The prediction of mortality from continuous non-invasive cardiovascular signals on standing: entropy was significant, but not the overall response profile

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***Abstract*— In this study, a novel approach is presented using principal component analysis and sample entropy (SampEn) for the analysis of continuous blood pressure (BP) data measured non-invasively during an active stand (AS) in a large sample of older adults. The method allows for the extraction of the bulk trends from these data in the form of principal components (PCs), which can be used as independent predictors of outcomes, and greatly increases the stationarity of the remaining data, allowing for secondary analyses such as SampEn. The relationship between AS BP measures (SampEn and first 6 PCs) and risk of all-cause 8-year mortality was investigated via Cox proportional hazards regression models in a sample of community-dwelling older adults (n = 4873, with 209 deaths) from The Irish Longitudinal Study on Ageing (TILDA). Higher SampEn in BP signals was found to be a significant predictor of mortality risk. PC scores, which characterize the overall bulk changes in response to standing, were not significantly predictive of mortality when controlling for age, sex, and educational attainment. The quantification of signal entropy in continuously measured BP signals during AS could provide a clinically useful predictor of risk of death.**

Keywords*— *Sample Entropy; Principal Component Analysis; Cardiovascular; Blood Pressure; Mortality

I. Introduction

The measurement of physiological resilience is of increasing interest in the field of ageing research, as this can help identify older persons at higher risk of negative outcomes when faced with a stressor [1, 2]. The assessment of resilience requires continuous tracking of a physiological signal related to the body's response to a stressor, for example the beat-to-beat response of the cardiovascular system when transitioning from a supine (lying down) to a standing position ('active stand' (AS)) [3, 4]. Upon standing, blood pressure (BP) sustains an initial decline within the first 10 to 15 seconds and following a stabilization phase that can last up to 30 to 40 seconds post-stand, the BP returns to baseline pre-stand values. Full recovery has in most cases occurred by 60 seconds post-stand [5].

To date, most of the research using continuous AS cardiovascular data has been focused on characterizing the bulk trends in these data, most commonly in order to identify individuals with orthostatic hypotension (OH), an important risk factor for falls and other adverse health outcomes [6]. OH is defined by consensus as a drop in systolic blood pressure (sBP) of $\geqslant$ 20 mmHg and/or a drop in diastolic blood pressure (dBP) of $\geqslant$10 mmHg within 3 minutes of standing [6]. Traditionally, this was measured at discrete time points using a sphygmomanometer or oscillometric device; however, improvements in non-invasive technology mean that this response can now be monitored continuously at high temporal resolutions via beat-to-beat acquisition, allowing for an individual's response profile to be examined in much greater detail.

It has been previously demonstrated that principal component analysis (PCA) can be used to identify common bulk trends in large AS datasets [7]. In the present work, we expand on this by demonstrating that the inverse is also possible, i.e., PCA can also be used to detrend AS data, which greatly improves data stationarity, while retaining individual-specific BP patterns in the data. The motivation for doing this is to allow for the measurement of the amount of disorder in these detrended data using sample entropy (SampEn), which requires the data to be stationary for accurate quantification. We hypothesized that abnormalities in physiological control mechanisms that are responsible for the dynamic regulation of BP may be detectable and quantifiable by the level of disorder in continuously measured BP signals during an AS challenge.

Signal entropy is a measure of irregularity or unpredictability, assigning lower entropy values to periodic, predictable data, and higher entropy values to irregular, unpredictable data. In 2000, Richman and Moorman [8] introduced SampEn. Briefly, given a time-series of length N, SampEn is defined as the negative natural logarithm of the conditional probability that two trajectories of length m remain similar for $m + 1$, within a tolerance specified as $\pm r$ * standard deviation (SD) of the timeseries. For SampEn, self-matches are not considered in the probability calculation, unlike the also widely used approximate entropy (ApEn). Additionally, it has been demonstrated that SampEn is largely independent of the data length and can potentially provide more consistent results than ApEn [8].

