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IOP Publishing Physiol. Meas. 44 (2023) 035004 https://doi.org/10.1088/1361-6579/acbc07

Physiological Measurement

IPEM Institute of Physics and Engineering in Medicine

OPEN ACCESS

RECEIVED
15 November 2022

REVISED
1 February 2023

ACCEPTED FOR PUBLICATION
14 February 2023

PUBLISHED
8 March 2023

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PAPER

Characterization of autonomic states by complex sympathetic and parasympathetic dynamics*

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Keywords: autonomic nervous system, heart rate variability (HRV), parasympathetic activity index, sympathetic activity index, sympathovagal balance, congestive heart failure (CHF), entropy

Abstract

Assessment of heartbeat dynamics provides a promising framework for non-invasive monitoring of cardiovascular and autonomic states. Nevertheless, the non-specificity of such measurements among clinical populations and healthy conditions associated with different autonomic states severely limits their applicability and exploitation in naturalistic conditions. This limitation arises especially when pathological or postural change-related sympathetic hyperactivity is compared to autonomic changes across age and experimental conditions. In this frame, we investigate the intrinsic irregularity and complexity of cardiac sympathetic and vagal activity series in different populations, which are associated with different cardiac autonomic dynamics. Sample entropy, fuzzy entropy, and distribution entropy are calculated on the recently proposed sympathetic and parasympathetic activity indices (SAI and PAI) series, which are derived from publicly available heartbeat series of congestive heart failure patients, elderly and young subjects watching a movie in the supine position, and healthy subjects undergoing slow postural changes. Results show statistically significant differences between pathological/old subjects and young subjects in the resting state and during slow tilt, with interesting trends in SAI- and PAI-related entropy values. Moreover, while CHF patients and healthy subjects in upright position show the higher cardiac sympathetic activity, elderly and young subjects in resting state showed higher vagal activity. We conclude that quantification of intrinsic cardiac complexity from sympathetic and vagal dynamics may provide new physiology insights and improve on the non-specificity of heartbeat-derived biomarkers.

1. Introduction

Dysfunction in autonomic nervous system (ANS) dynamics is a major marker of cardiovascular risk, including mortality. Congestive heart failure (CHF) and hypertension are characterized by sympathetic hyperactivity (Lanfranchi *et al* 1998). Any therapy that chronically stimulates sympathetic tone and/or decreases parasympathetic activity can increase the risk of cardiac events, especially in patients with cardiovascular diseases (Curtis and O'Keefe 2002). Therefore, in recent decades, the relationship between autonomic dynamics and cardiovascular health has been deeply investigated, and clinicians have developed a strong awareness of the importance of non-invasive monitoring of heart rate variability (HRV) as a crucial diagnostic and prognostic tool.

There is a large plethora of features that can be extracted from HRV time series, from standard statistical metrics and frequency domain analysis, to the study of complex cardiovascular dynamics through methodologies based on chaos theory (Acharya *et al* 2006, Shaffer and Ginsberg 2017, Castiglioni *et al* 2020). In

* Work partially supported by the Italian Ministry of Education and Research (MIUR) in the framework of the FoReLab project (Departments of Excellence).

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particular, the latter has been considered a way to uncover the nonlinear dynamics derived from the interplay between sympathetic and parasympathetic nervous systems, as well as between through interaction with central nervous system, occurring at different temporal and spatial levels (Sunagawa *et al* 1998, Captur *et al* 2017, Valenza *et al* 2018a, 2020).

