**RESEARCH ARTICLE**

# Imbalance in Cardiac Autonomic Nervous System Mediates Fatigue

**Authors**
Aaron I. Vinik, M.D., Ph.D.[1], Etta J. Vinik, MEd.[1], Ying-Chuen Lai, M.D.[2], Steven Morrison, Ph.D.[3], Sheri R. Colberg, Ph.D.[4], Serina Neumann, Ph.D.[5], Joshua Edwards, MS.[6], Scott Gerwe, M.D[1], Carolina Casellini, M.D.[1], Henri Parson, Ph.D.[1]

**Affiliations**
[1]Department of Internal Medicine, Strelitz Diabetes Center, Eastern Virginia Medical School, Norfolk, VA;
[2]Department of Internal Medicine, National Taiwan University Hospital Yun Lin Branch, Taiwan;
[3]School of Physical Therapy and Athletic Training, Old Dominion University, Norfolk, VA;
[4]Human Movement Sciences Department, Old Dominion University, Norfolk, VA;
[5]Department of Psychiatry and Behavioral Sciences, Eastern Virginia Medical School, Norfolk, VA;
[6] Health Care Analytic Institute Eastern Virginia Medical School
*This work was performed at Eastern Virginia Medical School and Old Dominion University, Norfolk, VA

**Corresponding Author:**
Etta Vinik, MEd, Strelitz Diabetes Center
Instructor, Community Faculty
Eastern Virginia Medical School, 855 West Brambleton Avenue, Norfolk VA 23510
Tel: 757-434-0837, Fax: 757-446-5868
Email: vinikej@evms.edu

**Brief Summary:**
High self-rated perceived exertion (cognitive fatigue) impacts sympathovagal imbalance even in healthy people; slows their heart rate and response to exercise, and reduces activities of daily living and quality of life.

**Disclosures and Conflict of Interest**
**Disclosures:** Aaron Vinik has received research funding from the NIH, and NINCDS, American Diabetes Association, Astellas Pharma US, Pfizer, Daiichi Sankyo. SJ and SC also have received prior grant support from the American Diabetes Association. None of these disclosures are conceived to be conflict of interest.
None of the other authors have any disclosures.

**Conflict of Interest:** All the authors declare no conflict of interest.
All authors listed were involved in the body of research resulting in the manuscript production and all have read and approved the final version.
All authors meet criteria for authorship as stated in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (see below individual contributions).

**Authorship and Acknowledgements:**
**Study concept and design:** Aaron I. Vinik
**Formal investigation:** Aaron I. Vinik, Carolina Casellini, Henri K Parson, Serina A. Neumann, Steven Morrison
**Study implementation and acquisition of data:** Carolina Casellini, Joshua Edwards, Henri K. Parson
**Analysis and interpretation of data:** Aaron I. Vinik, Joshua Edwards, Ying-Chuen Lai, Steven Morrison, Carolina Casellini
**Drafting of the manuscript:** Etta J. Vinik, Ying-Chuen Lai, Aaron I. Vinik, Carolina Casellini, Scott Gerwe
**Critical revision of the manuscript for important intellectual content:** Etta J. Vinik, Aaron I. Vinik, Sheri R. Colberg, Serina A. Neumann, Steven Morrison
**Final editing of the manuscript:** Etta J. Vinik and Sheri R. Colberg
**Management of the manuscript:** Etta J. Vinik

**Abstract**

***Aims*** To explore the impact of the autonomic nervous system function in "disease-free" people for testing and appropriate therapies in different age-groups.
***Methods*** Seventy-five disease-free volunteers who participated in a previous study were randomly selected from five age-groups (30-79 years) for a cross/sectional study to assess the impact of fatigue on cardiac/autonomic function by analysis of heart rate variability (HRV) and measures of cognitive and physical fatigue on quality-of-life-fatigue (QOLF) scores. Written informed consent was obtained and protocol approved. To induce fatigue, three 5-minute walking trials were performed on an instrumental treadmill, increasing the incline in increments of 2°/min to measure perceived exertion (RPE) at the beginning and end of each trial. Polar monitors measured heart rate (HR); a modified Borg 10-point scale measured RPE. Cardiac autonomic reflex tests (CART) with time/frequency domains analyzed HRV. QOLF scores were measured and analyzed for correlation with sympathetic/parasympathetic function on the Norfolk QOL-F fatigue scale.
***Results*** QOL-F scores were not significantly different among 5 age groups, likely due to wide standard deviations and small subject numbers. Significant correlations between overall fatigue severity and several indices of HRV *were* found, independent of age, gender, and body mass index ($p<0.05$). Self-rated physical fatigue and compromised activities of daily living (ADLs) were related to sympathetic hyperactivity and autonomic imbalance ($p=0.04$). Participants in the (70–79-year-olds) category had impaired scores.
***Conclusions*** The study identifies a relationship between autonomic nervous system function and cognitive and physical fatigue *even* in "disease-free" people in different age- groups and suggests that fatigue is impacted by somatic and autonomic nerve function. Higher self-ratings of perceived fatigue were associated with sympathovagal hyperactivity. Impaired HR response to exercise in older people corresponding with vagal over-activity, and paradoxically, best self-rated QOL-F, mandates clinical autonomic dysfunction testing and lifestyle therapies to prevent catastrophic events.

**Key words:** Autonomic imbalance, Cognitive, Physical Fatigue, Quality of Life.

 

## 1. Introduction

The reported prevalence of fatigue varies in different population settings and with the study methodology used. The worldwide prevalence rate of fatigue is between 7% and 45%, depending on the study.[1] Idiopathic chronic fatigue lasting for more than 6 months is more prevalent than the 0.2-2.6% estimated for chronic fatigue syndrome.[2] In England, a study reported chronic fatigue at 11%;[3] in the Netherlands it was even higher at 30.5%;[4] and a Korean study involving 1,648 subjects reported 8.4%.[5] Approximately 37.9% of the workforce in the United States has complained of fatigue with or without other chronic health conditions and had an increase in health-related loss of productivity, with fatigue being more prevalent in women and in workers under 50 years of age,[6] but the *mechanism* of fatigue had not been fully addressed, calling for further investigation and exploration of cardiac autonomic imbalance as a mediator of fatigue. An association between fatigue and cardiac autonomic dysfunction has been reported.[7-11]

