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Autonomic activity, frailty phenotype and risk of falling in the elderly: Study protocol

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ABSTRACT

Background: Generally, in the aging process, there is degradation of autonomic nervous control mechanisms, compromising the regulation of heart rate, which contributes to increased frailty and the risk of falls. This process is defined as a geriatric syndrome that leads to impairment of physiological systems and homeostatic imbalance. **Objective:** To correlate heart rate variability (HRV), frailty parameters, and the risk of falls in elderly people from a community center. **Methods:** This research will involve active seniors and participants from the Centro de Convivências de Praia Grande, São Paulo, Brazil. Clinical, demographic, and anthropometric data, psychological variables, and physical conditions will be collected through the International Physical Activity Questionnaire (IPAQ) and the risk of falls test. The heart rate R-R intervals will be analyzed using the H10 polar frequency meter and the HRV application, and transferred to the Kúbios software for further analysis.Results: Two hundred and fourteen participants are involved in this study, 181 (84.6%) of whom are female, 137 (64.0%) are white, with a mean age of 70.27 ± 7.07 years, a weight of 68.37 ± 11.15 kg, and a body mass index of 27.04 ± 4.04 kg/m2. **Conclusion:** A positive correlation is expected through the stratified analysis of frailty indices, risk of falls, and HRV, suggesting that the lower the HRV, the greater the risk of falls and the greater frailty in the elderly.
Keywords: Heart rate variability; Frailty; Falls; Elderly; Cardiac autonomic modulation

BACKGROUND

The pace of aging in the world's population has increased significantly compared to the past, considering that people are living longer. In 2020, it was observed that the number of people aged 60 years and over was higher than that of children under 5 years old. It is estimated that by 2030, one in six people will be 60 years or older, increasing from 1 billion in 2020 to 1.4 billion. By 2050, this number of elderly people will be 2.1 billion, of which 80% will live in low- and middle-income countries[(1)]. These global demographic changes bring with them a series of challenges in the face of population aging, especially regarding health care[(2)].

As people age, they are more likely to experience numerous adverse health conditions at the same time, a process that is irreversible and inexorable for the entire human population[(1, 3)]. The morphological, physiological, biochemical, and psychological changes lead to a reduction in the individual's ability to adapt to the environment[(4, 5)].

A healthy functioning of the human body requires the integration of a complex network of physiological systems, such as the nervous, endocrine, respiratory, cardiovascular, metabolic, and immune systems, which allow the body to maintain homeostasis in the face of intrinsic and extrinsic stressors. The impairment of the aging process on homeostatic regulatory mechanisms implies a reduction in the individual's ability to respond adequately to internal and external stressors[(6, 7)].

As individuals age, it is important to understand the adaptation of the autonomic nervous system (ANS) to meet the changing demands of the human body. The ANS plays an important role in maintaining homeostasis in almost all physiological functions[(7-9)]. The impairment of the ANS due to cardiovascular changes, such as increased blood pressure, dysfunction in heart rate regulation, and accelerated frailty, is noteworthy[(6,7,10-15)]. Frailty, described as a geriatric weakness syndrome, is characterized by reduced muscle strength, low levels of physical activity, and reduced walking speed, which consequently compromise functional capacity[(16-18)]. As homeostatic control mechanisms deteriorate, including the ANS, functional capacity exceeds the "frailty threshold" resulting in increased vulnerability to injuries, diseases, and ultimately, death. For this reason, older adults belonging to higher age groups and with lower levels of physical activity have a higher risk of falls[(19-23)].

However, the scientific literature is scarce in studies that investigated the behavior of autonomic nervous activity through VFC analysis, associating it with the frailty index (FI) and the risk of falls simultaneously in the elderly. In this scenario, this study aims to correlate VFC, frailty parameters, and the risk of falls in elderly individuals from a community center.