Looking at the literature, changes in complexity of heartbeat dynamics in the phase space have been hypothesized to be associated with aging and several cardiovascular dysfunctions (Goldberger *et al* 2002, Marmarelis 2004), e.g. sudden cardiac death (Mäkikallio *et al* 2001, Schulte-Frohlinde *et al* 2002, Glass 2009), ventricular and atrial fibrillations (Mäkikallio *et al* 1999, Corino *et al* 2006), congestive heart failure (Sassi *et al* 2009). However, despite the proven discriminative power of these techniques, their use in clinical settings is hampered by the lack of precise physiological correlates and specificity issues. In fact, the relationship between heartbeat metrics extracted through nonlinear analysis and the fluctuations in sympathetic and vagal tone underlying these dynamics are still unknown. Previous studies have performed complexity analyses of cardiovascular oscillations during a selective pharmacological blockade paradigm to understand whether changes in the extracted metrics were sympathetic- or vagal-driven (Berntson *et al* 1994, Beckers *et al* 2006). A major vagal involvement in regulating complex cardiovascular dynamics was hypothesized, given that a decrease in the fractal properties of the heartbeat series was reported after atropine administration (Tulppo *et al* 2001, Beckers *et al* 2006, Bolea *et al* 2014). Even if interesting, these findings can be misleading because a relevant theoretical issue is based on selective blockade paradigms: the effects of phasic autonomic modulation on heartbeat dynamics are considered additive. Features that can be extracted from HRV series lack of specificity for a particular physiological or pathological condition, leading to misinterpretation of the results for a particular individual and consequent non applicability in actual clinical setting (Saul and Valenza 2021). To illustrate, while a postural change in healthy humans leads to reproducible variations in the LF and HF powers, various types of physical and mental stress and cardiac conditions such as CHF can reasonably lead to similar changes in HRV power (Saul and Valenza 2021).

To disentangle the unique contribution of each autonomic branch in heartbeat oscillations, we recently proposed the sympathetic activity index (SAI) and the parasympathetic activity index (PAI) (Valenza *et al* 2018b). The calculation of these indices overcomes the limitations of standard spectral analysis of HRV based on the study of two main frequency bands, i.e. the low-frequency band (LF, from 0.04 Hz to 0.15 Hz) and the high-frequency band (HF, from 0.15 Hz to 0.4 Hz) (Malik 1996). In fact, if vagal activity strongly affects HF power, there is no clear relationship between the spectral indices and the phasic autonomic modulation of heart rate. Although sympathetic tasks often are associated with significant changes in LF power, it has been demonstrated that both autonomic branches can influence the magnitude of the spectrum in this band (Goldstein *et al* 2011, Billman 2013, Valenza *et al* 2018b). SAI and PAI rely on a proper weighted sum of primitives, defined from the discrete-time orthonormal Laguerre bases spanning the frequency domain. After convolving the Laguerre bases with the inter-beat (RR) interval series, an autoregressive model is identified without the need for a calibration procedure at a single subject level.

Aiming to overcome non-specificity issues in heartbeat dynamics analysis among clinical and normal populations, in this study we investigate changes in well-known entropy metrics extracted from time-varying SAI and PAI indices of healthy and pathological subjects referring to peculiar ANS conditions. We used three entropy algorithms, namely, sample entropy (SampEn) (Richman *et al* 2000), fuzzy entropy (FuzzyEn) (Chen *et al* 2007), and distribution entropy (DistEn) (Li *et al* 2015) to investigate the irregularity and complexity of cardiac sympathetic and vagal dynamics. To this end, we used three publicly available databases of cardiovascular signals gathered from Physionet (Goldberger *et al* 2000): the congestive heart failure (CHF) database (Baim *et al* 1986), the Fantasia dataset (Iyengar *et al* 1996), and the postural change dataset (Heldt *et al* 2003). Group-wise statistical differences were investigated in intrinsic sympathetic and vagal entropy values among patients with CHF, elderly and young subjects in the resting state, and young subjects undergoing a head-up tilt-table test.

2. Materials and methods

2.1. Experimental protocols

All three datasets used in this study were retrieved from the publicly-available Physionet repository (http://www.physionet.org/) (Goldberger *et al* 2000). More details regarding each dataset are provided below.

2.1.1. Congestive heart failure (CHF) database

The first dataset used in this study includes ECG signals from the BIDMC Congestive Heart Failure Database (Baim *et al* 1986). This database collects 15 long-term ECG recordings from 15 subjects (11 men, aged 22 to 71, and 4 women, aged 54 to 63) with severe congestive heart failure (NYHA class 3–4). Patient monitoring was

performed at Boston Beth Israel Hospital at a sampling rate of 250 Hz. After the first signal quality by visual inspection, we used 1-hour ECG signals from 13 subjects for further evaluations.

2.1.2. Fantasia dataset

The second dataset used in this study is the Fantasia database, the details of which are reported in (Iyengar *et al* 1996). This database includes autonomic signals from 20 young healthy subjects (10 females, 21-34 years) and 20 healthy elderly subjects (10 females, 68-85 years), who were monitored for 120 minutes in the supine position while watching the movie 'Fantasia' (Disney movie, 1940). The ECG signals were sampled at 250 Hz, the heartbeats were annotated using an automated arrhythmia detection algorithm, and each beat annotation was verified by visual inspection. For our analyses, we used 20 signals from 10 young and 10 elderly participants.

