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ORIGINAL RESEARCH

Complexity of preoperative blood pressure dynamics: possible utility in cardiac surgical risk assessment

Teresa S. Henriques[1,2] · Madalena D. Costa[2] · Pooja Mathur[1] · Priyam Mathur[1] · Roger B. Davis[3] · Murray A. Mittleman[4] · Kamal R. Khabbaz[5] · Ary L. Goldberger[2] · Balachundhar Subramaniam[1]

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Abstract

Complexity measures are intended to assess the cardiovascular system's capacity to respond to stressors. We sought to determine if decreased BP complexity is associated with increased estimated risk as obtained from two standard instruments: the Society of Thoracic Surgeons' (STS) Risk of Mortality and Morbidity Index and the European System for Cardiac Operative Risk Evaluation Score (EuroSCORE II). In this observational cohort study, preoperative systolic, diastolic, mean (MAP) and pulse pressure (PP) time series were derived in 147 patients undergoing cardiac surgery. The complexity of the fluctuations of these four variables was quantified using multiscale entropy (MSE) analysis. In addition, the traditional time series measures, mean and standard deviation (SD) were also computed. The relationships between time series measures and the risk indices (after logarithmic transformation) were then assessed using nonparametric (Spearman correlation, r_s) and linear regression methods. A one standard deviation change in the complexity of systolic, diastolic and MAP time series was negatively associated ($p < 0.05$) with the STS and EuroSCORE indices in both unadjusted (21–34%) and models adjusted for age, gender and SD of the BP time series (15–31%). The mean and SD of BP time series were not significantly associated with the risk index except for a positive association with the SD of the diastolic BP. Lower preoperative BP complexity was associated with a higher estimated risk of adverse cardiovascular outcomes and may provide a novel approach to assessing cardiovascular risk. Future studies are needed to determine whether dynamical risk indices can improve current risk prediction tools.

Keywords Blood pressure complexity · STS · EuroSCORE · Risk · Multiscale entropy

1 Introduction

Cardiovascular surgical procedures are increasingly being performed on patients who are at increased risk of major adverse events [1]. Two standard predictive risk assessment instruments, the Society of Thoracic Surgeons (STS) Risk of Mortality and Morbidity and the European System for Cardiac Operative Risk Evaluation Score (EuroSCORE II) indices incorporate information from population statistics and from individual static clinical measures, such as age [2, 3]. A notable health care priority, therefore, is the development of new measures of cardiac surgical risk [4]. One potential approach designed to foster "personalized" risk estimation would be to extract and quantify relevant measures from real-time physiologic signals that contain information about integrated cardiovascular control. Recent evidence [5] suggests that clinically important information, beyond a mean value or standard deviation (SD), is conveyed by the dynamical (beat-to-beat) fluctuations of such signals.

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✉ Balachundhar Subramaniam
bsubrama@bidmc.harvard.edu

1 Center for Anesthesia Research Excellence (CARE), Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02215, USA

2 Margret and H.A. Rey Institute of Nonlinear Dynamics in Physiology and Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA

3 Division of General Medicine and Primary Care, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA

4 Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA

5 Division of Cardiac Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

Surprisingly, even though radial arterial blood pressure (BP) is a key vital sign in cardiovascular monitoring, extracting "hidden" information from beat-to-beat fluctuations has been of only recent interest [5–10]. Furthermore, most of the literature on BP variability has limited its attention to conventional ("linear") measures related to the mean and SD. In this study, we expanded the analysis of BP signal to assess dynamical complexity, which reflects the system's capacity to adapt to changes and related stressors across multiple scales of time. The concept of physiologic complexity is closely related to that of system resilience and flexibility. For example, the complexity of beat-to-beat heart rate variations, reflecting the integrity of the underlying mechanical and neuro-autonomic control mechanisms, is highest in healthy young adults and degrades with cardiovascular pathology and senescence [5, 11–14]. To accomplish this, we employed a computational method, termed multiscale entropy (MSE) analysis [5, 11] derived from the study of complex (nonlinear) systems.

