Comparative Analysis of Generalized Multiscale Entropy Methods for Coarse-Grained Time Series Construction in Assessing Autonomic Balance in Peripheral Arterial Disease Patients

O. Barquero-Pérez[1] [a], R. Goya-Esteban[1] [b], E. Sarabia-Cachadiña[2] [c] and J. Naranjo-Orellana[3] [d]

[1]*Dept. Signal Theory and Communications, Universidad Rey Juan Carlos, Fuenlabrada, Madrid, Spain*

[2]*Centro de Estudios Universitarios Cardenal Spínola CEU, Sevilla, Spain*

[3]*Departamento Deporte e Informática, Universidad Pablo de Olavide, Sevilla, Spain*

{*oscar.barquero, rebeca.goyaesteban*}*@urjc.es, esarabia@ceu.es, jnarore@upo.es*

Keywords: Autonomic Nervous Systems, Heart Rate Variability, Generalized Multiscale Entropy, Peripheral Arterial Disease.

Abstract: Peripheral Arterial Disease (PAD) is a chronic condition that significantly impacts autonomic balance, as reflected in Heart Rate Variability (HRV). However, the characterization of autonomic balance in PAD patients using HRV is still unclear. Generalized Multiscale Entropy (GMSE) is a nonlinear method capable of characterizing the complexity of HRV across multiple time scales, offering a more nuanced understanding of autonomic dysfunction in PAD patients. 14 healthy male subjects (60±5 years) and 14 male intermittent claudication patients (64±6 years) underwent 10 minutes of ECG recording from which RR interval time series were obtained. This study provides a comparative analysis of different GMSE methods for constructing coarse-grained time series, specifically using the mean, mean absolute deviation (MAD), standard deviation (σ), and variance (σ^2) approaches. By applying these methods, we investigate their efficacy in differentiating between healthy individuals and PAD patients. Our results demonstrate that the variance coarse-grained method offers superior discriminatory power, revealing statistically significant differences. These findings suggest that the variance-based GMSE method is the most effective approach for assessing autonomic imbalance in PAD patients, with potential applications in improving diagnostic tools and treatment strategies.

1 INTRODUCTION

Peripheral Arterial Disease (PAD) is an atherosclerotic condition characterized by the occlusion of arteries located distal to the aortic bifurcation (Ramos et al., 2009). 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, often results in significant limitations in daily physical activities and negatively impacts the health-related quality of life of those patients (Feinglass et al., 1996; Crowther et al., 2007; Celis et al., 2009). PAD is a chronic and progressive disorder that can severely restrict an individual's mobility and independence, making it an important public health concern, particularly among the elderly population.

Atherosclerosis, and consequently PAD, is particularly prevalent among the elderly population. This condition is closely associated with several risk factors, including diabetes mellitus, hypertension, elevated body mass index, and dyslipidemia (Ramos et al., 2009; Diehm et al., 2009). Furthermore, the risk of developing PAD is further increased by both current and past smoking habits (Diehm et al., 2009).

Heart Rate Variability (HRV) is a fluctuation in the time intervals between consecutive heartbeats. It allows to non-invasively measure the autonomic nervous system regulation of the cardiovascular system. It provides valuable insight into the balance between sympathetic and parasympathetic nervous activity, making it a crucial tool for assessing autonomic function (Camm et al., 1996; Shaffer and Ginsberg, 2017). HRV analysis can reveal subtle abnormalities in the autonomic regulation of the heart, which may have important implications for understanding the physio-

[a] https://orcid.org/0000-0002-7235-3986
[b] https://orcid.org/0000-0002-0402-8487
[c] https://orcid.org/0000-0002-4444-6755
[d] https://orcid.org/0000-0001-9180-1732

Barquero-Pérez, O., Goya-Esteban, R., Sarabia-Cachadiña, E. and Naranjo-Orellana, J.
Comparative Analysis of Generalized Multiscale Entropy Methods for Coarse-Grained Time Series Construction in Assessing Autonomic Balance in Peripheral Arterial Disease Patients.
DOI: 10.5220/0013165000003911

In *Proceedings of the 18th International Joint Conference on Biomedical Engineering Systems and Technologies (BIOSTEC 2025) - Volume 1*, pages 893-898
ISBN: 978-989-758-731-3; ISSN: 2184-4305

logical mechanisms underlying various cardiovascular disorders, including peripheral arterial disease.