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In the present study, we utilised PCA and SampEn for the analysis of cardiovascular signal complexity during the entire AS (3 mins), 'pre-stand' during supine rest (-60 s to stand), at 'stand' (0 to 60 s), and during post-stand 'recovery' (60 to 120 s) sections of data. We then investigated the associations between these AS entropy measures and risk of mortality in a large cohort of older individuals (n = 4873, with 209 deaths) from the Irish Longitudinal Study on Ageing (TILDA).

II. Methods

A. Design and setting

This research was carried out as part of TILDA, an ongoing nationally-representative prospective cohort study of community-dwelling Irish adults, which collects information on their health, economic and social circumstances [9]. Wave 1 of the study took place between October 2009 and February 2011, and subsequent data was collected approximately every 2 years over four longitudinal waves. Wave 1 included a comprehensive health assessment conducted at a dedicated health assessment centre. The full cohort profile has been previously described in detail [9]. Ethical approval was granted for each wave from the Health Sciences Research Ethics Committee at Trinity College Dublin, Dublin, Ireland, and all participants provided written informed consent. All research was performed in accordance with the Declaration of Helsinki.

B. Cardiovascular measures

At wave 1 health assessment, beat-to-beat BP was measured at 200 Hz in 4873 individuals using a digital photoplethysmography device (Finometer MIDI, Finapres Medical Systems BV, Amsterdam, The Netherlands). All measurements were carried out in a comfortably lit room, at an ambient temperature between 21°C and 23°C. Data were acquired continuously while participants laid supine for 10 minutes (data from the last minute of rest was used) before transitioning to a standing position and remaining standing for 3 minutes (2-minute post-AS data was used). Signals for systolic blood pressure (sBP) and diastolic blood pressure (dBP) were extracted using MATLAB (R2021a, TheMathWorks, Inc, MA, USA). Beat-to-beat data were linearly interpolated to 5 Hz prior to analysis, providing N = 900 datapoints, and no filtering was applied.

C. PCA processing

PCA was performed using a built-in MATLAB function ('pca.m'). After applying PCA, the i^{th} curve ($\widehat{X}_i$) can be described by the mean ($\overline{X}$) plus a linear combination of k PCs where α is the score and U is the loading vector (Eq. 1).

$$\widehat{X}_i = \overline{X} + \alpha_1 U_1 + \ldots + \alpha_k U_k \quad (1)$$

In a similar way, the remaining PCs (k+1 to n) can be used to describe the remaining data ($\widehat{X}_r$), such that,

$$\widehat{X}_r = \alpha_{k+1} U_{k+1} + \ldots + \alpha_n U_n. \quad (2)$$

(Alternatively, one could also simply subtract each participant's $\widehat{X}_i$ from their raw data to obtain the same result in a less computationally demanding manner). A scree plot was produced to assess the cumulative variance explained by the first 20 modes for sBP, and visual representations of the first 6 components (± 2 SDs) were also produced using a previously described method termed 'single component reconstruction' [10]. The upper trace ($\widehat{X}_U$) for the R^{th} component is given by the mean ($\overline{X}$) plus the product of the loading vector (U_R) and twice the SD (σ_R) of the R^{th} PC (Eq. 3). The lower limit ($\widehat{X}_L$) is then given by the same equation with the addition replaced by a subtraction (Eq. 4).

$$\widehat{X}_U = \overline{X} + (2\sigma_R) U_R \quad (3)$$

$$\widehat{X}_L = \overline{X} - (2\sigma_R) U_R \quad (4)$$

Along with the graphical interpretation, scores were also leveraged for statistical inference by using them as independent variables in regression (i.e., PC regression).

D. Data stationarity assesment

Stationarity of the data was assessed via the augmented Dicky-Fuller test on both the original raw AS data (absolute and normalized to baseline) and transformed data ($\widehat{X}_r$).