In designing this study, we hypothesized that higher complexity indices of preoperative beat-to-beat BP fluctuations, as measured by MSE, would be inversely correlated with risk, as estimated from the Society of Thoracic Surgeons (STS) Risk of Mortality and Morbidity Index and the European System for Cardiac Operative Risk Evaluation Score (EuroSCORE II), two validated surgical risk prediction instruments, in a group of subjects undergoing major cardiovascular procedures. From a translational viewpoint, the observed correlations between the complexity indices of fluctuations in preoperative BP values and the two standard risk indices raise the possibility that the addition of real time dynamical information from such time series could enhance the precision of conventional (static) risk assessment tools.

2 Methods

2.1 Surgical study population

The patient data were collected from January to November 2013 with an informed consent, as part of an ongoing prospective, single tertiary care center observational study funded by the National Institute of Health (R01GM098406). The protocol was approved by the Institutional Review Board of Beth Israel Deaconess Medical Center. Two hundred adult patients (18 years. or older) undergoing elective cardiac surgery with cardiopulmonary bypass were included after obtaining informed consent. As part of standard protocol, a radial arterial catheter was placed preoperatively with intravenous midazolam titrated to anxiolysis. Patients found to be in paroxysmal atrial flutter or atrial fibrillation during final preoperative preparations were excluded from analysis.

2.2 Arterial blood pressure signal collection and analysis

Continuous radial BP recordings at least 10 min in duration (range 10–67 min) were obtained during the preoperative period. No other perturbations were allowed from the radial arterial catheter placement until the patient was transferred to the operating room. The recordings were collected at sampling rate of 125 Hz with 12-bit amplitude resolution (Philips Medical, Andover, MA). Systolic, diastolic, mean and pulse pressure time series were extracted from the BP waveforms, according to techniques previously described elsewhere [15–17] and pre-processed to remove artifacts [10]. We note that the extraction of these time series from the original waveform creates beat-to-beat time series. For each of these four extracted BP time

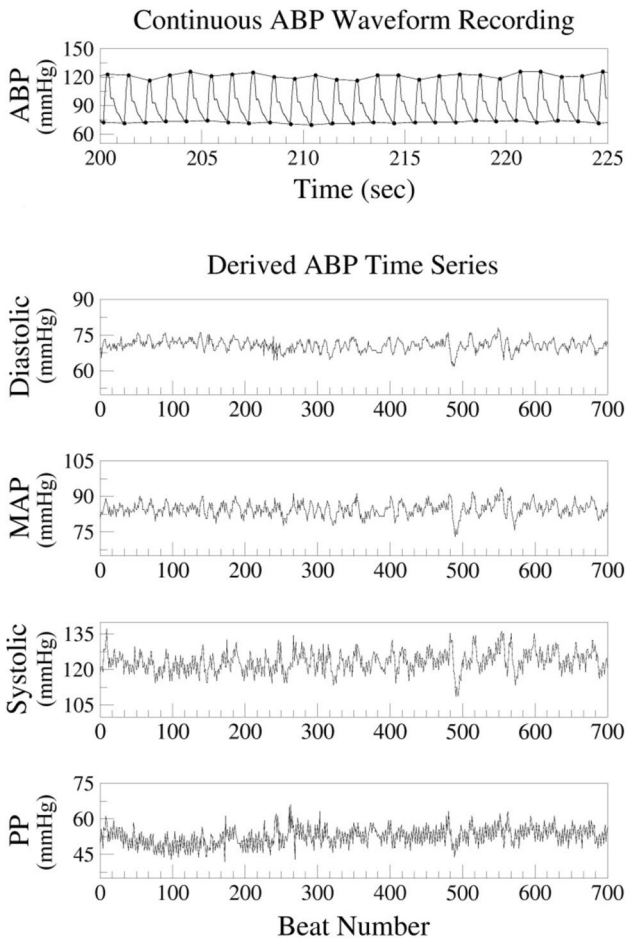

Fig. 1 Continuous arterial blood pressure (ABP) waveform (top panel) and derived systolic, diastolic, mean (MAP) and pulse pressure (PP) time series (lower panels) for one of the subjects. The black dots on the ABP waveform connected by solidlines represent the systolic and diastolic fiducial points, respectively

series (Fig. 1), we computed the mean and SD values and a set of complexity indices based on MSE analysis [11, 12].

