Assessing Autonomic Balance in Peripheral Arterial Disease Patients: A Generalized Multiscale Entropy Analysis of Heart Rate Variability

O Barquero-Pérez[1], E Cirugeda[1], L Jerónimo[1], R Goya-Esteban[1], E Sarabia-Cachadiña[2], A Sánchez-Sixto[2], B de la Cruz-Torres[3], J Naranjo-Orellana[4]

[1]Department of Signal Theory and Communications; University Rey Juan Carlos, Madrid, Spain
[2]Centro de Estudios Universitarios Cardenal Spínola CEU, Sevilla, Spain
[3]Department of Physiotherapy, University of Seville, Seville, Spain
[4]Departamento Deporte e Informática, Universidad Pablo de Olavide, Sevilla, Spain

Abstract

Peripheral arterial disease (PAD) is a chronic disorder that affects blood flow to the lower limbs. Many patients can develop intermittent claudication (IC) due to decreased blood flow in the lower limbs. Heart rate variability (HRV) assesses the autonomic balance through the cardiovascular system, however, the ability to predict IC in PAD patients using HRV is still unclear. We aim to assess if there are differences in resting HRV between patients with IC and healthy subjects using nonlinear analysis. 14 healthy male subjects (60±5 years) and 14 male IC patients (64±6 years) underwent 10 minutes of ECG recording from which RR interval time series were obtained. We characterized the HRV using Generalized Multiscale Entropy (GMSE), after removing artifacts. GMSE allows us to characterize the complexity of the HRV at different time scales. We computed GMSE for each patient, and then estimated the mean and standard deviation for each scale and group (PAD and healthy) using bootstrap. GMSE was significantly different for each scale between the healthy and PAD groups. Our findings suggest that GMSE was able to distinguish between IC PAD patients and healthy subjects using HRV, so there is clearly analteration in the autonomic balance due to PAD.

1. Introduction

Peripheral Arterial Disease (PAD) is an atherosclerotic condition characterized by the occlusion of arteries located distal to the aortic bifurcation [1]. This arterial blockage reduces the oxygen supply to the lower limb muscles during physical activity, leading to pain and forcing individuals to stop walking. This condition, known as intermittent claudication (IC), often results in significant limitations in daily physical activities and negatively impacts health-related quality of life [2–4].

Atherosclerosis, and consequently PAD, is particularly prevalent among the elderly and is closely associated with diabetes mellitus and other cardiovascular risk factors such as hypertension, elevated body mass index, and dyslipidemia [1, 5]. The risk of developing PAD is further increased by smoking, whether current or in the past [5].

Heart Rate Variability (HRV) is a non-invasive measure that reflects the autonomic nervous system (ANS) regulation of the cardiovascular system. It provides insight into the balance between sympathetic and parasympathetic nervous activity, making it a valuable tool for assessing autonomic function [6].

While HRV has been extensively studied in various cardiovascular diseases, and some studies on PAD patients, the role of non-linear characterization of HRV in predicting IC in PAD patients remains underexplored.

Traditional HRV analysis often focuses on linear methods, which may not fully capture the complex, nonlinear dynamics of the HRV. Therefore, nonlinear approach may be required to reveal subtle autonomic dysfunctions in PAD patients.

In some previous studies, the authors did not find a significant relation between HRV and improvement in walking ability [7, 8]. However, the authors of [9] found a positively relationship between HRV indices and maximal walking distance, but not with claudication distance, in symptomatic PAD patients. Therefore, it is clear that more research is needed to study the capacity of HRV characterizing PAD patients.

The objective of this study is to investigate whether resting HRV differs between IC patients and healthy controls by employing Generalized Multiscale Entropy (GMSE), a nonlinear method that characterizes the complexity of physiological time series over multiple temporal scales. We hypothesize that GMSE will detect significant differences in HRV patterns between PAD patients with IC and healthy individuals, potentially offering a new strategy for

understanding autonomic imbalance in this population.

The structure of the paper is as follows. In Section 2, the dataset is explained. In Section 3, HRV and exponential modeling are detailed. In Section 4, the statistical analysis is explained. In Section 5, results are reported. Finally, in Section 6, conclusions are presented.