Moreover, adults with postural orthostatic tachycardia syndrome (POTS),[12] a disease associated with underlying autonomic dysregulation, have increased severity of fatigue compared to those without autonomic dysfunction.[13] In healthy subjects, increased sympathetic activity and decreased parasympathetic activities have been noted after engaging in fatigue-inducing tasks[14] but the impact of aging has not been evaluated. Others have quantified individual perception of fatigue in response to normal activities and have evaluated the association between mental fatigue and cardiac autonomic dysfunction[15,16] using tools such as the Fatigue Symptom Inventory,[17] Fatigue Impact Scale,[18] Chalder's Fatigue Scale,[7,14] and the Multidimensional Fatigue Inventory.[8]

However, none of these scales fully incorporates and includes measurement of quality-of-life (QOL), nor are they sensitive to cognitive and physical fatigue. Additionally, they do not fulfill the requirement to measure the relationship between fatigue and autonomic function in a non-diseased population who might also be at risk due to autonomic imbalance. *To address these deficiencies, we utilized a QOL fatigue-specific questionnaire, the Norfolk QOL-F, to explore the relationship of cognitive and physical fatigue on the cardiac autonomic nervous system function in healthy (i.e., non-diseased) subjects of different age groups.*

## 2. Subjects

Seventy-five healthy volunteers were randomly selected from a previous study of 400 disease-free people and divided into five age-groups ranging from 30 to 79 years old. All participants were recruited from the local community by written invitation, newspaper advertisements, and strategically-placed flyers; included volunteers were men or women free of ocular or systemic disease (including diabetes) and with no recent or recurrent history of musculoskeletal injury, neurological conditions, history of vertigo, use of an aid while walking, difficulty with standing upright, or visible tremor or uncorrected visual deficits. This protocol was approved by the Academic Institutional Review Board (name undisclosed for anonymity) and was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from each subject prior to participation. Body weight, height, body fat, blood pressure (BP), and heart rate (HR) were measured at baseline. Body mass index (BMI) was calculated as weight (kg)/height ($m^2$). Participants also underwent a

 

complete history, physical examination, and neurological evaluation and were tested for time and frequency dependent cardiac autonomic balance using methods previously reported.[9,10]

## 3. Materials and Methods

### 3.1 Measurement of Fatigue

The Norfolk QOL-F questionnaire was used to measure perceived cognitive and physical fatigue and is sensitive to normative aging and its complications. The development of Norfolk QOL-F[19] encompassed validation of its construct, convergent and face validation, and reliability testing in 400 disease-free, multiethnic participant ranging from 30 to 79 years old (51% female). Its validation showed good internal consistency and strong inter-factor correlations, ranging from 0.690 to 0.830. Thirty-five items loaded clearly (0.617 or higher) on each of five factors and were designated as constituents of five scales: 1) subjective fatigue, 2) problems due to fatigue, 3) dysphoria/depression, 4) reduced activities, and 5) activities of daily living (ADL).

### 3.2 Induction of Fatigue

To induce fatigue, 75 randomly selected volunteers participated in a walking task on an instrumental treadmill (h/p/Cosmos Mercury 4.0; h/p/cosmos spores & medical gmbh, Nussdorf-Traunstein, Germany). This walking task of three 5-minute trials (with a 5-minute rest between) has been proven to determine the *physiological effort* on fatigue by of increasing the treadmill incline walking, as described in detail.[9] HR and rating of perceived exertion (RPE) values were recorded during the treadmill walking test. HR was measured using a Polar monitor (Polar Inc., Lake Success, NY). RPE was obtained at the beginning and end of each fatigue walking trial using a modified Borg 10-point scale (1 as "little or no exertion" to 10 as "maximal effort"), and the average change in RPE was calculated as RPE at the end of each fatigue trial minus baseline RPE.[9]

### 3.3 Autonomic Function Testing

During testing conducted on a separate day, *Cardiac Autonomic Reflex Tests* (CART) with Time and Frequency domain analysis of heart rate variability (HRV) were performed as previously described.[10,11] After resting for 15 minutes, HR and respiratory rate were continuously recorded for 15 minutes in a temperature-controlled room (22–24°C) using the ANSAR device (ANX 3.0 software; ANSAR Group, Inc., Philadelphia, PA). All subjects were fasting and had abstained from strenuous physical exercise, coffee, alcohol or cigarette consumption during the prior 12 hours. Time and Frequency domain analysis of HRV, and BP were determined at rest for 5 minutes with the patient sitting and breathing at a controlled rate (15 breaths per minute), and during deep breathing (six breaths per minute for 1 minute), Valsalva and standing from sitting position maneuvers to measure sympathetic and parasympathetic function, and autonomic balance, as described previously.[10,20,21] The following indices were recorded: resting HR and BP; E/I ratio (during deep breathing maneuver), Valsalva ratio (during Valsalva maneuver) and 30:15 ratio (during standing from sitting maneuver); ***frequency domain measures*** including total spectral power (TSP), low-frequency power (LF) which reflects primarily the oscillatory rhythm of the baroreceptors and is modulated by both the parasympathetic and the sympathetic nervous systems, high frequency power (HF) which mainly represents respiratory variation, is mediated by parasympathetic activity, and is highly correlated to the root mean square of successive R-R intervals (RMSSD) and LF/HF ratio; and ***time domain measures*** including sdNN (standard deviation of the beat to beat (NN) variability) that measures both sympathetic and parasympathetic action on

 

HRV and RMSSD, a measure primarily of parasympathetic activity.

## 4. Statistical Analyses

### 4.1 Sample Size Consideration

The G*Power 3.1 (Heinrich-Heine-Universitat Dusseldorf, Germany)[22] was used to predict the adequacy of sample size with an $\alpha$=0.05 and 1-$\beta$=0.8. The test demonstrated that a total of 74 subjects (this study included 75 randomly selected from 400[22]) would be sufficient to obtain significance of multiple linear regression models with 5 predictors. The Norfolk QOL-F questionnaire determined the relationship between fatigue and its domains and autonomic nerve function.