As detailed elsewhere [11, 12] (see also Online Appendix 1), the MSE method quantifies the information content of a signal over multiple scales of time. The basic algorithm comprises two steps: (1) a coarse-graining procedure that allows one to capture representations of the system's dynamics at different scales, and (2) the quantification of the degree of irregularity of each coarse-grained time series using a suitable measure, such as sample entropy (SampEn) [18]. We refer to the sequence of SampEn values for the derived set of coarse-grained time series as the "MSE curve". From this curve, the following three complexity indices were extracted (see Online Appendix 1): (i) $MSE_{\sum}$, the sum of the entropy values from scales 1 to 5; (ii) MSE_{slope}, the slope of the linear regression line best fitting the entropy values over scales 1–5 and (iii) the $MSE_{\sum_{slope}}$, defined as the product of $MSE_{\sum}$ and MSE_{slope} [12, 13]. Since the length of the recordings varied among subjects, we eliminated differences in SampEn that could be attributed to differences in time series' length by dividing the original signal into non-overlapping segments of 750 data points each and calculating the complexity indices for each of these segments. Mean indices were then computed for each subject.

2.3 Operative morbidity and mortality risk assessment

Two previously validated cardiac surgical risk scores, the STS risk index of morbidity or mortality [19] and the EuroSCORE II [20–27], were computed [22–27]. The EuroSCORE II scores were calculated for all the 147 patients. The STS indices, designed only for those undergoing coronary artery bypass grafting (CABG), mitral or aortic valve procedures, or combined CABG and valve procedures, were obtained for the qualified patients from the STS national database (Note: STS does not calculate a risk score for other procedures at the time of analysis, http://riskcalc.sts.org/stswebriskcalc/#/calculate accessed March 8, 2017). Time series analysis of the arterial BP data was done in a manner blinded to risk index values.

2.4 Statistical analysis

The summary information for each of the BP measures are presented using notched boxplots. To evaluate monotonic correlations between each of the BP signal measures and the two risk indices, the Spearman rank correlation coefficient (r_s) was computed. The Spearman correlation was used to allow for the non-normal distribution, as well as the presence of outliers, of the risk scores (see Online Appendix 2). Then, linear regression analyses were performed to further explore the relationship between the complexity measures (predictors) and the risk indices (outcomes) with and without adjusting for age, gender and SD. For all of these analyses, the risk indices were natural log transformed to accommodate the non-normal residual plots when using linear regression on the untransformed indices. Standardized coefficients are presented to facilitate comparison of the magnitude of the associations across measures. Results, unless otherwise stated, are reported as mean ± SD. For statistical hypothesis testing purposes, we considered 2-sided p-value < 0.05 as indicating statistical significance. All analyses were performed using R version 3.2.3 [28].

3 Results

Patient demographics and type of surgery are shown in Table 1.

From the initial 200 patients, 53 were excluded either due to the presence of atrial fibrillation (n = 22) or having fewer than 750 consecutive data points in the BP time series (n = 31). We note that the demographic characteristics were similar for the 31 subjects excluded because they did not have the minimum number of data points required to calculate the dynamical measures. The EuroSCORE II was computed for all the 147 subjects in the final dataset. The STS was obtained for the 115 qualifying patients (STS computes risk scores for only for patients undergoing CABG, aortic and mitral valve procedures). Histograms showing the distribution of the STS and EuroSCORE II scores and the correlation between the two risk indices in our patient population can be found in Online Appendix 2.

