Regulation of Cardiac Autonomic Nervous System Control across Frailty Statuses: A Systematic Review

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Key Words

Autonomic nervous system · Sympathovagal balance · Sympathetic nervous system · Parasympathetic nervous system · Heart rate · Heart rate variability · Frailty · Older adults · Geriatric population · Aging

Abstract

Background: Frailty is a geriatric syndrome that leads to impairment in interrelated physiological systems and progressive homeostatic dysregulation in physiological systems. **Objective:** The focus of the present systematic review was to study the association between the activity of the cardiac autonomic nervous system (ANS) and frailty. **Methods:** A systematic literature search was conducted in multiple databases: PubMed/MEDLINE, Embase, Cochrane Library, Web of Science, CINAHL, and ClinicalTrials.gov; the last search was performed in March 2015. Inclusion criteria were: (1) that the studied population was classified for frailty according to a standard definition, such as Fried's criteria; (2) that the study had a nonfrail control group, and (3) that heart rate (HR) and/or heart rate variability (HRV) were parameters of interest in the study. **Results:** Of the 1,544 articles screened, 54 were selected for full-text review and 6 studies met the inclusion criteria. Assessment of HRV using different standard time domain, frequency domain, and nonlinear domain approaches

confirmed the presence of an impaired cardiac ANS function in frail compared to nonfrail participants. Furthermore, HR changes while performing a clinical test (e.g., the seated step test or the lying-to-standing orthostatic test) were decreased in the frail group compared to the nonfrail group. **Conclusions:** The current systematic review provides evidence that the cardiac ANS is impaired in frail compared to nonfrail older adults, as indicated by a reduction in the complexity of HR dynamics, reduced HRV, and reduced HR changes in response to daily activities. Four out of 6 included articles recruited only female participants, and in the other 2 articles the effect of gender on impairment of cardiac ANS was insufficiently investigated. Therefore, further studies are required to study the association between cardiac ANS impairments and frailty in males. Furthermore, HRV was studied only during static postures such as sitting, or without considering the level of activity as a potential confounder. Accordingly, simultaneous measurement of both physiological (i.e., HRV) and kinematic (e.g., using wearable sensor technology) information may provide a better understanding of cardiac ANS impairments with frailty while controlling for activity.

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Introduction

Frailty is a geriatric syndrome defined as impairment in interrelated physiological systems, coupled with a decrease in physiological reserves [1, 2], which results in an increased vulnerability to stressors. Accordingly, frailty is associated with adverse health outcomes including mortality, morbidity, postoperative complications, institutionalization, and hospitalization [2–4]. Frail individuals are more susceptible to both acute and chronic conditions such as myocardial infarction, heart disease, and cardiac surgery [5, 6]. Frailty is higher in older adults with cardiovascular disease, with a prevalence range from 10 to 60% depending on the population studied and the frailty assessment approach [5, 7]. Also, the results of a recent study highlighted that early-stage frailty (i.e., prefrailty) contributes to development of cardiovascular disease [8]. An assessment of frailty and its impact on cardiovascular systems is, therefore, important in older vulnerable populations.

Frail elders are homeostenotic and have a decreased ability to maintain homeostasis under stress. The autonomic nervous system (ANS) including the cardiac ANS and its balanced functioning have a crucial role in maintaining homeostasis in almost all physiological functions [9]. This role becomes more pronounced when responding to internal or external stressors such as disease and activities of daily living [9, 10]. It has been postulated that frail older adults exhibit a progressive homeostatic dysregulation in physiological systems, including the cardiac ANS [8]. Also, impairment in the cardiac ANS, as highlighted in previous research studies [11, 12], may be a factor that accelerates the frailty process. For example, frailty and heart failure are frequently associated together, with a high prevalence of frailty in heart failure ranging from 15 to 74% [13]. It is known that both heart failure and its treatment can result in, or worsen, frailty [14]. An impact of heart failure on frailty status may occur due to changes in cardiac ANS activity (e.g., increased sympathetic activity) in order to restore cardiac output [15, 16], which in turn may add an excessive load on the cardiac ANS system, which already suffers from decreased physiological reserves. Also, the impairment of the cardiac ANS due to frailty may further worsen the heart failure because it is not able to maintain hemodynamic homeostasis.

As an aid to facilitate our understanding of the cardiac ANS mechanism in association with frailty status, noninvasive objective assessment methods based on heart rate (HR) and heart rate variability (HRV) have been intro-

duced [17, 18]. The degradation of cardiac autonomic control results in a loss of complexity in the HR and a reduction in HRV, which is associated with a higher morbidity and mortality in individuals with myocardial infarction and heart failure [19, 20]. Cardiac ANS parameters associated with frailty, such as HR and HRV, can capture the reduction in dynamics of the physiological system in order to distinguish between healthy and impaired heart functioning [18]. Also, HR and HRV parameters could be used to enhance the prediction of hospitalization outcomes and mortality, especially in older adults with heart disease, as well as to improve surgical risk assessment and to assess the benefits of interventions in order to prevent frailty or reverse the frailty process.

The objectives of this Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) literature review were to: (1) investigate protocols used for cardiac ANS assessment in individuals with different frailty levels as defined by standardized frailty criteria and (2) to study the relationship of cardiac ANS, as manifested in HR-derived parameters (HR and HRV), and frailty status. The findings of the current review could provide insight regarding cardiac ANS alterations with frailty that might assist in the evaluation and management of cardiac conditions in older adults. Also, its outcomes may highlight that measures of cardiac homeostatic integrity can be used as a complementary tool along with traditional approaches to improve frailty assessment.

