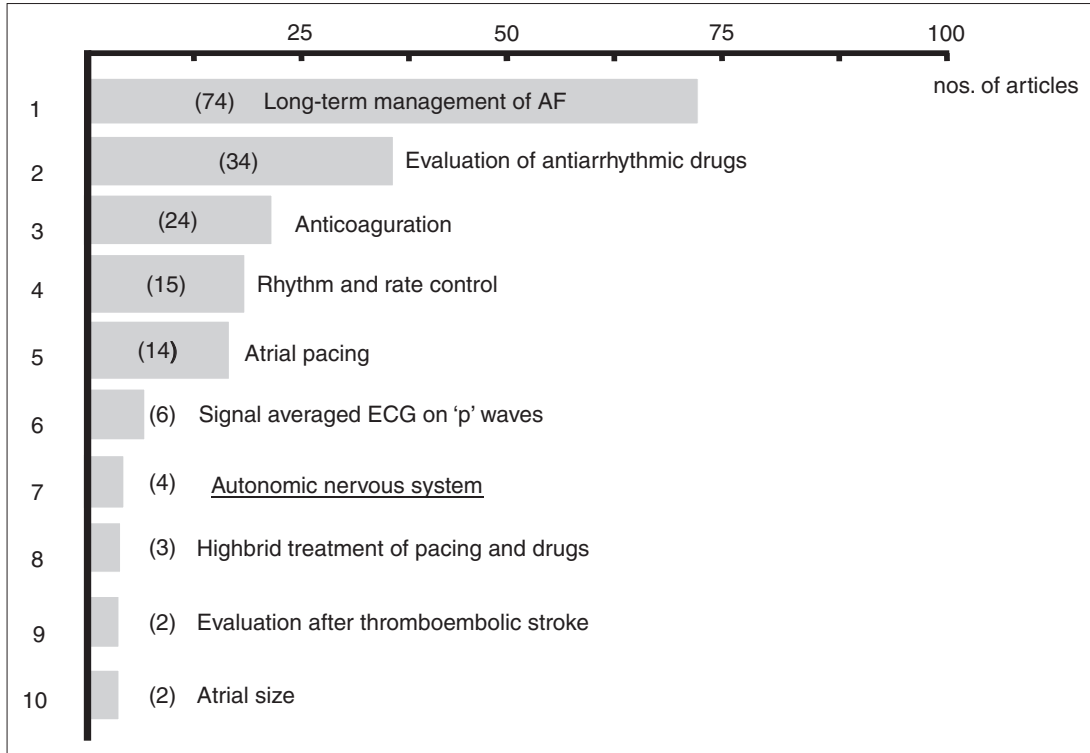


Figure 2 The 10 most prevalent topics among 618 articles in PUB/MED search for 'Holter monitoring and atrial fibrillation' between Jun 1, 2000 and March 31, 2007. AF: atrial fibrillation.

Circadian distribution of supraventricular tachyarrhythmias

1. Paroxysmal supraventricular tachycardia

PSVT, PAF and atrial flutter are well known supraventricular tachyarrhythmias with episodes of paroxysms. **Table 1** shows review literature investigating circadian variation in the onset of supraventricular tachyarrhythmias including PAF and PSVT. Irwin et al.¹⁴⁾ observed a peak incidence of PSVT in the afternoon and evening with a maximum at 4:00 pm. Regarding the PSVT, there is relatively broad consensus that episodes occur mainly during the afternoon.^{17,18)} However, there are studies demonstrating a double-peak with a peak occurring with PSVT in the morning in addition to the afternoon peak.^{16,19)} Plasma concentration was higher during the daytime (8:00 am to 6:00 pm) than at night in patients with essential hypertension.⁴⁰⁾ The reason for this high incidence of PSVT mainly in the afternoon or early morning may be based on an acceleration in electrophysiologic conduction of the atrioventricular node induced by adrenergic prevalence.⁴¹⁾ As a matter of fact, the abolition of the