Table 1 Patient demographic and surgical data

	All patients (n = 147)
Age (years), median [range]	67, [23–90]
Gender (male), n (%)	105 (71)
Diabetes mellitus, n (%)	43 (29)
CHF, n (%)	68 (46)
STS (%), median [range]	Median 13.04 Range [3.46, 55.38]
EuroSCORE II (%), median [range]	Median 1.53 Range [0.55, 42.75]
Surgery type	
CABG, n (%)	65 (44)
CABG + valve, n (%)	36 (24)
Valve, n (%)	42 (29)
Aortic surgeries, n (%)	4 (3)

CABG coronary artery bypass grafting; *CHF* congestive heart failure; *STS* Society of Thoracic Surgeons Risk of Morbidity or Mortality Index; *EuroSCORE II*, European System for Cardiac Operative Risk Evaluation Score; *Valve* cardiac valvular procedure

Figure 2 shows boxplots of the distribution of each of the BP measures including mean, SD, $MSE_{\sum}$, MSE_{slope} and $MSE_{\sum_{slope}}$. The Spearman rank correlation (r_s) between the risk indices and the BP measures are presented in Table 2.

We did not find a significant association between the SD of any of the BP time series and either risk index except for the SD of diastolic blood pressure. In contrast, the mean of the diastolic and pulse pressure showed a significant correlation with risk indices, such that lower values of mean diastolic pressure and higher values of mean pulse pressure were associated with higher risk scores.

A significant negative correlation was found between two of the complexity indices, MSE_{slope} and $MSE_{\Sigma_{slope}}$, and both of the risk indices for all BP time series but the pulse pressure one. For the latter time series only the correlation with the EuroSCORE score was statistically significant. Figure 3 shows the scatter plots of $MSE_{\Sigma_{slope}}$ for each of the four BP time series and the percentage change with the two logarithmically transformed risk indices. The linear regression coefficients between the complexity indices, MSE_{slope} and $MSE_{\Sigma_{slope}}$, and the risk scores, before and after adjusting for