E. Entropy measures

Entropy analyses were performed on $\widehat{X}_r$ in MATLAB using freely available scripts [11]. A detailed description of the algorithms used to compute SampEn has been previously reported in detail [8]; however, below we provide a brief overview. $B_i^m(r)$ is defined as the number of template vectors $\mathbf{x}_m(j)$ similar to $\mathbf{x}_m(i)$ (within r) divided by $N - m - 1$, where $j = 1...N - m$, with $j \neq i$ (to avoid self-matches). The average $B_i^m(r)$ for all i is given as

$$B^m(r) = \frac{1}{N-m} \sum_{i=1}^{N-m} B_i^m(r). \quad (5)$$

Similarly, we define $A_i^m(r)$ as the number of template vectors $\mathbf{x}_{m+1}(j)$ similar to $\mathbf{x}_{m+1}(i)$ (within r) divided by $N - m - 1$, where $j = 1...N - m$, with $j \neq i$. The average $A_i^m(r)$ for all i is given as

$$A^m(r) = \frac{1}{N-m} \sum_{i=1}^{N-m} A_i^m(r). \quad (6)$$

SampEn was then calculated as

$$\mathrm{SampEn}(m,r,N) = -\ln\left(\frac{A^m(r)}{B^m(r)}\right). \quad (7)$$

In this study, m (embedding dimension; the length of the data segment being compared) was set to 2 and an r (similarity criterion) of 0.15 was selected, in line with previous recommendations for similar physiological data [12]. N (the number of datapoints) was set at 900 for the entire AS and 300 for 'pre-stand', 'stand', and 'recovery' sections (Fig. 1(a)).

F. Mortality data linkage and covariates

The date and cause of death of deceased individuals was identified from official death registration data and linked to their TILDA survey and health assessment data. Linking was performed for all individuals who died between April 2010 and March 2017. Full details of the data linkage procedures are described elsewhere [13]. As part of the TILDA assessment, self-reported age, sex, and level of educational attainment were also recorded and were included as covariates in the models reported herein.

G. Statistical analysis

Statistical analysis was performed using STATA 15.1 (StataCorp, College Station, TX, USA). Cox proportional hazards regression models were utilized to estimate the hazard ratios (HRs) for the association between SampEn and all-cause 8-year mortality. Respondents lost to follow up were right-censored at the end of the follow-up-period (31st March 2017). Four sets of models were used: (1) unadjusted; (2) adjusted for first 6 PC scores (i.e., considering the overall

