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Cardiac sympathovagal modulation evaluated by short-term heart interval variability is subtly impaired in Alzheimer's disease

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Aim: Alzheimer's disease affects several nervous structures involved with the autonomic nervous system. Therefore, the still scarce evaluation of the cardiac autonomic function in this disease is of great functional, clinical, prognostic and therapeutic relevance.

Methods: Time- and frequency-domain variability of 5-min R-R interval series in supine and standing positions was comparatively evaluated in 22 Alzheimer's disease subjects, aged 60–87 years (mean ± standard error of the mean, 79.6 ± 1.4) with variable cognitive impairment, and 24 healthy individuals, aged 60–91 years (68.6 ± 1.6). The Student's *t*-test was used to compare the variability indices between the groups and logistic regression excluded the effects on these indices in the Alzheimer's group of confounding variables different from the control group (age, physical activity and caffeinated intake), at a significance level of $P \leq 0.05$.

Results: No difference was observed between the groups ($P = 0.12$–0.72) for each time-domain mean indices and for the frequency-domain indices of overall and absolute sympathetic modulation in both positions ($P = 0.21$–0.78). Absolute parasympathetic modulation showed borderline decrease in supine position ($P = 0.07$) and was reduced in the standing ($P = 0.05$). The sympathovagal balance was altered ($P = 0.05$) toward relative parasympathetic borderline depression ($P = 0.07$) and sympathetic exacerbation ($P = 0.04$) only in the supine posture.

Conclusion: Data indicate that Alzheimer's disease subjects with mild-to-severe cognitive dysfunction showed subtle, absolute and relative parasympathetic depression and relative sympathetic exacerbation, which may even so contribute to distinctive functional and cognitive disturbances.

Keywords: Alzheimer's disease, cardiac autonomic dysfunction, heart interval variability, neurocardiac interaction, sympathovagal balance.

Introduction

Alzheimer's disease is a common, progressively debilitating condition affecting millions of older persons worldwide, and is diagnosed on histopathological grounds or presumed on the basis of higher cerebral function deficits.[1–5] The disease primarily affects many central and peripheral nervous structures, such as the cerebral neocortex, hypothalamus, locus coeruleus, limbic system formations, insular cortex and lower brainstem,[3,6–11] and affects different neurotransmitter systems, principally the central and peripheral cholinergic systems with decrease of the acetylcholine neurotransmitter.[6,12,13] Many of these structures and systems are implicated in the function of the autonomic nervous system.[3,6,8–11,14,15] Furthermore, a link between the higher cerebral and autonomic functions appears to exist.[10,16,17]

In spite of this, the nature and extent of general or organ-specific autonomic involvement in Alzheimer's disease is still poorly investigated and characterized. In this context, cardiac autonomic function in Alzheimer's disease has been scarcely studied and the results reported are not rigorously similar or are conflicting. By using different methods of evaluation, including heart rate variability analysis, the majority of the studies indicate cardiac autonomic impairment represented mainly by variably reduced parasympathetic modulation,[18,19] or increased sympathetic activity in association with parasympathetic depression[20,21] or still by reduction in both autonomic components.[22,23] Markedly depressed baroreflex sensitivity reflecting abnormal cardiovascular autonomic regulation has also been described.[15] Association between neuropsychiatric deficits and altered heart rate responses to standing up has also been observed.[24] However, in one study, the cardiac autonomic function assessed by short-term heart rate variability was shown to be unaltered.[25] Furthermore, increased cardiovascular mortality was reported in Alzheimer's disease,[26–28] and it is possible that cardiac autonomic dysfunction may represent one mechanism implicated.[29–32]

Therefore, it may be relevant to extend the study of the cardiac autonomic function in Alzheimer's disease, which may be of interest for a better understanding of its pathophysiology and for complementing the diagnosis, monitoring the clinical progression and therapeutic and prognostic judgments.[10] Short-term time- and frequency-domain heart interval variability analysis is a suitable, simple and reliable noninvasive method widely used to evaluate overall cardiac autonomic modulation, the absolute sympathetic and parasympathetic influences and the sympathovagal balance that identify the relative influence of each separate component, under controlled conditions requiring minimal cooperation of the individuals,[29,31,33] as those with cognitive impairment.[34]

In the present study, we evaluated the cardiac autonomic modulation and the sympathovagal balance in the supine and active standing positions, based on short-term time- and frequency-domain heart interval variability analysis, in older subjects with probable Alzheimer's disease showing mild-to-severe cognitive deficit, in comparison with healthy older control individuals.