2.1.3. Physiological response to changes in posture dataset

The experimental protocol was based on sympathetic elicitation through a head-up tilt table test (Heldt *et al* 2003). Ten healthy volunteers (five males, aged 28.7± 1.2) provided informed consent to participate in the experiment. The study was carried out at the MIT General Clinical Research Center, and the experimental protocol was approved by the Advisory Board of the MIT-MGH General Clinical Research Center and MIT's Committee on the Use of Humans as experimental subjects. None of the participants showed signs of cardiovascular disease. The experimental protocol included six postural changes lasting three minutes: two stand-ups, two rapid head-up tilts, and two slow head-up tilts, administered in a randomized order across subjects, using a tilt table. Five minutes of the supine resting state preceded each postural change session. In this study, we investigated the first two-minutes of slow-tilt sessions and the last two minutes of the preceding resting-state sessions. During the entire duration of the experiment, single-lead ECG signals were continuously acquired using a BIOPAC MP System.

2.2. Sympathetic and parasympathetic activity indices

To automatically detect R-peaks from the ECG series included in the three datasets used in this study, we applied the Pan-Tompkins algorithm (Pan *et al* 1985). Our automated point process-based method was then used to detect and correct possible erroneous and ectopic heartbeats (Citi *et al* 2012).

Once the artifact-free HRV series was obtained, we estimated the SAI and PAI series following the procedure described in (Valenza *et al* 2018b).

As a first step, the jth-order discrete-time orthonormal Laguerre function $\phi_j(n, \alpha)$ was convolved with the RR series, as follows:

$$\ell_j(k) = \sum_{n=0}^{k-1} \phi_j(n, \alpha) RR(k - n - 1) \tag{1}$$

The jth-order discrete-time orthonormal Laguerre function $\phi_j(n, \alpha)$ was defined as:

$$\phi_j(n) = \alpha^{\frac{n-j}{2}}(1 - \alpha)^{\frac{1}{2}} \sum_{i=0}^{j} (-1)^i \binom{n}{i} \binom{j}{i} \alpha^{j-i}(1 - \alpha)^i \tag{2}$$

where α is the constant of decay, belonging to the range $0 < \alpha < 1$, and $n \geqslant 0$.

Then, we defined the following autoregressive model:

$$\mu_{RR}(k, \mathcal{H}_k, \xi(k)) = g_0(k) + \underbrace{\sum_{j=0}^{P_{\text{symp}}} g_{1,j}(k) l_j(k)}_{\text{Sympathetic}} + \underbrace{\sum_{j=P_{\text{Symp}}+1}^{P_{\text{ParSymp}}} g_{1,j}(k) l_j(k)}_{\text{Parasympathetic}} \tag{3}$$

where $\mathcal{H}_k = (u_k, \text{RR}_k, \text{RR}_{k-1}, \ldots, \text{RR}_{k-K+1})$ indicates the history of all the RR intervals before the kth and $\xi(t) = \{g_0(k), g_{1,0}(k), \ldots, g_{1,j}(k)\}$ is the vector containing the time-varying Laguerre coefficients. We use equation (3) as the observation model of a linear dynamic system with state transition model given by a random walk of the unknown time-varying Laguerre coefficients:

$$\begin{aligned} \boldsymbol{\xi}(k) &= \boldsymbol{\xi}(k - 1) + \varepsilon_{\boldsymbol{\xi}}(k) \\ RR(k) &= g_0(k) + \ell(k)^{\top} \boldsymbol{\xi}(k) + \varepsilon_{RR}(k) \end{aligned} \tag{4}$$

where $\varepsilon_{\boldsymbol{\xi}}(k)$ is the state noise and $\varepsilon_{RR}(k)$ is the observation noise. Finally, the disentangling Laguerre coefficients, Ψ_S and Ψ_P, are used to define the values of SAI and PAI metrics, as follows (Valenza *et al* 2018c):

$$SAI(k,\,\xi(k)) = \left[\Psi_{S_0} + \sum_{j=1}^{N_1} \Psi_{S_j} g_{1,j-1}(k)\right] / RR(k)^2 \tag{5}$$

$$PAI(k,\,\xi(k)) = \left[\Psi_{P_0} + \sum_{j=1}^{N_2} \Psi_{P_j} g_{1,j+1}(k)\right] 2RR(k) \tag{6}$$

A multiple regression analysis on physiological data acquired during postural changes with selective autonomic blockade was used to estimate Ψ_{S_0} and Ψ_{P_0} (see details in (Valenza *et al* 2018b)).