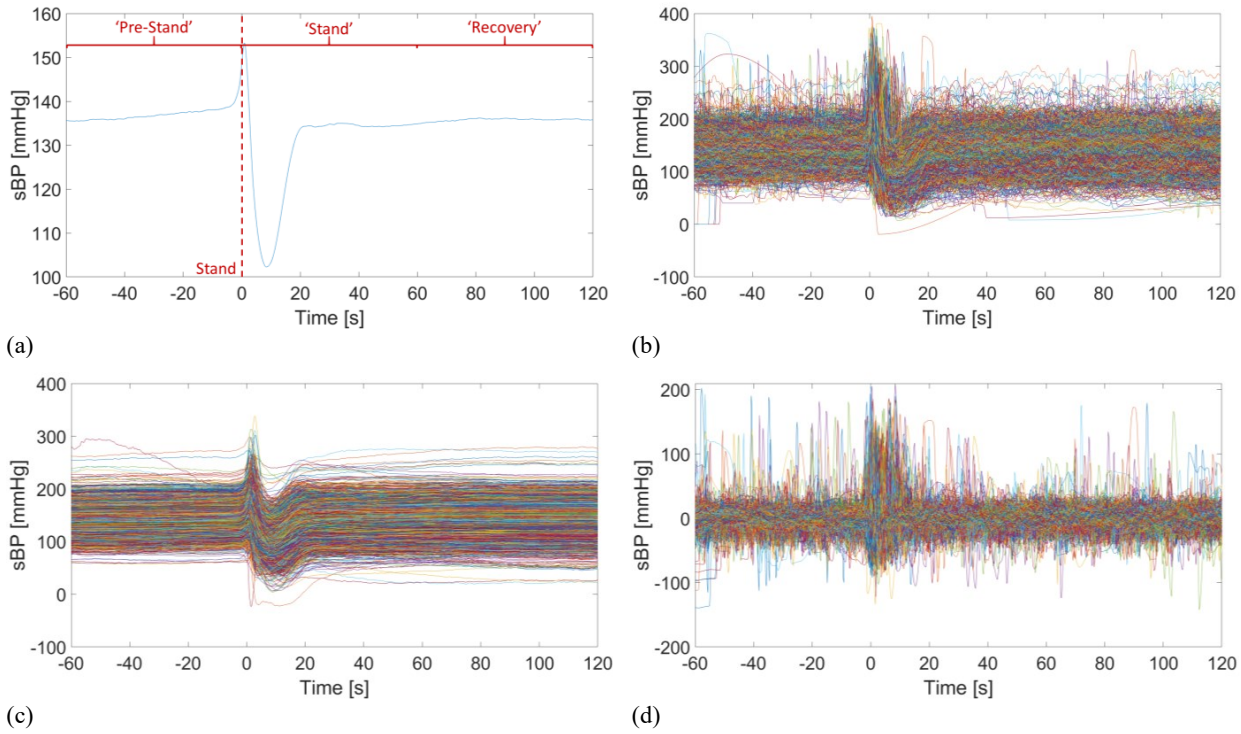

Fig. 1. Plots showing (a) the mean sBP AS data, with 'Pre-Stand', 'Stand', and 'Recovery' sections shown; (b) raw sBP data for all partispants; (c) data for all partisipants reconstructed using the first 6 PCs ($\widehat{X}_6$); and (d) data for all partisipants reconstructed using the last 894 componants ($\widehat{X}_r$).

participant-specific trend in response to standing); (3) adjusted for first 6 PC scores, age, sex, and education; and (4) for each section of the response to standing (pre-stand, stand, and recovery) adjusted for age, sex, and education. Results from models 1-3 are presented as forest plots and results from model 4 are tabulated.

III. Results

In total, 8175 participants over the age of 50 years were recruited at wave 1 of TILDA, of whom 5035 attended for a health centre assessment at wave 1, and adequate AS BP data were available for 4873 (209 deaths) individuals (mean (SD) age: 61.4 (8.2) years; 54.2% female). Raw AS data for the entire cohort is shown in Fig. 1(b).

Results from the PCA analysis for the entire cohort, with data reconstructed using the first 6 PCs ($\widehat{X}_6$), are presented in Fig. 1(c) and using the remaining 894 PCs ($\widehat{X}_r$) in Fig. 1(d). Scree plots, which show the variance explained by the first 20 PCs, are shown in Fig. 2(a) and the first 6 PCs (±2 SDs) are illustrated in Fig. 2(b). Augmented Dicky-Fuller tests revealed that for the raw data only 0.2% of participant's sBP and dBP data were stationary; this increased to 34.7% and 52.3%, respectively, when data were normalized to baseline (pre-stand), and further to 94.4% and 96.7%, respectively, for data reconstructed using the last 894 PCs ($\widehat{X}_r$; Fig. 1(d)).

Results from Cox proportional hazards regression models are presented as HRs in Fig. 3 (models 1-3) and Table I (model 4). Univariate analyses (model 1) of the entire stationary AS data ($\widehat{X}_r$) revealed that an increase in SampEn of 0.1 was associated with increased risk of mortality month-on-month, for both sBP (HR=1.14; 95%CIs=1.00 to 1.29; p=0.046) and dBP (HR=1.18; 95%CIs=1.07 to 1.31; p=0.001). Model 2 showed that in the absence of other confounders both the SampEn in $\widehat{X}_r$ and most PC scores (representing portions of the overall shape of the response to standing) were predictive of mortality, for both sBP and dBP.