Methods

Study groups

A group of 22 consecutively recruited older outpatients (two men and 20 women) aged 60–87 years old (mean ± standard error of the mean [SEM], 79.6 ± 1.4) with probable Alzheimer's disease and different degrees of cognitive impairment without any other ostensive clinical manifestations was compared with a control group of 24 apparently healthy older subjects (eight men and 16 women) aged 60–91 years old (mean ± SEM, 68.6 ± 1.6) ($P = 0.0001$). The patients were selected from our Geriatric Medicine Center at the Brasilia University Hospital. Probable Alzheimer's disease was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)[35] and the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association guidelines (NINCDS-ADRDA).[4] Except for the higher cerebral dysfunctions in the disease subjects, neither these nor control subjects had general or organ-specific abnormalities other than cardiac manifestations consistent with aging, as proved by extensive clinical and laboratory screening, and none were taking drugs. In 82% of the Alzheimer's disease subjects and 75% of the controls ($P = 0.72$) distinctive electrocardiographic alterations were founded, but were proportionally similar in both groups ($P = 0.10–1.00$).

The study protocol conformed to the guidelines of the Declaration of Helsinki and the Brazilian Ministry of Health and was approved by the University of Brasilia Faculty of Medicine Ethics Committee of Research in Human Beings. Healthy individuals and the attendant relatives of the Alzheimer's disease subjects were fully informed about the study. Each healthy subject gave signed personal consent to participate and the disease subjects were examined under signed consent by the relative.

Experimental session

The disease and control subjects participated in the experimental session coming from their routine activities, approximately 3–5 h after lunch, between 14.00 and 17.00 hours. All were instructed to avoid intake of

stimulant beverages, tea, coffee and alcoholic drinks, and not exercise, smoke or ingest drugs for at least 24 h before the examination.

Experimental sessions consisted of clinical characterization of the volunteers and acquisition of continuous electrocardiographic short strips of R-R interval series, and were performed in a quiet and isolated room, at ambient temperature (22–28°C). Clinical history and complete physical examination were initially obtained for each subject. Resting arterial pressure and heart rate were also registered and the 12-lead electrocardiogram was recorded in the supine position. In sequence, after 10–15 min of supine rest on the bed of examination for accommodation and stabilization of physiological variables, a continuous 5-min electrocardiogram strip was recorded in lead II at 25 mm/s. Subsequently, the subjects were asked to actively stand up at the bedside, and a new 5-min electrocardiogram tracing was obtained following 2 min in the active orthostatic position. In these recording periods, the subjects remained breathing regularly and had their spontaneous respiratory rate monitored and counted.

Cognitive function evaluation

At the beginning of the experimental session, the control and Alzheimer's disease subjects were similarly interviewed and submitted to a battery of conventional and standardized tests of cognitive function. The mean score of the modified CAMCOG,[36] the cognitive part of the Cambridge Examination for Mental Disorders of the Elderly (CAMDEX), was 24.14 (range, 0–74) for the disease subjects, against a cut-off score of 79–80 that discriminates healthy subjects (range, 80–107) from patients with cognitive deficit showing a low-to-mild educational attainment. In the Mini-Mental State Examination (MMSE), obtained as a subtest from within the CAMCOG,[1] the subjects with Alzheimer's disease showed a mean score of 6.77 (range, 0–20), which varied between 24 and 30 in the controls. The severity of dementia was judged according to the Washington University Clinical Dementia Rating (CDR),[2] with six patients showing a mild degree of dementia (CDR = 1), five patients moderate (CDR = 2) and 11 patients severe (CDR = 3). All patients could walk alone or with minimal assistance. The mean Katz Index of Activities of Daily Living activities[37] was 11.55 (range, 5–18). All disease subjects had Hachinski Ischemic Scores of 4 or less,[38] and showed a mean duration of illness of 5.36 years (range, 2–15).

In order to additionally corroborate the normality or not of the mental status, both groups of subjects were also submitted to the following tests of frontal function assessment: the Stroop test,[39] Digit Span and Digit Symbol (subtests of the Wechsler Intelligence Scale – Adult),[40] Trail Making A and B, Auditory Verbal Learn-

ing Test[41] and Mental Control (subtest of the Wechsler Memory Scale – Revised).[42] All of these tests proved to be within the limits of normality for each control subject.