While HRV has been extensively studied in various cardiovascular diseases, and some studies have examined HRV in peripheral arterial disease patients, the role of nonlinear characterization of HRV in predicting intermittent claudication 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, a nonlinear approach may be required to reveal more subtle autonomic dysfunctions in PAD patients and potentially improve our understanding of the relationship between HRV and symptoms like intermittent claudication.

Some previous studies have not found a significant relationship between heart rate variability and improvements in walking ability in peripheral arterial disease patients (Leicht et al., 2011; Sandercock et al., 2007), other research has revealed a positive association between HRV indices and maximal walking distance, though not with claudication distance, in symptomatic PAD individuals (Lima et al., 2016). These mixed findings suggest that further investigation is needed to better understand the capacity of HRV to characterize autonomic dysfunction in PAD patients and its potential relationship to clinical outcomes like walking performance.

The primary objective of this study is to investigate whether resting HRV differs between patients with intermittent claudication and healthy control subjects. To achieve this, we will employ Generalized Multiscale Entropy (GMSE), a nonlinear analysis method that characterizes the complexity of physiological time series over multiple temporal scales (Costa and Goldberger, 2015). We hypothesize that GMSE will detect significant differences in HRV patterns between PAD patients with intermittent claudication and healthy individuals. This could potentially offer a new strategy for understanding autonomic imbalance in this patient population, which may have important implications for managing and monitoring this chronic and debilitating condition.

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

2 DATASET

Fourteen male control individuals (60±5 years old, 90±12 kg, 174±7 cm) and 14 male PAD patients (64±6 years old, 83±17 kg, 168±7 cm) exhibiting intermittent claudication were recruited from two hospitals in Seville, Spain. The control subjects were selected based on the following criteria: absence of cardiovascular disease, no ongoing medical treatment, and an ankle-brachial index greater than 1. In contrast, the PAD patient group consisted of individuals referred by the vascular surgery departments of the participating hospitals, with a confirmed PAD diagnosis, no prior surgical interventions, and an ankle-brachial index less than 0.9 (Schroll and Munck, 1981; Aboyans et al., 2012). All participants, including both the control and PAD groups, were nonsmokers and had not taken any cardiovascular-related medications for at least three months prior to the study. The participants reported to the laboratory in the morning, two hours after breakfast, having abstained from caffeine consumption and exercise for 24 hours before the data recording. The RR interval time series were recorded for 15 minutes at rest in the supine position using a Firstbeat Bodyguard recorder. The initial five minutes of each recording were excluded to allow for participant relaxation (Chidean et al., 2018; Cachadiña et al., 2018).

3 GENERALIZED MULTISCALE ENTROPY FOR HEART RATE VARIABILITY

GMSE is an advanced nonlinear method used to quantify 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 (Richman and Moorman, 2000). Although effective, these measures may not fully capture the multiscale nature of physiological signals. Multiscale Entropy (MSE) extends this approach by evaluating entropy over a range of scales, providing a more comprehensive characterization of the underlying dynamics (Costa et al., 2005). GMSE further enhances MSE by allowing for flexible scaling parameters, which can be adjusted to fit specific types of data or clinical contexts (Costa and Goldberger, 2015). This type of methods has been used with success to characterize long-range correlated cardiovascular an respiratory signals (Martins et al., 2020; Silva et al., 2015)

In MSE definition, $\{y_j^{(\tau)}\}$ 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 $\{x_i\}$. The GMSE modifications use different statistical moments to build the coarse-grained time-series. In this work we are going to compare the following four approaches:

- **Averaging:** Each coarse-grained time series is constructed by averaging non-overlapping blocks of τ consecutive data points from the original time series $\{x_i\}$:

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

- **Mean Absolute Deviation (MAD)**: The coarse-grained time series can also be computed using the mean absolute deviation of τ consecutive data points:

$$y_j^{(\tau)} = \frac{1}{\tau} \sum_{i=(j-1)\tau+1}^{j\tau} |x_i - \hat{\mu}|$$

  where $\hat{\mu}$ is the sample mean of the τ data points in each block.

