

Diagnostic Value of Heart Rate Variability in the Indeterminate Chagas' Disease: Potential for an Early Detection of Cardiac Autonomic Dysfunction

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Summary

The aim of the study was to analyze the autonomic nervous system behavior of patients with the indeterminate form of Chagas' disease and to establish the utility of heart rate variability for the early diagnosis of cardiac autonomic dysfunction. It is well known that different activities of the ANS cause characteristic beat-to-beat variations of the heart rate, e.g., parasympathetic activities generate high-frequency fluctuations of the heart rate in the range from 0.15 to 14.0 Hz, whereas the low-frequency range from 0.04 to 0.15 Hz is affected by sympathetic influences. The study was performed on 261 subjects, of which 132 had indeterminate Chagas' disease (mean age: 52 ± 8 years) and 129 were healthy control subjects (mean age: 49 ± 11 years). All patients were monitored by 24h Holter ECG, and the data were analyzed in the time and spectral domain, with statistical and spectral analysis of beat-to-beat time intervals. In the Chagas group, we observed an impairment of vagal modulator activity (the high-frequency component and the pNN50 value that represents the percentage of large-scale beat-to-beat variations were significantly lower, $P = 0.0003$ and $P = 0.024$, respectively), together with signs of reduced capability to activate sympathetic responses (significantly decreased low-frequency component, $P = 0.0001$). These results point to the potential of heart rate variability analysis for detection of autonomic dysfunction and thus for early diagnosis of cardiac impairment.

Key Words

Indeterminate Chagas' disease, heart rate variability, autonomic dysfunction

Introduction

Chagas' disease is an immense public health problem in Latin America and responsible for many sudden cardiac deaths, affecting more than 16 million people. It is caused by *Trypanosoma cruzi*, which has a preference for muscle tissue and the nervous system, leading to an intrinsic denervation in organs such as heart, bowels, and peripheral nervous system. The disease manifests in three forms:

- Acute: general signs of acute infection;
- Indeterminate: asymptomatic (only immunological test results are altered);
- Chronic: cardiomyopathy, malignant arrhythmias, and thromboembolic syndrome.

Since recently, the indeterminate form of Chagas' disease has been studied intensely, in which function abnormalities in the autonomic nervous system (ANS) were found despite the lack of signs, symptoms, or any radiological evidence of the disease [1]. Heart rate variability (HRV) analysis may, in this context, be of a great promise as an additional noninvasive diagnostic concept. Normal RR intervals are measured from common Holter ECGs, after exclusion of extrasystoles and large-scale variations of RR intervals caused by pathological processes. It is well known that physiological effects lead to characteristic variations in the heart rate, which can be attributed to activities of the ANS [2-4].

| | Chagas group | Control group | P value |
|--|--------------------|--------------------|---------|
| Number of patients | 132 | 129 | |
| Laboratory test intermediate Chagas disease | positive (100 %) | negative (100 %) | |
| Age | 52 ± 8 years | 49 ± 11 years | ns |
| Sex | 60 % (m), 40 % (f) | 58 % (m), 42 % (f) | ns |
| Functional class NYHA - class - I | 100 % | 100 % | ns |
| Systemic hypertension | 16 % | 18 % | ns |
| Medication | none | none | |
| Coronary artery disease | absent | absent | |

Table 1. Clinical characteristics of study patients.

HRV analysis has shown to be a marker for the dysfunction of the autonomic tone and for risk stratification in cardiac failure patients.

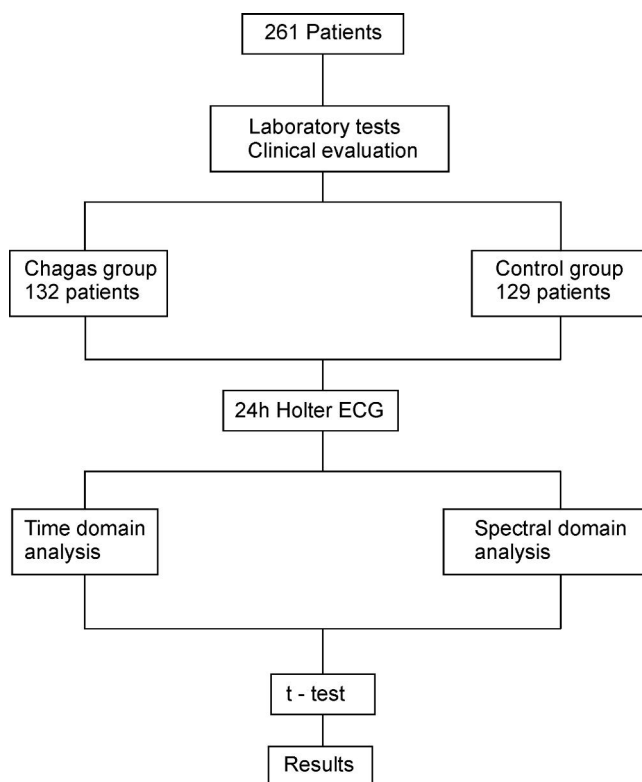


Figure 1. Study design.

Materials and Methods

We studied 261 patients divided into two groups: the indeterminate Chagas' disease group (132 patients, mean age: 52 ± 8 years) and the healthy control group in whom Chagas' disease tests were negative (129 patients, mean age: 49 ± 11 years). Clinical characteristics of study patients are shown in Table 1. There were no significant differences concerning age, sex, and state of health between the two groups, except for the presence or absence of the Chagas' disease.