Heart interval variability analysis

This analysis was performed according to the methodological standards recommended by the Task Force on Heart Rate Variability.[29] For each individual, one electrocardiographic 5-min series of R-R intervals was automatically recorded in the supine and standing positions and archived in real-time to a computer system using an analogical-digital converter, by means of a signal capturing dedicated software, while being visually monitored onscreen. Then, each R-R interval series was processed offline and analyzed for intervals variability. The software for the signal capturing and processing and analyses of the data were developed by using the MATLAB ver. 5.03 platform (The MathWorks, Natick, MA, USA), and also validated at our Cardiovascular Laboratory and the Department of Electrical Engineering of the University of Brasilia.[43]

Before the analysis, the R-R interval series were checked on a beat-to-beat basis for confirmation of sinus rhythm and detection of non-sinus and ectopic beats, artifacts and stability. When eventually present, spurious beats and their precedent and following intervals were deleted from the series without adding new intervals. Residual outlier beats were also removed. Artifacts were filtered by a specific module of the proper software. Edited R-R intervals were less than 3% of the series from the Alzheimer's disease subjects and 1% for the controls. As the R-R interval series were recorded in strictly controlled and stable experimental conditions, those qualified for analysis were highly stationary, as estimated by the percent differences of the mean and the standard deviation between each pair of three equal segments of the series. Subsequently, the series were processed and analyzed for variability in time- and frequency-domain by means of conventional different indices.[29,31,33]

The time-domain indices provided include the mean R-R interval series and two overall variability indices reflecting the extension of the combined cardiac sympathetic and parasympathetic modulation, which are the standard deviation (SDNN) and coefficient of variation (CV: SDNN/mean). Two other indices were the percentage of successive adjacent R-R intervals greater than 50 ms (pNN50%) and the square root of the mean of the squared of successive differences between adjacent R-R intervals (rMSSD), which reflect the rapid beat-to-beat changes in intervals that are dependent on the exclusive parasympathetic modulation associated with the respiratory sinus arrhythmia.

For the frequency-domain analysis, the non-uniform 5-min R-R interval series segments, without spurious and outlier beats, were initially normalized and re-sampled at 4 Hz by the cubic splines interpolation method to accomplish equidistance and continuity of the time intervals. In sequence, the segments were submitted to filtering with Hanning windowing to attenuate leakage side-effects and then processed by the fast Fourier transform algorithm for conversion of the signal oscillating components into power spectrum, which comprises an ultralow- plus very low-frequency (0–0.04 Hz), low-frequency (0.04–0.15 Hz) and high-frequency (0.15–0.50 Hz) spectral bands. The frequency domain indices provide include: (i) total power spectral area, which indicates the degree of the overall autonomic modulation; (ii) absolute and relative power areas of the very low-, low- and high-frequency bands; (iii) normalized or relative power areas of the low- and high-frequency bands, calculated as the absolute area of each band divided by the sum of both absolute area, multiplied or not by 100; (iv) ratio of the low- to high-frequency absolute areas, which is an estimative of the sympathovagal balance, where a ratio less than 1 indicates a predominant parasympathetic modulation and a ratio more than 1 the sympathetic dominance. The low-frequency band area is considered to be a marker of predominant sympathetic influence, and the high-frequency band area reflects the nearly exclusive parasympathetic influence on the sinus node.

Statistical analysis

Before analysis, the distribution of the functional variables was tested by the Kolmogorov–Smirnov and D'Agostino–Pearson tests of normality, and several proved to be non-normally distributed by at least one test. Therefore, all the variables were uniformly normalized by logarithmic transformation (log[x]) for subsequent parametric statistical analysis and then were back transformed for descriptive data. The variables were retested after transformation and showed a normal distribution. Thus, mean ± SEM of the time- and frequency-domain indices in each group were compared using the Student t-test. Multiple logistic regression analysis was employed to verify if the heart interval variability indices, as dependent variable in the Alzheimer's disease group, were affected by independent confounding variables that can influence the indices. The differences between the groups and the logistic regression coefficients were considered statistically significant when a two-tailed P-value was equal or less than 5% ($P \leq 0.05$) and with borderline or tendency to significance when between 5% and 10% ($0.05 \leq P \leq 0.10$). Processing, analysis and graphic design of the data employed the SigmaStat ver. 3.11/SigmaPlot ver. 9.01 for Windows (Systat Software, Chicago, IL, USA) and the Prism ver. 4 for Windows (GraphPad Software, San Diego, CA, USA) software packages.