### 4.2 Data Presentation

Descriptive data are presented as means ± standard deviations or as medians (interquartile range). Due to the skewed distribution of HRV measures, these values were log-transformed to improve normality for statistical testing. ANOVA was used to assess differences among the age groups, whereas differences between gender analyses were assessed with the Wilcoxon rank-sum test. We used Stata's command for the nonparametric test for trend across different age groups. Correlations between Norfolk QOL-F scores and HRV were examined by Pearson's correlation. Multivariate regression models were created to evaluate the relationship between Norfolk QOL-F scores and HRV. Age, gender, body mass index and hypertension are potential risk factors for autonomic neuropathy and were used as covariates.[23,24]. A p value of <0.05 was significant. The statistical analyses were performed using Stata/SE11.0 for Windows (Stata Corp LP, Texas).

## 5. Results

### 5.1 Baseline Data

Demographic characteristics of participants by age group are given in Table 1. They were subdivided into ethnic groups, with 50% self-identifying themselves as Caucasian, 47% as African-American, 14% as Asian, 10% as Hispanic, 2% as Native American and 3% as "other." The mean age of participants was 55.2±14.3 yr, 52% female. Most were overweight or obese with mean body mass index of 29.04 ± 5.17 kg/m$^2$, 81% with a BMI above 25 kg/m$^2$. Body fat, systolic BP, and corrected (QTc) intervals on the EKG were significantly higher in older participants. Most indices of cardiac autonomic function showed a significant decline from the youngest to oldest age groups, except for the rMSSD and Lfa/Rfa ratio. No significant difference was found by gender (p=0.32) or between age groups on mean fatigue (p=0.20), possibly due to the small number and wide SDs in the different age groups.

### 5.2 Exercise Effects

As reported previously,[9] a significant age effect for the treadmill walking speed was observed ($F_{4,70}$=12.23: p<0.001) with the oldest persons (70-79 yr) walking at a significantly slower self-selected speed compared to the other age groups. During walking, a significant age effect was observed for change in HR ($F_{4, 70}$+4.33: p<0.01) and overall change in RPE ($F_{4, 70}$= 4.86: p<0.001). For the RPE values, differences were found between age groups 1-3 (30-39, 40-49, and 50-59 yr) and age groups 4 (60-69 yr) and 5 (70-79 yr). Prior to the exercise intervention, no significant differences in HR values were seen across the age groups. The differences in HR and RPE at baseline and after treadmill exercise across the five age groups are illustrated in Figure 1.[9] Paradoxically, during the treadmill intervention, the increment and absolute HR

 

changes were significantly reduced in the 70-79 yr group (p=0.001), as shown in Figure 2.

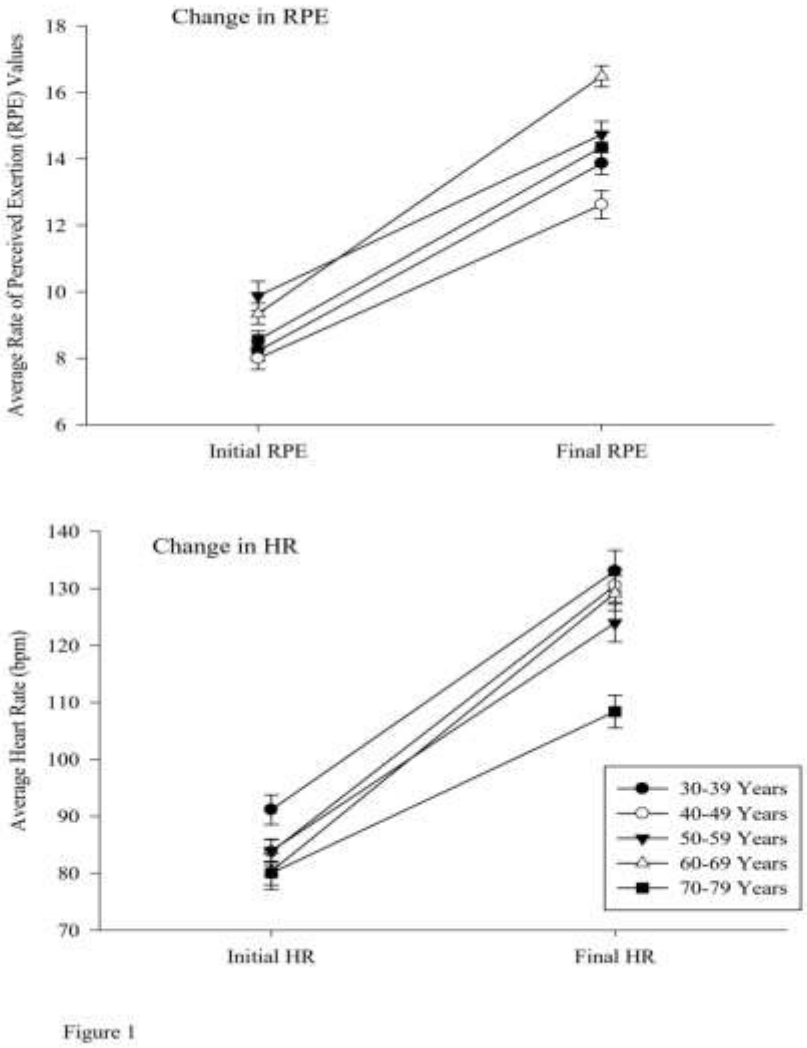


Figure 1

**Figure 1** shows the baseline heart (BPM) and the response to treadmill exercise compared with the baseline rate of perceived exertion and the change with exercise across the five age groups.[9]
Note: the oldest old (70-79 y) have a high rate of perceived exertion and the lowest increase in heart rate.