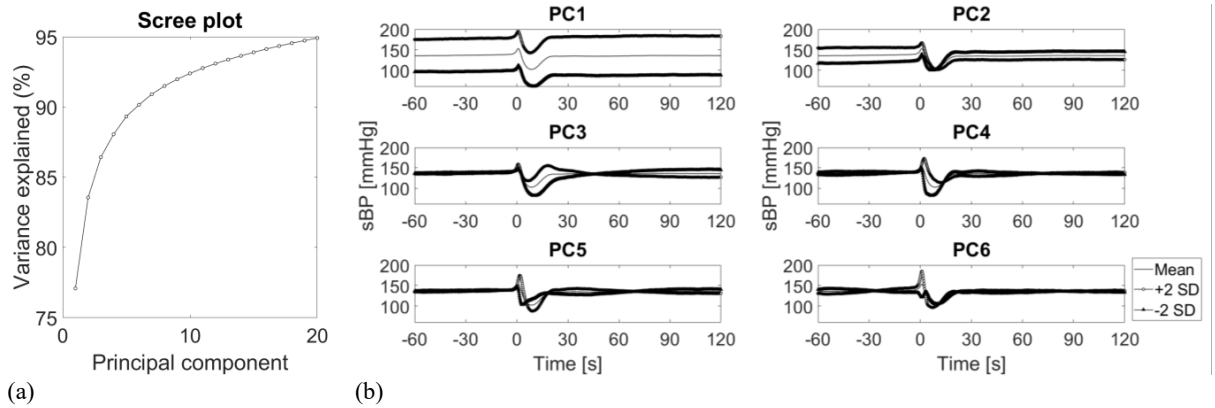

Fig. 2. (a) Scree plot showing the variance explained by the first 20 PCs for sBP and (b) graphical representations of the first 6 PCs for sBP (± 2 SDs) .

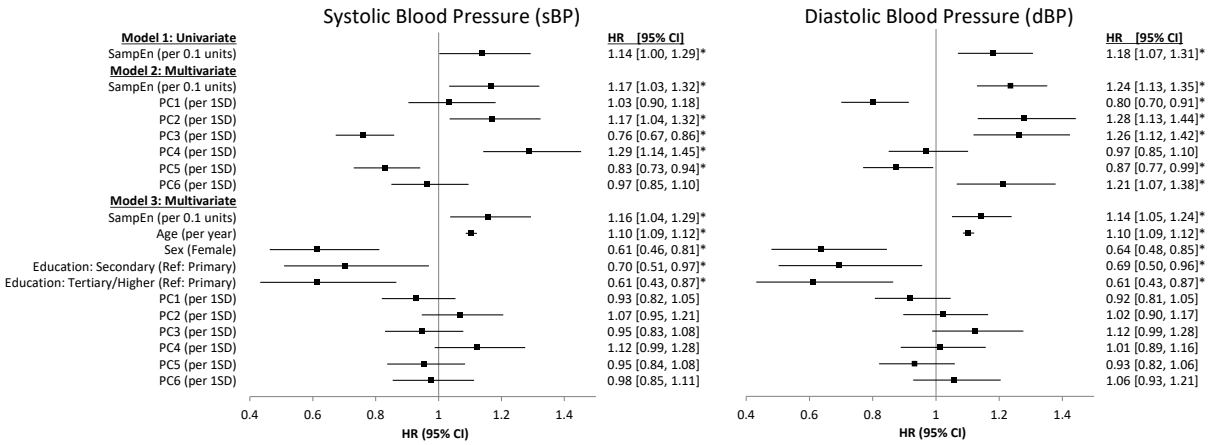

Fig. 3. Forest plots showing the results from Cox proportional hazards regression models 1-3.

When the models were extended to also control for age, sex, and education (model 3), the association between both sBP SampEn (HR=1.16; 95%CIs=1.04 to 1.29; p=0.009) and dBP SampEn (HR=1.14; 95%CIs=1.05 to 1.24; p=0.002) remained significant; however, the associations with PCs were all no longer significant. Model 4 (Table I) showed that SampEn calculated for each section of the data (pre-stand, stand, and recovery) were also individually associated with increased risk of mortality (models controlled for age, sex, and education), with the recovery section providing the highest HR for sBP (HR=1.16; 95%CIs=1.06 to 1.27; p=0.001) and pre-stand for dBP (HR=1.16; 95%CIs=1.06 to 1.26; p=0.001). Age, sex, and educational attainment were significantly associated with risk of mortality in all models that used these covariates; with increased age increasing the risk and being female or having a higher level of education reducing the risk.

TABLE I. RESULSTS FROM COX PROPORTIONAL HAZARDS REGRESSION MODEL 4.