Results

Table 1 summarizes clinical baseline and anthropometrical data and lifestyle habits obtained at the beginning of the experimental session for the two groups of subjects. No significant difference in mean resting systolic and diastolic arterial pressure, heart rate and respiratory rate was found between the groups

Table 1 Lifestyle habits and anthropometrical and baseline clinical functional variables of healthy control and Alzheimer's disease groups of subjects

	Control healthy group	Alzheimer's disease group	P
n	24	22	
Age (years)	68.6 ± 1.6	79.6 ± 1.4	0.0001
Sex (men/women) (%)	33.3/66.7	9.1/90.9	0.07
Body mass index (kg/m²)	23.3 ± 0.6	23.5 ± 1.1	0.86
Caffeinated beverages drinkers (%)	75	31.8	0.008
Alcoholic beverages drinkers (%)	33.3	9.1	0.07
Tobacco smokers (%)	4.2	9.1	0.60
Sedentary (%)	29.2	77.3	0.0001
Systolic blood pressure (mmHg)	121 ± 2.3	118 ± 2.6	0.44
Diastolic blood pressure (mmHg)	75 ± 1.4	74 ± 1.5	0.63
Mean blood pressure (mmHg)	91 ± 1.6	89 ± 1.82	0.51
Heart rate (b.p.m.)	64.6 ± 2.2	65.3 ± 2.2	0.83
Respiratory Rate (r.i.p.m.)	16.9 ± 0.5	17.3 ± 0.5	0.59

P-values were derived from the Student's t-test for continuous variables expressed as mean ± standard error of the mean (SEM), and from the χ^2-test or Fisher' exact tests for categorical variables expressed in percentage of subjects.

Table 2 Mean ± standard error of the mean of time-domain indices of short-term heart interval variability in healthy control and Alzheimer's disease groups of subjects in supine and active standing positions

	Supine Control group	Alzheimer's disease group	P	Standing Control group	Alzheimer's disease group	P
n	24	22		24	22	
n RRi	353 ± 11.3	340 ± 11.8	0.40	384 ± 10.0	398 ± 12.9	0.42
Mean RRi (ms)	862 ± 26.5	848 ± 28.1	0.72	779 ± 21.1	742 ± 26.1	0.23
SDNN (ms)	30.1 ± 2.9	25.7 ± 2.1	0.38	25.7 ± 1.9	21.6 ± 1.9	0.12
CV (%)	3.47 ± 0.3	3.00 ± 0.2	0.39	3.27 ± 0.2	2.90 ± 0.2	0.20
pNN50 (%)	2.58 ± 1.2	1.61 ± 0.7	0.72	1.17 ± 0.5	1.31 ± 0.5	0.13
rMSSD (ms)	17.6 ± 2.1	14.0 ± 1.6	0.15	15.3 ± 1.3	12.9 ± 1.7	0.09

P-values were derived from the comparison of the indices log-transformed, by the Student's t-test. Mean RRi, SDNN and CV indicate mean, standard deviation and coefficient of variation, respectively, of the R-R interval series; n RRi, number of R-R intervals; pNN50, percentage of successive R-R intervals >50 ms; rMSSD, square root of the mean of the squares of successive R-R intervals differences.

Table 3 Mean ± standard error of the mean of frequency-domain indices of short-term heart interval variability in healthy control and Alzheimer's disease groups of subjects in supine and active standing positions

