Heart Rate Variability Differentiates Between Vasovagal Syncope and Palpitation Related Fainting

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Abstract

Vasovagal syncope is a transient loss of consciousness, which can occur due to neurological, metabolic, psychiatric, and cardiac causes. Palpitations are characterized by abnormally rapid or irregular heartbeats and in some cases fainting. Determination of cause may be undertaken by patient history and physical examination including an ECG and head-up tilt testing (HUTT). However, HUTT bears some risks such as fainting and arrhythmia in syncope patients as well as being uncomfortable and unable to distinguish between palpitations and vasovagal syncope.

Alternative diagnostic tools are therefore of interest and this work examines the usefulness of Heart Rate Variability (HRV) obtained from 24-hour ECG recordings. A range of entropy measures were calculated for each recording and Mann-Whitney tests were used to compare groups. Rényi entropy provides a significant result for positive exponents, for q=5, where the 2-group comparison has a p-value of 0.00031. Tsallis, Norm, SB, Beta, and Gamma entropies show similar results.

These results suggest that short heart rate recordings, possibly during a clinic visit can differentiate between syncope and palpitations and hence HUTT is not required.

1. Introduction

Syncope is a sudden, ephemeral loss of consciousness due to brief cerebral hypoperfusion with an associated loss of postural tone and usually a fast natural recovery. Symptoms are often described as orthostatic intolerance, which includes dizziness, palpitations, diaphoresis, pallor, nausea, and loss of consciousness [1]. These symptoms are often resolved when the supine position is adopted. Syncope may be classified as reflex mediated (neurocardiogenic), cardiac, orthostatic, or neurologic [2]. Head up tilt testing (HUTT) is the most common method to diagnose and investigate syncope. However, tilt testing presents risks to patients with structural and arrhythmic cardiac abnormalities such as fainting and arrhythmia. Moreover, HUTT lacks sensitivity for the discrimination of vasovagal mediated syncope (NMS) in patients above 40 years of age including those presenting with palpitations [3].

Autonomic dysfunction is known to be associated with neurocardiogenic syncope with positive results from Valsalva and deep breathing cardiac autonomic reflex test (CARTs) [4]. For improved accuracy and patient experience, analysis of time and frequency domain as well as nonlinear heart rate variability (HRV) indices determined from ECG or heart rate recordings may prove to be valuable. Nonlinear analysis has been used more often recently due to the nonstationarity and nonlinearity characteristics inherent in ECG data and include diverse entropy measures [5]. Entropy measures such as sample entropy have been used to assess irregularities and complexities of HRV such as atrial fibrillation, heart failure, and fetal heart rate [6]. Sample entropy measures the regularity of a time series rather than the complexity. It defines the negative logarithm of conditional probability of sequences of data vectors [7].

A range of ECG sequence length recordings (from 10 seconds to 24 hours) have also been used to investigate cardiac autonomic modulation using HRV analysis [8] and syncopal events [9]. However, there is controversy associated with the use of HRV parameters for diagnostic syncope. Picirillo suggested that the high frequency (HF) spectrum may distinguish patients with negative or positive HUTT results, while Lipsitz et al. argue that predicting syncope from HRV parameters was impossible [10]. Nonlinear HRV methods that are robust for the inherent non-stationarity and nonlinearity of ECG data may shed new light on this controversy when combined with traditional HRV features in differentiating between

syncope and palpitations [11].

1.1. Methods

This study uses 24-hour Holter data collected from 147 patients of the Wangaratta Cardiology and Respiratory Centre in Wangaratta, Australia. The patients were classified into syncope and palpitations groups based on clinical data and review by a physician. All data were de-identified and an ethics approval for the study was obtained from the Charles Sturt University Human Ethics Committee under approval number H18161. All patients provided informed consent to take part in the study and for data disclosure in accordance with the principles of the 2001 Helsinki Declaration. The study included 98 females (21 syncope, and 72 palpitations) and 49 males (7 syncope, 23 palpitations). All patients had a normal sinus rhythm.

Heart Rate Variability (HRV) data were extracted from the Holter ECG recordings, yielding RR interval series. Common time domain features were calculated for each series: standard deviation of RR intervals, root mean square of RR intervals (rmssd) and the median RR interval. These measures were supplemented by the following generalised entropy measures.