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METHODS

Study design

The protocol of this study follows the recommendations of the SPIRIT - Standard Protocol Items: Recommendations for Interventional Trials[24]. This is an observational, cross-sectional study that will correlate HRV with frailty and fall risk, according to the recommendations of the STROBE - Strengthening the Reporting of Observational studies in Epidemiology[25] as shown in Figure 1.

Ethical aspects

This research was approved by the Research Ethics Committee of the Evangelical University of Goiás - UniEVANGÉLICA, under the opinion number 5.369.136. In order to participate in the study, all participants will be informed about the procedures and invited to sign the Informed Consent Form.

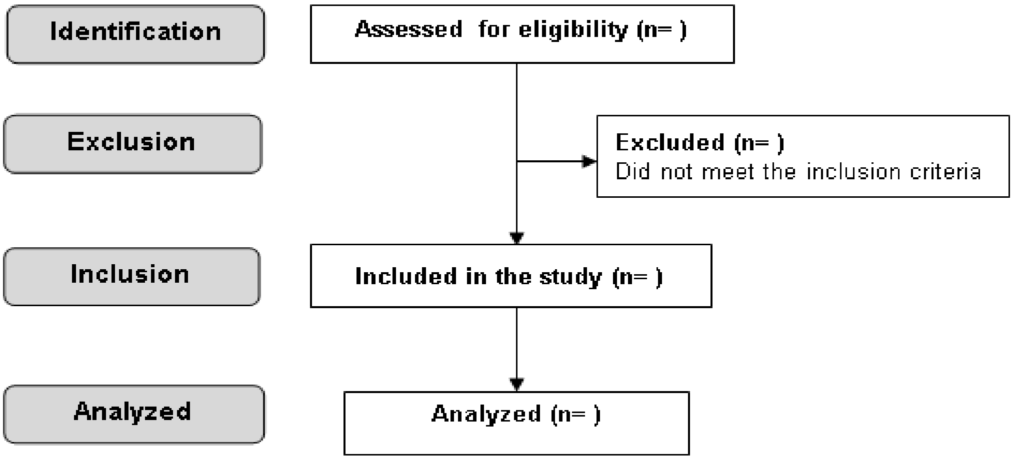

Figure 1. Study flowchart according to the Strengthening the Reporting of Observational studies in Epidemiology - STROBE.

Sample and participant

Selection Individuals aged 60 years or older who participate in activities at the Boqueirão de Praia Grande Center for Social Interaction, in São Paulo, Brazil, where data collection will take place, will be invited to participate in the study. The sample size was calculated based on the variance observed in a previous study by Giacomini et al. (2020)[20], considering a power of 90% and an alpha error of 0.05. Considering a possible loss of follow-up, 20% was added to the previous number of participants, resulting in a total of 208 participants.

According to the exclusion criteria, subjects with skeletal and/or joint limitations that prevent them from performing the walking test and those who use medication or drugs that influence autonomic nervous activity will not be included in the study. The score obtained in the Mini-Mental State Examination (MMSE) will also be used as a criterion for participation in the study, based on self-reported physical and mental health, functional performance, and subjective well-being. The following cut-off scores will be observed for participant exclusion: 17 points for illiterate participants, 22 points for those with 1-4 years of schooling, 24 points for those with 5-8 years of schooling, and 26 points for those with 9 years of schooling[26, 27].

Outcomes and Measures

Anthropometric measures

After signing the informed consent form, participant assessment will begin on the same day. Initially, individuals will undergo an anthropometric evaluation, which involves obtaining weight and height measurements for the subsequent calculation of body mass index (BMI), as well as for normalization of the measures needed to estimate the frailty phenotype. Weight and height variables will be verified using a Ramuza DP 200kg/50g anthropometric scale (RAMUSA Ltda, São Paulo, Brazil).

Height will be measured during inspiration and in an upright position, with the participant barefoot, ankles together, scapulae and head against the wall, and the head positioned according to the Frankfurt plane. Weight will be measured with participants wearing light clothing. BMI will be calculated using weight (kg) and height (m-2)[28].