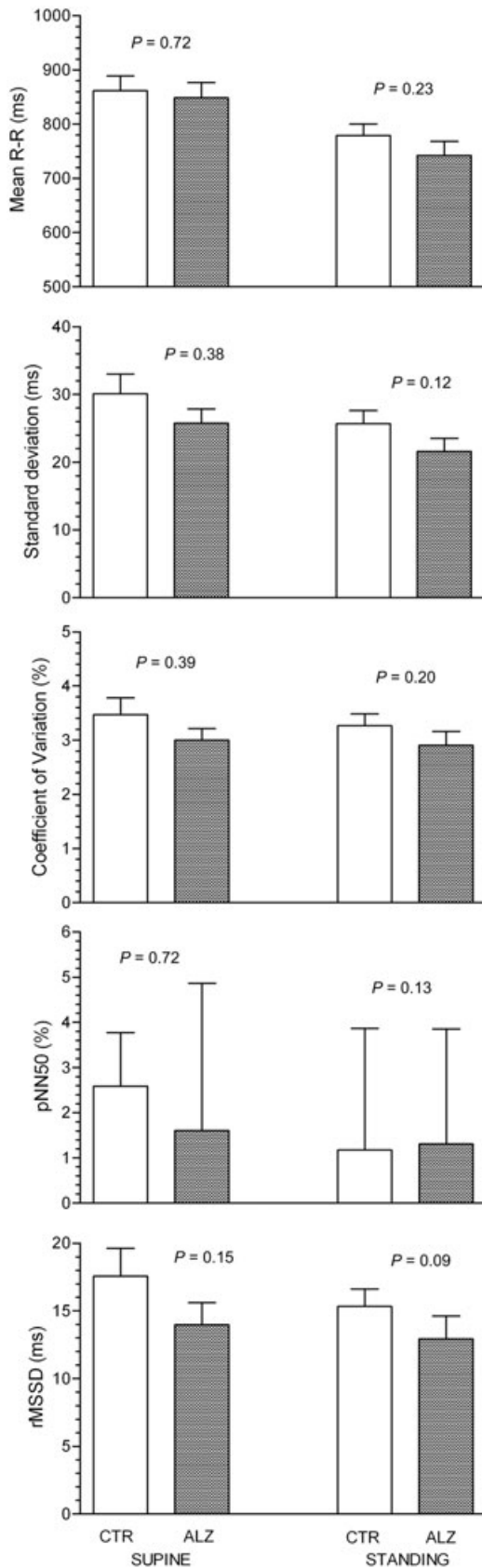|	Supine Control group	Alzheimer's disease group	P	Standing Control group	Alzheimer's disease group	P
n	24	22		24	22	
Total power spectral area (ms^2)	183 ± 33.7	125 ± 21.2	0.37	128 ± 20.5	99 ± 19.6	0.21
Low-frequency power spectral area (ms^2)	49.8 ± 12.0	41.9 ± 10.0	0.78	43.3 ± 9.3	37.7 ± 9.0	0.25
High-frequency power spectral area (ms^2)	28.0 ± 7.5	15.1 ± 3.9	0.07	15.3 ± 2.6	13.8 ± 4.4	0.05
Normalized low-frequency power area (uN)	0.62 ± 0.04	0.72 ± 0.03	0.04	0.66 ± 0.04	0.72 ± 0.03	0.19
Normalized high-frequency power area (uN)	0.38 ± 0.04	0.28 ± 0.03	0.07	0.34 ± 0.04	0.28 ± 0.03	0.51
Low-to-high-frequency power area ratio	2.61 ± 0.50	3.66 ± 0.51	0.05	4.11 ± 1.1	4.84 ± 1.3	0.38

P-values were derived from the comparison of the indices log-transformed, by the Student's t-test. See Methods for definition of the variability indices.

(P = 0.44–0.83), and all were within the normal range. The mean body mass index was also comparable (P = 0.86) and below 25 kg/m^2. Distribution of subjects in the two groups for gender and alcohol intake showed only a borderline lower proportion, respectively, of men (P = 0.07) and total individuals (P = 0.07) with Alzheimer's disease. Proportion of individuals with a smoking habit was similar in both groups (P = 0.60). However, higher mean age (P = 0.0001), and lower proportion in performing physical activity (P = 0.0001) and in caffeinated intake (P = 0.008) were observed in the Alzheimer's disease group.

The data of heart interval variability analysis in the time-domain for the two groups of subjects in supine and standing positions are presented in Table 2. No mean index showed by the Alzheimer's disease group was statistically different (P = 0.12–0.72) from that of the control group in both postures, except the rMSSD that showed a borderline reduction in the standing posture (P = 0.09).

The data of frequency-domain analysis are shown in Table 3. In both postures, the mean of the total and low-frequency absolute power areas were comparable in both groups of subjects (P = 0.21–0.78). Differently, the mean high-frequency power showed a statistically borderline reduction in the supine position (P = 0.07) and was significantly reduced in standing position (P = 0.05) in the disease group. The indices of sympathovagal

Figure 1 Mean ± standard error of the mean (SEM) of the time-domain heart interval variability indices of Alzheimer's disease (ALZ, $n = 22$) in comparison with control healthy (CTR, $n = 24$) groups in the rest supine and active standing positions. The groups were compared by the Student's t-test. The indices were normalized by logarithmic transformation before comparison between the groups and then back transformed. The P-values are from the comparison of the indices log-transformed.

balance (normalized power areas and ratio of low- to high-frequency power areas) showed significant or borderline alterations ($P = 0.04$–0.07) toward relative depression of parasympathetic and enhancement of sympathetic modulation in the supine but not in the standing posture ($P = 0.19$–0.51).