morning peak induced by β -blockers is consistent with this hypothesis.¹⁶⁾

2. Paroxysmal atrial fibrillation

There are many studies on circadian distribution of the onset of PAF.^{15-18,26-30)} Some of them have demonstrated a double-peak occurrence of PAF with morning and evening,^{16,29)} whereas the others showed peaks during midnight and in the morning,¹⁷⁾ or after lunch and at midnight.²⁷⁾ Also, there are studies demonstrating a much higher occurrence during the day than at night,^{26,28)} triple peaks—noon to 2:00 pm, 6:00 pm to 2:00 am and 4:00 am to 6:00 am,³⁰⁾ and no circadian distribution.¹⁸⁾ The data for PAF showing a peak incidence during the night are completely different from those for PSVT in which episodes mainly occurred in the afternoon. The mechanisms responsible for this difference are not clear.

Experimentally, atrial fibrillation can be initiated by application of acetylcholine to the localized region of the auricular surface.⁴²⁾ Clinically, in patients with frequent PAF episodes, especially with NHD, the onset of paroxysms is often associated with an increase in vagal tone.^{31,32)} Therefore, a

Table 1 Literatures reviewed from investigation of the circadian distribution of proxysmal atrial fibrillation atrial (PAF) and paroxysmal supraventricular tachycardia (PSVT).

Author	Publish (year)	Nos. of patients (men/women)	Mean age (y.o)	Arrhythmia (Nos. of episodes)	Underlying HD (Nos. of patients)	Drugs	symptomatic (S) or asymptomatic (A)	Peak time of incidence
Irwin JM, et al.	1988	52 (?)	46.2 ± 15.7	PSVT (52)	presence	non	S, telephone contact or regular clinic visits	PSVT: afternoon and evening, with peak at 4 pm
Kupari M, et al.	1990	251 (170/81)	49	PSVT (69), PAF (152)	presence (127) absence (82)	AAD, β -blocker	S, emergency room	PAF: double-peaking with evening and morning. PSVT: morning
Rawles JM, et al.	1990	72 (?)	72 (34-93)	PAF (139)	not described	AAD, β -blocker, Digoxin	S & A, Holter monitoring	PAF: more often by day than by night
Rostagno C, et al.	1993	1,118 (?)	not described	PSVT (348), PAF (726)	presence, absence	not described	S, mobile coronary care unit	PAF: with a peak between midnight and 2 am. With secondary peak in the morning (8 to 9 am). PSVT: during the daytime
Clair WK, et al.	1993	150 (79/71)	not described	PSVT (92), PAF (34)	presence, absence	drug free	S, event ECG recorder and telephone transmission	PAF: no circadian distribution. PSVT, with peak at approximately at 6 pm.
Yamashita T, et al.	1997	150 (120/30)	61.6 ± 12.8	407 PAF (407)	absence	drug free	S & A, Holter monitoring	PAF: with a double peak after lunch and at midnight
Huang JL, et al.	1988	57 (34/23)	66 ± 22	PAF (121)	presence (27) absence (30)	not described	S & A, Holter monitoring	PAF: the most common onset time between 4:00 am and 4:00 pm (40/63). No different circadian distribution pattern between vagal and sympathetic type PAF.
Lee SH, et al.	1999	105 (?)	not described	PAF (498)	not described	drug free	S & A, Holter monitoring	PSVT: with a peak during daytime, especially with peaks at 8:00 am to 9:00 am, 12:00 pm to 1:00 pm, and 5:00 to 6:00 pm.
Viskin S, et al.	1999	3,343 (1,872/1,471)	74.3 ± 12	PAF (9,989)	presence, absence	AAD and other drugs	S, event ECG recorder and telephonic transmission	PAF: with a double peak with a significant increase in the morning and a second rise in evening
Vincenti A, et al.	2005	90 (58/32)	67.7 (34-93)	PAF (233)	presence (28)	not described	S & A, Holter monitoring	PAF: triple peaks with noon to 2:00 pm, 6:00 pm to 2:00 am, and 4:00 am to 6:00 am.

subset of PAF has the increase in vagal tone as a partial mechanism since the above periods with a peak incidence of PAF during the night may be characterized by predominance of vagal tone.

