Circadian Heart Rate Variability in Permanent Atrial Fibrillation Patients

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Abstract. *Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia occurring in 1-2% of general population, and approximately 13% of AF patients suffer from diabetes. Cardiovascular autonomic control impairment is associated with total mortality, but current practical use of ECG-based risk predictors is limited in permanent AF (PAF) patients due to absolute irregularity of ventricular contractions. We assume that it is possible to use measurements of circadian heart rate (HR) changes for mortality risk and cardiac autonomic control assessment in PAF patients. In 327 symptomatic PAF patients (259 non-diabetic, 68 diabetic), exposed to Holter monitoring in 2007-2010, circadian HR variability and standard Heart Rate Variability (HRV) Time domain indices were calculated and compared in patients who died or survived, and non-diabetic and diabetic patients. Patients were followed for a median period of 39 months (1-60). It was found that circadian HR indices were significantly lower in the dead as compared with alive patients ($p < 0.001$); in diabetic patients as compared with those without diabetes ($p < 0.01$), and in diabetic patients with approved diabetic neuropathy diagnosis ($p < 0.05$). Measured HRV indices didn't show significant differences in studied patients groups. Circadian HR variability showed promising predictive value for risk assessment in PAF patients.*

Keywords: circadian heart rate variability; average day night heart rate ratio; average day night heart rate difference.

1. Introduction

Current practical use of heart rate variability (HRV) is limited in permanent atrial fibrillation (PAF) patients as there is a consensus of opinion as to which parameters of HRV to record and which method of assessing HRV is required [1]. Although autonomic dysfunction is likely to pose the same risks for death or electrical instability in patients with AF as in sinus rhythm, the relevance or significance of "traditional" time domain or spectral HRV parameters to assess autonomic function in PAF is uncertain. It may be possible to assess autonomic function in AF by measuring the circadian changes in electrophysiological parameters over a 24 h period [1].

Different measurements of HRV, in addition to traditional ones based on different calculation techniques, were studied and reported for different SR and PAF patient groups for risk assessment, such as delta HR [2], circadian rhythm of atrioventricular nodal functional refractory period [1], HRV Fraction [3], and so on.

The "National Russian Guidelines on Clinical Application of the method of Holter Monitoring in Clinical Practice", being a valuable tool for patients risk assessment, recommend the "circadian index" with an optimal cut off point 1.32 (range 1.24 – 1.44) with no reference to heart rhythm.

2. Subject and Methods

The aim of this study is to analyze circadian HR changes in PAF patients and to come up with working parameters to be further applied for non-invasive mortality risk assessment and cardiac autonomic control evaluation. Study cohort: 327 symptomatic PAF patients (mean age

74.6 (9.7), 148 (45.3%) male), exposed to Holter monitoring in 2007-2010, 259 non-diabetics (mean age 74.4 (10), 121 male (46.4%)) and 68 diabetic patients (mean age 75.7 (8.5), 28 male (40%)). Primary end-point: death for any reason.

Schiller MT200 Microvit and Seer Light Extend GE 3-channel Holter recorders with standard lead configurations were used for registration of recordings. Recordings were analysed by using accordingly Schiller MT200 and Mars Version 7.2 software with manual post processing of ventricular ectopic complexes, longest and shortest RR intervals and extreme heart rates.

Characteristics of 24 hour HR changes: average day and night HR ratio (AveDNHRratio) and difference (AveDNHRdif), with the day time from 9 a.m. to 21 p.m. , and night time – from midnight to 6 a.m., were compared between the groups and within the groups of patients who died before, or survived after 1.1.2011, as well as in patients with or without DM.

Table 1. Clinical characteristics of study patients

	N [%]
CHF NYHA class II/IV	277 [85]
Hypertension	219 [67]
Stroke/embolism	136 [42]
Diabetes	68 [21]
Cancer	45 [14]
COPD	65 [20]
CAD	114 [35]
CKD	90 [28]
Wide QRS >120ms	48 [15]
CHADS-VAS	5.04

Statistical analysis: IBM SPSS v.18.program was used. Data were presented as mean (M) (SD) or median (Me) ([IQR]) for continuous variables, and patient (%) for categorical variables. Comparisons were made using t-test, Mann-Whitney test in case of non-normality and chi-square test. All tests were two-sided and considered significant at $p < 0.05$. Receiver operating characteristic (ROC) curves were used for measurement of diagnostic effectiveness of circadian HR indices and for detection of diagnostic thresholds distinguishing between patients with high mortality risk and those without it. The Kaplan - Meijer method was used to test validity of the cut off points found for survival analysis.