As to the possible effects of the independent confounding variables that showed significant differences between the groups (mean age, physical activity and caffeinated intake), multiple logistic regression analysis proved that these differences were not responsible for the alterations in the dependent heart interval variability indices observed in the Alzheimer's group; that is to say, the confounding variables did not influence the alterations observed. Correlating each one of the indices altered with these variables simultaneously, the disease positively predicted the higher ratio of low-to-high-frequency power spectrum observed ($P = 0.05$) in the supine position and showed a tendency to inversely predict the high-frequency power ($P = 0.09$) in the standing posture. The normalized low-frequency power correlated positively with the disease both in supine ($P = 0.03$) and standing ($P = 0.01$) positions, while the normalized high-frequency power correlated inversely as much in supine ($P = 0.03$) as in standing ($P = 0.01$). For all the other indices, no correlation with the disease was noted in either posture ($P = 0.14$–0.90).

Figures 1 and 2 illustrate the mean ± SEM values, respectively, of the time- and frequency-domain indices for both groups in the supine and standing positions. The absolute and relative reductions of the mean frequency-domain indices indicating parasympathetic modulation and the relative increase of those expressing sympathetic activity may be observed in the Alzheimer's disease group. Although without statistical significance, a systematic reduction of the mean values of all the time-domain and the absolute frequency-domain indices was also noted in both postures.

Discussion

Alzheimer's disease peculiarly affects older people, encompassing variable disturbances of neural functions,
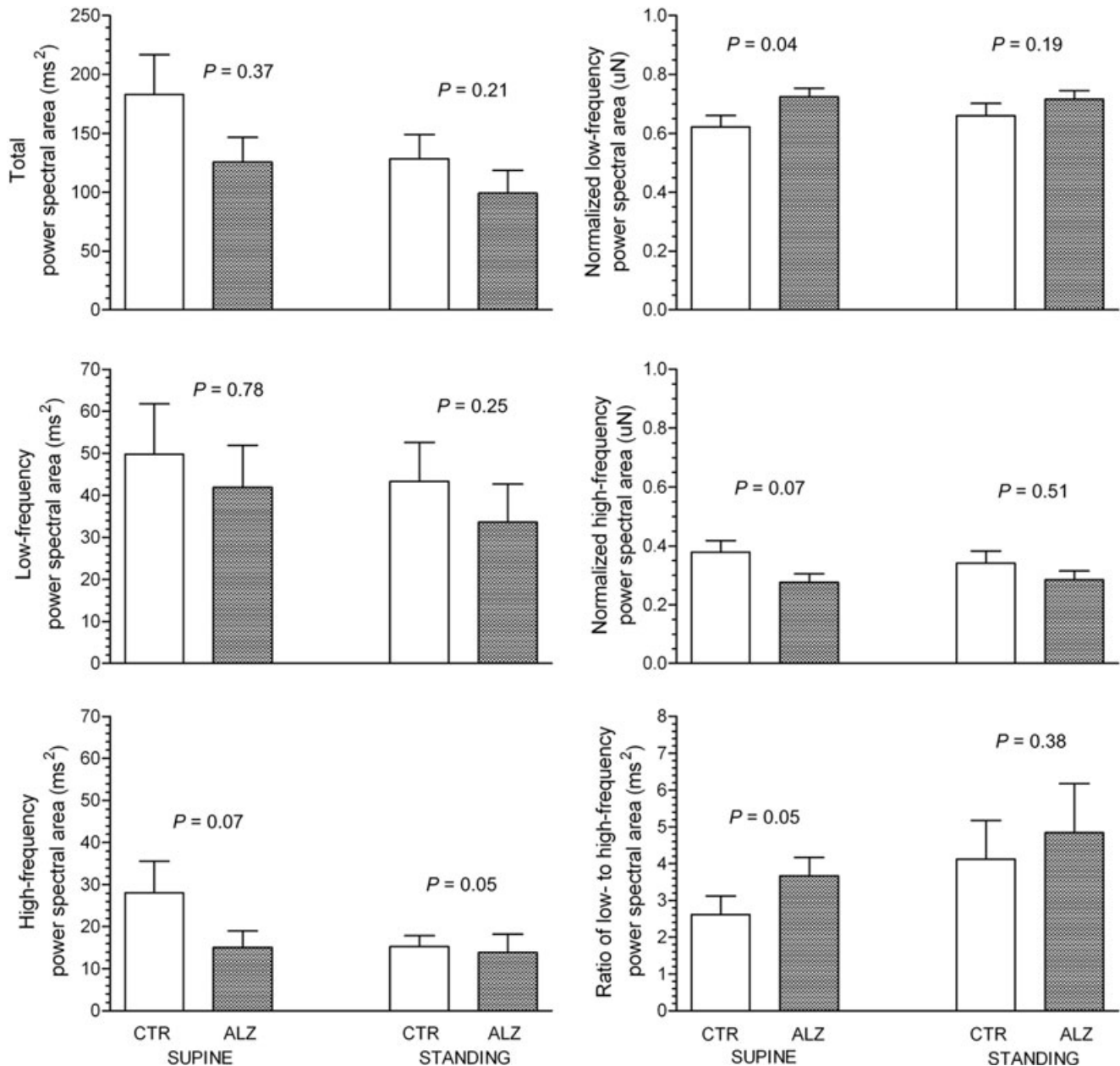
Figure 2 Mean ± SEM of the frequency-domain heart interval variability indices of Alzheimer's disease (ALZ, $n = 22$) in comparison with control healthy (CTR, $n = 24$) groups in the rest supine and active standing positions. The groups were compared by the Student's t-test. The indices were normalized by logarithmic transformation before comparison between the groups and then back transformed. The P-values are from the comparison of the indices log-transformed.

