Heart rate variability and falls in Huntington’s disease

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Abstract
Purpose Persons with Huntington’s disease (HD) have a high incidence of falls. Autonomic nervous system dysfunction has been reported even in early stages of this disease. To date, there has been no analysis of the relationship between heart rate variability (HRV) and falls in this patient population. The aim of the study reported here was to evaluate the relationship between HRV and falls in persons with HD.

Methods Huntington’s disease patients enrolled in a prospective study on fear of falling and falls were assessed using short-term HRV analyses and blood pressure measures in both the resting and standing states. Time–frequency domains and nonlinear parameters were calculated. Data on falls, the risk of falling (RoF) and disease-specific scales were collected at baseline and at the end of the 6-month follow-up.

Results Of the 24 HD patients who were invited to participate in the study, 20 completed the baseline analysis and 18 completed the 6-month follow-up. At baseline, seven (35%) HD patients reported at least one fall (single fallers) and 13 (65%) reported ≥ 2 falls (recurrent fallers) in the previous 12 months. At baseline, recurrent fallers had lower RMSSD (root mean square of successive RR interval differences) in the resting state (RMSSD-resting), higher LF/HF (low/high frequency) ratio in both states and higher DFA-α1 parameter (detrended fluctuation analyses over the short term) in both states. This association was similar at the 6-month follow-up for recurrent fallers, who showed lower RMSSD-resting and higher LF/HF ratio in the standing state (LF/HF-standing) than single fallers. Significant correlations were found between the number of falls, RMSSD-resting and LF/HF-standing. No differences were found between recurrent and single fallers for any blood pressure measures.

Conclusions The observed HRV pattern is consistent with a higher sympathetic prevalence associated with a higher RoF. Reduced parasympathetic HRV values in this patient population predict being a recurrent faller at 6 months of follow-up, independently of orthostatic phenomena.

Keywords Autonomic nervous system · Fall prediction · Heart rate variability · Huntington’s disease · Risk of falling

Introduction
Huntington’s disease (HD) is a neurodegenerative disorder characterized by progressive neural loss that primarily affects the caudate nucleus and putamen within the basal ganglia [1]. Persons with HD have an increased risk of frequent falls, which has a high impact on their quality of
life [2]. Among persons with early to mid-stage HD, single fall rates range from 21 to 75%, and recurrent falls range from 58 to 60% [3, 4]. It has been reported that being fall prone is one of the strongest predictors of nursing home placement [5].

Falling in persons with HD is multifactorial in origin. There is a complex interaction between chorea and bradykinesia, and their impact on balance, that increases the risk of falling (RoF) [4]. Reduced cognitive reserve for dual-tasking [2], behavioral disturbances, such as recklessness, reduced attention and lack of insight, and autonomic factors [6] may also have an effect on the RoF. The use of antidepressants, neuroleptics and/or cardiovascular medications, alcohol intake and the home environment are additional factors that may contribute to falls [3, 7]. Evaluation of the autonomic nervous system (ANS) as a tool for detecting the RoF is a relatively recent strategy. Different studies have used ANS evaluation and, in particular, heart rate variability (HRV) to detect and predict the RoF in other patient populations [6, 8, 9], but the association between recurrent falls and autonomic dysfunction has not yet been studied in sufficient detail in the general population. Also, to date, no studies have focused on HRV and its association with postural changes in the HD population.

ANS dysfunction in the HD patient population has been identified [10, 11]. Most studies conducted to date have shown early sympathetic hyperactivity in the HD population [10, 12–16]. The most likely mechanism underlying these findings is an apoptosis-induced structural defect in the central autonomic network, such as the limbic system, the brainstem or the hypothalamus [17, 18].

Although falls are multifactorial, evaluation of autonomic dysfunction in HD patients may be an important approach by which to investigate its role on RoF to minimize falls and to identify and monitor patients prone to falling [19]. Therefore, the main aim of this study was to investigate the association between the RoF and short-term HRV assessment in HD patients in different positions.

Patients and methods

Study design

A cross-sectional study was conducted between April 2016 and March 2019 to evaluate the association between clinical and autonomic variables and falls in HD patients. Falls in the previous 12 months and HRV were evaluated at baseline, and the study subjects were contacted by phone 6 months later to obtain information on the occurrence of falls in that 6-month period following the baseline evaluation.