Frailty phenotype

The elderly subjects involved in this study will be classified according to the frailty phenotype according to the criteria proposed by Fried et al. in 200[29]. The Measurement Criteria - Phenotype of Frailty is a screening test for frail individuals, evaluating the elderly in five items. Involuntary weight loss is observed - assessed by loss of 4.5 kg or more in the last year or at least 5% of body weight); Self-report of exhaustion (fatigue) – measured by the Center for Epidemiologic Studies-Depression Depression Scale[30, 31]; Weakness or reduced muscle strength of the upper limbs – assessed by the pressure generated by the palmar grip muscles of the dominant upper limb, measured by a dynamometer adjusted for gender and BMI[32]; Decreased speed when walking – decrease in walking speed verified by the time taken to walk a space of 4 measured meters, adjusted for gender and height; The low level of physical activity – measured by the International Physical Activity Questionnaire (IPAQ), an instrument validated in Brazil, recommended for national studies of prevalence an possibilities of international comparison. The indices will be calculated considering the minutes per week, 30' on most days of the week, adding at least 150' per week of moderate activity, and for vigorous at least 3 sessions of 20' per week seconds[22, 33]. After evaluating these five aspects, the elderly will be classified as frail - if three, four, or five items are present; Pre-frail - if one or two items were present and non-frail if no criteria were present[29].

Risk of falling

The estimate of the risk of falling will be obtained by a questionnaire with 21 items addressing stumbling, ability to climb stairs, decrease in walking speed, ability to cross the road during the green light, ability to walk 1 km continuously, ability to stand on just one leg for 5 seconds, use of a cane, ability to wring a bath towel, presence of dizziness, stooped back, knee pain, vision and/or hearing changes, memory lapses, anxiety related to falls, use the diary of more than five prescribed medications, presence of obstacles at home, presence of barriers on the floor, daily use of stairs at home, if there are steep paths close to the house. Each item will receive a score of 1 (presence of risk) or 0 (absence of risk) and the sum of all items will range from 0 (low risk of falling) to 21 (high risk of falling). The cutoff points for stratification

The HRV analysis through the time domain will be performed using the fast Fourier transform (FFT). All HRV analyzes will be performed using Kubios HRV

into low-risk (<10 points) and high-risk (≥ 10 points) falls will be adopted for comparison purposes, as previously established[34].

Heart Rate Variability

The HRV will be measured through the behavior of the R-R intervals. Volunteers will be seated, at rest for 15 minutes. After this period, the verification of the R-R intervals will be carried out with the Polar H10 sensor (Polar Electro Brasil Comércio, Distribuição e Exportação Ltda, Embu das Artes, São Paulo, Brazil), chest strap type and with the Elite HRV application (Gloucester, MA , USA). The tape will be moistened and placed in the anterior region of the chest, in the lower part of the sternum and the cell phone placed in front of the tape, on a table.

HRV analyzes will be performed in the time domain considering the SDNN indices (standard deviation of all normal RR intervals recorded in a time interval, expressed in ms), rMSSD (the square root of the mean square of the differences between normal RR intervals adjacent RR intervals, in a time interval, expressed in ms) pNN50 (percentage of adjacent RR intervals with a duration difference greater than 50ms).

The SDNN index represents sympathetic and parasympathetic activity, but it does not allow distinguishing when HRV changes are due to increased sympathetic tone or withdrawal of vagal tone. The rMSSD and pNN50 indices represent the parasympathetic activity, as they are found from the analysis of adjacent RR intervals[35].