However, most of the past studies vary greatly as to the circadian distribution of the onset of PAF, as described previously. Their weakness is that they do not measure the true circadian variation of PAF because they included only patients with symptomatic episodes,^{16-18,29)} those with unusual circumstances such as emergency room¹⁶⁾ or mobile coronary care unit,¹⁷⁾ those taking antiarrhythmic drugs including β -blockers,^{16,26,29)} those with event ECG recorder or

transtelephonic transmission of ECG,^{18,29)} and those with both structural heart disease (SHD) and NHD.^{16-18,28)} Furthermore, some studies did not describe whether the patients were on antiarrhythmic drugs including β -blockers,^{19,21,23,29)} although this is a very important aspect.

Nevertheless, only one paper, which was published by Yamashita et al.,²⁷⁾ precisely described the patient characteristics of NHD, absence of drug therapy and inclusion of both symptomatic and asymptomatic subjects. They analyzed the circadian variation not only at the onset of PAF but also the hourly total duration, maintenance and termination

of the arrhythmia from 150 Holter recordings with a total of 407 episodes of PAF in a drug-free state with NHD. They demonstrated non-uniformity of hourly total duration across the 24 hours, reflecting a non-random occurrence of PAF throughout the day, with an increase at night with a peak at about midnight and a decrease in the morning with a nadir at about 11:00 am. The incidence of onset was also non-uniformly distributed throughout the 24-hour period because it showed a double peak with increases after lunch and at midnight. However, the probability of onset could not be fitted to a single- or double-harmonic curve, although the incidence had a weak double-peaked diurnal rhythm (Figure 3A). In contrast, they observed significant circadian variations for both the maintenance period and termination of PAF: a sharp decline in the morning to a nadir at about 10:00 am and then a gradual increase after lunch in the maintenance period and a double-curve with peaks at 11:00 am to 12:00 pm and 10:00 pm to 11:00 pm. The authors suggested that the maintenance and termination of PAF showed more distinct circadian variations compared with the onset (Figure 3B, C).

There are very few reports which compare the circadian distribution of the onset of PAF between SHD and NHD. Kupari et al.¹⁶⁾ and Rostagno et al.¹⁷⁾ described that no significant differences in the circadian variation of the onset of PAF existed between the 2 groups. However, they included only patients with symptomatic episodes who were admitted to hospital in unusual circumstances such as emergency room or mobile coronary care unit, and took antiarrhythmic drugs including β -blockers.

We conducted a study of the circadian distribution of the hourly total duration, onset, maintenance and termination of PAF using Holter monitoring method in a drug-free state, which was similar to the protocol of Yamashita et al.²⁷⁾ comparing SHD and NHD patients. As a result, the circadian distribution at onset of PAF throughout 24 hours showed a marked difference between the 2 groups. The SHD group showed a triphasic circadian pattern with maximum peaks in the late afternoon, between late evening and night, and in the early morning, whereas the NHD group had a single harmonic peak between late evening and midnight (Figure 4). The coefficients of the two groups were significant ($p < 0.05$ in SHD and $p < 0.01$ in NHD). The circadian distribution of the probability of termination of PAF in SHD was demonstrated with a peak around noon and with a nadir at around midnight with a significant difference in the distribution ($p < 0.05$) (Figure 5). On the

