Commentary

Cardiovascular Risk Factors and Sympatho-vagal Balance: Importance of Time-domain Heart Rate Variability

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Abstract

Objective: Cardiovascular Disease (CVD) is the leading cause of death and disability worldwide. Dysregulation of the autonomic nervous system associated with various pathological conditions often occurs in presence of cardiovascular risk factors. Heart Rate Variability (HRV) may be used to assess autonomic imbalances. The aim of our study is to evaluate the correlation between HRV and the main cardiovascular risk factors in subject who underwent digital ambulatory 24 hours Holter ECG monitoring for clinical investigations.

Methods: We evaluated time domain parameters of HRV by Holter ECG monitoring in a large population categorized based on the presence or absence of the major cardiovascular risk factors.

Results: We found significant differences in time domain parameters of HRV in patients with and without common risk factor for CVD such as diabetes, family history for Coronary Artery Disease and dyslipidemia. We also analyzed our study population based on age and we found a positive correlation with the standard deviation of all NN intervals (SDNN), square root of the mean of the sum of the square of the differences between adjacent NN intervals (RMSSD), mean R-R intervals and by the number of adjacent NN intervals differing by more than 50 ms divided by the total number of all NN intervals (pNN50) and an inverse correlation for the others parameters.

Conclusion: Non-modifiable risk factors (age, gender, family history) along with dyslipidemia and diabetes, are related to a change in HRV, while modifiable risk factors (smoking, hypertension, overweight, hyperhomocysteinemia) showed no correlation. This would seem to indicate that the genetic components more than lifestyle habits and behavior act on the nervous control of the heart. Our study shows the possibility to find interesting clinical-prognostic data, analyzing simple parameters obtained from instrumental methods of investigation performed for other clinical reasons.

Introduction

Heart Rate Variability (HRV) is the beat-to-beat variation in either heart rate or the duration of the R-R interval - the heart period [1]. It has emerged as a practical, noninvasive tool to quantitatively investigate cardiac autonomic dysregulation and it has been proposed as a predictor of increased risk for cardiac mortality. There are two main approaches to measurement of HRV: analysis in the time or in the frequency domain. These measures are based on the analysis of interbeat intervals of normal beats determined from a digital ambulatory 24 hours Holter ECG monitoring [2]. Measures of HRV in both the time and frequency domains have been used successfully to index vagal activity. In the time domain, standard deviation of R-to-R intervals (SDNN) and the root mean square successive differences (RMSSD) have been shown to be useful indices of vagal activity.

Actually, a general consensus of the practical use of HRV in medicine has been reached only in two clinical scenarios: depressed HRV can be used as a predictor of risk after acute myocardial infarction and as an early warning sign of diabetic neuropathy [3].

In the ATRAMI study, a 3.2 greater risk of mortality was found in group of patients with SDNN<70 ms after a myocardial acute infarction [4]. This study confirmed that lower value of HRV is a powerful predictor of mortality and arrhythmic complications after myocardial infarction. In other several studies, a reduction of values of HRV was found in patients with diabetes mellitus type 2 and autonomic neuropathy correlates significantly with duration of disease and the

degree of neuropathic involvement. In diabetic patients, HRV has been used to recognize incipient cardiac autonomic dysfunction and to determine the severity of disease. That is the reason why it has been suggested as one of the diagnostic tests in a recent statement by the American Diabetes Association [5].

Furthermore, substantial evidence exists to support the notion that decreased vagal function is a common factor in all of the major risk factors for CVD, both modifiable and non-modifiable.

The aim of our study was to evaluate the correlation between HRV and the main cardiovascular risk factors, including a positive family history of Coronary Artery Disease (CAD) in subject who underwent digital ambulatory 24 hours Holter ECG monitoring for clinical investigations.

Methods

Study Population

The enrolled sample population consists of 569 patients who had no organic cardiovascular disease and underwent digital ambulatory 24 hours Holter ECG monitoring (delmar Reynolds) for clinical investigations. The collection of clinical data and HRV parameters of the study population was retrospectively performed using the database of the cardiologic ambulatory. The study is in line with the guidelines of Helsinki Declaration for Human Research and our local ethic committee guidelines.