For HRV analysis in the frequency domain, the high-frequency component indices (HF) will be used, which is an indicator of the action of the vagus nerve on the heart, the low-frequency component (LF), which is due to the joint action of the vagal and sympathetic components over the heart, with a predominance of the sympathetic and the LF/HF ratio, which reflects the absolute and relative alterations between the sympathetic and parasympathetic components, characterizing the sympathovagal balance over the heart. The triangular HRV index (a total number of all NN intervals divided by the height of the histogram of all NN intervals measured on a discrete scale with intervals of 7.8125 ms in a ratio of 1/128 seconds, which is between the geometric indices recommended by the task force, both measures reflect the general HRV and are more influenced by the lower frequencies than by the higher ones[35].

Standard version 3.5.0 software (Kubios software [free version], HRV analysis, University of Eastern Finland)[36].

Confidentiality and privacy

The information obtained in this study will have exclusive access to the researchers involved and will be used only for the purposes of scientific research and publication in scientific journals in the area. The name of the research participants will be replaced by numbers, and the data collected in the exams will be restricted, without any kind of posts and/or disclosures. All results obtained will remain stored on a central computer, with access only by authorized persons. The information obtained will be kept by the responsible researchers for 5 years and after that period incinerated.

Statistical analysis

Data normality will be tested by the Kolmogorov-Smirnov test, asymmetry, kurtosis, and graphic and histogram analysis. Descriptive analyses, measures of central tendency (mean and median), dispersion analyzes (standard deviation [SD] and interquartile range [IIQ]) and frequency calculations (absolute and relative) will be used. To compare the HRV indices, the frailty assessment parameters (weight loss, handgrip, exhaustion, walking speed, and level of physical activity), and the risk of falls, the Mann-Whitney U test will be used. The correlation of the HRV indices with the variables of the handgrip, gait speed, physical activity level, and with the risk score for the risk of falls will be verified using Spearman's correlation, whose effect size will be evaluated by Cohen's d, classified as weak (0.20 to 0.30), medium (0.40 to 0.70) and great (≥ 0.80)1.

The prevalence of the phenotypes of the frailty components will be presented in percentages. To compare the distribution of HRV indices with the frailty syndrome, the Chi-square test will be used. Therefore, the HRV indices will be dichotomized into low and high variability, using the 50th percentile value (median). To verify the associations of the HRV indices with the frailty assessment parameters and the risk of falls, the Generalized Linear Models (GzLM) will be used, with a confidence interval (CI) of 95% and an estimate of Odds Ratio (OR), using the principle of parsimony and the smallest value of the Akaike information criterion (AIC) regarding its distribution, using the Gamma distribution with link log for all tested models.All procedures will be performed using the Statistical Package for Social Sciences (SPSS) version 26.0 (IBM) software and the significance level adopted will be 5%.

PRELIMINARY RESULTS

The sociodemographic characteristics of the individuals who were initially invited to participate in the study are described in table 1.

Table 1. Sociodemographic Characteristics

Variables	**n = 214**
Gender	
Female	181 (84,58%)
Male	33 (15,42)
Ethnicity	
White	137 (64,02%)
Brow	55 (25,70%)
Black	17 (7,94%)
Asian	5 (2,34%)
Age (years)	70,27 ± 7,07
Weight (kg)	68,37 ± 11,15
BMI (kg/m²)	27,04 ± 4,04
Marital status	
Single	35 (16,36%)
Married	95 (44,39%)
Divorced	24 (11,21%)
Widower	60 (28,04%)

CONCLUSION

With this study, it is expected that through the stratified analysis of the frailty, risk of falls and HRV indices, comparing, correlating and individually associating each of the autonomic modulation indices, a positive correlation of these indices will be obtained, suggesting that the more the lower the HRV, the greater the risk of falls and the greater frailty in the elderly.

Author´s contributions: The authors confirm contribution to the paper as follows: study conception and design: RKP, and FSA; contributed to the acquisition of the data: FSA, APAFJ, GLR, KCSC, and EVC, LP, and GFS; participated in its design, coordination, and statistical analysis: MCO, SKAS, CNSN, and JPRA; performed the extra analyses; RKP, and FSA; drafted the manuscript: RKP, MCO, JPRA, and FSA. All authors read and approved the final manuscript.