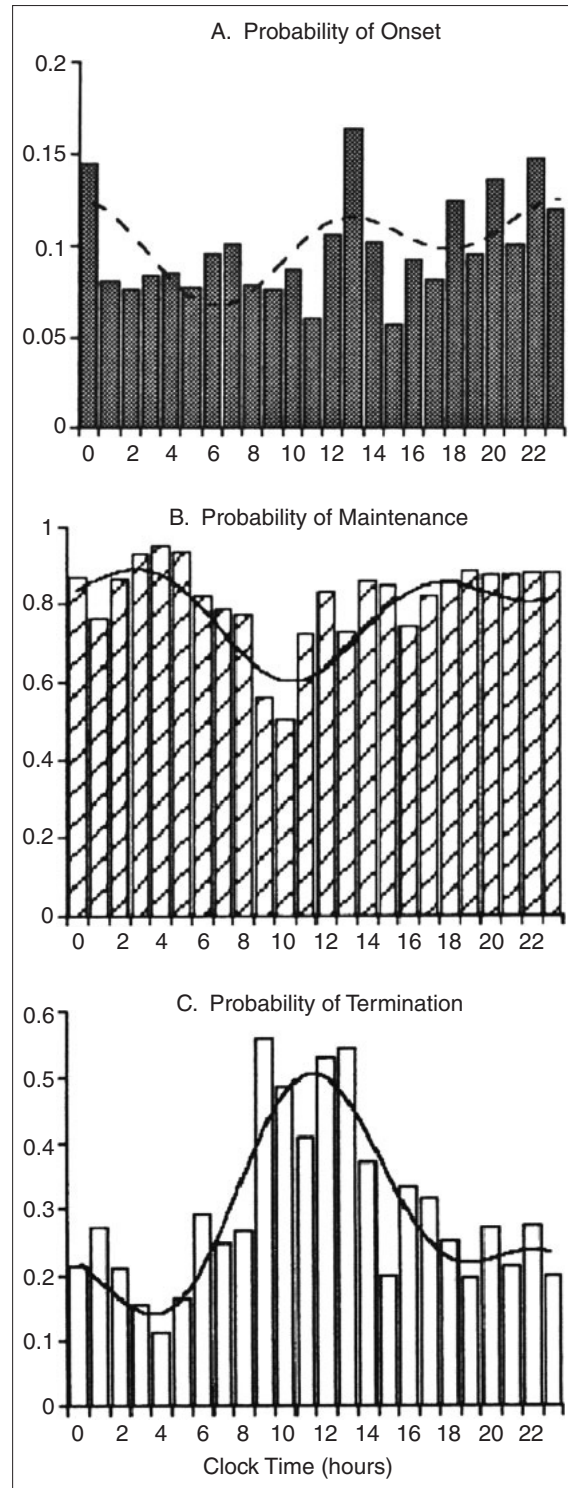


Figure 3 Hourly probability of paroxysmal atrial fibrillation episodes (A: onset, B: maintenance, C: termination) (from Yamashita T et al: Circadian variation of paroxysmal atrial fibrillation. *Circulation* 1997; 96: 1537–41 Reference No. 27).

other hand, in the distribution in the NHD group, a weak double-peaks at around 6:00 am–11:00 am and