Methods

Inclusion/Exclusion Criteria

A systematic literature review was performed based on the PRISMA guidelines for systematic reviews [21] (see Appendix A for the PRISMA checklist). Inclusion/exclusion criteria were chosen using a focused interview method by experts in the fields of aging and frailty, cardiology, clinical research, library science, and biomedical engineering. The inclusion criteria were: (1) that a frail sample, as explicitly defined according to a standard definition of frailty such as Fried's criteria [2], was studied; (2) that a control group (nonfrail) was considered, and (3) that HR and/or HRV were considered as parameters of interest. The following were considered as exclusion criteria: case reports, letters, systematic reviews/meta-analyses, data published in the form of abstracts instead of peer-reviewed articles, non-English studies, and animal studies.

Search Strategy

Search terms, including controlled vocabulary (e.g., MeSH) terms and key words, were compiled and iteratively refined by content experts in the fields of library science, geriatrics, and biomedical engineering. A medical librarian (C.L.H.) then constructed and performed the searches in the following databases: PubMed/

Fig. 1. Flowchart of the process of literature search and extraction of studies meeting the inclusion criteria.

MEDLINE (1946–2015), Embase (1947–2015), Cochrane Library (1898–2015), Web of Science (1898–2015), EBSCO/CINAHL (Plus with Full Text; 1981–2015), and ClinicalTrials.gov (1997–2015). The last literature searches were completed in March 2015. The complete PubMed/MEDLINE search strategy, upon which the other database searches were built, is available in Appendix B. Citations of and reference lists within the selected articles were also searched for studies that would meet the inclusion criteria. The World Wide Web (especially Google Scholar) was also perused for relevant articles.

Study Selection

Two independent reviewers performed the study selection (S.P. and B.H.). In case of disagreements, a third reviewer (J.M.) cast the deciding vote. Screening was done in two steps (fig. 1). Initially, the titles and abstracts of retrieved references were screened for inclusion in full paper review. Then, the full texts of the articles thus selected were further analyzed to see if they fulfilled the inclusion criteria or not.

Data Extraction

Two individuals (S.P. and B.H.) independently extracted the following data from the included articles: study goals; subjects and study design; definition of frailty used; protocol and equipment used to monitor HR and rhythm, and HR and HRV parameters (and their definitions). Any disagreements were resolved by consensus (tables 1, 3, 4).

Quality Assessment

The quality of the included studies was assessed using the Crombie criteria adapted for assessing cross-sectional studies [22]. Eight quality criteria – research design, recruitment strategy, response rate, sample representativeness, objective and reliable measures, power calculation performed, proper statistical analysis, and no evidence of bias – were considered. Two more components were added to the above-mentioned criteria, namely the clarity of the reported results and parameters and the reproducibility of a study. A higher overall score was an indicator of the methodological quality of a study.

Data Analysis

Values of HR and HRV in frail participants were compared with those of nonfrail and/or prefrail participants, where possible. In the absence of such data, a summary of the results was presented. Due to the lack of data and differences in study design and the parameters studied, a meta-analysis was not possible. Therefore, a narrative synthesis was employed to combine results and explain conflicting results.

Results

Study Selection

We found 1,903 articles through database searching and 12 additional articles through a citation analysis of the selected articles and perusal of the World Wide

Table 1. Study characteristics and research goals with respect to the assessment of an association between the cardiac ANS and frailty