such as the autonomic and higher cerebral ones, by the involvement of several central and peripheral nervous structures that implicate one another.[6–9,11,14,16,19,21] It shows a multiplicity of intriguing and unsolved aspects, one of which is the overall and organ-related autonomic nervous system involvement,[16,17] and it is important to characterize extensively the cardiac autonomic function, and the nature, and pathophysiological and clinical significance of its disturbances.

In the present work, we evaluated the momentary cardiac autonomic modulation, based on the analysis of

spontaneous short- or long-term heart rate variability in time- and frequency-domain, in ambulatory and active older subjects with Alzheimer's disease, and variable cognitive dysfunction, in comparison with older healthy controls. Taken together, the results showed that the group of disease subjects, in the supine rest position, showed subtle but consistent relative (reduced normalized high-frequency and enhanced ratio of low-to-high-frequency powers) and absolute (reduced high-frequency power) depression of parasympathetic modulation and only relative sympathetic exacerbation

(enhanced normalized low-frequency and ratio of low-to-high-frequency powers). The overall autonomic activity remained unaltered (unchanged time-domain indices and total power), but with the sympathovagal balance showing sympathetic dominance, in comparison with the control group in the supine position. In the standing position, borderline absolute parasympathetic depression was noted (tendency for reduction of the rMSSD index and the high-frequency power), with also preserved overall autonomic activity and unaltered sympathovagal balance.

Thus, the subjects with the disorder had no additional depression of the overall cardiac autonomic activity in either posture, superimposed on that usual to old age, but only a sympathovagal balance altered with absolute and relative parasympathetic depression plus sympathetic exacerbation in the supine position, and unchanged autonomic modulation balance in the standing posture. However, in those cases where the differences between the groups were not statistically significant, Alzheimer's disease subjects showed systematically small heart interval variability indices compared to control subjects. These data suggest that the standing posture appears to be more favorable than the supine posture for subjects with Alzheimer's disease in regard to the cardiovascular homeostasis dependent on the sympathovagal modulation of heart rate dynamics. Although the majority of our Alzheimer's disease subjects showed moderate-to-severe cognitive dysfunction, they had subtle cardiac autonomic impairment probably because the cardiac autonomic function is already at a low level in accordance with the aging of the subjects, which has been demonstrated by several works employing different tests, including heart interval variability analysis.[44–46]

Our results confirm and extend the majority of the previous observations about the cardiac autonomic dysfunction evaluated by the heart interval variability in Alzheimer's disease subjects, reinforcing the pattern of absolute and relative parasympathetic depression associated with relative sympathetic exacerbation,[18–21] with a sympathovagal imbalance toward the dominance of sympathetic activity. The difference is that we showed only borderline or subtle sympathovagal dysfunction, which proves that this disturbance is widespread and not consistently evident in Alzheimer's disease. These apparently contradictory findings are probably due to the variable pattern or severity of the functional disturbances in Alzheimer's disease in the different studies.