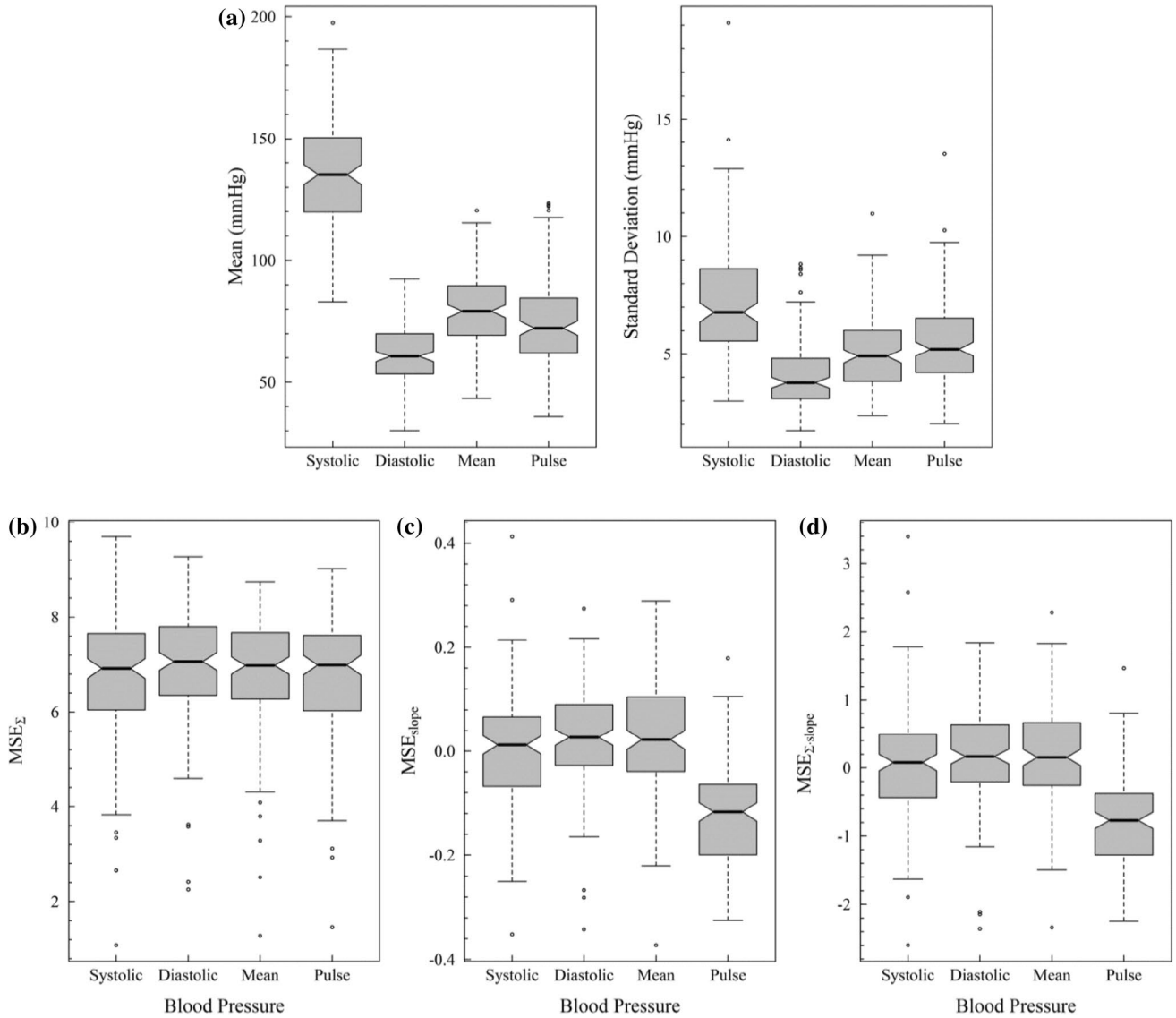

Fig. 2 Boxplots of arterial blood pressure values (**a** mean; **b** standard deviation; **c** $MSE_{\sum}$; **d** MSE_{slope}; **e** $MSE_{\sum_{slope}}$) per blood pressure time series (systolic, diastolic, mean arterial pressure, and pulse pressure). The gray box includes the interquartile range (values between the 25th and 75th percentiles). The line inside the box represents group median values. The whiskers bars indicate the minimum and maximum values excluding outliers (circles). The notch displays the 95% confidence interval around the median

Table 2 Spearman correlation coefficients: ABP measures and risk indices

	STS risk				EuroSCORE II			
	Systolic	Diastolic	MAP	PP	Systolic	Diastolic	MAP	PP
Conventional measures								
Mean	0.16	−0.20*	−0.03	0.30***	0.05	−0.24***	−0.11	0.23**
SD	−0.05	0.02	−0.01	0.12	−0.06	−0.05	−0.06	0.09
Dynamical measures								
MSE_{Σ}	−0.10	−0.16	−0.19*	−0.09	−0.16*	−0.20*	−0.19*	−0.13
MSE_{slope}	−0.34§	−0.35§	−0.28***	−0.12	−0.39§	−0.28§	−0.24***	−0.26***
$MSE_{\Sigma_{slope}}$	−0.35§	−0.35§	−0.27***	−0.10	−0.39§	−0.29§	−0.25***	−0.24***