3. Results

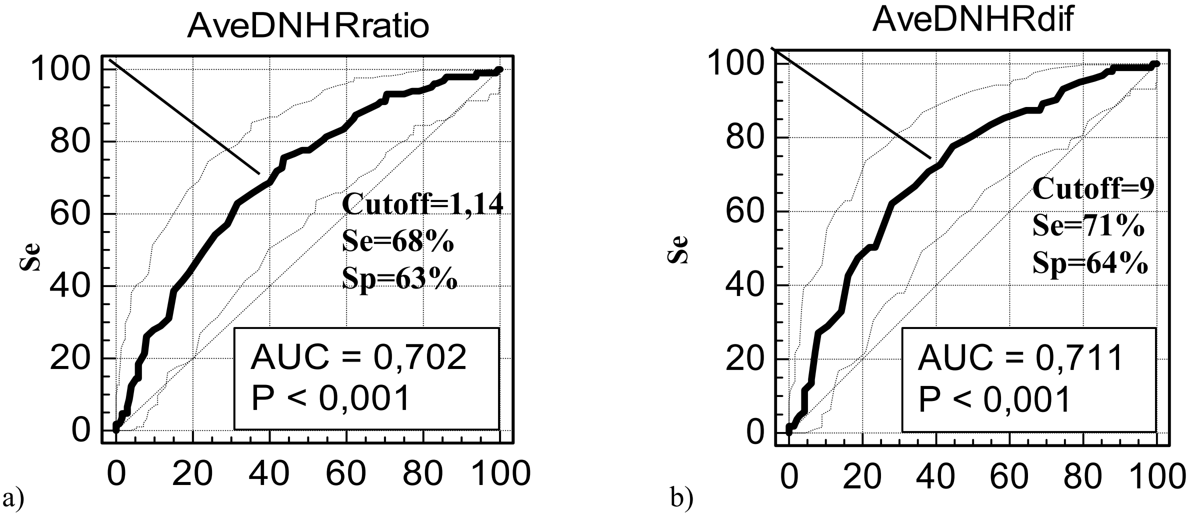
During the follow-up 103 (31.5%) patients (50 male (48.5%) died. The dead patients were older than the alive ones (77.9 y.o (7.9) vs. 73.1 y.o. (10.1)). Measured circadian HR changes were lower (the difference being statistically significant) in dead patient group, but standard HRV Time domain indices didn't show any significant differences in studied PAF cohort (Table 2). ROC curves used for detecting cut off points discriminating high risk patients from non- high risk ones showed fair diagnostic effectiveness of calculated circadian HR indices (Fig. 1).

Table 2 Comparison of standard Time domain and circadian HRV indices between dead and alive patient groups.

Variable	Dead [n=103]	Alive [n=224]	P value †	AUC	Cut off point
AveDNHRratio [M (SD)]	1.13 [0.14]	1.24 [0.16]	< 0.001	0.702 (0.642;0.761)***	1.14
AveDNHRdif [bpm][Me[IQR]]	8 [11]	15 [13]	< 0.001	0.711 (0.652;0.770)***	9
SDNN [ms] [Me [IQR]]	223 [89]	222 [68]	n.s.	0.522 (0.452;0.591)	-
SDANN [ms] [Me [IQR]]	86 [54]	89 [46]	n.s.	0.532 (0.462;0.599)	-
rMSSD [ms] [Me [IQR]]	212 [149]	227 [113]	n.s.	0.553 (0.485; 0.620)	-

† t-test or M-W test; *** p-value for area under the curve [AUC] < 0.001.

Decrease of circadian HRV indices under the estimated thresholds is acociated with higher death probability in studied patients. Cut off points for circadian HRV characteristics obtained from ROC curves showed an acceptable prognostic properties (Table 3).