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Conflict of interest: The authors of this manuscript declare that they have no conflicts of interest.

REFERENCES

1. World Health Organization (WHO). Ageing and health. Steverson M. WHO. 2022 [cited 2023 Mar 08]. Available from: https://www.who.int/news-room/fact-sheets/detail/ageing-and-health.
2. Dalgaard CJ, Hansen CW, Strulik H. Physiological aging around the World. PLoS One. 2022 Jun 8;17(6):e0268276.
3. Bernardi DF, Reis MAS, Lopes NB. O tratamento da sarcopenia através do exercício de força na prevenção de quedas em idosos: revisão de literatura. Ensaios e Ciência: Ciências Biológicas, Agrárias e da Saúde. 2008;12(2):197-213.
4. Almeida ST, Valentim AL, Diefenbach N. Lian Gong como prática fisioterápica preventiva do envelhecimento. Estudos Interdisciplinares do Envelhecimento. 2004;6(1):103-10.
5. Civinski C, Montibeller A, Braz ALO. A importância do exercício físico no envelhecimento. Rev. da Unifebe (Online). 2011;9(jan/jun):163-175.
6. Varadhan R, Chaves PHM, Lipsitz LA, Stein PH, Tian J, Windham BG, et al. Frailty and impaired cardiac autonomic control: new insights from principal components aggregation of traditional heart rate variability indices. J Gerontol A Biol Sci Med Sci. 2009;64:682-7.
7. Edwards IJ. Highlights in basic autonomic neurosciences: Changes to the autonomic nervous system associated with healthy ageing. Auton Neurosci. 2014;183:1-3.
8. Jänig W. Integrative Action of the Autonomic Nervous System: Neurobiology of Homeostasis. Cambridge: Cambridge University Press, 2006.
9. Freitas J, Santos RM, Figueiredo V, Teixeira E, Carvalho M, Freitas AF. Role of autonomic nervous system and hemodynamics in cardiovascular homeostasis after orthostatic stress. Rev Port Cardiol 2000;19(12):1241-74.
10. Arantes FS, Rosa Oliveira V, Leão AKM, Afonso JPR, Fonseca AL, Fonseca DRP, Mello DACPG, Costa IP, Oliveira LVF, da Palma RK. Heart rate variability: A biomarker of frailty in older adults? Front Med. 2022;9:1008970.
11. Pandey A, Kitzman D, Reeves G. Frailty is intertwined with heart failure: mechanisms prevalence prognosis assessment and management. JACC Heart Fail. 2019;7:1001–11.
12. Stewart R. Cardiovascular disease and frailty: what are the mechanistic links? Clin Chem. 2019;65:80–6.
13. Marengoni A, Zucchelli A, Vetrano DL, Aloisi G, Brandi V, Ciutan M, et al. Heart failure, frailty, and pre-frailty: a systematic review and meta-analysis of observational studies. Int J Cardiol. 2020;316:161–71.
14. Liperoti R, Vetrano DL, Palmer K, Targowski T, Cipriani MC, et al.. Association between frailty and ischemic heart disease: a systematic review and meta-analysis. BMC Geriatr. 2021;21:357.
15. Parvaneh S, Howe CL, Toosizadeh N, Honarvar B, Slepian MJ, Fain M, et al. Regulation of cardiac Autonomic Nervous System Control across Frailty Statuses: A Systematic Review. Gerontolgy. 2015;62:3–15.
16. Fried LP, Walston J. Frailty and failure to thrive . In: Hazzard WR, Blass JP, Ettinger WH Jr, Halter JB, Ouslander J. Principles of Geriatric Medicine and Gerontology. 4th ed. New York: McGraw Hill, 1998. p. 1387-402.
17. Morley JE, Vellas B, van Kan GA, Anker SD, Bauer JM, Bernabei R, et al. Frailty consensus: a call to action. J Am Med Dir Assoc. 2013;14(6):392-7.
18. Hoogendijk EO, Afilalo J, Ensrud KE, Kowal P, Onder G, Fried LP. Frailty: implications for clinical practice and public health. Lancet. 2019 Oct 12;394(10206):1365-1375.
19. Lipsitz LA. Physiological complexity, aging, and the path to frailty. Sci Aging Knowledge Environ. 2004(16):pe16.
20. Giacomini SB, Fhon JR, Rodrigues RA. Frailty and risk of falling in the older adult living at home. Acta Paul Enferm. 2020; eAPE20190124.
21. Zhou BY, Yu DN, Tao YK, Shi J, Yu PL. Relationship between fall and frailty index in older people adults of urban community in Beijing. Zhonghua liu xing bing xue za zhi Zhonghua liuxingbingxue zazhi. 2018;39(3):308–12.
22. Silva RA da, Brandão GS, Silva AS, Urbano JJ, Oliveira EF de, Oliveira LVF, Camelier AA, Brandão GS. Physical activity level, functional mobility and fall risk in the elderly. mtprehabjournal. 2017:1-6.
23. Dent E, Morley JE, Cruz-Jentoft AJ, Woodhouse L, Rodríguez-Mañas L, Fried LP, et al. Physical Frailty: ICFSR International Clinical Practice Guidelines for Identification and Management. J Nutr Health Aging. 2019;23(9):771-87.
24. Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 Statement: Defining standard protocol items