Participants

Patients with a genetically confirmed diagnosis of HD were enrolled in a study on fear of falling (FoF), and falls were assessed by short-term HRV analysis and blood pressure measures with the subject in different positions. Short-term HRV included time domain, frequency domain and nonlinear parameters. These variables were recorded for 5 min with the subject in the resting and standing positions, respectively, and the data collected on each state and the difference in data between the two states were analyzed. Demographic data, including age (years), weight (kg) and current medication, were obtained. Disease-specific and validated scales were used to measure RoF in the HD patient population. Information on falls was also collected by means of a retrospective questionnaire. Participants were divided into two groups at baseline, with one group comprising persons who reported ≥ 2 falls over the previous 12 months (recurrent fallers) and a second group comprising persons who reported ≤ 1 fall during the same period (single fallers) [20]. Patients were similarly classified based on the occurrence of falls during the 6 months of the follow-up.

Inclusion and exclusion criteria

Participants were eligible for the study if they met the following inclusion criteria: (1) genetically confirmed diagnosis of HD; (2) > 18 years of age; (3) stable medication regime for 4 weeks before baseline assessment. Exclusion criteria included: (1) the presence of diseases known to affect HRV (cardiac arrhythmia, heart failure, arterial hypertension, use of a pacemaker and kidney or liver disease); (2) diagnosis of dementia based on Diagnostic and Statistical Manual of Mental Disorders (DSM–5; American Psychiatric Association, Washington DC, USA) criteria; (3) inability to walk independently (use of a cane was allowed).

Whenever possible, cardiac medications that could affect the results of HRV (i.e. calcium-channel blockers, mineralocorticoids) were discontinued or reduced to the lowest dosage. Patients being treated with beta-receptor blockers were excluded from the study; those on angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers and diuretics were included.

Written informed consent was obtained from all the participants after a detailed explanation of the procedures. The local Ethics Committee approved the study, which followed all of ethical standards set out in the Declaration of Helsinki of 1964 and its later amendments.
Baseline assessment

All tests were performed in a single visit in a standardized order. A neurologist obtained the following clinical measures of disease severity: the Unified Huntington Disease Rating Scale (UHDRS), UHDRS-Total Motor Score (UHDRS-TMS; range 0–124; lower is better) and UHDRS-Total Functional Capacity (UHDRS-TFC; range 0–13; a higher score is better). Following the recommendations of The Kellog International Work Group on the prevention of falls in the elderly, a fall was defined as “an unintentional or unexpected event which results in the person coming to rest on the ground or another lower level” [21]. The history of falls was self-reported and confirmed by a family member or caregiver. Participants were asked to recall if they had any fall in the last 12 months and if the response was positive, to describe the circumstances and any associated injuries.

For a complete assessment of balance and gait, three tests validated for use in HD were performed:

1. The Berg Balance Scale (BBS) [22]. This is a 14-item objective measure of common everyday movement tasks related to balance control. Better balance is indicated by higher scores (range 0–56). The BBS is a suggested scale for screening for fall risk [23], with a cutoff score of 40 predicting being a faller [4].

2. The Timed up and Go test (TUG) [24]. This test measures (in seconds) the time taken by an individual to stand up from a standard armchair, walk a distance of 3 m, turn, walk back to the chair and sit down again. The TUG is suggested as a tool for assessing the severity of balance and mobility issues and for screening for fall risk; however, there is no sensitivity or specificity data for the reported cutoff point [23]. Mean scores for patients with manifest HD range from 9 to 17 s [25], and the cutoff score of 14 s has been reported to predict being a faller [4].

3. The Tinetti Mobility Test (TMT). This is a 16-item performance measure (range 0–28) which consists of balance and gait subscales that measure static and dynamic balance [26]. When the TMT is used to screen RoF in patients with HD, a cutoff value of 21 is applied to distinguish between those who are at high RoF (≤ 21) from those who are not (> 21) [23, 27].

Additionally, cognitive and neuropsychiatric symptoms were assessed using a comprehensive test battery, including the Montreal Cognitive Assessment (MoCA), the Frontal Assessment Battery (FAB), the Beck Depression Inventory (BDI), the Beck’s Anxiety Inventory (BAI), Starkstein’s Apathy Scale (SAS), Fear of Falling Scale (FES-I) and the Barthel Index.