 

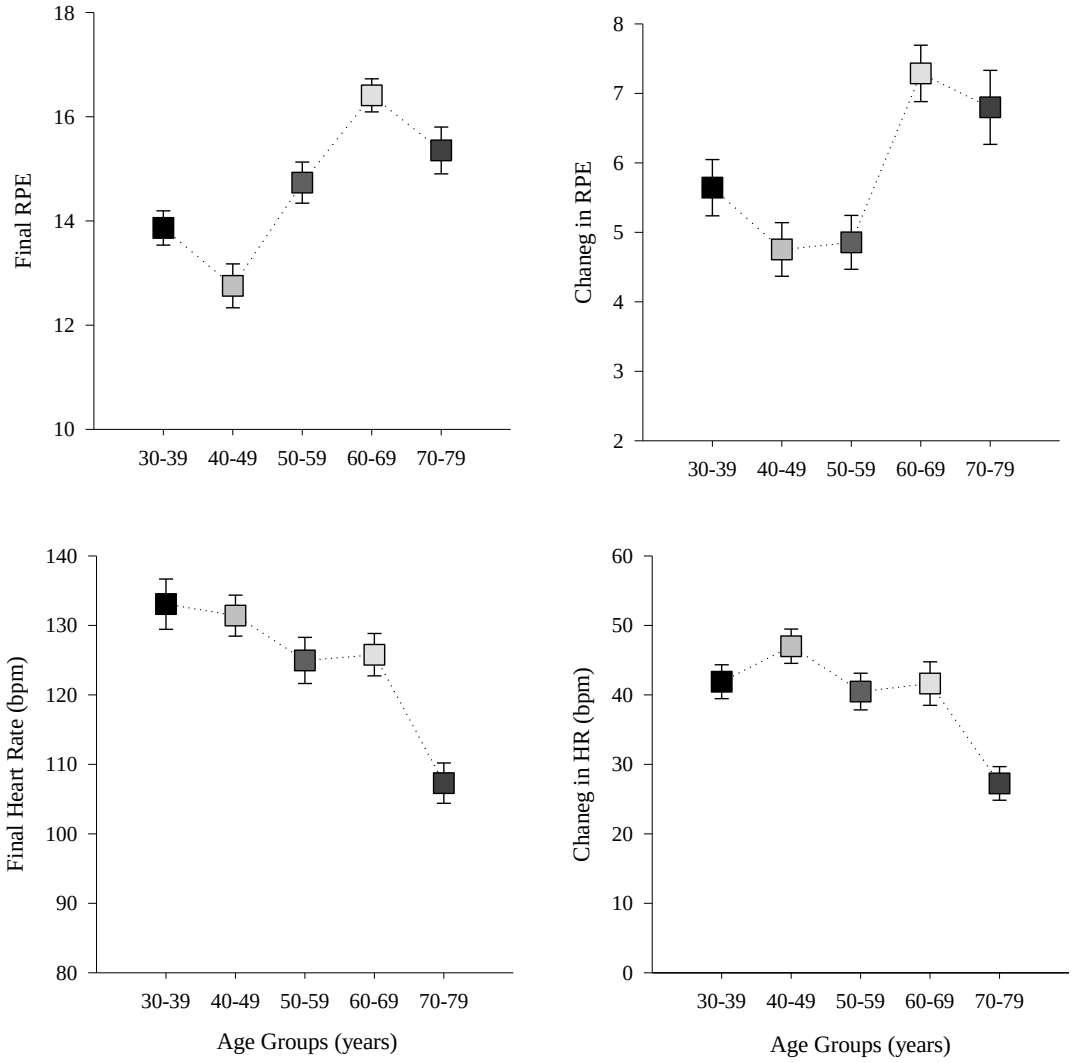


**Figure 2** illustrates the changes in the rate of perceived exercise (RPE) and the final RPE in the different age groups compared with the final heart rate and the change from baseline to that following exercise in the different age groups. [Note the rise in perceived exertion in the 70-79 y group with the fall in heart rate]. The differences between 70-79 y and the remaining age groups were significant ($p<0.001$).

### 5.3 Correlations between Fatigue and Autonomic Balance

Correlations between HRV measures and each fatigue scale are presented in Table 2. E/I ratio, postural 30:15 ratio, Lfa, and Rfa were significantly correlated with Norfolk QOL-F. For time-domain HR variation analysis, scale 2 (problem due to fatigue) was positively correlated with E/I ratio and scale 4 (reduced activities) was correlated with postural 30:15 ratio (r=0.25 and r=0.24; p=0.03 and p=0.04, respectively). Most scales were correlated with frequency domain HR variation. Scale 2 (problem due to fatigue) and scale 4 (reduced activities) were positively correlated Rfa (r=0.2549 and r=0.2608; p=0.03 and p=0.03, respectively). Scale 5 (ADL) was negatively correlated with L/R ratio (r=0.24, p=0.04). Multivariate linear regression analysis (Table 3) demonstrated that Norfolk QOL-F total and domain scores were significantly associated with the E/I ratio, postural 30:15 Lf, and Rf.

 

Adding age, sex, body mass index and hypertension as covariates did not impact correlations. Figure 3 illustrates the posited relationship between autonomic nervous system balance and fatigue.

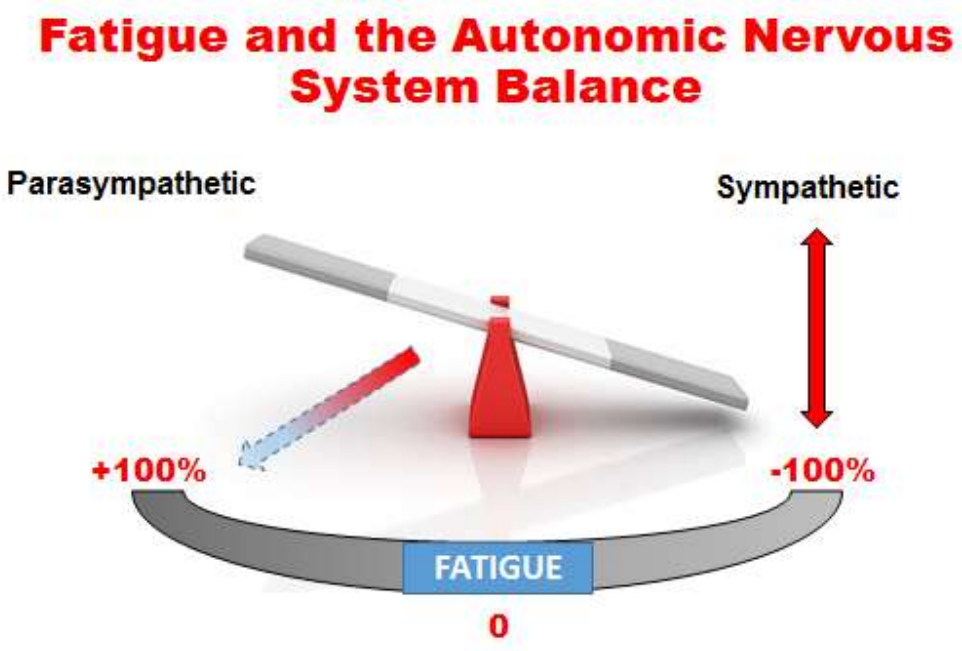


**Figure 3** illustrates the relationship between autonomic balance between the sympathetic and parasympathetic components of the autonomic nervous system and the impact on total fatigue score on the Norfolk QOLF tool. Note that with an increase in parasympathetic tone there is an increase in fatigue.