Study	Study goals	Subjects and study design	Frailty definition	Protocol for HR monitoring	Heart monitoring instrument	Comorbidities and medication considerations
Chaves et al. [11], 2008	To study the physiological complexity underlying the regulation of HR dynamics and its association with frailty	Total: 389 women; 259 nonfrail, 130 frail Age: 65–95 years Participants: moderate-to-severe physical disability Setting: WHAS I, community dwelling Design: cross-sectional, retrospective	Fried's criteria [2]	Assessment during physical tasks including walking, isometric exercise, and grip strength in diverse positions (lying, sitting, and standing)	Two-channel Holter monitoring – SpaceLabs (model 90205)	Adjusted their model based on the following medications and comorbidities: – medication: β -blockers – comorbidities: coronary heart disease, congestive heart failure, and diabetes
Varadhan et al. [12], 2009	To define a new measure of HRV to capture the impairment in cardiac autonomic control due to frailty	Total: 276 women Age: 65–101 years Participants: moderate-to-severe physical disability Setting: WHAS I, community dwelling Design: cross-sectional, retrospective	Fried's criteria [2]	Assessment during physical tasks including walking, isometric exercise, and grip strength in diverse positions (lying, sitting, and standing)	Two-channel Holter monitoring – SpaceLabs (model 90205)	Adjusted their model based on the following medications and comorbidities: – medication: β -blockers – comorbidities: cardiovascular disease and diabetes
Weiss et al. [26], 2010	(1) To assess the relationship between physiological systems (cardiac, pulmonary, and musculoskeletal) and exercise capacity (2) To assess the effect of the seated step test on exercise capacity in different frailty statuses	Total: 547 women; 416 nonfrail, 131 frail Age: ≥ 65 years Participants: moderate-to-severe physical disability Setting: WHAS I, community dwelling Design: cross-sectional, retrospective	Fried's criteria [2]	Assessment during the seated step test, i.e., performing a step-like motion while seated in a chair with 4 different heights of the step at each stage (each stage lasting 3 min)	Not mentioned	Medication (pulse blocking) and comorbidities (coronary artery disease and chronic lung disease) were not significantly different between the nonfrail and the frail group
Romero-Ortuno et al. [24], 2011	To classify a community sample of older people into three increasing frailty phenotypes and compare their orthostatic hemodynamics	Total: 442 (317 women); 198 nonfrail (age 70.5 ± 6.3 years, 66.7% women); 213 prefrail (age 72.9 ± 7.5 years, 76.1% women); 31 frail (age 76.6 ± 7.3 years, 74.2% women) Age: ≥ 60 years (mean age 72.1) Participants: nonfrail, prefrail, frail Setting: geriatric research clinic, community dwelling Design: cross-sectional	Modified Fried's criteria [28]	Assessment during the lying-to-standing orthostatic test	HR monitoring – Finapres Medical Systems BV (Finometer Pro device)	Subjects with following medications and comorbidities were excluded from the study: – medication: adrenergic antagonists – comorbidities: ventricular premature complexes, sinus or supraventricular tachycardia, atrioventricular blocks, and atrial fibrillation
Takahashi et al. [25], 2014	To evaluate the short-term complexity of HR dynamics in resting, supine, and standing positions and its association with frailty	Total: 80 (56 women); 38 nonfrail (age 67.1 ± 6.2 years, 76% women); 36 prefrail (age 70.4 ± 7.5 years, 64% women); 6 frail (age 86.0 ± 5.8 years, 67% women) Age: 60–94 years Participants: nonfrail, prefrail, frail Setting: community dwelling Design: cross-sectional	Fried's criteria [2]	Assessment during 10 min in the supine position and 10 min in the standing position; during monitoring, the participants were asked to speak only when necessary and to breathe spontaneously	12-lead ECG monitoring	Subjects with the following medications and comorbidities were excluded from the study: – medication: adrenergic antagonists – comorbidities: diabetes, Parkinson's disease, severe chronic renal failure, and vitamin B ₁₂ or red cell folate deficiency
Katayama et al. [23], 2015	To study the association of cardiac autonomic modulation with frailty status	Total: 23 women; 8 nonfrail (age 70.0 ± 2.2 years); 8 prefrail (age 67.0 ± 2.1 years); 7 frail (age 73.0 ± 3.5 years) Age: 65–77 years Participants: nonfrail, prefrail, frail Setting: community dwelling Design: cross-sectional	Fried's criteria [2]	Assessment during 10 min in the supine position with spontaneous breathing and without moving and speaking	HR monitoring – Polar Electro (RS800 CX)	Subjects with the following medications and comorbidities were excluded from the study: – medication: β -blockers, antiarrhythmics, tricyclic antidepressants and centrally acting antihypertensive agents, and/or hormone replacement therapy – comorbidities: neurological disease, Chagas disease, cardiovascular events during the previous year, and cardiac pacemaker

Web. Of the 1,544 articles remaining after duplicates had been removed, 1,490 were excluded during title and abstract screening because of their irrelevance with regard to the topic under review (fig. 1). The inclusion/exclusion criteria as outlined above were applied to the full texts of 54 articles, and 48 articles were excluded for

the following reasons: (1) lack of a standard definition of frailty ($n = 31$); (2) lack of HR or HRV measurements ($n = 8$); (3) conference abstracts ($n = 5$); (4) non-English articles ($n = 3$), and (5) systematic review ($n = 1$). Finally, 6 articles [11, 12, 23–26] met all the inclusion criteria (fig. 1).

Table 2. Quality assessment of articles using adapted Crombie criteria

Study	Appropriate research design	Appropriate recruitment strategy	Response rate, %	Sample representative	Objective and reliable measures	Power calculation/justification of numbers	Appropriate statistical analysis	No evidence for bias	Clarity and completeness of report	Reproducibility of study	Quality indicators met
Chaves et al. [11], 2008	✓	✓	NR	x ¹	✓	x	✓	✓	x ⁴	✓	6/10
Varadhan et al. [12], 2009	✓	✓	NR	x ¹	✓	x	✓	✓	x ⁴	✓	6/10
Weiss et al. [26], 2010	✓	✓	NR	x ¹	✓	x	✓	✓	x ⁵	✓	6/10
Romero-Ortuno et al. [24], 2011	✓	✓	NR	✓	✓	x	✓	✓	✓	✓	8/10
Takahashi et al. [25], 2014	✓	✓	NR	✓	✓	x	x ³	NC	✓	✓	6/10
Katayama et al. [23], 2015	✓	✓	64	x ²	✓	x	✓	✓	x ⁶	✓	7/10

NR = Not reported; NC = not clear.

¹ Only elderly women with severe-to-moderate disability were included.

² Only elderly women were recruited.

³ No suitable statistical test was used to assess pair-wise differences between nonfrail, prefrail, and frail groups.

⁴ No means and standard deviations of the extracted parameters for each group of nonfrail and frail subjects were reported. Also, no demographic information across the different groups (e.g. nonfrail and frail) was reported.

⁵ No means and standard deviations of the extracted parameters for each group of nonfrail and frail subjects were reported. Also, no numbers of participants and no corresponding demographic information for the two studied groups were reported.

⁶ No values for the different HR-derived parameters studied were reported across the different frailty groups.