2.3. Entropy measures

In this study, the nonlinear dynamics of the beat-to-beat SAI, PAI time series were analyzed using three well-known measures of entropy: SampEn, FuzzyEn, and DistEn. The first two measures, SampEn and FuzzyEn, were used to assess the irregularity of the time series, whereas DistEn was based on the estimation of the spatial complexity of the attractor in the phase space.

The first step was common to the three metrics: the phase space of the SAI, PAI time-varying series was reconstructed by setting the embedding dimension and time delay to $m = 2$, and $\tau = 1$. Starting from a time series $[u(i), u(i+1),\ldots,u(N)]$ of N samples, we construct $N - m + 1$ embedded vectors in a phase space of dimension m, defined as $x(i) = [u(i), u(i+1),\ldots,u(i+m-1)]$. In our case, points $x(i)$ constitute the trajectories described by the SAI or PAI dynamics.

2.3.1. Sample entropy (SampEn)

The procedure described in (Richman *et al* 2000, Lake *et al* 2002) was used to compute SampEn.

Considering each pair of vectors x_i and x_j in the phase space, the Chebyshev distance $d_{i,j}$ is computed by excluding self-matches ($i = j$). Then, $C^m(r)$, i.e. the probability that two vectors x_i and x_j of m coordinates will match, was estimated as follows:

$$C^m(r) = \frac{1}{N-m}\sum_{i=1}^{N-m}\left(\frac{1}{N-m-1}\sum_{i=1,i\neq j}^{N-m}\mathcal{O}(r - d_{i,j})\right) \tag{7}$$

where $\mathcal{O}$ is the Heaviside function. The parameter r represents the margin of tolerance used to compare the distance values between the vectors, and is usually chosen between 10-25% of the time series standard deviation (Castiglioni and Rienzo 2008). In this study, we set r equal to the 20% of the standard deviation of each series. The embedding dimension was then increased from m to $m + 1$, and $C^{m+1}(r)$ was calculated. Finally, the SampEn value was found as the negative natural logarithm of the conditional probability that two sequences similar for m points remain similar for $m + 1$ points (without self-comparisons), as follows:

$$\mathrm{SampEn(m,\ r,\ N)} = -\ln\frac{C^{m+1}}{C^m} \tag{8}$$

2.3.2. Fuzzy entropy (FuzzyEn)

Given that in the real physical world, the imposition of clear boundaries can lead to ambiguous results, the FuzzyEn algorithm uses a fuzzy function Γ to replace the Heaviside function $\mathcal{O}$, as the main novelty with respect to SampEn (Chen *et al* 2007). This Γ function assigns a membership degree to the Chebyshev distance value ($d_{i,j}$) between each pair of vectors in phase space. The higher the membership degree, the closer the value of Γ is to unity, and the closer the vectors are in the phase space. In this study, Γ function was defined as follows (Azami *et al* 2017, Nardelli *et al* 2019):

$$\Gamma(d_{i,j},\,n,\,r) = e^{-d_{i,j}^{f_p}/r} \tag{9}$$

where f_p is the power of the fuzzy function, which we set to 2 in accordance with previous evidence (Azami *et al* 2017, Nardelli *et al* 2019, Scarciglia *et al* 2022), and r was set to 20% of the standard deviation of the time series, as in the SampEn computation. In the remaining part, the algorithm for the calculation of FuzzyEn follows the steps described above for SampEn.