## 6. Discussion

Norfolk QOL-F has been shown to be a useful tool to identify fatigue severity and cardiac autonomic function status in all age groups and both women and men. Examination of the impact of autonomic function on the total Norfolk QOL-F score as well as the different domains revealed certain specificities for the individual domains and the sympathetic/parasympathetic functions. Norfolk QOL-F scores were associated with an increase in E/I ratio and Rfa, an index of cardiac parasympathetic activity, and Lfa, an index of cardiac sympathetic activity, independent of anthropometric characteristics and hypertension in healthy subjects. Furthermore, the severity of fatigue was associated with increased vagal activity.

Our findings are supported by Porges' polyvagal theory.[25,26] When the environment is perceived as safe, an increase of the vagal pathway regulates social engagement behavior. When danger is perceived, the sympathetic nerve system is activated and vagal system withdraws. Since fatigued patients reduce their physical activities and stay at a comfortable and safe level, a higher level of resting vagal activity is expected. In this study, problems due to fatigue and reduced activities correlated with E/I ratio and Rfa. Higher respiratory sinus arrhythmia (RSA) is correlated with greater emotional expressivity and vagal tone. Women with higher resting RSA experienced more negative emotion.[27] Scale 3 (dysphoria) of the Norfolk QOL-F includes psychological items to evaluate negative thoughts, emotional stress and

 

reaction, such as "Have you felt that you could not shake off blues?" and "Have you been bothered by things that usually did not bother you?" These questions also correlated with measures of increased vagal function.

In contrast, reduced activities and ADL scales correlated with the increase of Lfa and postural 30:15 ratio, and were considered as cardiac indices of sympathetic nerve activity and baroreflex sensitivity[28,29]. The relationship between physical fatigue and sympathovagal imbalance suggests an important role of cardiac autonomic regulation in the pathophysiology of chronic fatigue. When sympathetic nerve activity increases as a function of cognitive and emotional stress, adrenergic effects lead to coronary artery constriction and arrhythmias.[30]. In addition, other studies have shown that adults with chronic fatigue syndrome have a higher risk of postural tachycardia than controls (70% vs 5%).[31] Recently, the association between sleep quality and HRV was studied in postural orthostatic tachycardia syndrome (POTS). Reduction of LF/HR ratio variability was found during different sleep stages.[32] People with insomnia reported more fatigue than people without it.[33] The consequence of insomnia were measured in the question "Do you feel sleepy during the day?" which is mostly induced by poor sleep quality. This question correlated strongly with the Total QOL-F score and the domain of subjective fatigue, implicating an important role of sleep quality and fatigue.

Of particular interest is the change in total QOL with age, as shown in Table 1 QOL-F scores. Lower scores in the Norfolk QOL-F relate to better perceived QOL. RPE was greater for the 60-69 and the 70-79 yr age groups, but paradoxically the 70-79 yr group had a lower HR and the smallest rise in HR with exercise (see Figure 1). Participants who reported the lowest RPE were those in the 70-79 yr age group, yet the QOL fatigue scores for this age group were the best of all age groups and the overall change in HR the lowest. One suggested reason for this is that in older individuals, perceived exertion is driven by the autonomic nervous system, and they may have dominance of the parasympathetic nervous system. Older people scored lower on cognitive fatigue ratings than their younger counterparts. Thus, older adults may be reluctant to admit cognitive disabilities or, alternatively, they might just have a different frame of reference. In our study, the "oldest old" reported a better QOL score, likely attributable to a diminished RPE associated with vagal dominance.

Also in keeping with Porges theory,[25,26] which states that fatigued people reduce their ADL and slow their HR and HR response to exercise, our response showed that problems due to fatigue and reduced activities correlated with E/I ratio and Rfa, i.e., a parasympathetic effect. Dysphoria also correlated with measures of parasympathetic vagal function. Therefore, we believe that in the "oldest old" participants, vagal hyperactivity is reflected in acceptable rates of perceived exertion accompanied by reduced HR and the HR response to exercise.

Many studies on the association between autonomic function and fatigue have been controversial. Patients with chronic fatigue syndrome, breast cancer, or biliary cirrhosis, and veterans of Gulf War were reported in the literature to have autonomic dysfunction.[17,18,31,34] However, in these studies most participants have small fiber neuropathy related to neuropathic POTS in chronic fatigue syndrome, chemotherapy treated breast cancer, and toxin exposure during the Gulf War veterans. This contrasts with our studies in normal healthy subjects and demonstrates that there is a specific regulation of fatigue components sensitive to the branches of the

 

autonomic nervous system. We anticipate that the fatigue scales developed in our study will be sensitive to the disease states reported above that will be examined in future studies, in particular studies in patients with diabetes.

To our knowledge, this study is the first to evaluate the effect on both cognitive and physical fatigue on autonomic nervous system imbalance in healthy subjects. Norfolk QOL-F has been shown to be a useful tool to measure fatigue severity and the impact of fatigue on cardiac autonomic function and a means of quantification of the impact of autonomic intervention on fatigue. The strength of this study is use of the validated Norfolk QOL-F questionnaire in evaluating the relationship between fatigue and autonomic function in participants in our study who were selected to exclude the effects of neuromuscular disorders on fatigue.

Its limitations are that data are cross-sectional and cannot be attributed to a causal relationship between autonomic dysfunction and fatigue and its domains without perturbation of the autonomic nervous system. Our study design did not determine the biologic factors responsible for fatigue, only its relationship with autonomic function. However, both sympathetic and parasympathetic nervous systems play an important role in regulation of the immune system.[35] We have also reported on the role of vagal activity on the neuroinflammatory reflex and impaired vagal function results in unbridling of inflammatory reflexes.[35] It will be interesting to examine the fatigue components of chronic inflammatory disorders and their relationship with autonomic function.