- **Standard Deviation, σ**: Alternatively, each block of τ data points can be used to compute the standard deviation:

$$y_j^{(\tau)} = \sqrt{\frac{1}{\tau} \sum_{i=(j-1)\tau+1}^{j\tau} (x_i - \hat{\mu})^2}$$

- **Variance, σ^2**: Finally, the coarse-grained series can be based on the variance of the data points within each block:

$$y_j^{(\tau)} = \frac{1}{\tau} \sum_{i=(j-1)\tau+1}^{j\tau} (x_i - \hat{\mu})^2$$

  Where N is the length of the original time series, and τ is the scale factor.

Once the coarse-grained time series are generated, the entropy of each is calculated using a method such as Sample Entropy (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 (typically a percentage of the time series standard deviation), and $A(m+1)$ and $B(m)$ represent the number of matching template vectors of length $m+1$ and m, respectively.

GMSE is defined as the entropy measure computed across all scales τ, producing a profile that reflects the time series complexity at various temporal resolutions. This approach is particularly effective in HRV analysis, where entropy at different scales can reveal the balance between sympathetic and parasympathetic influences on the heart (Costa and Goldberger, 2015).

4 STATISTICAL ANALYSIS

To statistically analyze the differences between the control and PAD patients groups, we will employ a combination of bootstrap resampling and exponential curve fitting to the GMSE curve. This approach will allow us model the complexity and autonomic balance of heart rate variability measured by GMSE.

First, we will perform bootstrap resampling with replacement on the GMSE curves for both the control and PAD groups. This will generate multiple resampled GMSE curves for each group, allowing us to compute the average GMSE curve and assess the variability within each group.

For each average GMSE curve from the bootstrap resampling, we will then fit an exponential curve using the equation:

$$GMSE(\tau) = C \cdot \mathrm{e}^{-\kappa\tau}$$

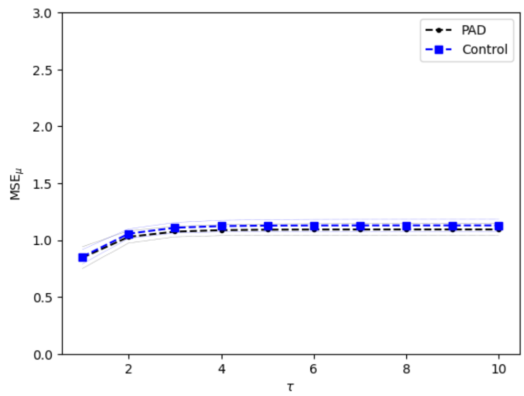
where C and κ are constants of the model determined by optimization methods. Whereas τ represents the different time scales.

This exponential curve fitting will allow us to extract the values of C_c and C_{pad} as well as κ_c and κ_{pad} for the control and PAD patient groups, respectively, from the bootstrap resampling process. We can then assess whether there are significant differences in these exponential model parameters between the two groups by comparing the distributions of the fitted model parameters obtained from the bootstrap resampling procedure.

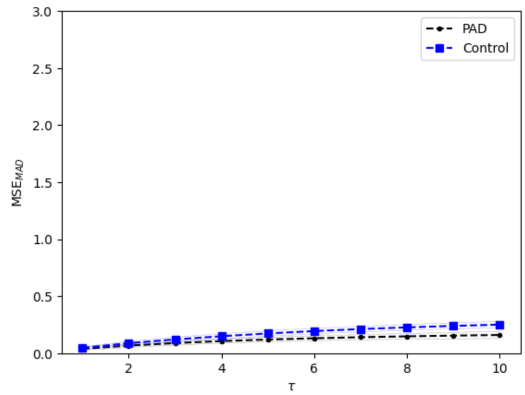
Specifically, this statistical analysis will provide insights into the underlying differences in the complexity and autonomic balance of heart rate variability between the healthy control subjects and the PAD patients. The exponential curve fitting and comparison of the model parameters between the groups can shed light on the specific alterations in the cardiovascular autonomic regulation associated with peripheral arterial disease, potentially leading to a better understanding of the disease and improved diagnostic or prognostic tools.