An exponential entropic definition without any physical interpretation but fulfilling the axiomatic criteria for an entropy is given by [12]:

$$SE = \sum_i p_i \left(1 - e^{\frac{p_i - 1}{p_i}}\right)$$

Graph entropies are a rather new concept using the term $(p_i)^{p_i}$, but again follow the axiomatic conditions for generalised entropies [13]. Three different entropy measures of this class were used:

$$H_1 = \sum_i \left(1 - \left(p_i\right)^{p_i}\right)$$

$$H_2 = \exp\left(\sum_i \left(\ln\left(2 - \left(p_i\right)^{p_i}\right)\right)\right)$$

$$H_3 = \sum_i \left(p_i + \ln\left(2 - \left(p_i\right)^{p_i}\right)\right)$$

The well known Rényi entropies for negative and positive q's are defined with

$$SRényi(q) = \frac{1}{1-q} \ln \sum_i p_i^q$$

and similarly, the Tsallis entropies with

$$STsallis(q) = \frac{1}{1-q}\left(\sum_i p_i^q - 1\right)$$

Following Tsallis [14] another two possibilities for negative and positive q's are

$$SNorm(q) = \frac{1}{1-q}\left(1 - \left(\sum_i p_i^q\right)^{-1}\right)$$

$$SEscort(q) = \frac{1}{q-1}\left(1 - \left(\sum_i p_i^{1/q}\right)^{-q}\right)$$

All four of these measures were used, with the exponent q taking integer values in the range of -5 to +5.

An entropy can also be defined by using Gamma functions:

$$SEta = \sum_{i=1}^{N} \Gamma\left(\frac{\eta+1}{\eta}, -\ln p_i\right) - p_i \Gamma\left(\frac{\eta+1}{\eta}\right)$$

with $\Gamma(a,b)$ the complementary incomplete Gamma function, $\Gamma(a)$ the Gamma function and η any positive real number [15].

The Kappa entropy is defined for distributions with power law tails by

$$SKappa(p) = \sum_i p_i \ln_\kappa\left(\frac{1}{p_i}\right)$$

with $0<\kappa<1$ [16]. In this work SEta and SKappa were calculated using κ = 0.1 to 1.0 in increments of 0.1.

The SB entropy is defined by

$$SB(b) = \sum_i \left(1 - e^{-b\,p_i}\right) + e^{-b} - 1$$

for all $b > 0$ [17].

A definition which might be seen as a mixture of Rényi and Tsallis entropies is

$$SBeta() = \sum_i p_i^{\beta} \ln p_i$$

with $0 < \beta < 1$ [18].

And finally, another form of generalised entropy defined by Tsallis is

$$SGamma() = \sum_i p_i \ln^{1/\beta}$$

with $0 < \beta < 1$ [14].

For this study, the probability distribution p_i was

computed from the individual signal values. All entropy measures were computed with ComsystanJ software (https://comsystan.github.io/comsystanj and https://github.com/comsystan/comsystanj). Shapiro-Wilk tests with p=0.05 revealed that not all distributions for the two groups (syncope, palpitation) and various heart rate variability parameters were normally distributed. Therefore, the Mann-Whitney test was used.

2. Results

Tests of entropy measures show a mixture of non-significant and significant results. The following tables include only those measures comparing Syncope with Palpitations that are significant at the p<0.01 level. None of the time domain features showed significant results. Each table row provides the p-value for one entropy measure. The best results are indicated by an asterisk and are shown in figures.

Table 1 shows that the Rényi entropy provides a significant result for positive exponents, especially for q=5, where the 2-group comparison has a p-value of 0.000306 obtained from the Mann-Whitney test. This result is illustrated in Figure 1, where the separation of medians and the overlap of the inter-quartile range can be seen. The p-values for Tsallis entropy show a similar pattern to those of Rényi entropy, as provided in table 1.

Table 1. Results for Rényi and Tsallis entropies.

Entropy	p-value	Entropy	p-value
Renyi_q2	0.000995	Tsallis_q2	0.000995
Renyi_q3	0.000610	Tsallis_q3	0.000610
Renyi_q4	0.000481	Tsallis_q4	0.000481
Renyi_q5	0.000306*	Tsallis_q5	0.000306

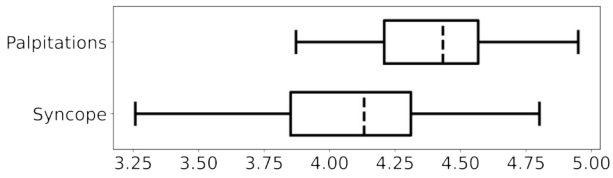

Figure 1. Box and whisker plot representing the range of values calculated for the Rényi entropy with q=5. Median (IQR) for Palpitations is 4.433 (0.359), while for Syncope is 4.132 (0.459). Linear discriminant gave sensitivity of 0.652 and specificity of 0.786.