2. Dataset

14 male control subjects (age 60±5 years, weight 90±12 kg, height 174±7 cm) and 14 male PAD patients presenting IC (age 64±6 years, weight 83±17 kg, height 168±7 cm) were recruited from two Hospitals in Seville, Spain. Control subjects were selected based on the following inclusion criteria: absence of cardiovascular disease, no ongoing medical treatment, and an Ankle Brachial Index (ABI)>1. For the PAD group, patients were referred by the vascular surgery departments of the participating hospitals, with documented PAD diagnosis, no prior surgical interventions, and an ABI< 0.9 [10, 11]. All participants, including both controls and PAD patients, were non-smokers and had not taken any cardiovascular-related medications for at least three months prior to the study. Subjects reported to the lab in the morning, two hours after breakfast, having abstained from caffeine consumption and exercise for 24 hours before data recdording. RR intervals time series were recorded for 15 minutes at rest in supine position using a Firstbeat Bodyguard recorder (Firstbeat Technologies Ltd, Jyväskylä, Finland). The initial five minutes of each recording were excluded to allow for participant relaxation [12, 13].

3. Heart Rate Variability Indices

HRV refers to the natural fluctuations in the intervals between successive heartbeats, reflecting the dynamic interplay between the sympathetic and parasympathetic branches of the ANS. HRV is a widely recognized index for evaluating neurocardiac function, owing to the complex, non-linear interactions that occur between the heart, brain, and autonomic nervous system.

In HRV analysis, it is generally accepted that short-term and long-term variations in heart rate arise from distinct physiological mechanisms. The extent of these variations provides valuable insight into the autonomic state, serving as a key indicator of overall cardiovascular health and adaptability [6].

HRV is typically quantified using time-domain and frequency-domain indices derived from NN-interval time series, which are often obtained from 24-hour Holter monitor recordings. Numerous studies have demonstrated that both short-term (approximately 5 minutes) and long-term (over 24 hours) HRV measurements correlate with physiological adaptability, health status, and the mobilization of limited regulatory resources [6]. Additionally, recent research has validated that ultra-short-term HRV measurements (lasting 5 minutes or less) can reliably capture meaningful HRV data, providing a convenient and efficient alternative for clinical and research applications [14].

GMSE is an advanced nonlinear analysis technique that quantifies the complexity of physiological time series across multiple temporal scales. Traditional entropy measures, such as Sample Entropy (SampEn), quantify the unpredictability or irregularity of a time series on a single scale [15]. While effective, these measures can be limited in their ability to capture the multiscale nature of physiological signals. Multiscale Entropy (MSE) extends this approach by evaluating entropy over a range of scales, thus providing a richer characterization of the underlying dynamics [16]. GMSE further enhances MSE by generalizing the scaling process, allowing for a broader set of parameters that can be adjusted to tailor the analysis to specific types of data or clinical contexts [17].

To compute GMSE, the first step is to generate a set of coarse-grained time series, $\{y_j^{(\tau)}\}$ where each coarse-grained time series at scale τ is constructed by averaging non-overlapping blocks of τ consecutive data points from the original time series $\{x_i\}$.

$$y_j^{(\tau)} = \frac{1}{\tau} \sum_{i=(j-1)\tau+1}^{j\tau} x_i, \quad j = 1, 2, \ldots, \left\lfloor \frac{N}{\tau} \right\rfloor$$

where N is the length of the original time series, and τ is the scale factor. The entropy of each coarse-grained time series is then calculated using a method such as SampEn.

$$\text{SampEn}(m, r, N) = -\ln\left(\frac{\text{A}(m+1)}{\text{B}(m)}\right)$$

where m is the embedding dimension, r is the tolerance (usually a percentage of the standard deviation of the time series), and $A(m+1)$ and $B(m)$ are the number of matching template vectors of length $m+1$ and m, respectively. GMSE is then defined as the entropy measure computed across all scales τ, providing a profile that reflects the complexity of the time series at different temporal resolutions.

GMSE is particularly effective in analyzing HRV, where the entropy values at different scales can reveal the balance between sympathetic and parasympathetic influences on the heart [17].

4. Statistical Analysis

To statistically analyze the differences between the control and PAD patient groups, we will employ a combination of bootstrap resampling and exponential curve fitting to the GMSE curve.