5 RESULTS

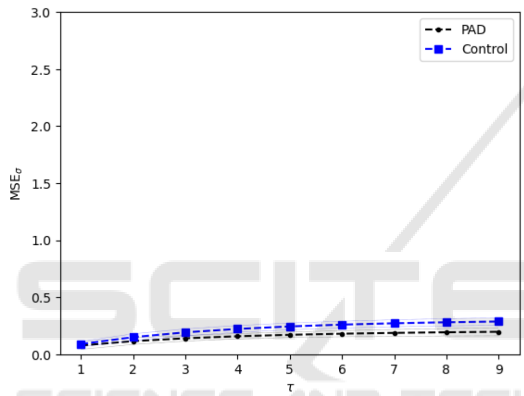
Figure 1 shows the average value and standard deviation of the GMSE curve obtained from the bootstrap resamplings for the different methods to build the coarse-grained time series, in particular, (a) using the average MSE_{μ}, (b) using the MAD MSE_{MAD}, (c) using the standard deviation MSE_{σ}, and (d) using the variance MSE_{σ^2}. From scale two, the curves are statistically different, showing that GMSE, with variance, is able to distinguish control subjects from PAD



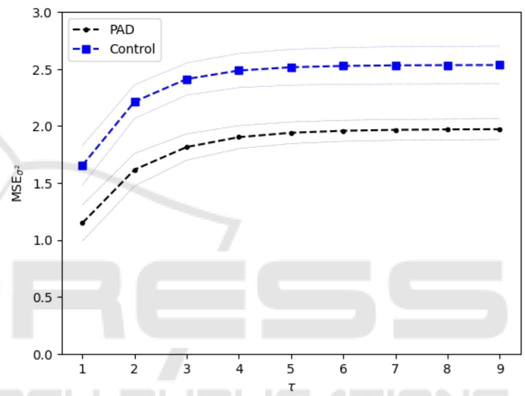
(a) GMSE average values for healthy subjects and PAD patients, using average to build coarse-grained time series.



(b) GMSE average values for healthy subjects and PAD patients, using MAD to build coarse-grained time series.



(c) GMSE average values for healthy subjects and PAD patients, using σ to build coarse-grained time series.



(d) GMSE average values for healthy subjects and PAD patients, using σ^2 to build coarse-grained time series.

Figure 1: GMSE comparison of methods to build the coarse-grained time series for healthy subjects (dots) and PAD patients (squares) with mean and standard deviation curves obtained from the bootstrap resampling.

patients. It is clear, that using the variance to create the coarse-grained time series allows to better distinguish healthy subjects and PAD patients.

Figure 2 shows the mean and standard deviation for the *C* parameter of the exponential model. Among the methods evaluated for constructing coarse-grained time series, only the σ^2 approach demonstrates sufficient discriminatory power to reliably differentiate between healthy individuals and PAD patients, yielding statistically significant differences.

6 CONCLUSIONS

The findings of this study provide significant insights into the autonomic dysfunction associated with PAD and its manifestation in patients with intermittent claudication. 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 (Cachadiña et al., 2018; Leicht et al., 2011; Sandercock et al., 2007; Lima et al., 2016).