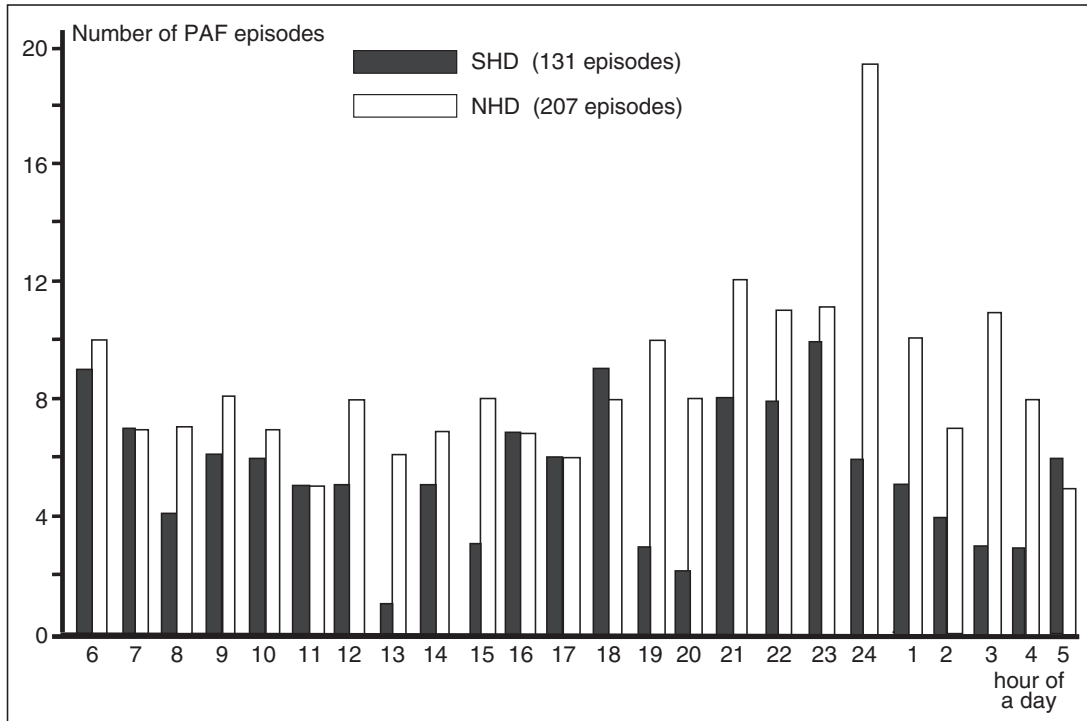


Figure 4 Circadian distribution of the onset of paroxysmal atrial fibrillation—comparison between structural (SHD) and non-structural (NHD) heart diseases.

8:00 pm–0:00 am were demonstrated although not significant ($p = 0.063$). This observation in the NHD group was similar to the outcome obtained by Yamashita et al.²⁷⁾ with a double-curve with peaks at 11:00 am to 12:00 pm and 10:00 pm to 11:00 pm. Therefore, it may be an indication that spontaneous cessation of PAF occurs in the morning until around noon and in the late evening.

Dynamic changes in autonomic tone in the onset and termination of PAF

In recent years, autonomic tone has been easily and noninvasively measured by heart rate variability (HRV) analysis. In particular, the measurement of autonomic tone in humans plays a critical role because reduced vagal and augmented sympathetic activities are reported to be an independent predictor of sudden cardiac death and total mortality in patients with prior myocardial infarction^{43–45)} and chronic heart failure.^{46,47)} On the other hand, HRV analysis is also important for investigating alterations of neural regulatory mechanisms in the genesis of arrhythmias. As a matter of fact, changes in autonomic tone before the onset of spontaneous idiopathic ventricular tachycardia has been investigated and the relationship between autonomic

nerve activity and life-threatening ventricular arrhythmias has been studied in patients with a variety of underlying heart disorders.²³⁾

Coumel^{31–33)} is the first to demonstrate PAF related to vagotonic or sympathetic activity from initiation and its relation to fluctuation in autonomic tone, but his classification was done from clinical observations without HRV analysis. **Table 2** shows authors, underlying heart disease, drugs administered and outcome of HRV analysis in reviewed literature of studies on HRV before the onset of PAF. Huang et al.²⁸⁾ classified 3 subtypes according to the HRV analysis before the onset of PAF: onset of PAF accompanied with increased high-frequency component (HF) and decreased low-frequency component (LF)/HF ratio before the PAF onset designated as the vagal type; decreased HF component and increased LF/HF ratio designated as the sympathetic type; and other episodes which did not belong to vagal or sympathetic type designated as the non-related type. As a result, vagal type was predominant (41/63 episodes, 63.5%) in NHD PAF group (idiopathic PAF) whereas sympathetic type was predominant (39/58 episodes, 67.2%) in SHD PAF group.

Other studies also demonstrated strong connection between an increase in HF or increased vagal