Follow-up assessment

Participants were contacted by phone to collect the records of any fall incidence during the 6 months after the baseline assessment. The participants were asked to complete a falls diary in which they recorded every fall experienced during this period as soon as it occurred. To ensure an accurate reporting of falls and to verify data and check for patients’ missing data, family members and/or caregivers were contacted by phone monthly by the same investigator who recruited and assessed the patients at baseline. This method is considered to be an appropriate method to collect fall incidence data [28]. The FES-I scale to assess concerns about falling was also completed by phone during the follow-up evaluation.

HRV assessment

Heart rate variability examinations were always performed between 1400 and 1700 hours. To avoid variations in circadian HRV, all participants were instructed to have only a light meal and to sleep for at least 7 h before the HRV examination, and to abstain at least 3 h from drinking caffeine-containing beverages. Participants were asked to remain in the same position without talking during the HRV recording. The HRV tests were performed in a standardized order, as described below.

Signal recording

Participants were connected to the electrocardiogram (ECG) recording device and then left to rest in a sitting position for 10 min, following which the ECG signal was recorded for 5 min under the same conditions (resting state). After this first ECG recording, the participants were asked to stand up, and the ECG was again recorded for 5 min under these conditions (standing state). Blood pressure was measured twice under both conditions. Orthostatic hypotension was defined as a sustained reduction in systolic blood pressure of at least 20 mmHg or in diastolic blood pressure of at least 10 mmHg, or both, within 3 min of standing, in accordance with the recommendations of the international consensus statement [29]. The ECG signal was recorded using a digital Holter device (Holter HCAA 348; Holtech Servicios Computados S.A., Buenos Aires, Argentina) and stored in a memory card. Ventricular depolarizations (R waves) were detected by the software of the Holter device. Kubios® software [30] (Kubios HRV 2.1; Biosignal Analysis and Medical Imaging Group, Kuopio, Finland) was used to import and analyze all RR series [31, 32].
HRV analyses

We analyzed 5-min periods of resting-state and 5-min periods of standing-state RR intervals resulting from sinus beats. Medium threshold correction was used to detect artifacts (missed, extra and misaligned beat detections) as well as ectopic beats [30]. The artifacts and ectopic beats were corrected by comparing every RR interval value against a local average interval (0.25 ms). Detected ectopic beats were corrected by replacing corrupted RR times with interpolated RR values. Missed beats were corrected by adding new R-wave occurrence time, and extra beats were corrected by removing extra R-wave detection and recalculating the RR interval series [30]. All records included in this study comprised > 80% valid data [31]. For the slow linear or more complex trends within the time-series analyses, the smoothness prior approach for removing time-series non-stationarities was applied. The strong stationarity was visually checked. The cutoff frequency was below the low-frequency (LF) band (< 0.04 Hz) [30].

HRV linear analyses

**Time domain (non-spectral).** Time-domain measurements of HRV included the mean heart rate (HRM), the mean RR interval (RRM), with the RR interval defined as the time distance between nearest R peaks in a human electrocardiogram, the standard deviation (SD) of all regular RR intervals (SDNN) and the root mean square of the successive differences in regular RR intervals (RMSSD) [32]. RRM is a measure that quantifies the HRM, SDNN represents a coarse quantification of overall variability and RMSSD measures high-frequency (HF) variations in heart rate [17, 30, 32].

**Frequency domain (spectral).** In the frequency-domain methods, a spectrum estimate was calculated for the RR interval series. Prior to spectrum estimation, the RR interval series was converted to equidistantly sampled series by cubic spline interpolation. The spectrum was estimated by Welch’s periodogram [30]. In Welch’s periodogram, the RR series was divided into overlapping segments, each segment was windowed to decrease the leakage effect and the spectrum estimate was obtained by averaging the fast Fourier transform spectra of these windowed segments. The spectrum estimates are then divided into very LF (VLF), LF and HF bands. The generally used limits for these bands in the case of short-term HRV recordings in healthy human subjects are 0–0.04 Hz (VLF), 0.04–0.15 Hz (LF) and 0.15–0.4 Hz (HF) [32–34]. HRV measures extracted from these frequency bands included absolute powers, expressed as the natural logarithm for each band (in ms²) and the LF/HF power ratio [30, 32]. All HRV indices were calculated for the resting and standing states, and the difference between both states.