One of the very probable mechanisms of the subtle cardiac autonomic dysfunction in Alzheimer's disease, which can act exclusively or in association with others, is the degenerative damage of central nervous structures related to the autonomic nervous system, besides their involvement in the higher cerebral functions.[3,6–11,14]

Involvement of peripheral nervous structures, including afferent nervous terminations and the intrinsic autonomic innervation of the heart, is also a possibility that may play a role.[15] It has also been demonstrated that cardiovascular regulation-related centers are damaged.[6,11] Different central and peripheral neurofunctional systems may also be involved, including the cholinergic, serotonergic, noradrenergic and dopaminergic neurons and neurotransmitters, but the cholinergic appears to be the principal system affected with increase in acetylcholinesterase activity and consequent cholinergic synaptic transmission deficiency.[12,13,20]

The pathophysiological and clinical significance of the subtle cardiac autonomic impairment can only be conjectured. The autonomic nervous system exerts important modulation on all the electrophysiological properties of the heart. The parasympathetic influence exerts depressive or stabilizing electrophysiological effects promoting anti-arrhythmogenic effects, while the sympathetic activity determine a pro-arrhythmogenic stimulating effect on different properties. Absolute or relative modifications of the sympathovagal balance, particularly toward dominance of sympathetic influence, triggered or exacerbated by different factors, in association with damage and disturbances of the myocardium and excite-conducting tissue, may result in electrophysiological instability and induce different arrhythmias.[47] Because individuals with Alzheimer's disease are older, it is plausible to consider that they may have variable pathological and functional involvement of the excite-conducting system, myocardium contractile and the intrinsic autonomic innervation of the heart, especially as a consequence of atherosclerotic degeneration and coronary ischemia, which may result in electrical, mechanical and neural regulatory disturbances. The even subtler autonomic dysfunction observed in these individuals, superimposed on the already depressed cardiac autonomic of aging, may be an additional factor for electrical and mechanical cardiac disturbances.[30,31,46–48] Cardiac autonomic impairment in association with these disturbances can propitiate the development of arrhythmias able to provoke even sudden death, as well as the installation of ventricular dysfunction resulting in heart failure.[47]

Even discrete deficiencies in cardiac autonomic adjustments to different stimuli might also affect the moment-to-moment cardiovascular adaptation, reflecting poor homeostasis and vulnerability to functional disturbances and disease states.[30,32,33,45,47] Thus, individuals with Alzheimer's disease may not be fully capacitated for adequate performance of their physical, physiological and even psychological activities, showing subtle or ostensive consequent disturbances and deficient cardiovascular adaptation.

Cardiac autonomic dysfunction may additionally be a risk factor for adverse overall and cardiovascular outcomes, because inappropriate sympathovagal balance or depressed heart interval variability have been firmly recognized to be independent markers of enhanced cardiovascular morbidity and mortality, higher risk of arrhythmias, sudden death and other cardiac events, and of poor prognosis in different clinical conditions and in some mental states.[28,29,31–33,47,48] In fact, Alzheimer's disease subjects show increased cardiovascular mortality,[26–28,32] and therefore it is possible that even the subtle cardiac autonomic dysfunction with sympathovagal imbalance disrupting the homeostatic adaptive capacity dependent on changes of heart rate, may be one mechanism for this worse outcome. Thus, cardiac autonomic impairment in this disease might be not of minor value, but instead an important cause of different disturbances and clinical manifestations, including those concerned with higher cerebral functions.[16,19,24,30]

A limitation in our study is that patients showing greater severity of the disease and/or with neuropsychiatric symptoms could not be included because of the difficulties found in performing the examinations. Also, the selection of subjects in this age range with no clinical disturbances and not making use of any drug is a very difficult task. These difficulties have led to a relatively small but reliable number of patients evaluated; however, they did not invalidate the results and their significance.

In conclusion, Alzheimer's disease subjects in this study showed subtle cardiac autonomic dysfunction. In the supine position, no alteration was observed in the overall cardiac autonomic modulation, reflecting the associated sympathetic and parasympathetic influences, as indicated by unaltered time-domain indices. That is to say, although at a low level as expected for older subjects, the degree of heart interval variability was similar in both groups. As to the sympathovagal balance in this position, the Alzheimer's disease group showed absolute and relative reduction of parasympathetic and relative increase of sympathetic modulation, resulting in an alteration toward the sympathetic dominance. In the standing position, a borderline result toward reduction of the parasympathetic modulation, reflected by lower rMSSD and high-frequency power, was noted with preserved sympathovagal balance. The cardiac autonomic impairment might be related to damage of autonomic-related nervous structures and/or disturbed cholinergic mechanisms. The probable effects that the subtle cardiac autonomic impairment may provoke in subjects with Alzheimer's disease should be investigated, but they may include arrhythmias, sudden cardiac death, increase of overall and cardiovascular mortality and morbidity, inappropriate cardiovascular adaptation, and worsening of cognitive and other higher cerebral dysfunctions.

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