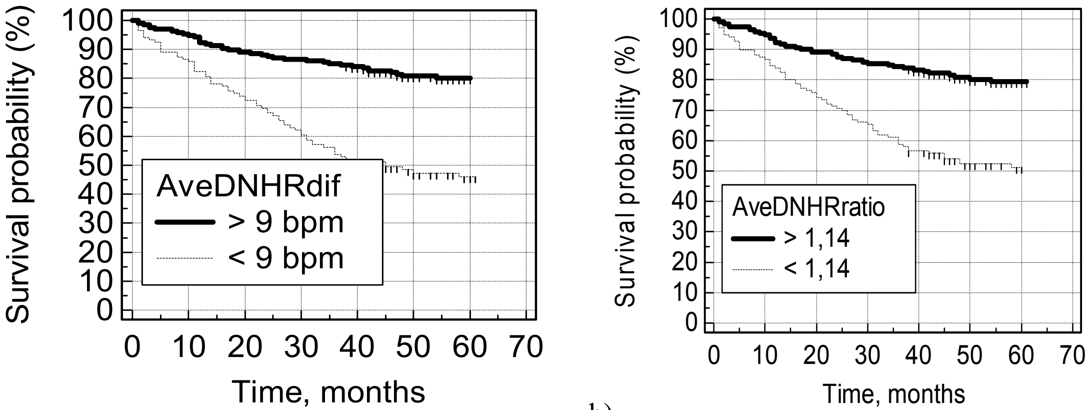


a) b)

Fig. 1 ROC curves for AveDNHRratio (a) and AveDNHRdif (b) diagnostic effectiveness evaluation and optimal cut off points detection.

Table 3 Diagnostic characteristics for circadian HRV cut off points estimated from ROC curves

Variable	Dead [n=103]	Alive [n=224]	p-value	OR [95% CI]	Sensitivity [%]	Specificity [%]
AveDNHRratio < 1,14 [patients [%]]	65 [63.1]	71 [31.7]	< 0.001	3.69 [2.26; 6.01]	68	63
AveDNHRdif < 9 bpm [patients [%]]	63 [61.2]	56 [25%]	< 0.001	4.73 [2.87; 7.79]	71	64



a) b)

Fig. 2 Circadian HR parameters cut-off thresholds AveDNHRdif (a) and AveDNHRratio (b) tried for survival analysis showed promising prognostic value for survival prediction in studied cohort

Circadian HRV in Diabetic Patient Group

Community studies showed prevalence of DM in 13% of patients with AF [5]. Prevalence of DM in studied cohort was higher - 21%. During the follow-up, 65 (25%) patients in the non-diabetic group and 38 (54.3%) diabetic ones died (OR – 2.97 (1.73; 5.09 95% CI)).

Cardiac autonomic neuropathy is significantly associated with total mortality [6]. In study cohort the measurements of circadian HR changes were significantly lower in diabetic patient group as compared with the non-diabetics (Table 4). Measurements of circadian HRV compared between dead and alive diabetic patients were low in both groups and didn't show any statistically significant differences (1.15 [0.15] vs. 1.19 [0.19] for AveDNHRratio and 9 [15] vs. 12 [20] for AveDNHRdif), which may be due to the underlying diabetic autonomic neuropathy and cardiomyopathy.

Table 4. Circadian HRV indices are significantly lower in the diabetic patient group

Variable	Non-diabetic [n=259]	Diabetic [n=68]	p-value
AveDNHRratio [M (SD)]	1.22 [0.16]	1.16 [0.16]	< 0.01
AveDNHRdif [Me[IQR]]	13 [14]	9 [14]	< 0.01

In the studied diabetic patient cohort AveDNHRratio was significantly lower in patient group (n = 12) with recognised diabetic neuropathy diagnosis (1.08 [0.13] vs. 1.16 [0.17], p – .036).

4. Conclusions and discussion

Circadian HR variability showed promising properties to be a relevant ECG-based diagnostic and predictive tool for patient risk assessment irrespectively of AF presence. Indices of circadian HR variability could be easily measured and analysed for every patient exposed to long-term (24 hours and more) ECG monitoring. In the studied aging patient group including patients with mostly more than one dichotomous high risk predictor, application of additional dynamic risk parameters could help to distinguish between two patients with equally high dichotomous risk the one with higher immediate risk. The important question still remaining open, especially for clinicians, is validity period of the dynamic risk stratification parameters and optimal time interval for high risk patients follow-up. The challenge would be to identify a parameter with a certain threshold value, which could be informative enough for a certain patient group within a certain (validity) time period. And of course, the impact of antiarrhythmic drug on dynamic parameters derived from heart rate measurements can't be underestimated. Additional prospective studies with more patients included in dynamic evaluation are required to find answers to at least part of clinical questions.

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