2.3.3. Distribution entropy (DistEn)

The DistEn algorithm investigates the probability distribution of the intervector distances without the need for a preliminary estimation of the parameter r (Karmakar *et al* 2015, Li *et al* 2015, Nardelli *et al* 2019). Specifically, following the procedure described in (Li *et al* 2015), all Chebyshev distances d_{ij} among all pairs of embedded vectors in the phase space were computed without considering self-comparisons. Then, the related empirical probability distribution was studied using the histogram approach. The number of bins B was set to 512 as suggested in previous studies (Li *et al* 2015, Shi *et al* 2019). In the case of the postural change dataset, we used

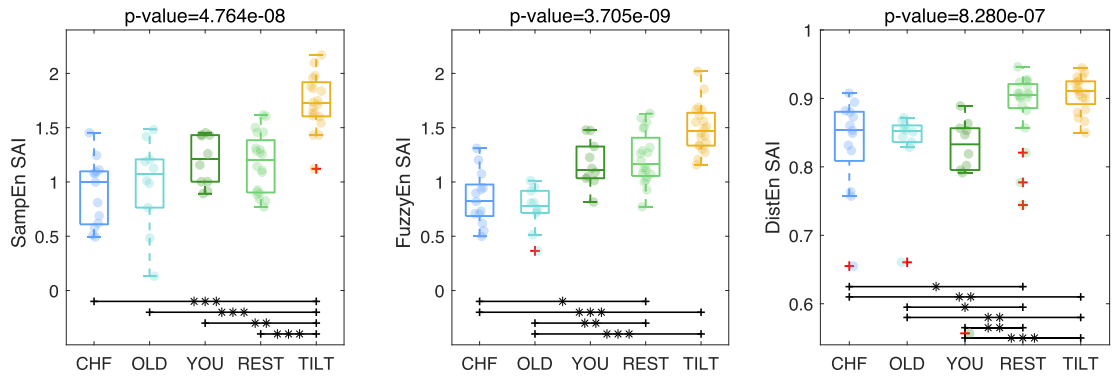

Figure 1. Group-wise statistics for SampEn, FuzzyEn, and DistEn computed on SAI series acquired from the five groups (CHF = congestive heart failure patients, OLD = elderly healthy subjects in resting state watching Fantasia movie, YOU = young healthy subjects in resting state watching Fantasia movie, REST: healthy subjects in resting state session during head-up tilt-table test, TILT: healthy subjects during slow-tilt). The p-values reported on the top are refereed to Kruskal-Wallis test. One asterisk (*) indicates a p-value lower than 0.05, two asterisks (**) indicate a p-value lower than 0.01, and three asterisks (***) indicate a p-value less than 0.001 from the Mann-Whitney test after Bonferroni correction.

$B = 256$, according to our previous study on ultra-short series (Nardelli *et al* 2019). Considering p_b as the probability value associated with each bin b ($b = 1,...,B$), i.e. $p_b = \frac{\text{count in bin b}}{\text{total number of distances } d_{ij}}$, DistEn is computed using the Shannon entropy formula as follows:

$$DistEn(m,\ B) = -\frac{1}{\log_2(B)}\sum_{t=1}^{B} p_b \log_2(p_b) \tag{10}$$

Note that DistEn shows normalized values in the range [0, 1] since the Shannon Entropy formula is normalized by the factor $\log_2(B)$ (Li *et al* 2015).

2.4. Statistical analysis and multivariate linear regression analysis

Considering SampEn, FuzzyEn, and DistEn metrics, the Kruskal-Wallis non-parametric statistical test was used to statistically compare group-wise medians for the SAI and PAI in the following five experimental groups: CHF patients, elderly Fantasia subjects, young Fantasia subjects, healthy subjects during tilt-table resting state sessions, and healthy subjects during slow-tilt sessions. The use of non-parametric tests was justified by the non-Gaussian distribution of the samples ($p < 0.05$ from the Shapiro-Wilk test). In the post-hoc analysis, we compared the entropy values of each pair of experimental groups using the Mann-Whitney test. The Bonferroni procedure for multiple-comparison correction was applied by multiplying the Mann-Whitney p-values by the number of pairwise comparisons.

In order to evaluate the role of sympathetic and vagal dynamics and its complexity in predicting mean RR interval, we performed a multivariate linear regression analysis considering two sets of predictors:

(1) SAI, PAI, SampEn-SAI, SampEn-PAI

(2) SAI, PAI

The SAI and PAI information in time has been averaged, obtaining one sample per subject. Each regression is evaluated through R^2 statistic, adjusted R^2 statistic, the F-statistic and its p-value, and an estimate of the error variance. The likelihood ratio test is used to evaluate statistical differences between the models, considering that the difference in log-likelihood between models follow a one degree-of-freedom chi-square distribution.