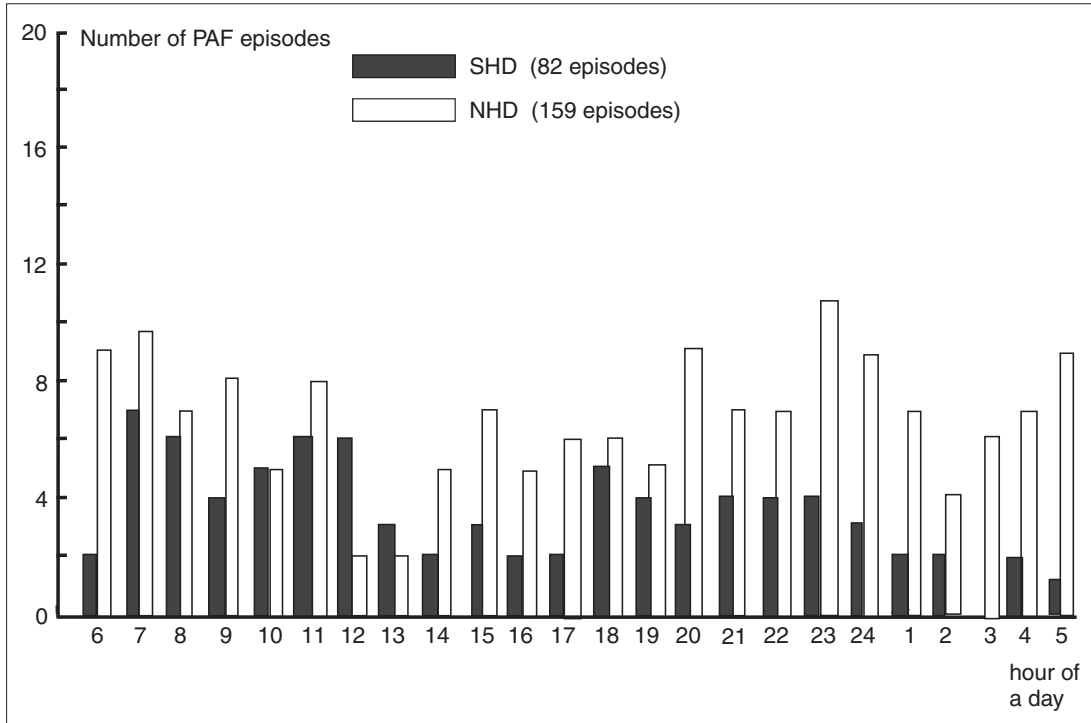


Figure 5 Circadian distribution of the termination of atrial fibrillation: comparison between structural (SHD) and non-structural (NHD) heart diseases.

activity with nighttime initiation PAF, and that of an increase in LF/HF and an decrease in HF or increased sympathetic activity with daytime initiation PAF in patients in a drug-free state with structurally normal heart.^{34,38)} Fioranelli et al.³⁵⁾ investigated changes in sympatho-vagal balance only within 5 minutes before the onset of PAF in patients in a drug-free state without structural cardiac diseases. They observed two types of abrupt changes in sympatho-vagal balance even in the last 5 minutes preceding an episode of PAF; Type A with an increase of LF and LF/HF and a decrease of HF, and Type B with a reduction of LF and LF/HF and an increase of HF.

An increase in vagal tone reportedly shortens the atrial refractory period, augmentation of heterogeneity of refractoriness and facilitate intraatrial reentry.⁴⁸⁾ Strengthened sympathetic tone is likely to induce automaticity and delayed afterdepolarization.⁴⁹⁾ Therefore, any changes in individual vagal or sympathetic tone, or sympatho-vagal imbalance may initiate PAF.

It is widely recognized that premature beat foci located at or near the orifice of the pulmonary veins are often involved in the genesis of PAF.⁵⁰⁻⁵²⁾ Zimmemann and Kalusche³⁶⁾ analyzed dynamic changes in autonomic tone preceding the onset of

PAF with proven pulmonary vein origin. They concluded that episodes of focal PAF originating from pulmonary veins are mainly dependent on variations of autonomic tone, with a significant shift toward vagal predominance before PAF onset.

Bettoni and Zimmermann³⁷⁾ analyzed dynamic change in autonomic tone preceding the onset of PAF by measuring HRV in a total of 147 episodes of the arrhythmia; the 24-hour period, one hour before the PAF onset and the 20 minutes before PAF divided into four 5-minute periods. Their observations were interesting with regards to suggesting a primary increase in adrenergic tone followed by a marked modulation toward vagal predominance before the onset of PAF. The reason for this interpretation was that the LF/HF ratio showed a linear increase until 10 minutes before the arrhythmia, followed by a sharp decrease immediately before it. They also demonstrated a significant alteration in SDANN (standard deviation of RR intervals) and SDNN (standard deviation of the averages of RR intervals for 5 minute segments) parameters of time domain analysis of HRV, and an increase in atrial ectopy in the minute before the PAF onset in more than 50% of patients. Increased frequency of atrial premature beats before the onset

Table 2 Literatures reviewed from investigation of heart rate variability before the onset of paroxysmal atrial fibrillation (PAF).