MAP Mean arterial pressure; *PP* pulse pressure; *SD* standard deviation

p-values: *< 0.05; **<0.01; ***< 0.005; §<0.001

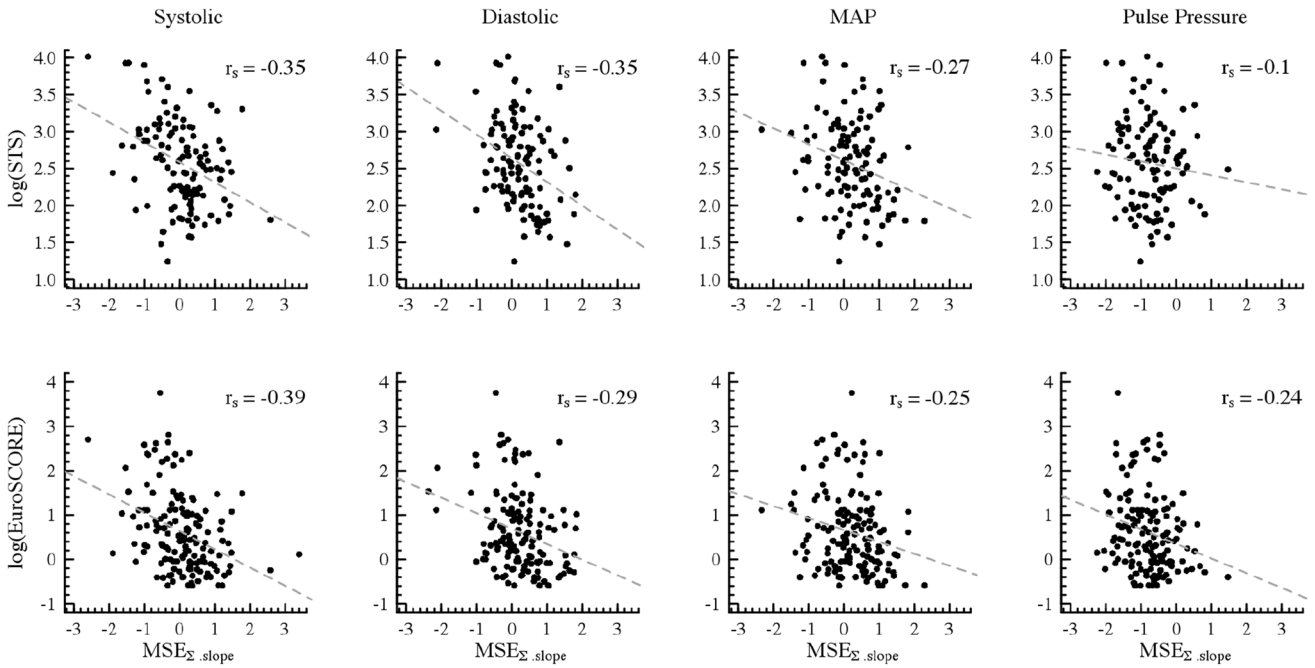

Fig. 3 Scatter plot of the $MSE_{\Sigma_{slope}}$ and the STS risk (top row) and the EuroSCORE II (bottom row) for the systolic (first column), diastolic (second column), mean arterial (third column), and pulse (fourth column) pressures

age, gender, SD of the BP time series are presented in Table 3.

In models adjusted for age, gender, and SD of the BP time series, a one SD increase in the MSE slope was associated with a 19%(MAP), 28% (systolic), and 29% (diastolic) lower STS risk, respectively. In these types of models (adjusted for age, gender and SD of the BP time series), a one SD increase in the MSE slope was also associated with a 16% (MAP), 31% (systolic), and 21% (diastolic) lower EuroSCORE risk. Mean systolic, diastolic, MAP and PP values were not significantly associated with any of the risk scores. Concerning the traditional measure of BP variability, i.e., the SD of the BP fluctuations, a significant association with the risk indices was only observed for the diastolic time series in the adjusted models. Specifically, a one SD increase in the value of the diastolic time series' SD was associated with a 23 and 19% higher STS and EuroSCORE risks, respectively. Of note, the results of both unadjusted and age and gender adjusted linear correlation analyses were similar to those obtained using Spearman (non-parametric) correlation analyses.

4 Discussion

The two main findings of the study were: (1) the observed modest to moderate inverse relationships between the complexity of the fluctuations in systolic, diastolic, mean and

Table 3 Percentage change (with 95% confidence intervals) in the risk scores associated with increase of one standard deviation of the ABP complexity indices and the risk indices

