Atrial Ectopy, Autonomic Dysfunction, and Cardioembolic Risk: Holter Insights From the ES²CRYP Stroke Cohort

Ectopie atriale, dysfonction autonome et risque cardioembolique : Données du Holter Rythmique à partir de la cohorte ES²CRYP Stroke

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Summary

This paper explored the role of Holter monitoring in the characterization of atrial cardiomyopathy. Excessive atrial ectopy, supraventricular runs, and autonomic nervous system abnormalities provide valuable information regarding electrical instability and arrhythmogenic substrate.

In ES²CRYP Stroke Cohort, a PAC burden ≥400/day emerged as one of the strongest predictors of cardioembolic stroke and occult atrial fibrillation and was incorporated into the ES²CRYP score. Furthermore, patients with cardioembolic stroke exhibited a distinct autonomic profile characterized by increased vagal modulation, reflected by higher SDNN, RMSSD, pNN50, and HF power and lower LF/HF ratios.

Keywords

Atrial cardiomyopathy; Cardioembolic stroke; Premature atrial contractions (PACs); Occult atrial fibrillation; Holter monitoring; Heart rate variability; Autonomic dysfunction; ES²CRYP score.

Résumé

Ce travail a exploré l'apport de l'enregistrement Holter rythmique dans la caractérisation de la cardiomyopathie atriale. Une ectopie atriale excessive, la présence de salves supraventriculaires ainsi que les anomalies du système nerveux autonome fournissent des informations précieuses sur l'instabilité électrique atriale et le substrat arythmogène.

Au sein de la cohorte ES²CRYP Stroke, une charge en contractions atriales prématurées (PAC) ≥ 400/jour est apparue comme l'un des plus puissants prédicteurs d'accident vasculaire cérébral (AVC) cardioembolique et de fibrillation atriale occulte. Ce paramètre a ainsi été intégré au score ES²CRYP.

Par ailleurs, les patients ayant présenté un AVC cardioembolique se distinguaient par un profil autonome spécifique caractérisé par une augmentation de la modulation vagale, objectivée par des valeurs plus élevées de SDNN, RMSSD, pNN50 et de la puissance HF, associées à un rapport LF/HF plus faible.

Le score ES²CRYP comprend les composantes suivantes : âge ≥ 75 ans, sexe féminin, PALS ≤ 26,5 %, absence de maladie coronarienne, charge en PAC ≥ 400/jour, dispersion de l'onde P ≥ 55 ms et indice PTFV1 ≥ 3100 ms·µV.

Ce travail met particulièrement en évidence la composante arythmogène de la cardiomyopathie atriale, représentée par l'ectopie atriale excessive et la dysfonction du système nerveux autonome, comme déterminants potentiels du risque cardioembolique.

Mots-clés

Cardiomyopathie atriale ; Accident vasculaire cérébral cardioembolique ; Contractions atriales prématurées ; Fibrillation atriale occulte ; Holter ECG ; Variabilité de la fréquence cardiaque ; Dysfonction autonome ; Score ES²CRYP.

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INTRODUCTION

The traditional role of ambulatory electrocardiographic monitoring has been the detection of arrhythmias, particularly paroxysmal atrial fibrillation (AF). However, contemporary evidence indicates that Holter monitoring provides a far more comprehensive assessment of atrial disease. Beyond AF detection, Holter-derived parameters offer unique insights into atrial electrical remodeling, ectopic activity, sinus node behavior, and autonomic nervous system (ANS) regulation (1–4).

Atrial cardiomyopathy is increasingly recognized as a multidimensional disorder involving structural remodeling, electrical abnormalities, mechanical dysfunction, and autonomic imbalance (5,6). Continuous ECG monitoring allows simultaneous exploration of these different components and may identify patients with advanced atrial disease before the occurrence of overt AF.

PREMATURE ATRIAL CONTRACTIONS: THE ELECTRICAL SIGNATURE OF ATRIAL REMODELING

Pathophysiological Basis

Premature atrial contractions (PACs) arise from ectopic foci located outside the sinoatrial node. While occasional PACs are common in healthy individuals, an increased PAC burden is now considered a hallmark of atrial electrical remodeling (5,7).