Authors	Publish year	Nos. of patients (men/women)	Mean age y.o.	Underlying HD (Nos. of patients)	Drugs	Outcome of HRV analysis
Huang JL, et al.	1998	57 (34/23)	66 ± 22	presence (27) absence (30)	not described	A significant increase in HF in majority of idiopathic PAF (41/63 episodes) and a significant increase in LF/HF ratio (39/58 episodes) in organic heart disease PAF.
Herweg B et al.	1998	29 (18/11)	61 ± 13	presence (16 including 6 HT) absence (13)	Digoxin, β-blockers, Ca-blockers	Contrary to daytime PAF, an increase in vagal activity preceded predominantly nocturnal PAF, mostly in younger patients with structurally normal heart.
Fioranelli M et al.	1999	28 (20/8)	60 ± 11	absence (28)	drug-free	Abrupt HRV changes in the last 5 minutes before the onset of PAF. One group revealed an increase in LF and LF/HF, and a decrease in HF suggesting an enhancement of sympathetic drive. The other demonstrated a reduction of LF and LF/HF, and an increase in HF consistent with an enhancement of vagal drive.
Zimmermann M et al.	2001	13 (10/3)	53 ± 5	absence and pro ven pulmonary vein origin (13)	drug free (11 pts, 85%)	Pulmonary vein origin AF are mainly dependent on variations of autonomic tone, with a significant shift toward vagal predominance before AF onset.
Bettoni M et al.	2002	77 (63/14)	58 ± 12	absence	amiodarone (9 pts), β-blockers (18 pts), digoxin (10 pts)	PAF onset greatly depends on variations of autonomic tone, with a primary increase in adrenergic tone followed by an abrupt shift toward vagal predominance.
Tomita T et al.	2003	23 (12/11)	65 ± 2	absence	drug-free	PAF was preceded by a gradual increases in HF and LF component without changes of LH/HF ratio in the nighttime initiation PAF. Conversely, daytime initiation PAF group demonstrated a significant increase in the LF/HF ratio before PAF without changes in HF.

of PAF may result in an enlarged standard deviation of RR intervals and a subsequent incorrect interpretation as an increase of vagal predominance. Therefore, HRV should be evaluated without preceding atrial premature beats before the onset of PAF. In this regard, we studied PAF patients with NHD in untreated state and having one or zero premature beats every minute for 5 minutes before the onset of the arrhythmia divided into 4 time periods: morning (6:01 am to 12:00 pm), afternoon (12:01 pm to 6:00 pm), evening (6:01 pm to 0:00 am) and night (0:01 am to 6:00 am). **Figure 6** shows the changes in HF and LF/HF in the evening onset PAF from just before to 120 minutes before the onset of the arrhythmia. Significantly accelerated HF power and reduced LF/HF ratio just before the PAF onset as compared to 5 to 10 minutes before the onset are observed. Interestingly, note that accelerated HF just before the onset of PAF is preceded by a reduction in HF and reduced LF/HF just before the onset of arrhythmia is preceded by an increase in LF/HF ratio

as compared to those parameters 15 to 30 minutes before the onset. These observations may be an indication that the initiation of PAF needs a reduction in vagal tone or an increase in sympathetic tone, or both about 20 minutes before the onset, and then a sharp increase in vagal tone just before the onset, especially in evening onset PAF.

Tomita et al.³⁸⁾ evaluated HRV parameter changes in a 10-minute segments at 60 minutes, 20 minutes, and at time of onset, not only before the onset of PAF but also after its termination in 23 patients with NHD. They showed a significant decrease in HF and LF components after the termination of PAF in group N (n = 14), in which PAF began at night and was preceded by a gradual increase in HF and LF. This group, however, demonstrated no changes in the LF/HF ratio both before and after the arrhythmia. In contrast, group D (n = 9), in which PAF occurred during the daytime, showed a significant increase in the LF/HF ratio before PAF and a decrease in LF and the LF/HF ratio after PAF,