Study Design and Quality Assessment

All included articles were cross-sectional studies, with various research aims with respect to the cardiac ANS, as summarized in table 1. Using adapted Crombie criteria, the study conducted by Romero-Ortuno et al. [24] had the highest score (8 out of 10) among all the included studies. As reported in table 2, all these studies had an appropriate research design, appropriate recruitment strategy, and objective and reliable measures and were reproducible. Only in the study by Takahashi et al. [25] a statistical analysis was not performed to assess pairwise differences between nonfrail, prefrail, and frail groups. Interestingly, none of the included studies had performed a power calculation. The study by Katayama et al. [23] was the only one that reported response rates. Four research studies lacked a sufficient report of the parameters utilized [11, 12, 23, 26], and statistical values (e.g., means and standard deviations) for the extracted parameters were not reported; in 3 of these studies, demographic information was not reported individually for each frailty group [11, 12, 26].

Participants

The sample sizes of the selected articles ranged from 23 to 547, and the participants' ages ranged from 60 to 101 years. A total of 919 nonfrail and 305 frail subjects were

studied in the selected articles (excluding that by Weiss et al. [26], in which the numbers of frail and nonfrail participants were not provided). Interestingly, in 4 out of the 6 studies, only female participants were recruited [11, 12, 23, 26]. Three of these studies [11, 12, 26] retrospectively analyzed different data subsets from the Women's Health and Aging Study (WHAS), which was originally designed for investigation of the epidemiology of disability progression in noninstitutionalized women aged 65 years and older [27]. Katayama et al. [23] did not explain the reason for recruiting only women.

In 3 studies [11, 12, 26], the participants were categorized into nonfrail and frail, and in 2 studies [23, 25] into nonfrail, prefrail, and frail according to Fried's criteria. In 1 study [24], the participants were categorized into three categories (nonfrail, prefrail, and frail) using a modified version of Fried's criteria. Since some measures based on Fried's criteria were not available in this study, they were substituted with similar measures extracted from the experiment (e.g., frequency of going outdoors was used as a surrogate of the Minnesota Leisure Time Activity questionnaire used in Fried's criteria) [24, 28]. Of note, evaluated outcomes such as gait speed and hand grip strength used age- and sex-adjusted norms in all studies in accordance with frailty criteria (Fried's or modified Fried's criteria).

Table 3. HR and HRV parameters reported in the studies included in this review

Study	Assessment	Duration of monitoring	HR indices	HRV indices
Chaves et al. [11], 2008	HRV	2–3 h	–	Time domain: SDNN, SDANN, and RMSSD Frequency domain: TP, pVLF, pLF, pHF, and LF/HF Nonlinear domain: ApEn _{HR}
Varadhan et al. [12], 2009	HRV	2–3 h	–	Time domain: SDNN, RMSSD, and pNN50 Frequency domain: pVLF, pLF, pHF, and LF/HF PC1 and PC2: principal component of HRV measures
Weiss et al. [26], 2010	HR	During the test	Baseline HR (beats/min) Δ HR (beats/min): change in HR beginning to end	–
Romero-Ortuno et al. [24], 2011	HR	From beginning of the test until 3 min after standing	Baseline HR (beats/min) Δ HR (beats/min): max. HR within 30 s – baseline HR Max. HR by 30 s (% of baseline HR) HR by 120 s (% of baseline HR)	–
Takahashi et al. [25], 2014	HRV	Stationary sequence of 256 heartbeats during each condition (supine and standing)	–	Nonlinear domain: ApEn _{HR} and CE _{HR}
Katayama et al. [23], 2015	HR HRV	Stationary 5-min period	Mean RR (ms)	Time domain: SDNN and RMSSD Frequency domain: pLF, pHF, and LF/HF Nonlinear domain: symbolic analysis, ApEn _{HR} , and SE _{HR}

TP = Power across all frequency bands (<0.4 Hz); PC1 = mean of log-transformed HRV indices; PC2 = linear combination of log-transformed indices; ApEn_{HR} = approximate entropy for an HR time series; CE_{HR} = conditional entropy for an HR time series; SE_{HR} = sample entropy for an HR time series; RR = time between consecutive R-waves in the ECG; has a reciprocal relation to HR.

Equipment and Protocols Used for Assessment of Cardiac Autonomic Control

Table 1 summarizes the equipment and protocols that were used for assessment of the cardiac ANS. In 1 study, no information about the equipment utilized for assessment of heart response was reported [26]; all others used one of the two methods described below:

- 1 HR data extraction from electrocardiograms (ECG) – in 2 studies [11, 12], two-channel Holter monitoring, and in 1 study [29], 12-channel ECG recording equipment were utilized. In 1 study [23], a one-channel ECG monitor (a belt worn around the thorax) was used; using this device, beat-to-beat HRs from the ECGs were recorded without providing the raw ECG data.
- 2 Optical HR monitoring – 1 study [24] used an optical method based on the measurement of changes in light absorption to estimate HR.

Weiss et al. [26] and Romero-Ortuno et al. [24] measured HR while participants were performing the seated step test and the lying-to-standing orthostatic test, respective-

ly. Takahashi et al. [29] assessed their participants during supine and standing postures (10 min in each position). Measurement of ECGs in the supine position for 10 min was done by Katayama et al. [23]. In the other 2 studies, the participants were free to perform any physical tasks such as walking, lying, sitting, or standing [11, 12].