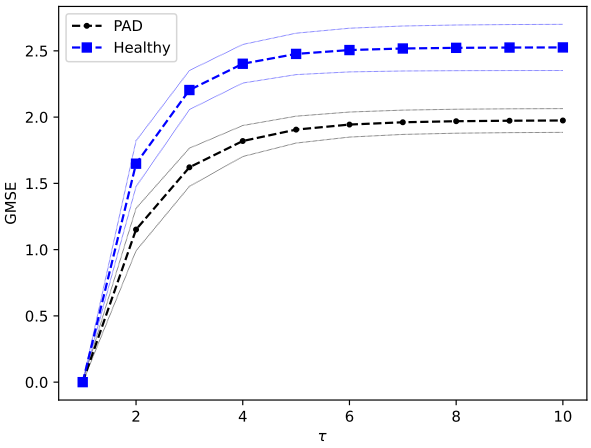

Figure 1. GMSE average values and standard deviation obtained from bootstrap resampling, for healthy subjects (dots) and PAD patients (squares)

First, we will perform bootstrap resampling with replacement on the GMSE curves for both the control and PAD groups. Thus, for each complete resample, we will compute the average GMSE curve. For each average GMSE curve from the bootstrap resampling, an exponential curve will be fitted using the following exponential equation:

$$u = C(1 - \mathrm{e}^{-\kappa\tau})$$

where C and κ are constants of the model find by optimization methods. τ represents the scales.

In this way, at the end of the bootstrap resampling process, we will obtain B values of C_c and C_{pad} as well as κ_c and κ_{pad}, for the control and PAD patient groups, respectively. Thus, we can assess whether there are significant differences in the exponential model parameters between the two groups.

5. Results

Figure 1 shows the average value and standard deviation of the GMSE curve obtained from the bootstrap resamplings. From scale two, the curves are statistically different, showing that GMSE, with variance, is able to distinguish control subjects from PAD patiens.

Table 1 show the mean values and standard deviation from the exponential model fitted for the average GMSE curve for each bootstrap resample. Results show that the parameters of the exponential model are statistically different for health subjects. and PAD patients. The values indicates that the entropy values are lower for each scale τ in PAD patients.

6. Conclusions

The findings of this study provide significant insights into the autonomic dysfunction associated with PAD and its manifestation in patients with IC. By employing GMSE analysis of HRV, we were able to discern notable differences in autonomic regulation between PAD patients and healthy controls. This study underscores the utility of nonlinear methods in capturing the complexity of physiological signals, which traditional linear methods may overlook. In fact, previous studies using linear methods (both time and frequency domain) and nonlinear (SampEn, DFA) did not show strong differences in HRV [7–9, 13].

Our results indicate that PAD patients exhibit a reduced complexity in HRV across multiple time scales, as evidenced by lower GMSE values compared to healthy subjects. This reduction in complexity suggests a diminished adaptability of the autonomic nervous system in PAD patients, potentially due to chronic ischemic conditions affecting the cardiovascular system. Our study uniquely contributes by utilizing a multiscale entropy approach to provide a more strong prove of these alterations.

The clinical implications of these findings are substantial. The ability to distinguish PAD patients from healthy individuals based on HRV complexity could pave the way for new diagnostic tools and therapeutic strategies aimed at improving autonomic function in this population. Furthermore, the use of GMSE as a diagnostic marker could enhance the monitoring of disease progression and the efficacy of interventions aimed at restoring autonomic balance.

However, this study is not without limitations. The sample size was relatively small, and the study population was limited to male subjects, which may affect the results. Future research should aim to include a larger and more diverse cohort to validate these results.

In conclusion, this study demonstrates that GMSE analysis of HRV is a powerful tool for assessing autonomic dysfunction in patients with Peripheral Arterial Disease. The significant differences in HRV complexity between PAD patients and healthy controls highlight the potential of GMSE as a diagnostic and monitoring tool in clinical settings.

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Subject	C **(m** $\pm$ **std)**	κ **(m** $\pm$ **std)**	C 95% CI	κ 95% CI
Health	2.531 ± 0.172	1.095 ± 0.258	$[2.52, 2.54]$	$[1.08, 1.11]$
PAD	1.684 ± 0.227	0.996 ± 1.248	$[1.67, 1.69]$	$[0.94, 1.05]$

Table 1. Mean and standard deviation of parameters C and K for Health and PAD groups and the 95% confidence interval for each parameter.

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Address for correspondence:

O Barquero-Pérez
Department of Signal Theory and Communications
University Rey Juan Carlos. DIII:D-217, Camino del Molino s/n
28943 - Fuenlabrada (Madrid), Spain
Phone: +34 91 488 84 62
oscar.barquero@urjc.es