Data	Measure	HR	P	95% CIs
Model 4a – Age, Sex, Education Controlled – sBP				
Pre-Stand (-60 to 0s)	SampEn (per 0.1)	1.13	**0.025**	1.02 to 1.25
	Age (per 1 year)	1.11	**<0.001**	1.09 to 1.13
	Sex (Female)	0.64	**0.002**	0.49 to 0.85
	Education*			
	Secondary	0.70	**0.030**	0.51 to 0.97
	Tertiary/Higher	0.60	**0.004**	0.43 to 0.85
Stand (0 to 60s)	SampEn (per 0.1)	1.10	**0.049**	1.00 to 1.20
	Age (per 1 year)	1.11	**<0.001**	1.09 to 1.13
	Sex (Female)	0.63	**0.001**	0.48 to 0.84
	Education*			
	Secondary	0.69	**0.023**	0.50 to 0.95
	Tertiary/Higher	0.60	**0.003**	0.42 to 0.84
Recovery (60 to 120s)	SampEn (per 0.1)	1.16	**0.001**	1.06 to 1.27
	Age (per 1 year)	1.11	**<0.001**	1.09 to 1.13
	Sex (Female)	0.62	**0.001**	0.47 to 0.81
	Education*			
	Secondary	0.68	**0.021**	0.50 to 0.94
	Tertiary/Higher	0.59	**0.003**	0.42 to 0.84
Model 4b – Age, Sex, Education Controlled – dBP				
Pre-Stand (-60 to 0s)	SampEn (per 0.1)	1.16	**0.001**	1.06 to 1.26
	Age (per 1 year)	1.11	**<0.001**	1.09 to 1.13
	Sex (Female)	0.66	**0.004**	0.50 to 0.88
	Education*			
	Secondary	0.70	**0.029**	0.51 to 0.96
	Tertiary/Higher	0.61	**0.005**	0.43 to 0.86
Stand (0 to 60s)	SampEn (per 0.1)	1.10	**0.012**	1.02 to 1.18
	Age (per 1 year)	1.11	**<0.001**	1.09 to 1.13
	Sex (Female)	0.66	**0.003**	0.50 to 0.86
	Education*			
	Secondary	0.68	**0.019**	0.49 to 0.94
	Tertiary/Higher	0.58	**0.003**	0.42 to 0.83
Recovery (60 to 120s)	SampEn (per 0.1)	1.14	**0.001**	1.06 to 1.23
	Age (per 1 year)	1.11	**<0.001**	1.09 to 1.13
	Sex (Female)	0.65	**0.002**	0.49 to 0.86
	Education*			
	Secondary	0.69	**0.024**	0.50 to 0.95
	Tertiary/Higher	0.60	**0.004**	0.43 to 0.85

* Reference: primary level education

IV. DISCUSSION

This study demonstrated a novel application of PCA to AS data, as a method for both extracting the overall bulk participant-specific trends in the data, as well as increasing the stationarity of the remaining data, to allow for secondary analyses that require the data to be stationary, such as SampEn. The study also reported associations between BP SampEn measurements and risk of 8-year all-cause mortality. It was found that for both sBP and dBP, higher SampEn was significantly associated with a higher risk of mortality. By also utilizing the first 6 PCs in the Cox regression models (removed from the stationary data for SampEn calculation), it was also possible to extend this investigation to see whether the overall, bulk change in AS profiles was also associated with mortality risk, within the same models. SampEn in BP data during standing predicted mortality, but not overall response profiles (when controlling for age, sex, and education). Additionally, SampEn was calculated for each section of the data (pre-stand, stand, and recovery). It was found that SampEn in sBP data during the recovery from stand section, and in dBP data during the pre-stand, supine stage of the experiment, provided the highest HRs for predicting risk of mortality for each BP measure. Age, sex, and educational attainment were all significantly associated with risk of mortality, with older age increasing the risk and being female or having a higher level of education (a proxy for socioeconomic status) reducing the risk.

Most previous work using AS data have been focused on investigating the bulk response of neurocardiovascular to transitioning from a supine to standing position. Often, to simplify the analysis, or to characterize specific physiological groupings, such as OH, data are decimated into temporal bins of 5-10 seconds [7], or even longer. However, there is a growing interest in using more data-driven approaches, which draw on the richness of data available as non-invasive continuous physiological monitoring technology has evolved. In a previous study, we demonstrated the utility of PCA for extracting bulk trends from AS data [7]. To the best of our knowledge, this is the first study to utilize PCA to both increase the stationarity of these types of timeseries data, for the purposes of increasing the accuracy of secondary analyses (such as SampEn), as well as allowing for bulk trends in the

data to be simultaneously investigated within the same models. This technique is not only applicable to these specific BP AS data, but to any large timeseries dataset, where there is a common experimental paradigm or seasonality that produces a trend shared across repeated measures. One of the big advantages of such an approach is that it allows for the use of *all* of the data, and as we have demonstrated in the present work, this can be advantageous, since for certain data there can be information contained within parts of data which might otherwise be discarded.