In the articles reviewed, HR was monitored during the clinical test by Weiss et al. [26] and during the test and 3 min after the test by Romero-Ortuno et al. [24]. Takahashi et al. [29] reported HRV parameters based on stationary sequences of 256 heartbeats during each condition of supine positioning and standing. Katayama et al. [23] used a stationary 5-min period for reporting HR and HRV measures. Furthermore, Chaves et al. [11] and Varadhan et al. [12] reported HRV based on 2–3 h of recorded data.

HR and HRV Parameters Reported

The definition of HR and HRV measures and their physiological interpretation are summarized in Appen-

dix C. Detailed information about their calculation can be found in the references provided there. As summarized in table 3, 2 studies reported only HR parameters [24, 26], 3 studies reported only HRV measures [11, 12, 25], and 1 study provided both HR and HRV measures [23]. In the 3 studies that measured HR [23, 24, 26], different outcome measures were calculated, including baseline HR [24, 26], the mean of beat-to-beat intervals (RR intervals), which has a reciprocal relation to HR [23], and changes in HR (Δ HR), with different definitions as explained in table 3 [24, 26].

Among the studies that provided HRV assessments, outcome measures included:

- 1 time domain HRV measures – the standard deviation of all normal-to-normal intervals (SDNN) [11, 12, 23], the square root of the mean squared differences between successive normal-to-normal intervals (RMSSD) [11, 12, 23], the standard deviation of the average normal-to-normal intervals over 5-min periods (SDANN) [11], and the percentage of successive normal-to-normal intervals with differences >50 ms (pNN50) [11] (see Appendix C for definitions);
- 2 frequency domain measures of HRV derived using a fast Fourier transform – the power density in the very-low-frequency [11, 12], low-frequency [11, 12, 23], and high-frequency bands [11, 12, 23] and the ratio of low-frequency to high-frequency bands (LF/HF) [11, 12, 23], as well as total power density [11]);
- 3 nonlinear measures of HRV – approximate entropy [11, 29], conditional entropy [29], and sample entropy [23] as measures of cardiac ANS complexity as well as symbolic dynamics [23] (definitions of the frequency bands and nonlinear measures are presented in Appendix C).

Alterations in HR and HRV Parameters with Frailty

A summary of the HR-derived parameter values across the frailty groups or a summary of the findings is presented for the reviewed studies in table 4. Chaves et al. [11] demonstrated that the approximate entropy (the amount of regularity and the unpredictability of fluctuations over time) of HR is significantly reduced in frail as compared to nonfrail adults. Also, a significant reduction of SDNN, SDANN, total power density, power density in the very-low-frequency band (pVLF; <0.04 Hz), power density in the low-frequency band (pLF; 0.04 – 0.15 Hz), and LF/HF in individuals with a higher probability of frailty was reported by Chaves et al. [11]. Varadhan et al. [12] proposed that an aggregate of HRV measures by second principal component analysis had a stronger associa-

tion with frailty because it captures the impairment in the cardiac ANS while discarding any redundancies in the highly correlated HRV parameters. Approximate entropy marked differences between nonfrail and prefrail/frail groups in the study by Takahashi et al. [29]. They reported a higher approximate entropy in prefrail and frail individuals as compared to nonfrail subjects, which is conflicting with the results of Chaves et al. [11]. Katayama et al. [23] reported a trend for reduction in SDNN and RMSSD from nonfrail to prefrail and frail individuals. The assessment of HRV in the frequency domain [pLF and power density in the high-frequency band (pHF; 0.15 – 0.4 Hz)] and nonlinear domain (symbolic analysis) highlighted a higher sympathetic and a lower parasympathetic modulation in frail subjects when compared to nonfrail and prefrail groups. A nonsignificant trend towards a lower sample entropy in prefrail and frail groups as compared to the nonfrail group was observed. Also, the authors have shown that the mean HR in the supine position is higher in frail than in prefrail and nonfrail individuals.

In 2 studies, the analysis of HR in response to activity during a clinical test demonstrated a higher baseline HR in the frail than in the nonfrail group [24, 26]. Also, in both studies, the change in HR in response to activity (Δ HR) was smaller in the frail group. Romero-Ortuno et al. [24] also reported a significant decrease in maximum HR by 30 s after orthostatic lying-to-standing in frail as compared to prefrail and nonfrail subjects.

Discussion

The purpose of the present systematic review was to study the relationship between the frailty syndrome and the cardiac ANS. The results demonstrated a reduction in HRV and complexity as well as an impairment in HR response to physical activity in the frail group as compared to the nonfrail group. These observations provide evidence of cardiac ANS impairments in frail versus nonfrail subjects.

Measurement Equipment

The findings from the current review revealed that HR as extracted from ECGs recorded by ECG monitoring equipment (e.g., Holter monitor, standard 12-lead ECG, and chest-worn ECG monitoring equipment) was the most common approach to assessing HR in older adults. Optical HR monitoring was also employed for recording

Table 4. Mean values of HR and HRV parameters for the different frailty categories