Table 2 lists p-values obtained from Mann-Whitney tests applied to Gamma entropies. In contrast to Rényi and Tsallis, these data suggest that significance decreases as the parameter β increases. The best result of p=0.000239 was obtained using β=0.1 and is illustrated in figure 2. Here, the distribution for Syncope is very wide compared to that of palpitations.

Table 2. Results for Gamma entropies.

Entropy	p-value	Entropy	p-value
Gamma_0.1	0.000239*	Gamma_0.5	0.001640
Gamma_0.2	0.000326	Gamma_0.6	0.003101
Gamma_0.3	0.000550	Gamma_0.7	0.009784
Gamma_0.4	0.000815	Gamma_0.9	0.003101

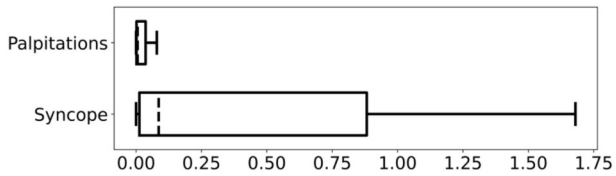

Figure 2. Box and whisker plot representing the range of values calculated for the Gamma entropy with β=0.1 (scale in units of E-14). Median (IQR) for Palpitations is 0.0057E-14 (0.035E-14), while for Syncope is 0.087E-14 (0.87E-14). Linear discriminant gave sensitivity of 0.246 and specificity of 0.464.

Table 3 summarises p-values obtained using other entropy measures. The best result of 0.000246 was obtained for the Beta entropy using a value of 1.2. This result is illustrated in figure 3, where the increased size of distribution for Syncope can be observed, although the difference in size of distributions is less than that of Gamma entropy.

Table 3. Results for other entropies.

Entropy	p-value	Entropy	p-value
SE	0.00102	SNorm_q2	0.000995
SB_1.0	0.00102	SNorm_q3	0.000610
Beta_1.1	0.00381	SNorm_q4	0.000481
Beta_1.2	0.000246*	SNorm_q5	0.000301*

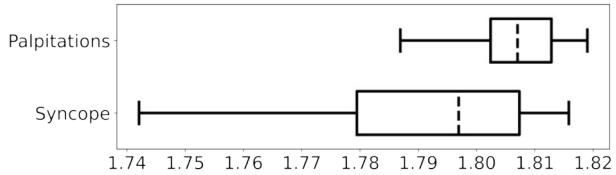

Figure 3. Box and whisker plot representing the range of values calculated for the Beta entropy with β =1.2. Median (IQR) for Palpitations is 1.807 (0.010), while for Syncope is 1.797 (0.279). Linear discriminant gave sensitivity of 0.710 and specificity of 0.678.

Results for SNorm entropy show statistical significance increasing with increasing values of parameter q. The smallest p-value obtained was 0.000301 for q=5. This result is illustrated in figure 4, where the

medians appear well separated as expected from the p-value obtained by Mann-Whitney test. However, in this figure it is the Palpitations group that appears to have a much wider distribution than that of Syncope.

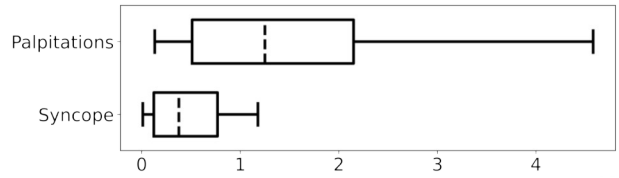

Figure 4. Box and whisker plot representing the range of values calculated for the SNorm entropy with q=5 (scale in units of E+7). Median (IQR) for Palpitations is 1.25E+7 (1.64E+7), while for Syncope is 0.377E+7 (0.646E+7). Linear discriminant gave sensitivity of 0.652 and specificity of 0.786.

6. Conclusions

A range of entropy measures were evaluated to compare Heart Rate Variability (HRV) data collected from patients presenting with Syncope or Palpitations. Significant differences were found between Syncope and Palpitations groups for a range of entropy measures and for a range of parameter values for each of these measures. This suggests a possible route for a diagnostic test for Syncope based on non-invasive HRV. Further research is required including determination of the diagnostic accuracy for individual patients attending the clinic with unknown syncope or palpitation based on HRV and entropy analysis. In particular, future work will focus on time-of-day analysis after dividing up the 24 hour recording into day/night sections, in order to investigate circadian rhythms. Another approach that will be considered is the division of the recording into hourly segments in order to identify whether differences between groups are restricted to short term effects, as this could affect requirements for the timing of any diagnostic test.