## 7. Conclusions and Implications

In conclusion, using the Norfolk QOL-F as a tool to evaluate physical and cognitive fatigue in a normal healthy subset of the general population, we demonstrate that increasing fatigue severity is associated with sympathovagal imbalance in healthy subjects, and with impaired parasympathetic tone, there is an increase in fatigue. Fatigued people reduce their ADLs and slow their HR and HR response to exercise, which correlates with E/I ratio and Rfa measures of vagal activation. The Norfolk QOL-F too, was able to determine differences in physical and cognitive fatigue in different age groups. Noteworthy, in the "oldest old" participants, vagal hyperactivity is reflected in reduced HR and the HR response to exercise. Further studies on the impact of autonomic dysfunction (e.g., diabetic autonomic neuropathy) and the impact of modulation of the specific arm of the autonomic nervous system and its impact on Norfolk QOL-F and its domains will further define a possible cause-effect relationship. The impaired HR response to exercise in older people corresponding with vagal over activity, suggests that the Norfolk QOL-F tool, which captures fatigue related to autonomic dysfunction, could be used in future clinical studies designed to mitigate fatigue in both healthy and diseased populations. In conclusion, we reiterate the importance of identifying the loss of parasympathetic integrity, which if undiagnosed can lead to unfortunate consequences.

**Implications:** Our study promotes autonomic testing in the clinic but we are cognizant of the importance of acting on the results of the diagnostic procedures. Therefore, we recommend the introduction of lifestyle changes and safety measures (as listed below) to prevent catastrophic events and use of agents that modulate sympathetic parasympathetic balance.

- Attention to lifestyle issues encompasses changes to body composition as well as the introduction of strength and balance training.
- Regarding body composition, the results of studies on the correlation between obesity,

 

adipose tissue, cytokines and autonomic function suggest the need for weight loss medical programs and gastric bypass surgery.

- Regarding other lifestyle measures, sedentary habits and smoking cessation are difficult to achieve but not impossible, and group programs for smoking cessation and fun social groups with dancing and music have proven to be successful (e.g., "Dance out Diabetes" and local line dancing).
- To prevent falls and fractures strength and balance training is highly recommended for people with diagnosed autonomic imbalance and such programs are available now virtually recommended by physical therapists in place of, or in addition to formal classes.
- Daily walking has been shown to restore autonomic balance as well, and walking with a buddy has added social and emotional benefits. Of great interest is always the possible therapeutic benefits – the "magic bullet!"
- In the case of autonomic dysfunction, because of its complexities there are many different suggestions but no single therapy. In severe cases, immune therapy for patients with antibodies has been used to relieve postural hypotension.
- Antioxidant therapy, in particular, has been an employed therapy. Alpha lipoic acid has been shown to target the nervous system, but for now it is clear that multifactorial intervention is needed.

## 8. Acknowledgments

**Funding Sources:**

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The research team thanks the diabetes research laboratory at Eastern Virginia Medical School and School of Physical Therapy and Athletic Training, at Old Dominion University for the use of the facility, supplies and access to the patients recruited from a previous study.

 

**References**


1. Lewis G, Wessely S. The epidemiology of fatigue: more questions than answers. *J Epidemiol Community Health* 1992;46:92-7.
2. Ranjith G. Epidemiology of chronic fatigue syndrome. *Occup Med (Lond)* 2005;55:13-9.
3. Wessely S, Chalder T, Hirsch S, Wallace P, Wright D. The prevalence and morbidity of chronic fatigue and chronic fatigue syndrome: a prospective primary care study. *Am J Public Health* 1997;87:1449-55.
4. van't Leven M, Zielhuis GA, van der Meer JW, Verbeek AL, Bleijenberg G. Fatigue and chronic fatigue syndrome-like complaints in the general population. *Eur J Public Health* 2010;20:251-7.
5. Kim CH, Shin HC, Won CW. Prevalence of chronic fatigue and chronic fatigue syndrome in Korea: community-based primary care study. *J Korean Med Sci* 2005;20:529-34.
6. Ricci JA, Chee E, Lorandeau AL, Berger J. Fatigue in the U.S. workforce: prevalence and implications for lost productive work time. *J Occup Environ Med* 2007;49:1-10.
7. Gibbons CH, Bonyhay I, Benson A, Wang N, Freeman R. Structural and functional small fiber abnormalities in the neuropathic postural tachycardia syndrome. *PLoS One* 2013;8:e84716.
8. Smets EM, Garssen B, Bonke B, De Haes JC. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J Psychosom Res* 1995;39:315-25.
9. Morrison S, Colberg SR, Parson HK, et al. Walking-Induced Fatigue Leads to Increased Falls Risk in Older Adults. *J Am Med Dir Assoc* 2016;17:402-9.
10. Vinik AI, Ziegler D. Diabetic cardiovascular autonomic neuropathy. *Circulation* 2007;115:387-97.
11. Casellini CM, Parson HK, Richardson MS, Nevoret ML, Vinik AI. Sudoscan, a Noninvasive Tool for Detecting Diabetic Small Fiber Neuropathy and Autonomic Dysfunction. *Diabetes Technol Ther* 2013;15:948-53.
12. Sheldon RS, Grubb BP, Olshansky B, et al. 2015 heart rhythm society expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope. *Heart Rhythm* 2015;12:e41-e63.
13. Bagai K, Song Y, Ling JF, et al. Sleep disturbances and diminished quality of life in postural tachycardia syndrome. *J Clin Sleep Med* 2011;7:204-10.
14. Tanaka M, Mizuno K, Yamaguti K, et al. Autonomic nervous alterations associated with daily level of fatigue. *Behav Brain Funct* 2011;7:46.
15. Mizuno K, Tanaka M, Yamaguti K, Kajimoto O, Kuratsune H, Watanabe Y. Mental fatigue caused by prolonged cognitive load associated with sympathetic hyperactivity. *Behav Brain Funct* 2011;7:17.
16. Togo F, Natelson BH. Heart rate variability during sleep and subsequent sleepiness in patients with chronic fatigue syndrome. *Auton Neurosci* 2013;176:85-90.
17. Crosswell AD, Lockwood KG, Ganz PA, Bower JE. Low heart rate variability and cancer-related fatigue in breast cancer survivors. *Psychoneuroendocrinology* 2014;45:58-66.
18. Newton JL, Okonkwo O, Sutcliffe K, Seth A, Shin J, Jones DE. Symptoms of autonomic dysfunction in chronic fatigue syndrome. *QJM* 2007;100:519-26.
19. Vinik EJ, Vinik AI, Neumann SA, et al. Development and Validation of the Norfolk Quality of Life Fatigue Tool (QOL-F): A New Measure of Perception of