From a physiological perspective, being able to extract measures of 'disorder' (such as signal entropy) from cardiovascular data during 'rest', 'challenge', and 'recovery' is very informative, since these measures can be differentially indicative of dysregulation in the body, leading to reduced resilience when faced with a stressor [1, 2]. One potential cause for this dysregulation could be abnormally modified baroreflex sensitivity and/or vagal tone. Another plausible cause might be an increase of sympathetic activity and/or modulation directed to the heart and/or blood vessels. Other possible influencing factors could be changes in arterial structure (e.g., increased stiffness, decreased compliance, and endothelial dysfunction), modified cardiac reserve, as well as changes of diastolic filling and increased collagen in the left ventricle. In fact, the entropy measure described in this study may be influenced by a composite of the above potential factors [14]. Further work will be required elucidate the physiological origins of this potential measure of cardiovascular dysregulation.

Although several previous studies have shown higher neurovascular and cardiovascular entropy measures, calculated in a similar way to that used in the present study, to be associated with detrimental health conditions, such as frailty, cognitive performance, and accelerated brain aging [16-18], this is the first study to demonstrate the utility of short-length BP SampEn, calculated in this fashion, for the prediction of mortality. There are several strengths to this approach, namely: all measures were non-invasive and non-ionizing; the potentially short data length required (60 seconds) would be feasible and practical for use in a busy clinic; and SampEn provides a single-number measure, which is easily tracked and is interpretable to clinicians. Further work is required however to fully investigate the possible value of this measure as a potential early maker of mortality risk.

There are several limitations to this study which should be kept in mind when interpreting the results. Six PCs were chosen to demonstrate this approach, since these explained >90% of the common variance in the sBP data; however, this may not be the optimal amount, as some of the bulk trend from the 'stand' portion of the experiment is still apparent for some participants (as seen in Fig. 1(d)); further work will explore the effects of using different numbers of components on data stationarity, entropy calculations, and associations with clinical markers.

In conclusion, in this study overall BP response profiles to standing were not significantly predictive of mortality risk, however, the level of signal entropy in BP signals during AS was. This may provide a clinically useful marker to help identify those at higher risk of premature death.

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REFERENCES

[1] G. A. Kuchel, "Frailty and Resilience as Outcome Measures in Clinical Trials and Geriatric Care: Are We Getting Any Closer?," (in eng), *J Am Geriatr Soc,* vol. 66, no. 8, pp. 1451-1454, Aug 2018, doi: 10.1111/jgs.15441.

[2] R. Varadhan, J. D. Walston, and K. Bandeen-Roche, "Can a Link Be Found Between Physical Resilience and Frailty in Older Adults by Studying Dynamical Systems?," (in eng), *J Am Geriatr Soc,* vol. 66, no. 8, pp. 1455-1458, Aug 2018, doi: 10.1111/jgs.15409.

[3] M. D. O'Connell, G. M. Savva, C. Finucane, R. Romero-Ortuno, C. W. Fan, and R. A. Kenny, "Impairments in Hemodynamic Responses to Orthostasis Associated with Frailty: Results from The Irish Longitudinal Study on Ageing (TILDA)," (in eng), *J Am Geriatr Soc,* vol. 66, no. 8, pp. 1475-1483, Aug 2018, doi: 10.1111/jgs.15327.

[4] R. Romero-Ortuno, L. Cogan, D. O'Shea, B. A. Lawlor, and R. A. Kenny, "Orthostatic haemodynamics may be impaired in frailty†," *Age and Ageing,* vol. 40, no. 5, pp. 576-583, 2011, doi: 10.1093/ageing/afr076.