**HRV nonlinear analyses** The scaling exponent αs and sample entropy (SampEn) were used as nonlinear HRV indexes. αs, based on the “detrended fluctuation analysis” (DFA), quantifies the short-term fractal correlation properties of the interbeat time data [35]. DFA measures the correlations within the data for different time scales and is divided into short-term and long-term fluctuations, which are characterized by parameters α1 (range 4–16 beats) and α2 (range 16–64 beats), respectively [30]. Values of α close to 0.5 are associated with white noise (no correlation between values), whereas values close to 1.5 are associated with Brownian noise (strong correlation between values). Values near 1 are characteristic of fractal-like processes, associated with the dynamic behavior of time series generated by complex systems, such as the autonomic regulation of the sinus rhythm of a healthy subject. SampEn [36] estimated the irregularity of the RR interval time series as a measure of system complexity. Regular sequences will result in lower SampEn values, whereas random behavior is associated with larger SampEn values. These methods have been previously described [34–36]. Uncorrelated and irregular behavior is usually associated with parasympathetic prevalence [37].

**Statistical analyses**

The sample size was decided based on the expected differences between risk groups (early-mid/late stages of HD, and faller/no faller) and estimated population SD for the selected HRV variable: LF mean difference 1.5 ms², SD 1.1 ms²; HF mean difference 1.4 ms², SD 1.0 ms²; LF/HF ratio mean difference 0.4 ms²), SD 0.3 ms². Thus, a sample size of eight participants per group was decided (statistical power 80%; alpha 0.05; STATA 13v, StataCorp LLC, College Station, TX, USA). The values of references used for the calculation have been published previously [8, 15]. Median and interquartile range (IQR; 25 and 75%) or proportions were compared between single and recurrent fallers through the unpaired Mann–Whitney U tests or X² tests, respectively. Correlation coefficients between the number of falls and HRV were calculated with Spearman’s rho. The statistical significance for these comparisons was set at p < 0.05. A false discovery rate (FDR 0.25) correction was applied to multiple intergroup comparisons (https://www.sdmproject.com/utilities/?show5FDR). Logistic regression models were used to assess the independent predictive value of RoF outcome measures and HRV to identify recurrent fallers. Faller status at 6 months (single faller/recurrent faller) was included as the dependent variable, while RoF measured by BBS, TUG or TMT (high risk = 1, low risk = 0), and
significant HRV parameters were included as independent variables. Taking into account the small sample size of our study, models were constructed with only two independent variables as predictors: a clinical scale that measures RoF in HD was the first independent variable (BBS, TUG or TMT), and the HRV variable that had been significant in the univariate analysis (RMSSD in the resting state [RMSSD-resting] or LF/HF ratio in the standing state [LF/HF-standing]) was the second independent variable. Thus, each model included two independent predictors that were included as follows: (1) RMSSD-resting and BBS; (2) RMSSD-resting and TUG; (3) RMSSD-resting and TMT; (4) LF/HF-standing and BBS; (5) LF/HF-standing, and TUG; (6) LF/HF-standing and TMT. The variance inflation factor (VIF) was used to discard collinearity between independent variables; all variables included in the logistic regression models had VIF values lower than 10 (data not shown). In addition, we double-checked the absence of collinearity with low VIF measures for all our variables using the command Collin on STATA 13v. Associations were expressed as the coefficient of regression with the standard error (SE) and as odds ratios (OR) with 95% confidence intervals (CIs). Statistical analyses were performed using IBM SPSS Statistics version 23.0 (IBM Corp., Armonk, NY, USA).