Fibrosis and atrial structural disorganization create areas of conduction slowing and heterogeneity that facilitate triggered activity and micro-reentry. Consequently, PACs should be viewed not only as triggers of AF but also as markers of the underlying arrhythmogenic substrate (5,6,8).

Quantification of PAC Burden

Several parameters can be derived from Holter recordings:

Total PAC Count : The total number of premature atrial contractions recorded during 24 hours.

PAC Burden : The percentage of supraventricular ectopic beats relative to total heartbeats.

PAC Density : The number of PACs per hour

Prognostic Thresholds

In ES^{2}CRYP Stroke Cohort (9), receiver operating characteristic analysis identified the following thresholds as markers of advanced atrial cardiomyopathy:

- PAC count ≥ 400 PACs/24 h
- PAC burden ≥ 0.45%

Patients exceeding these thresholds exhibited a significantly higher probability of cardioembolic stroke and occult AF.

The threshold of 400 PACs/day was ultimately incorporated into the ES^{2}CRYP score and assigned a weight of three points, reflecting its strong independent predictive value.

EXCESSIVE SUPRAVENTRICULAR ECTOPIC ACTIVITY (ESVEA)

Excessive supraventricular ectopic activity represents a more advanced stage of atrial electrical instability.

Traditionally, ESVEA has been defined as:

- ≥720 PACs/day
- or ≥20 consecutive supraventricular beats

However, these thresholds vary considerably between studies.

Clinical Significance

ESVEA is associated with:

- Incident AF
- Cardioembolic stroke
- Increased mortality
- Progression of atrial remodeling

Several authors have proposed that ESVEA constitutes an electrophysiological manifestation of atrial cardiomyopathy (10–13)

SHORT ATRIAL RUNS

Short atrial runs are episodes of three or more consecutive supraventricular beats lasting less than 30 seconds. These arrhythmias represent an intermediate phenotype between isolated PACs and sustained AF.

Prognostic Threshold

In our study, the optimal ROC-derived cut-off was supraventricular runs ≥6 runs/24 h

Patients exceeding this threshold demonstrated significantly greater prevalence of cardioembolic stroke and occult atrial disease.

This finding suggests that short atrial runs should be regarded as markers of advanced electrical remodeling rather than benign rhythm disturbances.

HEART RATE VARIABILITY: A WINDOW INTO AUTONOMIC REGULATION (FIGURE 1)

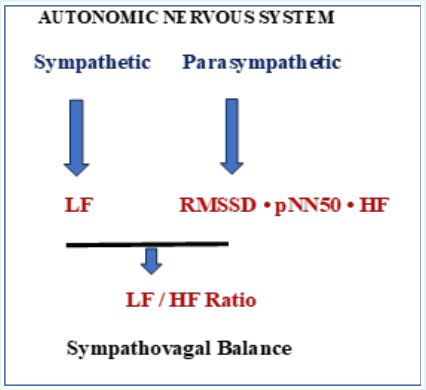


Figure 1. Relationship between HRV parameters and autonomic nervous system.

Physiological Background

Heart rate variability (HRV) refers to the physiological fluctuations in consecutive sinus RR intervals and reflects the dynamic interaction between the sympathetic and parasympathetic branches of the autonomic nervous system (ANS) (14,15). The sinoatrial node is continuously modulated by autonomic inputs, which influence heart rate, atrial refractoriness, conduction velocity, and susceptibility to arrhythmias (8,14,16,18).

Accumulating evidence indicates that autonomic dysfunction plays a pivotal role in atrial fibrillation initiation and maintenance. Increased vagal activity shortens atrial refractory periods and promotes reentrant circuits, whereas sympathetic activation enhances automaticity and triggered activity (8,16,18). Consequently, HRV analysis provides a non-invasive assessment of autonomic remodeling, which may represent an additional component of atrial cardiomyopathy beyond structural and electrical abnormalities (5,19).

Time-Domain Analysis

SDNN : The standard deviation of all normal-to-normal RR intervals (SDNN) represents the overall variability of sinus rhythm during the recording period and is considered the most robust measure of global autonomic modulation (14,15).