The entire population underwent the following examinations: medical history and family anamnesis, focusing major cardiovascular risk factors (age, gender, hypertension, diabetes mellitus, hypercholesterolemy, smoke, family history of CAD, overweight and hyperhomocysteinemia). Hypertension was defined as a blood pressure>140/90 mmHg or by the use of antihypertensive medications. About the habit of smoking, we considered smokers those who smoked daily for 1 year at least. The diagnosis of dyslipidemia was based on blood levels of total cholesterol (>200 mg/dl), LDL (>130 mg/dl), HDL (<40 mg/dl in men and <50 mg/dl in women) and/or triglycerides (>150 mg/dl). It was also defined in patients already undergoing a therapy with either statin or other hypolipemiant drugs. The presence of hyperhomocysteinemia was assessed on the basis of plasma values ≥ 16 mmol/l. Diabetes mellitus was diagnosed in patients already taking oral hypoglycemic therapy or insulin or when fasting plasma glucose >126 mg/dl was found. The body mass index was calculated as weight divided by the square of height. Patients with 18.5<BMI≤24.9 were considered normal weighted, overweight if 25 ≤ BMI ≤ 29.9, obese in BMI ≥ 30. A family history of CAD was identified in relation to the presence of at least one relative with an early coronary event or treated revascularization procedures at a young age (under 65 years of age for males, under 55 years for females).

Besides continuous electrocardiographic ECG monitoring for 24 hours, all study population also underwent physical examination, basal electrocardiogram of 12 derivations, blood pressure measurement, and echocardiographic examination with special regard to left ventricular ejection fraction, diastolic thickness of interventricular septum and posterior wall.

The exclusion criteria were lack of clinical-anamnestic information or of echocardiographic examination and cardiac valvular pathology.

HRV parameters

Twenty-four hour ECG monitoring was performed in all patients enrolled in the study, using a three-channel tape recorder (V1-V2-V3). All the tapes were analyzed with the Holter Delmar Reynolds Pathfinder system. The variation in heart rate was evaluated by the time domain measures, according to the guidelines of the Task Force of the European society of Cardiology and North American Society of Pacing and Electrophysiology [3]. Mean RR intervals and the following HRV parameters were calculated as 24 hours values: mean RR intervals (mean RR), standard deviation of all NN interval (SDNN), standard deviation of differences between adjacent NN, square root of the mean of the sum of the square of the differences between adjacent NN intervals (RMSSD), mean standard deviation of NN intervals for all 5 minutes segments (SDNN index), number of adjacent NN intervals differing by more than 50 ms divided by the total number of all NN intervals (pNN50), and the geometric measures: HRV triangular index and TINN.

Statistical analyses

Continuous variables were expressed as median ± standard deviation for normally distributed data. Paired data were analyzed using the t test of Student and linear regression analysis. Correlations were performed through Pearson coefficient. The hypothesis that HRV is reduced in male, patients with diabetes, hypertension and familial history of CAD was confirmed by an overall MANOVA (Multivariate Analysis of Variance).

Results

The clinical characteristics of the population studied were shown in Table 1.

Our study population of 569 patients was categorized according to major cardiovascular risk factors: diabetes mellitus, hypertension, family history of CAD, smoking, dyslipidemia, overweight and hyperhomocysteinemia. The correlation analysis between HRV parameters and risk factors show the absence of significant correlation between HRV and risk factors such as smoking, hypertension, overweight and hyperhomocysteinemia.

Conversely time domain parameters of HRV were found to be definitely lower in diabetic patients than in population without diabetes, with statistically significant difference as to SDNN, RMSSD, pNN50 and triangular HRV index ($p<0.05$ for each of them) (Table 2). In particular, there were statistically significant differences in SDNN, mean RR and TINN ($p<0.05$ for each of them). We also found similar results about family history for CAD and gender. In the first case, RMSSD and pNN50 were lower in patients with positive family history ($p<0.05$ for both of them). For what concerns gender, a significant difference between parameters, such as SDNN, mean RR and mean HR (Table 3). SDNN was higher in men than women (respectively 135.1 ± 48.3 ms e 128 ± 44.5 ms, $p <0.0001$). The same occurred for mean RR (884.9 ± 161 ms in men versus 840.5 ± 169.3 in women ms, $p= 0.023$). On the contrary, mean HR was higher in women (73.3 ± 11.1 bpm) than in men (69 ± 12.7 bpm) with p value<0.0001.

Finally, we analyzed our study population based on age and we found a positive correlation between RMSSD, mean RR e pNN50 and aging and an inverse correlation for the others parameters.

Overall multivariate ANOVA revealed significant differences across the log-trasformed HRV measures in diabetic patients relative to non-diabetic ones ($F_{(7, 551)}=2.34$, $p=0.023$) as well as significant differences between males compared to females ($F_{(7, 551)}=2.53$, $p=0.0144$) and young subjects compared to older ones ($F_{(7, 551)}=8.87$, $p<0.0001$).