3. Results

Figure 1 shows group-wise statistics of SampEn, FuzzyEn, and DistEn computed for the SAI series of the five experimental groups considered in this study. After applying the Kruskal-Wallis non-parametric test, we found significant statistical differences among the groups using all three entropy algorithms ($p < 10^{-6}$, see figure 1). Concerning the results obtained through the Mann-Whitney test during the post-hoc analysis, we found that the group of healthy subjects who underwent slow-tilt sessions presented values of SampEn extracted from the SAI series significantly different from those of the other groups, with higher median values. Using FuzzyEn computed on the SAI series, we were able to distinguish both groups taken from the postural change dataset from CHF patients and elderly subjects in the Fantasia database. In this case, the sympathetic index series of CHF

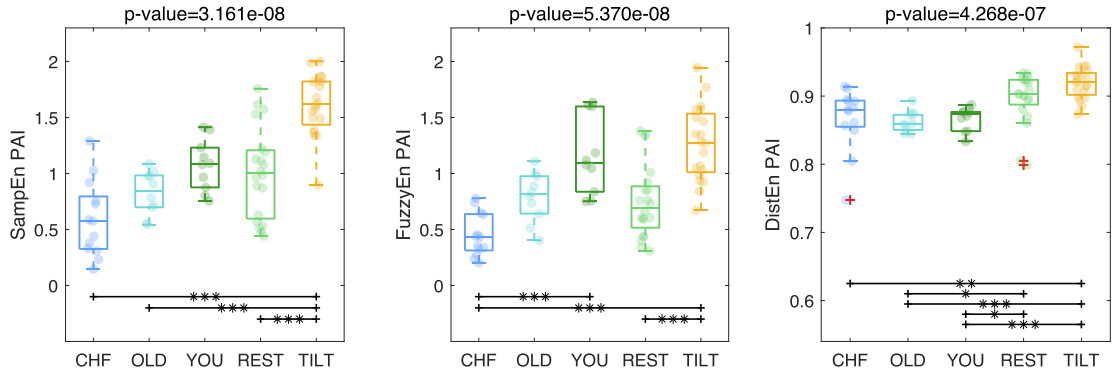

Figure 2. Group-wise statistics for SampEn, FuzzyEn, and DistEn computed on PAI series acquired from the five groups (CHF = congestive heart failure patients, OLD = elderly healthy subjects in resting state watching Fantasia movie, YOU = young healthy subjects in resting state watching Fantasia movie, REST: healthy subjects in resting state session during head-up tilt-table test, TILT: healthy subjects during slow-tilt). The p-values reported on the top are refereed to Kruskal-Wallis test. One asterisk (*) indicates a p-value lower than 0.05, two asterisks (**) indicate a p-value lower than 0.01, and three asterisks (***) indicate a p-value less than 0.001 from the Mann-Whitney test after Bonferroni correction.

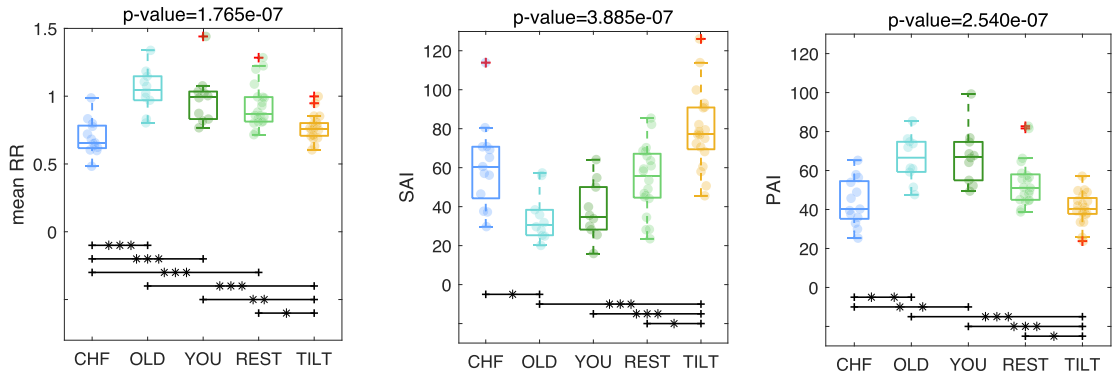

Figure 3. Group-wise statistics for the mean values of RR, SAI and PAI series acquired from the five groups (CHF = congestive heart failure patients, OLD = elderly healthy subjects in resting state watching Fantasia movie, YOU = young healthy subjects in resting state watching Fantasia movie, REST: healthy subjects in resting state session during head-up tilt-table test, TILT: healthy subjects during slow-tilt). The p-values reported on the top are refereed to Kruskal-Wallis test. One asterisk (*) indicates a p-value lower than 0.05, two asterisks (**) indicate a p-value lower than 0.01, and three asterisks (***) indicate a p-value less than 0.001 from the Mann-Whitney test after Bonferroni correction.