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

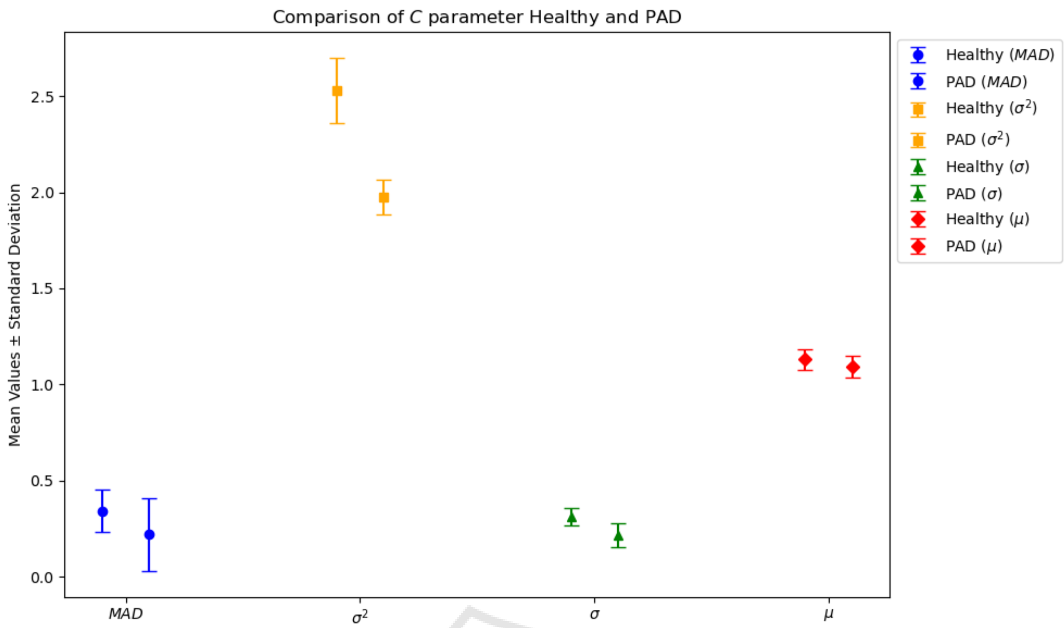


Figure 2: Mean and standard deviation for the *C* parameter of the exponential model for the different methods to build the coarse-grained time series in GMSE.

by utilizing a MSE approach to provide a more strong proof of these alterations. Moreover, among all the possible ways to build the coarse-grained time series in GMSE, the best option to be able to distinguish between healthy and PAD patients is using the σ^2. The results indicated a reduction in the complexity of HRV time series in PAD patients, which is in agreement with previous results.

The clinical implications of these findings are substantial. The ability to distinguish PAD patients from healthy individuals based on HRV complexity could help to the search 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 and explore the potential sex-based differences in the autonomic dysfunction associated with PAD. As a future work, it would be worth to compare these results with other multiscale entropy measures (Bari et al., 2014; Valencia et al., 2009)

In conclusion, this study demonstrates that GMSE analysis, using σ^2 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.

ACKNOWLEDGEMENTS

This work was partially funded by Grant PID2022-136887NB-I00 by MCIN/AEI/10.13039/501100011033.

REFERENCES

Aboyans, V., Criqui, M. H., Abraham, P., Allison, M. A., Creager, M. A., Diehm, C., Fowkes, F. G. R., Hiatt, W. R., Jönsson, B., Lacroix, P., Marin, B., McDermott, M. M., Norgren, L., Pande, R. L., Preux, P.-M., Stoffers, H. J., and Treat-Jacobson, D. (2012). Measurement and Interpretation of the Ankle-Brachial Index: A Scientific Statement From the American Heart Association. *Circulation*, 126(24):2890–2909.

Bari, V., Valencia, J. F., Vallverdú, M., Girardengo, G., Marchi, A., Bassani, T., Caminal, P., Cerutti, S., George, A. L., Brink, P. A., Crotti, L., Schwartz, P. J., and Porta, A. (2014). Multiscale Complexity Analysis of the Cardiac Control Identifies Asymptomatic and Symptomatic Patients in Long QT Syndrome Type 1. *PLoS ONE*, 9(4):e93808.

Cachadiña, E. S., De la Cruz Torres, B., Sánchez Sixto, A., Floria Martín, P., Berral de la Rosa, F. J., and

Naranjo Orellana, J. (2018). Heart Rate Variability is Lower in Patients with Intermittent Claudication: A Preliminary Study. *Archivos de medicina del deporte*, 35(186):218–221.

Camm, A. J., Malik, M., Bigger, J., Breithardt, G., Cerutti, S., Cohen, R. J., Coumel, P., Fallen, E. L., Kennedy, H. L., Kleiger, R. E., et al. (1996). Heart Rate Variability: Standards of Measurement, Physiological Interpretation and Clinical Use. *Circulation*, 93(5):1043–1065.

Celis, R., Pipinos, I. I., Scott-Pandorf, M. M., Myers, S. A., Stergiou, N., and Johanning, J. M. (2009). Peripheral Arterial Disease Affects Kinematics during Walking. *Journal of Vascular Surgery*, 49(1):127–132.

Chidean, M. I., Barquero-Pérez, O., Goya-Esteban, R., Sánchez Sixto, A., De La Cruz Torres, B., Naranjo Orellana, J., Sarabia Cachadiña, E., and Caamaño, A. J. (2018). Full Band Spectra Analysis of Gait Acceleration Signals for Peripheral Arterial Disease Patients. *Frontiers in Physiology*, 9:1061.

Costa, M. and Goldberger, A. (2015). Generalized Multiscale Entropy Analysis: Application to Quantifying the Complex Volatility of Human Heartbeat Time Series. *Entropy*, 17(3):1197–1203.