 

Fatigue. *J Am Med Dir Assoc* 2020; 21(9):1267-1272.e2.
20. Spallone V, Bellavere F, Scionti L, et al. Recommendations for the use of cardiovascular tests in diagnosing diabetic autonomic neuropathy. *Nutr Metab Cardiovasc Dis* 2011;21:69-78.
21. Cardiology TFotESo. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation* 1996;93:1043-65.
22. Faul F, Erdfelder E, Buchner A, Lang AG. Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. *Behav Res Methods* 2009;41:1149-60.
23. Christou DD, Jones PP, Jordan J, Diedrich A, Robertson D, Seals DR. Women have lower tonic autonomic support of arterial blood pressure and less effective baroreflex buffering than men. *Circulation* 2005;111:494-8.
24. Ge X, Pan SM, Zeng F, Tang ZH, Wang YW. A simple Chinese risk score model for screening cardiovascular autonomic neuropathy. *PLoS One* 2014;9:e89623.
25. Porges SW. The polyvagal theory: new insights into adaptive reactions of the autonomic nervous system. *Cleve Clin J Med* 2009;76 Suppl 2:S86-S90.
26. Porges SW. Social engagement and attachment: a phylogenetic perspective. *Ann N Y Acad Sci* 2003;1008:31-47.
27. Butler EA, Wilhelm FH, Gross JJ. Respiratory sinus arrhythmia, emotion, and emotion regulation during social interaction. *Psychophysiology* 2006;43:612-22.
28. Convertino VA. Neurohumoral mechanisms associated with orthostasis: reaffirmation of the significant contribution of the heart rate response. *Front Physiol* 2014;5:236.
29. Moak JP, Goldstein DS, Eldadah BA, et al. Supine low-frequency power of heart rate variability reflects baroreflex function, not cardiac sympathetic innervation. *Heart Rhythm* 2007;4:1523-9.
30. Schachinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. *Circulation* 2000;101:1899-906.
31. Freeman R, Komaroff AL. Does the chronic fatigue syndrome involve the autonomic nervous system? *Am J Med* 1997;102:357-64.
32. Mallien J, Isenmann S, Mrazek A, Haensch CA. Sleep disturbances and autonomic dysfunction in patients with postural orthostatic tachycardia syndrome. *Front Neurol* 2014;5:118.
33. Gradisar M, Lack L, Richards H, et al. The Flinders Fatigue Scale: preliminary psychometric properties and clinical sensitivity of a new scale for measuring daytime fatigue associated with insomnia. *J Clin Sleep Med* 2007;3:722-8.
34. Li M, Xu C, Yao W, et al. Self-reported post-exertional fatigue in Gulf War veterans: roles of autonomic testing. *Front Neurosci* 2014;7:269.
35. Vinik AI. The conductor of the autonomic orchestra. *Front Endocrinol* 2012;71:1-13.

 

**Table 1.** Demographic data in different age groups

| | **All subjects** | **Group 1** | **Group 2** | **Group 3** | **Group 4** | **Group 5** | |
|---|---|---|---|---|---|---|---|
| | | **30-39 y** | **40-49 y** | **50-59 y** | **60-69 y** | **70-79 y** | ***p value*** |
| **N** | 75 | 15 | 15 | 15 | 15 | 15 | |
| **Ethnicity (AA/Non-AA)** | 35/40 | 7/8 | 8/7 | 7/8 | 6/9 | 7/8 | |
| **Age (years)** | 55.2 ± 14.3 | 35.2 ± 2.5 | 45.6 ± 2.8 | 55.0 ± 2.8 | 65.0 ± 2.8 | 74.9 ± 2.1 | |
| **Gender (Female/male)** | 39/36 | 7/8 | 8/7 | 8/7 | 8/7 | 8/7 | 0.75 |
| **Body Mass Index (kg/m$^2$)** | 29.04 ± 5.17 | 29.60 ± 7.61 | 27.87 ± 4.47 | 30.47 ± 3.57 | 29.28 ± 5.00 | 27.97 ± 4.52 | 0.97 |
| **Body Fat (%)** | 32.73 ± 8.21 | 28.18 ± 8.83 | 28.71 ± 7.23 | 35.79 ± 7.52 | 35.19 ± 8.17 | 35.79 ± 6.04 | 0.001 |
| **Waist/Hip Ratio** | 0.90 ± 0.07 | 0.90 ± 0.09 | 0.88 ± 0.07 | 0.91 ± 0.08 | 0.89 ± 0.06 | 0.92 ± 0.07 | 0.30 |
| **Norfolk QOL-F Score** | 39.18 ± 24.41 | 48.20 ± 32.87 | 34.60 ± 19.22 | 40.0 ± 23.06 | 40.64 ± 26.03 | 31.21 ± 17.25 | 0.27 |
| **SBP sitting (mmHg)** | 132.3 ± 18.0 | 124.4 ± 11.6 | 123.7 ± 14.1 | 131.0 ± 17.5 | 132.9 ± 14.6 | 149.5 ± 20.0 | <0.001 |
| **DBP sitting (mmHg)** | 81.6 ± 8.9 | 82 ± 8.4 | 81.4 ± 9.0 | 83.8 ± 10.7 | 80.7 ± 9.4 | 80.1 ± 7.5 | 0.59 |
| **Heart Rate sitting (bpm)** | 67.0 ± 11.8 | 77.5 ± 17.6 | 70.9 ± 5.6 | 70.9 ± 11.8 | 64.4 ± 9.7 | 66.3 ± 7.0 | 0.006 |
| **EKG QTC interval (ms)** | 413.4 ± 17.4 | 401.4 ± 15.0 | 414.2 ± 15.8 | 416.9 ± 14.3 | 409.7 ± 18.0 | 425.0 ± 16.6 | 0.004 |
| **E/I ratio** | 1.2 (1.12-1.27) | 1.28 (1.18-1.31) | 1.23 (1.16-1.26) | 1.18 (1.17-1.3) | 1.15 (1.09-1.27) | 1.13 (1.06-1.20) | 0.003 |
| **Valsalva ratio** | 1.34 (1.20-1.62) | 1.60 (1.35-1.74) | 1.38 (1.25-1.72) | 1.29 (1.19-1.42) | 1.38 (1.20-1.65) | 1.18 (1.12-1.59) | 0.003 |
| **Postural 30:15** | 1.27 (1.16-1.43) | 1.43 (1.17-1.60) | 1.39 (1.27-1.44) | 1.19 (1.11-1.32) | 1.22 (1.15-1.35) | 1.20 (1.14-1.41) | 0.01 |
| **SdNN (ms)** | 40 (27-53) | 49 (34-64) | 43 (34-51) | 46 (27-59) | 39 (28-49) | 28 (20-53) | 0.03 |
| **rMSSD (ms)** | 28 (21-39) | 34 (21-46) | 27 (22-39) | 34 (15-42) | 26 (21-33) | 23 (16-34) | 0.10 |
| **Lfa (beats per minute$^2$)** | 1.15 (0.57-2.75) | 2.60 (1.15-4.18) | 1.14 (0.74-2.75) | 1.27 (0.83-2.10) | 0.83 (0.38-1.59) | 0.45 (0.14-2.09) | 0.001 |
| **Rfa (beats per minute$^2$)** | 1.05 (0.49-2.34) | 2.89 (1.64-3.75) | 1.78 (1.00-2.34) | 0.84 (0.49-3.25) | 0.53 (0.26-0.95) | 0.68 (0.26-1.41) | <0.001 |
| **L/R ratio** | 1.35 (0.51-2.10) | 1.42 (0.39-1.67) | 1.07 (0.46-1.50) | 1.62 (1.00-3.34) | 2.03 (0.73-3.52) | 0.86 (0.41-2.06) | 0.32 |
| **Total spectral power (ms$^2$)** | 640 (311-1283) | 1149 (408-1899) | 748 (516-1316) | 768 (232-1283) | 512 (303-945) | 311 (118-767) | 0.009 |