Results

Demographic and clinical characteristics of patients

Twenty-four HD patients were invited to participate in the study, of whom three refused to participate and one was excluded due to the use of beta-receptor blockers, leaving a total study sample of 20 patients who completed the baseline analysis and 18 patients who completed the 6-month follow-up. At baseline, there were 12 (60%) women. According to the results from the UHDRS-TFC, 16 (80%) patients were in the early-mid stage of HD (early stage, n = 14; mid-stage, n = 2) and four (20%) were in the late stage of the disease. Due to the small number of patients in the mid-stage, this group was merged with the early-stage group, forming the early-mid group (n = 16). The rationale of forming the early-mid group derives from the clinical similarity in early stages of the disease with respect to the mid-stage. Medians and IQR (25–75%) of all clinical and demographics variables at baseline are presented in Table 1. The BBS classified seven patients (2 single fallers vs. 5 recurrent fallers; p = 0.658) at high RoF (HRF); the TUG classified 14 patients (5 single fallers vs. 9 recurrent fallers; p = 0.919) as HRF; and the TMT classified ten patients (3 single fallers vs. 7 recurrent fallers; p = 0.639) as HRF (Table 1).

At baseline, seven patients (35%) were classified as single fallers and 13 (65%) patients as recurrent fallers (reporting ≥ 2 falls). In the single fallers group, three patients (43%) reported only one fall and four (57%) reported no falls. Compared to recurrent fallers, single fallers had a significantly fewer total number of falls in the past 12 months (Mann–Whitney U = 91.0, p < 0.001) and a lower level of FoF based on FES-I scores [Mann–Whitney U test = 71.0, p = 0.043] (Table 1). There were no differences in age, weight, gender, MoCA test score and the remaining clinical and demographic variables between those who were classified as recurrent fallers and those classified as single fallers (Table 1).

At the 6-month follow-up, the median number of falls was 0.5 (IQR 0–2), and the median FES-I was 23.5 (IQR 18.5–33). Eleven patients (61%) were classified as single fallers, of whom nine (82%) reported no falls and two (18%) reported only one fall. Seven patients (39%) were categorized as recurrent fallers at follow-up. As a baseline, significant differences were found in the number of falls between fallers type at follow-up (Mann–Whitney U = 71.0, p = 0.003). There were no differences in the FoF level between single and recurrent fallers at follow-up.

Association between HRV, RoF and falls

At baseline, recurrent fallers had a significantly lower RMSSD-resting (p = 0.011) and higher LF/HF ratio in both states (resting p = 0.006; standing p = 0.019) and a higher DFA-α1 in both states (resting p = 0.024; standing p = 0.006) than single fallers. No significant differences in the HRV values of the differences between states were found in the comparison of patients by groups (single vs. recurrent fallers) (Table 2). Similarly, at the 6-month follow-up, recurrent fallers had a significantly lower RMSSD-resting (p = 0.027) and a higher LF/HF-standing (p = 0.035) (Table 3). When the association between number of falls and HRV measures was assessed significant correlations were observed in the resting state between the RMSSD and number of falls (r = −0.493; p = 0.027) (Fig. 1a) and between LF/HF-standing and number of falls (r = 0.496, p = 0.026) (Fig. 1b) (Electronic Supplementary Material [ESM] Appendix 1). Assessment of the RoF based on the BBS, TUG and TMT scores and of HRV measures revealed no significant correlations in any state (ESM Appendix 3).

Blood pressure measures and falls

No significant differences were found in any blood pressure measures between recurrent and single fallers (ESM Appendix 2).
The results of logistic regression indicated that RMSSD-resting and the LF/HF-standing ratio are significantly associated with the odds of being a recurrent faller in the next 6 months at a level of significance of \( p < 0.05 \). The regression coefficients (SE) of the RMSSD-resting and LF/HF-standing ratio were \(-0.084 (0.044)\) and \(1.580 (0.758)\), respectively. The estimated OR (95% CI) of the RMSSD-resting and LF/HF-standing ratio were \(0.917 (0.849–0.996; p < 0.036)\) and \(4.899 (1.099–21.436; p = 0.043)\), respectively. In other words, lower values of the RMSSD-resting and higher values of the LF/HF-standing ratio increase the risk of being a recurrent faller in the next 6 months.