and elderly subjects was more predictable than the corresponding series of young subjects during the tilt table experiment. When the complexity of sympathetic dynamics was quantified through DistEn, we found that CHF and elderly subjects presented statistically different and lower values with respect to young subjects in the fantasia and postural change datasets.

In figure 2 we report the results of the statistical analysis computed on the entropy indexes extracted from the PAI series. The Kruskal-Wallis test yielded significant results for all three metrics ($p < 10^{-6}$). Concerning SampEn, vagal dynamics were more irregular in the slow-tilt sessions than in CHF patients, elderly subjects, and the preceding resting-state sessions ($p < 0.001$ after Mann-Whitney n test). Using FuzzyEn, patients with CHF presented significantly lower median values than young subjects during rest and slow tilt. Post-hoc analysis of DistEn values of the PAI series yielded the same results obtained for the SAI series in terms of pairs of groups that were significantly different. The only difference was that patients with CHF and healthy subjects during the resting sessions in the tilt protocol were not statistically discernible. Figure 3 shows the statistical results obtained after the application of Kruskal-Wallis and Mann-Whitney tests on the mean values of the RR series, and SAI and PAI series extracted from each of the five datasets. The mean values of RR series acquired from the CHF patients and young subjects during the tilt table test were significantly lower than the mean values of the RR series acquired during the resting state sessions in supine position recorded before the postural changes, and during the Fantasia experimental protocol for both young and elderly subjects. While SAI showed higher values in CHF patients and slow-tilt sessions, PAI was lower in CHF and slow-tilt groups with respect to Fantasia groups and subjects in supine resting position. For both SAI and PAI, a significant statistical difference was

observed between CHF and elderly Fantasia subjects and between the group of healthy subjects during the slow tilt when compared to the supine position sessions in resting state and to the two groups belonging to Fantasia dataset. Furthermore, the mean values of PAI were statistically different between CHF and young subjects.

The multiple linear regression analysis for the feature set 1) comprising {SAI, PAI, SampEn-SAI, SampEn-PAI} showed an $R^2 = 0.772$, adjusted $R^2 = 0.7587$, $F = 57.59$ ($p < 10^{-6}$), and error variance of 0.0085. The multiple linear regression analysis for the feature set 2) comprising {SAI, PAI} showed an $R^2 = 0.7068$, adjusted $R^2 = 0.6985$, $F = 84.3884$ ($p < 10^{-6}$), and error variance of 0.0107. The likelihood ratio test shows differences between models with $p < 10^{-6}$.

4. Discussion

This study reports the investigation of complex sympathetic and vagal dynamics in healthy and pathological subjects. Three entropy metrics were extracted from the recently proposed time-varying SAI and PAI (Valenza *et al* 2018b, 2018c), which overcome the limitations of standard spectral analysis and provide more reliable measures of phasic autonomic modulation of heart rate. The irregularities of the SAI and PAI dynamics were quantified using two well-known algorithms: SampEn (Richman *et al* 2000) and FuzzyEn (Chen *et al* 2007). Changes in the spatial complexity of the trajectories in phase space were investigated using DistEn (Karmakar *et al* 2015, Li *et al* 2015). While SampEn and FuzzyEn quantify the conditional probability that two vectors in the phase space remain close by increasing the embedding dimension, DistEn studies the probability distribution of all inter-vector distances.