Discussion

Heart Rate Variability analysis in our sample population, obtained from digital ambulatory 24 hours Holter ECG monitoring, showed significantly lower time domain parameters in patients affected by

Cardiovascular risk factors	Patients n=569
Diabetes Mellitus	96 (16.1%)
Hypertension	396 (69.6%)
Family history for Coronary Artery Disease	150 (26.4%)
Ever Smoking	145 (25.5%)
Dyslipidemia	339 (59.6%)
Overweight	141 (24.8%)
Hyperhomocysteinemia	70 (12.3%)

Table 1: Clinical characteristics of the study population.

	Diabetic	Non-diabetic	Dyslipidemic	Non-dyslipidemic	Family history of CAD	No family history of CAD
SDNN (ms)	115.2 ± 44.2*	133.8 ± 46.6	130.8 ± 46.8*	131.35 ± 46.6	126.4 ± 44.4	131.9 ± 47.3
RMSSD (ms)	37.9 ± 26.9*	45.9 ± 32.9	42.8 ± 33.5	44.95 ± 33.8	38.3 ± 24.7*	46.4 ± 56
pNN50 (%)	5.95 ± 15.9*	39.8 ± 17.8	8 ± 16.9	8.7 ± 7.5	6.8 ± 4.1*	8.9 ± 18.5
mean RR (ms)	850.6 ± 169.5	960.2 ± 165.5	871.1* ± 153.2	845.7 ± 180.2	834.3 ± 139.7	870.4 ± 174.7
mean HR (bpm)	72.3 ± 10.3*	64.45 ± 12.4	70.3 ± 11.7	72.7 ± 12.5	73.7 ± 12.1	70.4 ± 12.1
triangular HRV	15 ± 5.01*	18.1 ± 6.4	17.6 ± 6	17.4 ± 6.4	17.5 ± 5.9	17.6 ± 6.3
TINN (ms)	468.8 ± 171.5	562.5 ± 213.3	546.9* ± 199.2	531.3 ± 211.3	531.3 ± 204.7	546.9 ± 201.3

*All P value<0.05

SDNN: standard deviation of all NN interval; RMSSD: Standard deviation of differences between adjacent; NN: Square root of the mean of the sum of the square of the differences between adjacent NN intervals; pNN50: number of adjacent NN intervals differing by more than 50 ms divided by the total number of all NN intervals; mean RR: mean RR intervals; mean HR: mean Heart Rate; TINN: triangular interpolation of NN interval

Table 2: Median value of the HRV parameters studied in patients divided based on cardiovascular risk factors.

	Male n=303	Female n=266	p value
SDNN (ms)	135.1 ± 48.3	128 ± 44.5	<0.0001
RMSSD (ms)	44.2 ± 5.42	43.1 ± 34.9	Ns
SDNN index (ms)	45.6 ± 31	41.3 ± 35.2	Ns
pNN50 (%)	9 ± 7.2	7.7 ± 6.9	Ns
mean RR (ms)	884.9 ± 161	840.5 ± 169.3	0.023
mean HR (bpm)	69 ± 12.7	73.3 ± 11.1	<0.0001
Triangular HRV	17.6 ± 6.4	17.5 ± 5.9	Ns
TINN (ms)	531.3 ± 212.5	546.9 ± 203.1	Ns

SDNN: Standard deviation of all NN interval; RMSSD: Standard deviation of differences between adjacent NN, square root of the mean of the sum of the square of the differences between adjacent NN intervals; pNN50: Number of adjacent NN intervals differing by more than 50 ms divided by the total number of all NN intervals; Mean RR: Mean RR intervals; Mean HR: Mean Heart Rate; TINN: Triangular Interpolation of NN Interval

Table 3: median value of the HRV parameters studied in patients divided on the basis of gender.

diabetes mellitus, dyslipidemia and with family history of coronary artery disease when compared to those of the control population without these risk factors.

The guidelines of the Task Force of the European society of Cardiology and North American Society of Pacing and Electrophysiology admit the utility of HRV in patients with diabetes [3]. The detection of lower values of HRV parameters suggests the presence of a hyperactive sympathetic system and/or a hypoactive parasympathetic system [5-7]. By means of spectral analysis, it is partially possible to distinguish the influence of the sympathetic system from that of the vagal system on the heart, giving important information about pathogenesis of diabetic autonomic neuropathy, a complication of diabetes mellitus, characterized by early and widespread neuronal degeneration of small nerve fibres of both sympathetic and parasympathetic tracts [8,9]. Its clinical manifestations are ubiquitous with functional impairment and include postural hypotension, persistent tachycardia, gastroparesis, bladder atony and nocturnal diarrhea. Once clinical manifestations of diabetic autonomic neuropathy supervene, the estimated 5-year mortality is approximately 50%. Thus, early subclinical detection of autonomic dysfunction is important for risk stratification and subsequent management [3].