Physiological Significance

SDNN reflects the combined influence of sympathetic and parasympathetic activity on the sinus node. Lower values generally indicate autonomic impairment, whereas higher values reflect greater variability and preserved autonomic responsiveness (14,15). Normal 24-hour SDNN values generally range between 102 and 180 ms (14,15).

Clinical Evidence

Reduced SDNN has historically been associated with increased cardiovascular mortality and adverse outcomes in the Framingham and ARIC cohorts (20,21). However, in atrial cardiomyopathy, autonomic remodeling may follow a different pattern. Several studies suggest that enhanced vagal modulation contributes to atrial vulnerability and promotes atrial fibrillation initiation (16,18).

In ES^{2}CRYP Stroke Cohort , patients with cardioembolic stroke exhibited significantly higher SDNN values than patients with non-cardioembolic stroke. An SDNN value >120 ms was associated with cardioembolic stroke and occult atrial fibrillation in our population, suggesting increased vagal modulation as a characteristic feature of advanced atrial cardiomyopathy

RMSSD : The root mean square of successive differences (RMSSD) between adjacent RR intervals quantifies short-term beat-to-beat variability and is considered one of the most reliable markers of parasympathetic activity (14,15).

Physiological Significance

RMSSD predominantly reflects vagal modulation of the sinoatrial node and is relatively independent of sympathetic influences (14,15). Normal values generally range between 15 and 39 ms (15).

Clinical Evidence

Increased vagal activity has been implicated in the initiation of paroxysmal atrial fibrillation, particularly in patients without significant structural heart disease (8,16,18). RMSSD values above 50 ms identified patients with a higher probability of occult AF and cardioembolic stroke (16,18).

pNN50 : pNN50 represents the percentage of adjacent normal RR intervals differing by more than 50 milliseconds (14).

Physiological Significance

Like RMSSD, pNN50 primarily reflects parasympathetic modulation and is considered a marker of vagal predominance (13,14). Values below 10% are generally considered normal in middle-aged adults, although substantial age-related variation exists (15).

Clinical Evidence

Increased pNN50 values have been associated with enhanced vagal tone and may identify individuals susceptible to vagally mediated atrial arrhythmias (16,18).

ES²CRYP Stroke Cohort showed that patients with cardioembolic stroke exhibited significantly higher pNN50 values.

Frequency-Domain Analysis

Low-Frequency Power (LF) : Low-frequency power corresponds to spectral oscillations between 0.04 and 0.15 Hz (14).

Physiological Significance

Although historically considered a marker of sympathetic activity, LF is currently recognized as reflecting both sympathetic and parasympathetic influences, including baroreflex modulation (13,14). Typical 24-hour values range from 754 to 1586 ms^2 (15).

Clinical Relevance

LF provides information regarding autonomic responsiveness but should not be interpreted as an isolated measure of sympathetic activity (14,15).

High-Frequency Power (HF) : High-frequency power corresponds to oscillations between 0.15 and 0.40 Hz and reflects respiratory sinus arrhythmia (15).

Physiological Significance

HF is considered the most specific frequency-domain marker of parasympathetic activity (14,15). Normal values generally range between 772 and 1178 ms^2 (15).

Clinical Evidence

Enhanced vagal modulation, reflected by elevated HF values, has been linked to atrial fibrillation susceptibility and vagally mediated atrial arrhythmias (16,18).

In Our Cohort (9), HF power was significantly higher in patients with cardioembolic stroke.

Elevated HF values (HF power >200 ms^2) were independently associated with advanced atrial disease.

LF/HF Ratio : The LF/HF ratio represents the relationship between low-frequency and high-frequency oscillations and is commonly used as an indicator of sympathovagal balance (14,15).

Physiological Significance

Higher values suggest relative sympathetic predominance, whereas lower values indicate relative parasympathetic predominance (14,15). Normal values generally range between 1.5 and 2.0 (15).

Clinical Evidence

Several investigations have demonstrated that vagal predominance facilitates atrial fibrillation initiation by shortening atrial refractory periods and increasing electrical heterogeneity (8,16,18).