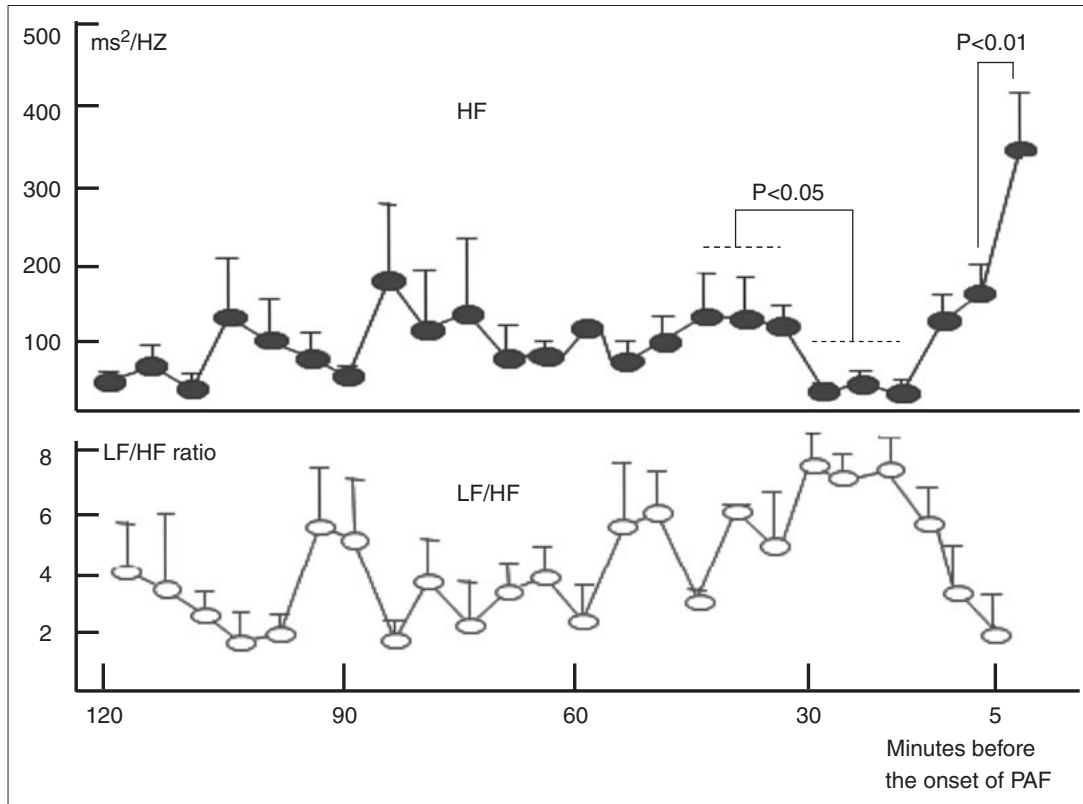


Figure 6 Fluctuation in HF component power (top panel) and LF/HF ratio (bottom panel) from 120 to 0 minutes preceding the onset of paroxysmal atrial fibrillation (PAF) in evening initiation PAF. One hundred twenty minutes were divided into twenty-four 5-minute segments from 120 to 0 minutes before the onset of the arrhythmia.

but no changes in HF. Consequently they suggested that the autonomic nervous system played an important role in both the initiation and termination of PAF.

By looking at the variety of studies mentioned above, there is a consensus on the onset mechanism of PAF regarding the fluctuation of autonomic tone in patients with NHD. It frequently initiates during the night and is strongly associated with a sharp increase in vagal tone just before the onset. Some studies emphasize that such a sharp increase of vagal tone is often preceded by a reduction of vagal tone or an increase of sympathetic tone. Very few studies are reported on the autonomic initiation mechanism of PAF in patients with SHD. Some studies demonstrate no change in circadian distribution of PAF onset between NHD and SHD patients. In contrast, our SHD patients showed a triphasic circadian pattern with maximum peaks in the late afternoon, between late evening and night, and in the early morning. Therefore, the autonomic onset mechanism in SHD seems very complicated compared to that in NHD. Further study is needed regarding this.

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