Three datasets were retrieved from the publicly available repository Physionet (Goldberger *et al* 2000) and five different groups of subjects were studied: patients affected by CHF (Baim *et al* 1986), elderly subjects in supine position watching a movie, young subjects in supine position watching a movie, young subjects during resting state in supine position, and young subjects during slow-tilt. We reported an ascending trend of irregularity measures, especially in SAI and PAI dynamics, going from CHF patients to young healthy subjects undergoing passive postural changes, passing through healthy subjects in old age (see SampEn and FuzzyEn boxplots in figures 1, 2). Specifically, when we used SampEn, we were able to statistically discern short-term autonomic modulation elicited during the slow-tilt sessions from other subjects in the resting state, whereas with FuzzyEn, we were also able to distinguish more predictable SAI dynamics in patients with CHF and elderly subjects with respect to young subjects in the resting state. Concerning vagal dynamics, patients with CHF also presented significantly lower FuzzyEn values than the young subjects. If we consider the DistEn results, both sympathetic and vagal dynamics of subjects undergoing postural changes were significantly more complex than the corresponding dynamics in pathological and elderly subjects. Note that such entropy and complexity metrics may be modulated not only by the amplitude range of the series, but also by its temporal and spatial evolution. Accordingly, a heartbeat time series with smaller amplitude on average may be associated with a greater irregularity or complexity (i.e, greater entropy). Indeed, while sympathetic (vagal) activity increases (decreases) during tilt with respect to a previous resting state, tilt-related activity of both autonomic branches show more irregular and/or complex dynamics.

The multiple linear regression analysis confirms that sympathetic and vagal activity, as estimated through SAI and PAI, as well as the intrinsic SAI and PAI complexity, are fundamental predictors of the mean RR interval.

Patients with CHF are known to have higher sympathetic activity than controls (Hasking *et al* 1986, Kaye *et al* 1995, Lanfranchi *et al* 1998, Curtis and O'Keefe 2002, Valenza *et al* 2018c). However, several previous studies have provided HRV-derived markers to distinguish patients with CHF from healthy subjects, e.g. significantly lower LF and HF powers (Malik 1996, Van De Borne *et al* 1997, Guzzetti *et al* 2000, Acharya *et al* 2006). Through speculation, these changes have been associated with specific pathophysiological mechanisms, such as central autonomic impairment (Van De Borne *et al* 1997), low responsiveness of the failing heart to sympathetic modulation (Bristow *et al* 1982) and augmented chemoreceptor sensitivity (Ponikowski *et al* 1997). Applying SAI and PAI indices, we were able to identify the activity of the two main ANS branches in patients with CHF, finding augmented SAI and reduced PAI values, and confirmed the sympathetic hyperactivity (Valenza *et al* 2018c). In the field of nonlinear metrics, CHF disease is characterized by a breakdown of physiological fractal correlations and an overall decrease in the complexity of heartbeat dynamics (Woo *et al* 1992, Butler *et al* 1997, Ho *et al* 1997, Guzzetti *et al* 2000, Costa *et al* 2002, Wang *et al* 2018). A similar loss of information and complexity was found in the heartbeat dynamics of elderly subjects when compared to young subjects (Costa *et al* 2002), but also in healthy subjects during passive upright postural changes with respect to the resting state in the supine position (Porta *et al* 2001, Heldt *et al* 2003, Valenza *et al* 2014, Nardelli *et al* 2019).

Finally, if we consider the groups of CHF, elderly, and young subjects in the resting state, the PAI results are in agreement with previous knowledge about the loss of predictability in neurophysiological dynamics from

pathological to healthy young subjects (see figure 2). However, in the comparison between pathological and healthy subjects, we could hypothesize a direct relationship between vagal activity entropy and heartbeat entropy values; the additional increase in irregularity during slow-tilt sessions showed the opposite behavior.

4.1. Conclusion and future works

Our promising findings show the potential diagnostic power of entropy and complexity assessment applied to SAI and PAI measurements for the clinical monitoring of ANS dynamics, despite cardiac autonomic non-specificity. Compared to all the standard and nonlinear HRV features proposed in the literature, they offer the advantage of presenting monotonic-like trend that allows distinguishing anomalous autonomic modulation due to a pathological state or age from a response to passive stimulation in a healthy condition. In this regards, our approach complements current non-invasive state-of-the-art measurements of autonomic control on heartbeat dynamics. Future studies will be directed towards the investigation of autonomic complexity through the search for optimal parameters (e.g. m, τ, r, and B), as well as towards the application of these methodologies to other datasets related to different cardiovascular pathologies and experimental setups, also in comparison with further complexity measurements (Nardelli *et al* 2019, Scarciglia *et al* 2022).

Data availability statement

The data that support the findings of this study are openly available at the following URL/DOI: https://physionet.org/content/prcp/1.0.0/. Data will be available from 30 January 2023.

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