In ou cohorts , patients with cardioembolic stroke exhibited significantly lower LF/HF ratios than non-cardioembolic stroke patients.

This finding supports the hypothesis that autonomic remodeling characterized by increased vagal modulation contributes to advanced atrial cardiomyopathy and thromboembolic risk.

Table 1 indicates normal values of sinus variability parameters (8,14-18).

Table 1. Normal values of sinus variability parameters

Variables	Unity	Normal values
FC - max	bpm	101 - 70
FC - min	bpm	49 - 59
FC - moy	bpm	60 - 100
SDNN	ms	102 - 180
SDANN	ms	92 - 162
RMSSD	ms	15 - 39
BF	ms^2	754 - 1586
HF	ms^2	772 - 1178
BF/HF		1 - 5 - 2

AUTONOMIC DYSFUNCTION AS A COMPONENT OF ATRIAL CARDIOMYOPATHY

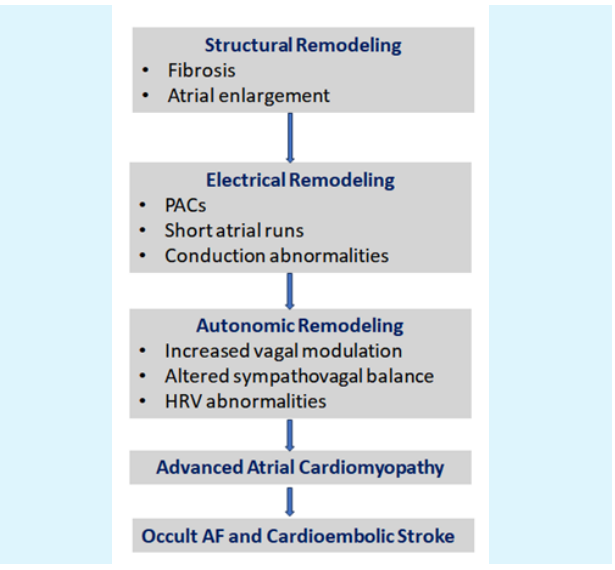
Traditionally, atrial cardiomyopathy has been conceptualized as a structural and electrical disease characterized by fibrosis, atrial enlargement, and conduction abnormalities.

Our findings support a broader paradigm.

Autonomic imbalance appears to represent a third major component of atrial remodeling.

The progression may be summarized as follows:

This model closely parallels Coumel's triangle (figure 2) :



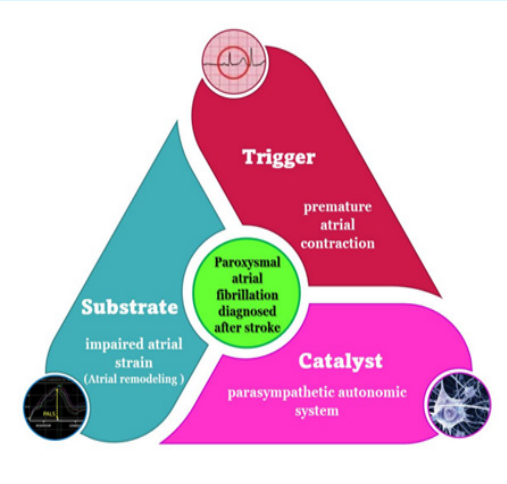


Figure 2. Coumel's triangle in atrial cardiomyopathy

PROPOSED HOLTER MARKERS OF ADVANCED ATRIAL CARDIOMYOPATHY (TABLE 2)

These markers may contribute to the identification of a high-risk atrial phenotype characterized by advanced remodeling, autonomic dysregulation, and increased thromboembolic potential.

Table 1. Holter Markers values of Advanced Atrial Cardiomyopathy

Parameter	Proposed Cut-off
PAC count	≥400/day
PAC burden	≥0.45%
Supraventricular runs	≥6/day
SDNN	>120 ms
RMSSD	>50 ms
pNN50	>10%
HF power	>200 ms²
LF/HF ratio	<2.5

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