Study	Parameters and results				
Chaves et al. [11], 2008	– Median $ApEn_{HR}$ was lower in frail than in nonfrail subjects ($p = 0.03$) – Analysis of HRV revealed that lower SDNN, SDANN, TP, pVLF, pLF, and LF/HF were associated with a higher probability of frailty ($p < 0.05$); however, no significant association was observed for RMSSD and pHF				
Varadhan et al. [12], 2009	– PC2 used for aggregation of the recorded traditional HRV measures was the best predictor of frailty ($p < 10^{-5}$) – PC2 can capture the long-range correlations in heartbeat fluctuations across frequency bands (VLF to HF) – pVLF, pLF, SDNN, LF/HF, and PC2 had a significant and negative association with frailty ($p < 0.05$)				
Weiss et al. [26], 2010	Baseline HR, beats/min Δ HR, beats/min	Nonfrail 74 16	Frail 75 13	p value 0.486 0.001*	n.s. ↓ in frail
Romero-Ortuno et al. [24], 2011	Baseline HR, beats/min Δ HR, beats/min Max. HR by 30 s, % of baseline HR HR by 120 s, % of baseline HR	Nonfrail 67.7 ± 10.7 15.5 ± 6.2 123.7 ± 10.9 110.1 ± 10.5	Prefrail 68.8 ± 10.6 13.7 ± 10.5 120.6 ± 18.0 109.0 ± 10.8	Frail 73.0 ± 9.2 13.3 ± 7.1 118.8 ± 11.2 111.8 ± 28.3	p value 0.008* <0.001* <0.001* 0.675 ↑ in frail ↓ in frail ↓ in frail n.s.
Takahashi et al. [25], 2014	CI (supine) CI (standing) $ApEn_{HR}$ (supine) $ApEn_{HR}$ (standing)	Nonfrail 0.73 ± 0.08 0.67 ± 0.08 3.90 ± 0.48 3.55 ± 0.58	Prefrail 0.74 ± 0.08 0.69 ± 0.12 3.86 ± 0.46 3.58 ± 0.67	Frail 0.79 ± 0.09 0.73 ± 0.08 4.07 ± 0.33 3.93 ± 0.46	p value >0.05 >0.05 <0.05* <0.05 n.s. n.s. ↑ in frail ↑ in frail
Katayama et al. [23], 2015	– Nonsignificant higher mean RR (lower mean HR) observed in nonfrail as compared to prefrail and frail subjects in the supine position – A nonsignificant trend towards lower HRV as captured by SDNN and RMSSD in the frail group as compared to the prefrail and frail groups was found; the reduction in SDNN and RMSSD in the frail group may be an indicator of reduced global HRV and a decrease in parasympathetic activity, respectively – The frail group showed a significant decrease in pHF as compared to the nonfrail group ($p < 0.05$), which is an indicator of a reduction in activity of the parasympathetic nervous system – The frail group presented a significant increase in pLF and LF/HF as compared to the other groups ($p < 0.05$) – Using nonlinear methods, symbolic analysis revealed that the frail group had a significantly lower incidence of patterns in the 2LV family as compared to the nonfrail group ($p < 0.05$); this suggests that parasympathetic activity is decreased in frail as compared to nonfrail individuals – A nonsignificant trend towards a lower SE_{HR} in the prefrail and frail groups as compared to the nonfrail group was observed; this suggests that frailty is linked to lower physiological complexity				

Summaries of findings are presented for studies that do not provide quantitative values. ↑ = Significant increase; ↓ = significant decrease; n.s. = not significant; * = statistically significant; TP = power across all frequency bands (<0.4 Hz); PC2 = second principal component; VLF = very-low-frequency band; HF = high-frequency band; $ApEn_{HR}$ = approximate entropy for an HR time series; CI = complexity index (minimum of the conditional entropy with respect to L past value); 2LV = patterns with two like variations; SE_{HR} = sample entropy for an HR time series; RR = time between consecutive R-waves in the ECG; has a reciprocal relation to HR.

HR. Of these two approaches, using an ECG device which reports both HR and raw ECG data that are used for extraction of HR is more efficient for excluding noisy data segments and heartbeats originating from an ectopic location and/or arrhythmia and noisy data.

HR and HRV Measures for Assessing Frailty

Of different HR measures, baseline HR and Δ HR were the most commonly used parameters. Δ HR was the most effective parameter, significantly differentiating frail from nonfrail groups. Furthermore, SDNN, RMSSD, and power densities at different frequency bands (e.g.,

very low frequency, low frequency, and high frequency) were the main parameters that were used to study HRV, which showed a reduction in global HRV and an imbalance in activity between the sympathetic and the parasympathetic nervous system in the frail group compared to the nonfrail group. Different definitions of entropy (e.g., approximate entropy, conditional entropy, and sample entropy) were also reported for assessing the complexity underlying the cardiac ANS. These measures showed a reduction in complexity of the cardiac ANS in frail compared to nonfrail groups in long-term measurement.

Conflicting Results across Studies

Two conflicting results among the studies included in the current systematic review were observed:

- 1 Increased pLF and LF/HF as well as a decreased pHF were observed in the frail group as compared to the nonfrail group in the study by Katayama et al. [23], which was not in line with the findings of Chaves et al. [11].
- 2 An increased approximate entropy (an indicator of increase in complexity of the cardiac ANS) in the frail group as compared to the nonfrail and prefrail groups was reported by Takahashi et al. [25], which was in disagreement with the results provided by Chaves et al. [11].

The main source of the above-mentioned disagreement may be constituted by the implemented methodological approaches: the measures of Takahashi et al. [25] and Katayama et al. [23] were based on short-term HR series (~5 min) while their participants were in a controlled static position (e.g., supine position). On the other hand, Chaves et al. [11] calculated the same parameters for longer data recordings (2–3 h) during physical tasks in diverse positions (e.g., lying, sitting, and standing).