Acknowledgments

The authors would like to acknowledge the contribution of the clinical and administrative staff at the Wangaratta clinic in assisting with data collection.

References

[1] M.J. Hilz, H. Marthol, B. Neundörfer, “Syncope - a systematic overview of classification, pathogenesis, diagnosis and management”, Fortschr Neurol Psychiatr, vol. 70, no. 2, pp. 95-107, Feb. 2002.

[2] C. Chen-Scarabelli, T.M. Scarabelli, “Neurocardiogenic syncope”, BMJ, vol. 329, no. 7461, pp. 336-341, Aug. 2004.

[3] A. Ungar, P. Sgobino, V. Russo et al., “Diagnosis of neurally mediated syncope at initial evaluation and with tilt table testing compared with that revealed by prolonged ECG monitoring. An analysis from the Third International Study on Syncope of Uncertain Etiology (ISSUE-3),” Heart, vol. 99, no. 24, pp. 1825-31, Oct. 2013.

[4] R. Sutton. “Diagnostic tools to assess dysfunction of autonomic control of the heart,” J Atr Fibrillation, vol. 13, no. 1, pp. 2402, Jun-Jul. 2020.

[5] H. F. Jelinek, D. J. Cornforth, M. P. Tarvainen et al. “Investigation of linear and nonlinear properties of a heartbeat time series using multiscale Rényi entropy,” Entropy, vol. 21, no. 8, pp. 727, Jul. 2019.

[6] M. Ribeiro, J. Monteiro-Santos, L. Castro et al. “Non-linear methods predominant in fetal heart rate analysis: A systematic review,” Front Med, vol. 8, no. 661226, Nov. 2021.

[7] D. E. Lake, J. S. Richman, M. P. Griffin et al. “Sample entropy analysis of neonatal heart rate variability,” Am J Physiol Regul Integr Comp Physiol, vol. 283, no. 3, pp. R789-97, Sept. 2002.

[8] D. Wehler, H. F. Jelinek, A. Gronau et al. “Reliability of heart-rate-variability features derived from ultra-short ECG recordings and their validity in the assessment of cardiac autonomic neuropathy,” Biomed. Sig. Proc. Con, vol. 68, no. 102651, Jul. 2021.

[9] S. H. Shim, S. Y. Park, S. N. Moon et al. “Baseline heart rate variability in children and adolescents with vasovagal syncope,” Korean J Pediatr , vol. 57, no. 4, pp. 193-198, Apr. 2014.

[10] G. Piccirillo, C. Naso, A. Moisè et al. “Heart rate and blood pressure variability in subjects with vasovagal syncope,” Clin Sci, vol. 107, no. 1, pp. 55-61, Jul. 2004.

[11] G. Georgieva-Tsaneva, E. Gospodinova,M. Gospodinov et al. “Cardio-Diagnostic Assisting Computer System,” Diagnostics, vol. 10, no. 5, May 2020.

[12] G. A. Tsekouras, and C. Tsallis. “Generalized entropy arising from a distribution of q indices,” Phys. Rev. E, vol. 71, no. 4, pp. 046144, Apr. 2005.

[13] J. M. Amigó, S. G. Balogh, and S. Hernández. „A Brief Review of Generalized Entropies,”. Entropy , vol. 20, no. 11, pp. 813, Oct. 2018.

[14] C. Tsallis, “Introduction to Nonextensive Statistical Mechanics”; Springer: New York, NY, USA, 2009.

[15] C. Anteneodo, A. R. Plastino, “Maximum entropy approach to stretched exponential probability distributions,” J. Phys. A Math. Gen., vol. 32, no. 1999, pp. 1089–1098, Feb. 1999.

[16]G. Kaniadakis, “Statistical mechanics in the context of special relativity,” Phys. Rev. E vol. 66, no. 5, pp. 1089-1097, Nov. 2002.

[17] E. M. F. Curado, and F. D. Nobre. “On the stability of analytic entropic forms“. Physica A: Stat. Mech. App., vol. 335, no. 1, pp. 94–106, Apr. 2004.

[18] F. Shafee, “Lambert Function and a New Non-Extensive Form of Entropy,” IMA J App. Math. Vol. 72, no. 6, pp. 785-800, Dec. 2007.

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