[5] R. Romero-Ortuno, M. D. O'Connell, C. Finucane, C. Soraghan, C. W. Fan, and R. A. Kenny, "Insights into the clinical management of the syndrome of supine hypertension--orthostatic hypotension (SH-OH): the Irish Longitudinal Study on Ageing (TILDA)," (in eng), *BMC Geriatr,* vol. 13, p. 73, Jul 15 2013, doi: 10.1186/1471-2318-13-73.

[6] R. Freeman *et al.*, "Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome," (in eng), *Clin Auton Res,* vol. 21, no. 2, pp. 69-72, Apr 2011, doi: 10.1007/s10286-011-0119-5.

[7] J. D. O'Connor *et al.*, "Functional Analysis of Continuous, High-Resolution Measures in Aging Research: A Demonstration Using Cerebral Oxygenation Data From the Irish Longitudinal Study on Aging," (in eng), *Front Hum Neurosci,* vol. 14, p. 261, 2020, doi: 10.3389/fnhum.2020.00261.

[8] J. S. Richman and J. R. Moorman, "Physiological time-series analysis using approximate entropy and sample entropy," (in eng), *Am J Physiol Heart Circ Physiol,* vol. 278, no. 6, pp. H2039-49, Jun 2000, doi: 10.1152/ajpheart.2000.278.6.H2039.

[9] O. A. Donoghue, C. A. McGarrigle, M. Foley, A. Fagan, J. Meaney, and R. A. Kenny, "Cohort Profile Update: The Irish Longitudinal Study on Ageing (TILDA)," *Int J Epidemiol,* vol. 47, no. 5, pp. 1398-1398l, Oct 1 2018, doi: 10.1093/ije/dyy163.

[10] S. C. Brandon, R. B. Graham, S. Almosnino, E. M. Sadler, J. M. Stevenson, and K. J. Deluzio, "Interpreting principal components in biomechanics: representative extremes and single component reconstruction," (in eng), *J Electromyogr Kinesiol,* vol. 23, no. 6, pp. 1304-10, Dec 2013, doi: 10.1016/j.jelekin.2013.09.010.

[11] V. Martínez-Cagigal. "Sample Entropy." MATLAB Central File Exchange. https://uk.mathworks.com/matlabcentral/fileexchange/69381-sample-entropy (accessed accessed on 10 January 2020, 2020).

[12] Z. Turianikova, K. Javorka, M. Baumert, A. Calkovska, and M. Javorka, "The effect of orthostatic stress on multiscale entropy of heart rate and blood pressure," (in eng), *Physiol Meas,* vol. 32, no. 9, pp. 1425-37, Sep 2011, doi: 10.1088/0967-3334/32/9/006.

[13] M. Ward *et al.*, "Linking death registration and survey data: Procedures and cohort profile for The Irish Longitudinal Study on Ageing (TILDA) [version 2; peer review: 3 approved]," *HRB Open Research,* vol. 3, no. 43, 2020, doi: 10.12688/hrbopenres.13083.2.

[14] S. O'Callaghan and R. A. Kenny, "Neurocardiovascular Instability and Cognition," (in eng), *Yale J Biol Med,* vol. 89, no. 1, pp. 59-71, Mar 2016.

[15] D. Bajić and N. Japundžić-Žigon, "On Quantization Errors in Approximate and Sample Entropy," *Entropy,* vol. 24, no. 1, p. 73, 2022. [Online]. Available: https://www.mdpi.com/1099-4300/24/1/73.

[16] S. P. Knight, L. Newman, J. D. O'Connor, J. Davis, R. A. Kenny, and R. Romero-Ortuno, "Associations between Neurocardiovascular Signal Entropy and Physical Frailty," *Entropy,* vol. 23, no. 1, p. 4, 2021. [Online]. Available: https://www.mdpi.com/1099-4300/23/1/4.

[17] S. P. Knight *et al.*, "Associations between Cardiovascular Signal Entropy and Cognitive Performance over Eight Years," *Entropy,* vol. 23, no. 10, p. 1337, 2021. [Online]. Available: https://www.mdpi.com/1099-4300/23/10/1337.

[18] S. Knight *et al.*, "Higher neurovascular signal entropy is associated with accelerated brain ageing," *Age and Ageing,* vol. 50, no. Supplement_3, 2021, doi: 10.1093/ageing/afab219.78.