The most frequent cause and direction of falls were tripping (60%) and forward (65%), respectively. The place of occurrence of falls most frequently reported was the bathroom when showering in a stand-up position (30%). Thirteen (65%) fallers suffered injuries by falling, of which the most frequent injury reported was bruising (62%), followed by sprains or dislocations (31%). Finally, eight (40%) fallers required medical assistance for physical damage related to falls.
Table 2  Association between falls and parameters of heart rate variability during postural changes at baseline

| HRV parameters | Resting state | Standing state | Differences between resting and standing states |
|---------------|--------------|----------------|-----------------------------------------------|
|               | Single fallers (n = 7) | Recurrent fallers (n = 13) | p value | Single fallers (n = 7) | Recurrent fallers (n = 13) | p value |
| HRM (bpm)     | 77.2 (59.3–87.3) | 77.4 (67–86.6) | 0.877 | 89 (65.9–94.8) | 78.4 (73.3–88.8) | 0.817 |
| RRM (ms)      | 777.1 (687–1011.1) | 774.8 (692.7–895.1) | 0.877 | 674 (633–910.9) | 765.6 (675.6–818.9) | 0.817 |
| SDNN (ms)     | 64.8 (41.1–68.6) | 43.8 (32.8–64.3) | 0.351 | 58.9 (46–106.1) | 42.1 (35.2–57) | 0.115 |
| RMSSD (ms)    | 52.7 (39.3–73.2) | 26.3 (19.6–46.1) | 0.011* | 55.7 (37.3–67.1) | 22.7 (17.7–53.3) | 0.081 |
| LnVLF (ms²)   | 7.4 (5–7.7) | 6.6 (5.6–7.3) | 0.393 | 6.8 (5.5–8.2) | 6.5 (6.1–7.1) | 0.757 |
| LnLF (ms²)    | 6.9 (5.1–7.2) | 6.5 (6–7.5) | 0.877 | 5.4 (5.1–7.1) | 6.5 (5.7–7.4) | 0.485 |
| LnHF (ms²)    | 7.3 (4.9–7.4) | 5.4 (4.5–5.7) | 0.081 | 6.9 (5.2–7.1) | 5.2 (4.3–6.3) | 0.157 |
| LF/HF         | 0.9 (0.6–1.2) | 2.6 (1.9–4) | 0.006* | 0.9 (0.4–1.3) | 2.7 (1–3.2) | 0.019* |
| DFA-α1        | 0.9 (0.7–1) | 1.2 (1–1.4) | 0.024* | 0.9 (0.7–0.9) | 1.3 (1.2–1.4) | 0.006* |
| SampEn        | 1.2 (0.9–1.9) | 1.3 (1–1.5) | 0.643 | 1.2 (0.9–1.3) | 1.2 (1–1.4) | 0.183 |

Data are expressed as the median with the IQR in parenthesis

*Significant difference between single faller and recurrent faller groups at p < 0.05 according to the Mann–Whitney U test

HRV Heart rate variability, HRM mean heart rate (beats per minute [bpm]), RRM mean RR interval, SDNN standard deviation of the RR intervals, RMSSD square root of the mean squared differences between successive RR intervals, VLF very low-frequency power, LF low-frequency power, HF high-frequency power, LF/HF ratio of low-frequency and high-frequency power, DFA-α1 detrended fluctuation analysis short-term parameter, SampEn sample entropy
Discussion

To our knowledge, this is the first study whose findings suggest a relationship between faller status and short-term HRV in patients with HD in different postural positions. We found that the patients in the early-mid stages of HD who participated in this study did regularly fall (only 20% of participants did not report any fall in the previous 12 months) and that the HRV pattern was consistent with a higher sympathetic prevalence associated with a higher frequency of falls. The observed decrease in parasympathetic HRV values adequately identified being a recurrent faller, independently of orthostatic phenomena, in this specific population.

HRV measurement is a complementary non-invasive method commonly used to estimate activity of the ANS. The LF/HF ratio should be interpreted as a measure of relative sympathetic predominance [32, 38]. Other changes in HRV observed in our study (increased DFA-$\alpha_1$, decreased RMSSD) suggest that these measures point in the same direction; therefore, these results may instead be indicating decreased vagal modulation. Results from previous studies support our findings since they show an underlying structural alteration in persons with HD, i.e. degeneration in central vagal nuclei [39–41].

Melillo et al. [8] showed that a depressed HRV increased the RoF by fivefold since the depressed HRV would reflect a reduced ability to react to risk situations [8]. Similarly, Nocera et al. [6] found a positive predictive value of 73.8% when they included ANS activity in their measures to improve the detection rate of fall sensors during simulated falls [6]. In line with our results, other authors [12, 40] found that the LF/HF ratio should be interpreted as a measure of relative sympathetic predominance [32, 38]. Other changes in HRV observed in our study (increased DFA-$\alpha_1$, decreased RMSSD) suggest that these measures point in the same direction; therefore, these results may instead be indicating decreased vagal modulation. Results from previous studies support our findings since they show an underlying structural alteration in persons with HD, i.e. degeneration in central vagal nuclei [39–41].