In our diabetic patients, we found lower values of SDNN, RMSSD, pNN50 and triangular index values of mean HR higher than in non-diabetic population. According to the literature, the degree of decrease of these parameters correlates significantly with duration of disease. Because the decrease in variability of HR is the earliest sign of diabetic autonomic neuropathy, beat-to-beat HR variability is suggested as one of the diagnostic tests in a recent statement by the American Diabetes Association [5].

Few studies have examined the relationship between HRV and Cholesterol levels Christensen et al. previously found that plasma total-cholesterol and low-density-lipoprotein (LDL)-cholesterol were inversely correlated with 24-h HRV [10-13]. In our study we found that the dyslipidemic population has lower HRV values compared to non dyslipidemic patients, confirming the existing evidences that low HRV is associated with high cholesterol levels.

We also researched a possible relation between HRV and family history of CAD. Recent evidence confirmed the genetic determination of heart rate regulation and suggested that genetic factors may also contribute to the beat-to-beat variability in heart rate. Genetic effects and household effects accounted for 37% to 61% of the total phenotype variability in most of the HRV measurements [14]. The variance in heart rate due to the genetic effect accounted for a relatively larger proportion of the phenotypic variability (2- to 3-fold) than that of measured covariates. The reduction in the genetic variance of the HRV measures after inclusion of HR in the model could be explained by the possibility that HR and HRV may share common genes. In our study population, we found a significant reduction of RMSSD and pNN50 values in subjects with positive family history. Beside the presence of other risk factors associated with decreased variability in the population with family-associated increased risk for CAD, a genetic component on rhythm modulation could account for the correlation found between positive family history and altered HRV.

Different studies demonstrated an involvement of age in reduction of HRV. It is important to consider that these studies are based on different approaches to measurement of HRV (time domain and frequency domain) and different recording duration. In 2003, Bonnemeier et al. found an inverse correlation between every parameter of HRV in the 24 h and age [14]. Also in our study, there is an inverse correlation with age and many parameters analyzed. Nevertheless a positive correlation was found between RMSSD, mean RR, pNN50 and age. Aging is associated with deterioration in cardiac autonomic nervous system, and this situation is linked to many changes in autonomic nervous control, for example in baroreceptor output, afferent neural conduction and efferent autonomic outflow, and sinoatrial node responsiveness.

There are not many studies about gender differences and HRV, and the ones analyzing the frequency domain gave conflicting results. However, some studies in time domain showed results that are more consistent. We evaluated parameters of time domain in our study population (as recommended by Task Force ESC and NASPE) and we found significant differences between men and women in SDNN, mean RR and mean HR. The first two parameters were higher in men, while mean HR was higher in women. Our data partially confirm the results of the study of Bonnemeier H et al., who demonstrated the same

significant association between SDNN, mean RR and gender [14]. In addition, the study of Van Hoogenhuyze et al. showed that SDANN and SDNN index were significantly higher in men [15].

In conclusion, our study confirms a significant correlation between the major cardiovascular risk factors (age, gender, dyslipidemia, diabetes and family history) and HRV determined by Holter ECG monitoring. HRV, which is an indicator of symphatovagal equilibrium, seems to be altered in pathological conditions like hypertension or diabetes mellitus type 2. It is well known that a positive family history of CAD conveys greater cardiovascular risk. The relationship between HRV and family history of CAD is of great interest, indicating that a positive family history is also associated with non-traditional risk factors such as altered HRV. The fact that non-modifiable risk factors (age, gender, family history) along with dyslipidemia and diabetes, are related to a change in HRV, while modifiable risk factors (smoking, hypertension, overweight, hyperhomocysteinemia) showed no correlation would seem to indicate that the genetic components more than lifestyle habits and behavior act on the nervous control of the heart.

Moreover, our study shows that it is possible to find interesting clinical-prognostic data through the analysis of simple parameters obtained from instrumental methods of investigation performed for other clinical reasons. Thus, the presence of lower HRV value imposes a close monitoring for those patients with risk factors for CAD, because this population seems to have higher risk to develop CAD.

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