for clinical trials. Ann Intern Med. 2013;158(3):200-7

25. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007 Oct 20;370(9596):1453-7.
26. Bertolucci PHF, Brucki SMD, Campacci S, Juliano Y. The Mini-Mental State Examination in an outpatient population: influence of literacy. Arq Neuropsiquiatr 1994; 52:1-7.
27. de Melo DM, Barbosa AJ. Use of the Mini-Mental State Examination in research on the elderly in Brazil: a systematic review. Cien Saude Colet. 2015;20(12):3865-76.
28. Peterson CM, Thomas DM, Blackburn GL, Heymsfield SB. Universal equation for estimating ideal body weight and body weight at any BMI. Am J Clin Nutr. 2016;103(5):1197-203.
29. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in Older Adults: Evidence of a Phenotype. J. Gerontol. A Biol Sci Med Sci. 2001;56(3):146-56.
30. Liu CJ, Marie D, Fredrick A, Bertram J, Utley K, Fess EE. Predicting hand function in older adults: evaluations of grip strength, arm curl strength, and manual dexterity. Aging Clin Exp Res. 2017;29(4):753-60.
31. Tavares BS, Neri AL, Cupertino APFB. Validity of the Center for Epidemiological Studies – Depression Scale (CES-D) among Brazilian elderly. Cad Saúde Pública. 2007;41(4):598-605.
32. Kim SY, Park JH, Lee MY, Oh KS, Shin DW, Shin YC. Physical activity and the prevention of depression: A cohort study. Gen Hosp Psychiatry. 2019;60:90-7.
33. Matsudo S, Araújo T, Matsudo V, Andrade D, Andrade E, Oliveira LC, et al. Questionário internacional de atividade física (IPAQ): estudo de validade e reprodutibilidade no Brasil. Ativ Fis Saude. 2001;6(2):5-18.
34. Ishimoto Y, Wada T, Kasahara Y, Kimura Y, Fukutomi E, Matsubayashi K, et al. Fall Risk Index predicts functional decline regardless of fall experiences among Community dwelling elderly. Geriatr Gerontol Int 2012;12(4):659-66.
35. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Circulation. 1996;93(5):1043-65
36. Tarvainen MP et al. Kubios HRV – Heart rate variability analysis software. Comp Meth Programs Biomed. 2014; 113(1):210-20.