Data are presented as mean ± SD or median (IQR). AA, African American; SBP, systolic blood pressure; DBP, diastolic blood pressure
Note: The lowest and best Norfolk QOL-F scores were in the oldest group (70-79 y).
The rate of perceived exertion (RPE) was greater for 60-69 y and 70-79 y age-groups.
Yet, 70-79 y age group had lowest HR and smallest rise in HR with exercise. See Fig 1.

 

**Table 2.** Pearson's correlations between Norfolk QOL-F and heart rate variability in five fatigue subscales

| | Scale 1 Subjective Fatigue | Scale 2 Problems due to Fatigue | Scale 3 Dysphoria | Scale 4 Reduced Activities | Scale 5 Activities of Daily Living | Norfolk QOL-F |
|---|---|---|---|---|---|---|
| **E/I ratio** | 0.203† | 0.250* | 0.169 | 0.169 | 0.169 | 0.256* |
| **Valsalva ratio** | -0.008 | 0.006 | -0.059 | -0.051 | -0.104 | 0.049 |
| **Postural 30:15** | 0.198† | 0.199† | 0.173 | 0.240* | 0.040 | 0.243* |
| **SdNN** | 0.110 | 0.159 | 0.102 | 0.169 | 0.114 | 0.169 |
| **rMSSD** | 0.077 | 0.162 | 0.133 | 0.198† | 0.212† | 0.180 |
| **Lfa** | 0.200† | 0.209† | 0.143 | 0.196† | 0.072 | 0.258* |
| **Rfa** | 0.201† | 0.255* | 0.217† | 0.260* | 0.214† | 0.321** |
| **L/R ratio** | 0.041 | -0.062 | -0.099 | -0.166 | -0.239* | -0.087 |
| **Total spectral power** | 0.157 | 0.197† | 0.135 | 0.196† | 0.156 | 0.229† |

* $p<0.05$, ** $p<0.01$, † $p<0.1$

 

**Table 3.** Multivariate analysis of the influence of heart rate variability indexes on Norfolk QOL-F.

| | **Ln(E/I ratio)** | | | **Ln(Postural 30:15)** | | | **Ln(Lfa)** | | | **Ln(Rfa)** | | | **Ln(TSP)** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Beta Coefficient** | **SE** | ***p*** | **Beta Coefficient** | **SE** | ***p*** | **Beta Coefficient** | **SE** | ***p*** | **Beta Coefficient** | **SE** | ***p*** | **Beta Coefficient** | **SE** | ***p*** |
| **Unadjusted** | 0.002 | 0.001 | 0.031 | 0.003 | 0.002 | 0.041 | 0.015 | 0.007 | 0.03 | 0.189 | 0.007 | 0.006 | 0.011 | 0.006 | 0.054 |
| **Model 1: age and sex** | 0.002 | 0.001 | 0.051 | 0.003 | 0.002 | 0.076 | 0.015 | 0.007 | 0.041 | 0.017 | 0.007 | 0.015 | 0.01 | 0.006 | 0.077 |
| **Model 2: age, sex and BMI** | 0.002 | 0.001 | 0.051 | 0.003 | 0.002 | 0.082 | 0.014 | 0.007 | 0.047 | 0.017 | 0.007 | 0.018 | 0.010 | 0.006 | 0.086 |
| **Model 3: age, sex, BMI and history of hypertension** | 0.002 | 0.001 | 0.049 | 0.003 | 0.002 | 0.086 | 0.014 | 0.007 | 0.051 | 0.016 | 0.007 | 0.02 | 0.010 | 0.006 | 0.087 |

The beta coefficient represents the difference in heart rate variability measures between dichotomous variables (sex, history of hypertension) or per unit of continuous variables (age, BMI); SE=standard error.

The unadjusted correlation between log natural (Ln) indices of HR variability but not QOL-F were sign for the E/I ratio; Postural 30:15; (LF), (RS) and (TSP)
TSP - Total Spectral Power
(Rf) - Respiratory frequency
(Lf) - Low frequency
E/I - ratio Expiration/Inspiration
Postural 30:15 = Ratio of the RR interval of $30^{th}$ beat to $15^{th}$ beat after changing from supine to erect position

 