The dynamics of blood pressure and heart rate, particularly the ability to restore homeostasis after standing, depend largely on the state of the ANS [43]. Interestingly, our results do not identify orthostatic hypotension as a significant risk factor for falls. These results are important evidence that HRV is an independent cardiac factor isolated from changes in blood pressure during postural changes, at least in the population with HD at the early and middle stages, as has previously been reported [12].

Table 3  Association between falls and parameters of heart rate variability during postural changes at the 6-month follow-up

| HRV parameters | Resting state | Standing state | Differences between resting and standing states |
|----------------|--------------|---------------|-----------------------------------------------|
|                | Single fallers ($n = 11$) | Recurrent fallers ($n = 7$) | $p$ value |
|                | Single fallers ($n = 11$) | Recurrent fallers ($n = 7$) | $p$ value |
|                | Single fallers ($n = 11$) | Recurrent fallers ($n = 7$) | $p$ value |
| HRM (bpm)      | 71.1 (59.3–84.5) | 79.1 (56.8–95.5) | 0.596 |
| RRM (ms)       | 843.9 (710–1011.1) | 774.8 (828–1055.5) | 0.596 |
| SDNN (ms)      | 64.3 (41.8–68.6) | 43.8 (24.8–74.7) | 0.246 |
| RMSSD(ms)      | 46.1 (31.7–59.5) | 25.3 (19.4–41.8) | 0.027* |
| LnVLF (ms$^2$) | 7.3 (6.6–7.7) | 6.4 (5.6–7.3) | 0.211 |
| LnLF (ms$^2$)  | 6.8 (5.7–7.2) | 6.5 (4.9–7.6) | 0.791 |
| LnHF (ms$^2$)  | 7.1 (4.9–7.4) | 5.3 (4.3–6.1) | 0.069 |
| LF/HF          | 1.2 (0.9–2.1) | 2.6 (1.2–7.6) | 0.085 |
| DFA-$\alpha_1$ | 1 (0.7–1.4) | 1.2 (0.8–1.5) | 0.375 |
| SampEn         | 1.2 (0.9–1.6) | 1.3 (1.1–1.6) | 0.536 |

Data in table are expressed as the median with the IQR in parenthesis

*Significant difference between single faller and recurrent faller groups at $p < 0.05$ according to the Mann–Whitney $U$ test.
Little is known about possible alterations in vascular sympathetic regulatory activity in patients without orthostatic hypotension or symptoms of orthostatic intolerance in other neurodegenerative diseases [44]. While not well documented in HD patients, orthostatic hypotension has been extensively examined in patients with Parkinson’s disease. In one study, a certain degree of sympathetic cardiac abnormalities could be identified in patients in the supine position, of whom about 50% were without hypotension [45]. In this sense, we would have to weigh some aspects of the analysis of this dissociation. First, the exact origin of the damage of the ANS function in individuals with HD has not yet been elucidated [10, 15]; second, it has been postulated that HD-related cardiac alterations are also likely driven by dysfunctions of the central nervous system [46, 47]; and third, there is no reason to suspect damage to the peripheral nervous system [10, 15] nor vascular dysfunction in animal models [46]. Therefore, it is possible to assume that, as in Parkinson’s disease, the initial impairment of the sympathetic vasomotor control could mainly affect the variability of blood pressure and that only subsequently are changes induced in the mean values of systolic blood pressure that cause orthostatic hypotension? [44]. In this respect, other mechanisms may explain the blood pressure values maintained by patients with Parkinson’s disease during the standing position, including a noradrenergic hypersensitivity [44]. Unfortunately, blood pressure variability and changes in catecholamines during gravitational stimulation were not addressed in our study. Therefore, we hypothesized that the dissociation between HRV and orthostatic phenomena should not be so surprising in the early-mid stages of HD. This dissociation allows us to postulate that the autonomic changes registered with the ECG are probably more sensitive to predicting RoF than those dependent on orthostatic hypotension. However, additional research is needed to test this hypothesis.