Clinical Implications

The results of the current review demonstrate that most HRV measures (e.g., SDNN and power across all frequency bands as well as those calculated for longer data recordings, including pVLF, pLF, LF/HF, and approximate entropy) decline with frailty. The reduction in SDNN and total spectral power in the frail group compared to the nonfrail group is an indicator of reduced global HRV in the frail group. Furthermore, a different LF/HF in frail compared to nonfrail individuals is an indicator of an increased imbalance between the sympathetic and the parasympathetic nervous system [11, 12, 23]. The reduction in entropy measures (approximate entropy [11] and sample entropy [23]) reported in frail individuals suggests a reduction in the physiological complexity underlying HR dynamics. This finding is in agreement with previous research that demonstrated a reduction in the complexity of HR with aging [29, 30]. This reduction in complexity may be associated with an impaired interaction between subsystems and regulatory mechanisms and was observed in pathological conditions [29]. Therefore, it can be concluded that frail individuals are at a higher risk of cardiac disease, and better medical care is required for them to prevent cardiac complications.

The significantly smaller alterations in HR in response to a postural transition in the frail group [24, 26] indicate that the instantaneous response of the cardiac system is less robust and competent in frail compared to nonfrail individuals. This finding suggests that frail people, especially those with heart problems, are more susceptible to adverse health conditions when performing strenuous tasks such as climbing the stairs; therefore, more rest between performances of more dynamic activities is required.

Previous studies have demonstrated that prehabilitation or rehabilitation prior to, or after, cardiac surgery leads to fewer postoperative complications and a shorter postoperative length of stay [31, 32]. The clinical findings of the current systematic review provide evidence that using detectable alterations in the cardiac ANS can assist in clinical monitoring. Cardiac ANS assessment may be used, specifically in cardiac patients, as a complementary measurement in addition to current subjective/semisubjective methods (e.g., Fried's criteria) or walking-based frailty assessment methods (e.g., 5-meter gait speed) that assess physical performance and are the most common frailty assessment approaches utilized in cardiovascular care for older adults [5]. As such, monitoring of HRV measures may serve as a potential tool for guiding prescriptive prehabilitation and rehabilitation programs. Further, by extension, this may offer additional benefits for reducing hospital stay and health care costs and for improving the quality of life of older adults.

Future Research Directions

The small number of studies included in this systematic review highlights the fact that published research on the association of frailty and cardiac autonomic control is limited. Also, the variety of protocols and parameters for assessing the cardiac ANS employed suggests a lack of standardized protocols for the evaluation of cardiac autonomic control. Therefore, suggesting a guideline for the standardized assessment of the cardiac ANS in frail older adults would be helpful for cross-study comparisons.

Although different HRV measures including time domain, frequency domain, and nonlinear approaches have been used to study the cardiac ANS across frailty groups, no study has quantitatively evaluated the relationship between the degree of autonomic dysfunction (the range of HR and HRV) and the frailty level. Providing such information in future studies could help to better understand the underlying mechanism of HR and HRV alterations

with frailty. Since each HR and HRV measure assesses the cardiac ANS from a specific standpoint, an extraction of different HR and HRV measures can better characterize the cardiac ANS and increase the confidence in the interpretation of the results. For example, both RMSSD and pHF carry information about the activity of the parasympathetic nervous system, and implementing both parameters may increase the confidence in the interpretation of the effect of frailty on the parasympathetic nervous system.

Interestingly, only one study monitored HRV in male older adults [25], and another study that provided a cardiac ANS assessment in both males and females only focused on the monitoring of HR response and HR recovery [24]. Therefore, further studies of the effect of frailty on the cardiac ANS in males are warranted.

Of 4 studies that utilized a standardized definition of frailty for assessing HRV, 2 studied short-term HRV (5-min measure) [23, 25] and the other 2 assessed HRV for a longer duration (2–3 h) [11, 12]. Future studies are warranted which evaluate the agreement between short-term and long-term HRV assessments in frail populations as well as find the most reliable approach to assessing HRV in frail older adults.

All reviewed articles studied heart response and cardiac autonomic control in static positions (e.g., sitting and standing) [23, 25] or without considering positioning or the level of activity [11, 12]. Previous studies have recommended that frailty be identified with greater precision by studying the heart response to physical activity (e.g., sit-to-stand test) [24, 26]. Wearable technologies can provide a tool for simultaneously measuring physiological (e.g., ECG) and kinematic data (e.g., body posture using accelerometers), which can then be used to assess the HR response to and recovery from tasks such as sit-to-stand or lie-to-stand testing during activities of daily living. Also, this coupling of activity and physiologic response could help to better study heart response and recovery during different phases of the activity studied (e.g., the leaning forward part of sitting to standing or the transition from a leaning position to standing).

No study to date has explored longitudinal changes in performance of cardiac autonomic control in response to frailty progression. Future longitudinal studies are recommended to explore this relationship. Also, the predictive value of the cardiac ANS in combination with current frailty assessment methods such as Fried's criteria for the prediction of prospective frailty status changes is another area that could be explored.

Previous studies in the area of aging have shown that HRV was more pronounced during the night [33]; this result warrants research studies assessing the cardiac ANS in individuals with different frailty statuses, as defined by a standardized definition, during nighttime sleeping. It should be noted that the effect of confounders such as movement and change in posture can be minimized during sleep.

Further, the effect of exercise on the cardiac ANS of frail individuals has not previously been explored. Designing studies to systematically explore the effect of exercise on the cardiac ANS based on objective frailty levels is worth pursuing.