Costa, M., Goldberger, A. L., and Peng, C.-K. (2005). Multiscale Entropy Analysis of Biological Signals. *Physical Review E*, 71(2):021906.

Crowther, R. G., Spinks, W. L., Leicht, A. S., Quigley, F., and Golledge, J. (2007). Relationship between Temporal-Spatial Gait Parameters, Gait Kinematics, Walking Performance, Exercise Capacity, and Physical Activity Level in Peripheral Arterial Disease. *Journal of Vascular Surgery*, 45(6):1172–1178.

Diehm, C., Allenberg, J. R., Pittrow, D., Mahn, M., Tepohl, G., Haberl, R. L., Darius, H., Burghaus, I., and Trampisch, H. J. (2009). Mortality and Vascular Morbidity in Older Adults With Asymptomatic Versus Symptomatic Peripheral Artery Disease. *Circulation*, 120(21):2053–2061.

Feinglass, J., McCarthy, W. J., Slavensky, R., Manheim, L. M., Martin, G. J., and the Chicago Claudication Outcomes Research Group (1996). Effect of Lower Extremity Blood Pressure on Physical Functioning in Patients who Have Intermittent Claudication. *Journal of Vascular Surgery*, 24(4):503–512.

Leicht, A. S., Crowther, R. G., and Golledge, J. (2011). Influence of Peripheral Arterial Disease and Supervised Walking on Heart Rate Variability. *Journal of Vascular Surgery*, 54(5):1352–1359.

Lima, A., Soares, A., Cucato, G., Leicht, A., Franco, F., Wolosker, N., and Ritti-Dias, R. (2016). Walking Capacity Is Positively Related with Heart Rate Variability in Symptomatic Peripheral Artery Disease. *European Journal of Vascular and Endovascular Surgery*, 52(1):82–89.

Martins, A., Pernice, R., Amado, C., Rocha, A. P., Silva, M. E., Javorka, M., and Faes, L. (2020). Multivariate and Multiscale Complexity of Long-Range Correlated Cardiovascular and Respiratory Variability Series. *Entropy*, 22(3):315.

Ramos, R., Quesada, M., Solanas, P., Subirana, I., Sala, J., Vila, J., Masiá, R., Cerezo, C., Elosua, R., Grau, M., Cordón, F., Juvinyà, D., Fitó, M., Isabel Covas, M., Clarà, A., Ángel Muñoz, M., and Marrugat, J. (2009). Prevalence of Symptomatic and Asymptomatic Peripheral Arterial Disease and the Value of the Ankle-brachial Index to Stratify Cardiovascular Risk. *European Journal of Vascular and Endovascular Surgery*, 38(3):305–311.

Richman, J. S. and Moorman, J. R. (2000). Physiological Time-Series Analysis Using Approximate Entropy and Sample Entropy. *American Journal of Physiology-Heart and Circulatory Physiology*, 278(6):H2039–H2049.

Sandercock, G. R. H., Hodges, L. D., Das, S. K., and Brodie, D. A. (2007). The Impact of Short Term Supervised and Home-Based Walking Programmes on Heart Rate Variability in Patients with Peripheral Arterial D. *Journal of Sports Science and Medicine*, (6):471–476.

Schroll, M. and Munck, O. (1981). Estimation of Peripheral Arteriosclerotic Disease by Ankle Blood Pressure Measurements in a Population Study of 60-Year-Old Men and Women. *Journal of Chronic Diseases*, 34(6):261–269.

Shaffer, F. and Ginsberg, J. P. (2017). An Overview of Heart Rate Variability Metrics and Norms. *Frontiers in Public Health*, 5:258.

Silva, L. E. V., Cabella, B. C. T., Neves, U. P. D. C., and Murta Junior, L. O. (2015). Multiscale entropy-based methods for heart rate variability complexity analysis. *Physica A: Statistical Mechanics and its Applications*, 422:143–152.

Valencia, J. F., Porta, A., Vallverdu, M., Claria, F., Baranowski, R., Orlowska-Baranowska, E., and Caminal, P. (2009). Refined Multiscale Entropy: Application to 24-h Holter Recordings of Heart Period Variability in Healthy and Aortic Stenosis Subjects. *IEEE Transactions on Biomedical Engineering*, 56(9):2202–2213.