A relevant result of the study was the demonstration of the association between decreases in parasympathetic prevalence measured by HRV and being a recurrent faller independently of orthostatic phenomena. One possible explanation of this association would be a state of reactivity (hyperarousal) due to a early hyper-sympathetic state in HD that has been well determined [15–17]; this in turn would be associated with having a greater awareness of motor disability in tasks that challenge balance and could potentially be translated by the patient into FoF [48]. Within this framework, another hypothesis states that the activity of the ANS is a major component of the emotional response to stress, with large differences that range from undifferentiated excitation to the recognition of a highly specific response for certain stressful emotions, such as the fear [49]. In line with our results, experimental models have demonstrated that different fearful events rapidly increase heart rate and decrease parasympathetic activity coupled with uninhibited sympathetic activities and indexed by low HRV [50, 51]. Future studies are required to better explain the proposed mechanisms.

Contrary to our expectations, we found that the number of self-reported falls in the previous 12 months did not correlate with any of the balance variables recommended for measuring the RoF in HD patients (BBS, TUG, TMT) [23] (data not shown). We hypothesize that this lack of correlation could potentially be related to two reasons. First, methodologically, it is difficult to obtain accurate falls data from people with HD due to recall bias, cognitive deficits and behavioral issues that may impact on the accuracy of retrospective data [2, 52] Second, the RoF assessment is
used to measure and classify patients at high or low RoF; unfortunately, therefore, administrating a functional test may be affected by responder bias and inter-observer variability. A few studies have found the TUG test [4, 23, 25], the BBS [4, 22, 23] and the TMT [23, 26, 27], with cutoffs of ≥ 14 s, ≤ 40 points and ≤ 21 points, respectively, have been associated with increased fall risk in patients with HD. These data demonstrate that simple physical outcome measures cannot accurately predict falls and that other intrinsic and extrinsic factors should be considered. In this regard, after the logistic regression analysis, our results showed that two indexes of HRV, namely RMSSD-resting and LF/HF-standing, were better predictors of the odds to be a recurrent faller in the next 6 months than the three most commonly used scales to measure RoF in HD (e.g. the odds to be a recurrent faller was increased by almost fivefold if a higher LH/HF-standing value was registered).

The strengths of this study were the use of an easy and useful tool to measure short-term HRV through postural changes; the use of an extensive balance, gait and neuropsychological testing battery that captures multiple possible risk factors and their potential correlations with fall risk; and a novel description of the qualitative aspects of falls in patients with HD.

We acknowledge that this is an exploratory study. Shortcomings that could affect the accuracy of our conclusions should be mentioned. First, the small sample size and the clinical heterogeneity of our participants must be considered. Second, unfortunately, and due to the exploratory nature of the study, neither baroreflex sensitivity nor any dynamic interaction index of cardiac period systolic blood pressure was available for baroreflex control analysis during the postural challenge. These indices would have characterized the cardiac baroreflex from the spontaneous fluctuations of the cardiac period and the systolic blood pressure when the patient was facing the orthostatic challenge and variations in the blood pressure buffer [53]. Third, the results of the logistic regression analysis must be interpreted with caution due to the small sample size. Although binary logistic regression recommendations propose a minimum of five to nine events per variable [54, 55], the current sample size might not avoid type I or II errors. Fourth, the obtained results of HRV analysis should be interpreted with caution since the effect of the consumption of caffeine-containing beverages is usually longer than the 3 h recommended in the study. Hence, these results should be corroborated by cross-validated further investigations, using larger samples across different stages of the disease and a longer prospective follow-up.

In conclusion, our findings suggest that an increased sympathetic prevalence, as detected by HRV measures, is associated with the odds of being a recurrent faller in persons at the early-mid stages of HD, independent of orthostatic phenomena. Future studies should address whether HRV measures may represent a predictive parameter for RoF in the early-mid stages of HD and whether such an association persists in more advanced stages of the disease. Inclusion of a short registry of HRV in the early assessment of HD patients may be relevant to early detection of the disease and reducing the number of recurrent falls as well to identify and monitor those patients at high RoF who would benefit from fall prevention programs.

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Conflict of interest None of the authors have any conflicts of interest to report.

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