Limitations

There is a limited body of evidence on cardiac autonomic functions such as HR and HRV in frail groups as defined by a standard definition. In addition to the scarcity of articles, two factors limited the comparability between the studies included: (1) different parameters were used for assessing the cardiac ANS, and (2) confounders, such as posture [34, 35] and the level of activity [36, 37], which may influence HR-derived parameters and outcomes, were not controlled for in all studies. Also, due to the above-mentioned factors as well as missing values [11, 12, 23, 26], we were unable to perform a meta-analysis. Finally, different subsets of the same sample were used in 3 out of the 6 studies included [11, 12, 26], reducing the total number of unique participants and their independence. Thus, the results need to be interpreted with caution.

Conclusions

The current systematic review provides evidence of cardiac autonomic nervous impairments in frail as compared to nonfrail older adults. These impairments are characterized by a reduction in the complexity of HR dynamics, a reduction in HRV, or an impaired HR response to daily physical activities. The lack of methodological rigor limits the generalizability of the study findings (i.e., different measures and study designs). Thus, more rigorous studies, incorporating systematic measures and methods, are required to better assess associations between the cardiac ANS and different frailty statuses in older adults.

Appendix A: PRISMA 2009 Checklist Adapted from Moher et al. [21]

Section/topic	No.	Checklist item	Reported on section
<i>Title</i>			
Title	1	Identify the report as a systematic review, meta-analysis, or both	Article title
<i>Abstract</i>			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	Abstract
<i>Introduction</i>			
Rationale	3	Describe the rationale for the review in the context of what is already known	Introduction
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	Introduction
<i>Methods</i>			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number	–
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale	Methods – Inclusion/Exclusion Criteria
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	Methods – Search Strategy
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	Appendix B
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	Methods – Study Selection
Data collection process	10	Describe the method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	–
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made	Methods – Data Extraction
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	–
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means)	N/A
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis	N/A
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies)	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	N/A
<i>Results</i>			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	Results – Study Selection (fig. 1)
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations	Results – Participants Results – Study Design and Quality Assessment (tables 1, 3, 4)
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12)	N/A
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot	N/A
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15)	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression; see item 16)	N/A
<i>Discussion</i>			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers)	Discussion

Section/topic	No.	Checklist item	Reported on section
Limitations	25	Discuss limitations at the study and outcome levels (e.g., risk of bias), and at the review level (e.g., incomplete retrieval of identified research, reporting bias)	Discussion – Limitations
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	Conclusions
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review	Acknowledgements

Appendix B

The following search strategy was used in the PubMed database:

“Frail Elderly”[MeSH] OR frail*[tw] OR pre-frail[tw] OR pre-frailty[tw] OR prefrail*[tw] AND ((heart OR cardiac[Text Word])) AND (rate OR rhythm OR conduction[Text Word]) OR ((adren-erg* OR noradrenerg* OR cholinerg*)) OR ((autonomic[Text Word]) AND (control OR system[Text Word])) OR ((sympathetic OR parasympathetic[Text Word])) OR ((vasovagal OR vagal OR

vagus[Text Word])) OR (((“Hemodynamics”[MeSH]) OR “Heart Conduction System”[MeSH]) OR “Autonomic Nervous System”[MeSH])

The search strategies applied in the other databases (Embase, Cochrane Library, Web of Science, CINAHL, and ClinicalTrials.gov) were derived from the PubMed search. The database searches were conducted without using language or publication date restrictions (though non-English articles were excluded during the screening process).

Appendix C: Definition of HR and HRV Parameters and the Physiological Interpretation of HRV Measures

	Parameter	Definition	Physiological interpretation
HR	Baseline HR (bpm)	HR before starting the test [24, 26]	–
	ΔHR (bpm or %)	Change in HR compared to the baseline after completing a test [24, 26]	–
HRV	SDNN (ms)	Standard deviation of normal-to-normal intervals [38]	Global HRV
	SDANN (ms)	Standard deviation of the average normal-to-normal intervals over 5-min periods [38]	Sympathetic and parasympathetic nervous system interactions (autonomic tone)
	RMSSD (ms)	Square root of the mean squared differences between successive normal-to-normal intervals [38]	Parasympathetic activity
	pNN50 (%)	Number of successive normal-to-normal intervals with differences >50 ms divided by the total number of RR intervals [38]	Parasympathetic activity
	Total power density (ms ²)	Power across all frequency bands (<0.4 Hz), which is a net effect of all possible physiological mechanisms contributing to HRV [20, 38]	Global HRV
	pVLF (ms ²)	Power in the very-low-frequency band (<0.04 Hz) [20, 38]	Overall activity of various slow mechanisms of sympathetic function
	pLF (ms ²)	Power in the low-frequency band (0.04–0.15 Hz) [20, 38]	Both sympathetic and parasympathetic tone
	pHF (ms ²)	Power in the high-frequency band (0.15–0.4 Hz) [20, 38]	Parasympathetic tone
	LF/HF	Ratio of the power in the low-frequency band to the power in the high-frequency band [20, 38]	Balance between sympathetic and parasympathetic tone
	Approximate entropy/ conditional entropy/ sample entropy	Measures the irregularity or complexity of the HR series [23, 25, 29]	–
	Symbolic analysis	Converts cardiac RR intervals into different levels (symbols) and analyzes the pattern of symbols [23]	–

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Disclosure Statement

The authors have no conflicts of interest to disclose.

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