The study design is illustrated in Figure 1. All patients underwent the 24h Holter ECG recording, allowing heart rate and ANS activity analysis during daily-life activities. The beat-to-beat intervals from the Holter ECG recordings were analyzed in the time and spectral domain. The nature of the extracted values in the HRV analysis is described in Tables 2 and 3. [4]. The time domain variables (SDNN, pNN50, and rMSSD) and the spectral domain variables (VLF, LF, HF) were compared for the two groups using the Student's t-test, with a confidence interval of 95 % ($\alpha = 0.05$).

Results

Results of the HRV analysis in the time domain are shown in Figure 2 and in the spectral domain in Figure 3. A statistically significant difference ($P < 0.05$) was found between the two groups in the time domain data:

- Standard deviation of normal-to-normal intervals (SDNN): $P = 0.0031$

| Variable | Definition | Neural mechanisms |
|------------|---|---|
| SDNN (ms) | standard deviation of the mean of all normal RR intervals | total neural activities, unspecific indicator |
| pNN50 (%) | percent of difference between adjacent normal RR intervals that are greater than 50 ms | parasympathetic system |
| rMSSD (ms) | root mean square successive difference, the square root of the mean of the sum of squares of differences between adjacent normal RR intervals | parasympathetic system |

Table 2. Variables used for HRV time domain analysis.

- Root mean square successive differences (rMSSD): P = ns
- Proportion of cycles where the difference is > 50 ms (pNN50): P = 0.024

From the significantly lowered standard deviation of normal RR intervals (SDNN), it is evident that physiological HRV is decreased in the indeterminate Chagas' disease even though there are no actual limitations in the state of health in general. More specific, lower rMSSD and pNN50 values can be interpreted as an impairment of vagal activity.

The spectral domain variables (Figure 3) also exhibited statistically significant differences for the two groups:

- Very low frequency (VLF): P = 0.010
- Low frequency (LF): P = 0.0001
- High frequency (HF): P = 0.0003

Low-frequency power, LF, and the high-frequency power, HF, decreased substantially in Chagasic patients, which is a result related to the reduced activity of both the sympathetic and parasympathetic branches of the ANS.

Discussion

In the present study, we selected patients for the Chagas group and the control group as homogeneously as possible, to exclude bias effects on the HRV from parameters changing the autonomic nervous regulation, such as hypertension, medication, and others (Table 1). As a consequence of the specific study collective, the potential of HRV analysis for the early diagnosis and future prognosis of cardiac failure [5,6] could not be investigated in detail. Nevertheless, the initial findings presented here suggest a simultaneous effect of indeterminate Chagas' disease on both sympathetic (LF component) and parasympathetic (decreased changes in HF and pNN50 variables) modulations, which is in accordance with clinical and morphological studies.

Conclusion

We were able to observe differences in the parameters of autonomic function in the two groups, reflecting an impairment of vagal and sympathetic response in

| Variable | Definition | Neural mechanisms |
|------------------------|--|--------------------------------------|
| VLF (ms ²) | power in the very low frequency range: 0.003 - 0.04 Hz | renin - angiotensin system |
| LF (ms ²) | power in the low frequency range: 0.04 - 0.15 Hz | sympathetic system |
| HF (ms ²) | power in the high frequency range: 0.15 - 0.4 Hz | parasympathetic system |
| LF/HF | ratio between the power of the LF and HF components | sympathetic & parasympathetic system |

Table 3. Variables used for HRV spectral domain analysis.

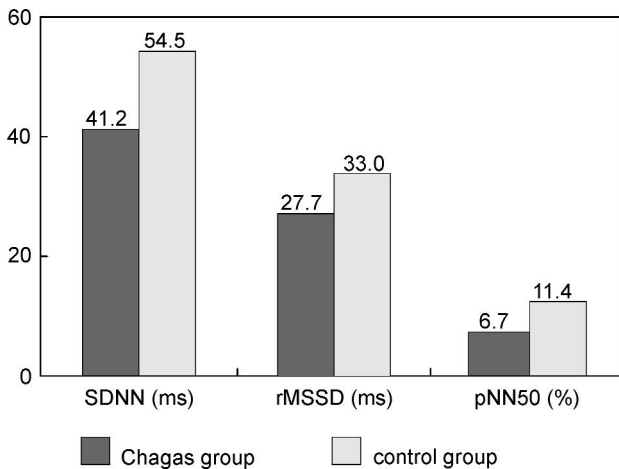


Figure 2. Mean values of HRV time domain variables.

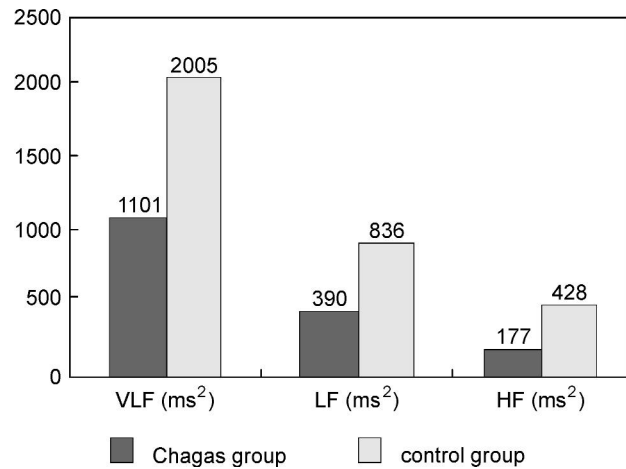


Figure 3. Mean values of HRV spectral domain variables.

patients with the indeterminate Chagas' disease. The study demonstrated the potential value of the noninvasive, easy to handle HRV analysis for an early diagnosis of cardiac autonomic dysfunction. Further research is necessary to establish absolute values of HRV variables for classification of the form of Chagas' disease and for future prognosis.

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