	STS risk (N = 115)				EuroSCORE II (N = 147)			
	Systolic	Diastolic	MAP	PP	Systolic	Diastolic	MAP	PP
MSE_{Σ}	−3 (−20, 16)	−6 (−21, 14)	−10 (−25,9)	−4 (−20, 16)	−9 (−20, 16)	−10 (−23, 6)	−10 (−23, 6)	−10 (−23, 6)
MSE_{slope}	−32§ (−44, −18)	−31§ (−42, −16)	−24*** (−37, −9)	−10 (−25, 8)	−34§ (−44, −22)	−25§ (−0.36, −0.11)	−21*** (−33, −7)	−23*** (−34, −9)
$MSE_{\Sigma_{slope}}$	−33§ (−44, −18)	−32§ (−43, −18)	−25*** (−38, −10)	−10 (−25, 8)	−34§ (−44, −22)	−26§ (−37, −13)	−21*** (−33, −7)	−22*** (−34, −8)
Age and gender adjusted								
MSE_{Σ}	−5 (−21, 14)	−11 (−26, 7)	−13 (−28, 5)	−4 (−20, 16)	−11 (−24, 5)	−14 (−27, 2)	−12 (−25, 4)	−11 (−24, 6)
MSE_{slope}	−27§ (−39, −12)	−31§ (−42, −17)	−20* (−33, −3)	−2 (−19, 18)	−30 § (−40, −17)	−24*** (−35, −10)	−16* (−29, −1)	−30* (−40, −5)
$MSE_{\Sigma_{slope}}$	−28§ (−40, −14)	−31§ (−43, −17)	−21* (−34, −3)	−3 (−19, 17)	−30 § (−40, −17)	−23 *** (−35, −10)	−16* (−28, −1)	−30* (−40, −4)
Age, gender, SD adjusted								
MSE_{Σ}	−4 (−20, 16)	−6 (−22, 13)	−11 (−26, 7)	−1 (−18, 19)	−10 (−24, 6)	−10 (−23, 7)	−10 (−24, 6)	−10 (−24, 8)
MSE_{slope}	−28§ (−40, −13)	−29§ (−41, −15)	−19* (−33, −3)	−3 (−20, 16)	−31§ (−41, −19)	−21*** (−33, −7)	−16* (−29, −1)	−31** (−41, −7)
$MSE_{\Sigma_{slope}}$	−29§ (−41, −15)	−29§ (−41, −14)	−20* (−34, −4)	−4 (−20, 15)	−31§ (−41, −18)	−21** (−33, −7)	−15* (−28, 0)	−31** (−41, −6)

MAP Mean arterial pressure; *PP* pulse pressure

p-values: *< 0.05; **<0.01; ***< 0.005; §<0.001

pulse pressure time series, and risk, estimated from the two standard instruments STS morbidity and mortality and EuroSCORE II is consistent with the complexity framework of aging and disease [29], (2) even after the adjustment for conventional measure of BP variability, namely SD, the increase in complexity measures such as MSE (slope and the product) showed a reduction in the STS and EuroSCORE risk. In concert, these findings highlight the limitations of "static" measures of variability that do not incorporate information encoded in the temporal sequence of the values and, therefore, are unable to detect differences in signals with the same amount of variability but different dynamical patterns. Furthermore, from a translational viewpoint, these findings support the possibility that the extraction of real time information from the dynamics of BP time series ("dynamical assays") might enhance the performance of risk indices that otherwise solely rely on static measures.

From a computational viewpoint, the MSE method was devised to quantify the information content of a signal over a designated range of scales. Since the output of the MSE analysis is a "curve," i.e., a set of values (one per time scale analyzed), we summarized the results by presenting three summary indices: MSE_{Σ}, the summation of the entropy values over pre-defined range of scales; MSE_{slope}, a measure of the rate of change of entropy with scale and $MSE_{\Sigma_{slope}}$ that combines the two previous measures into a single index. In terms of their individual associations with the risk indices, we found that MSE_{slope} and $MSE_{\Sigma_{slope}}$ outperformed the traditional complexity index MSE_{Σ}.

The entropy of a time series quantifies its degree of irregularity, or, in other words, how unpredictable each new observation is. Traditional (single scale) entropy measures do not allow differentiating between (uncorrelated) random signals and complex signals because both are variable and unpredictable. The development of MSE showed that if the entropy analysis was extended to a wide range of time scales, such discrimination was possible. While the entropy of an uncorrelated random signal monotonically decreases with time scale, that of a complex (fractal) signal remains approximately constant. Thus, information about how entropy values change with time scale, in addition to their magnitude, is important for understanding the dynamical structure of the original signal and therefore, the complexity indices are more informative than the traditional one.

The most informative time series, in terms of detecting an association between its dynamical properties and the risk indices, was the diastolic time series. It presented correlations both with the mean value and complexity indices. A possible explanation is the likelihood that the other signals present a lower signal-to-noise ratio. For example, a plausible source of noise in the systolic time series is the failure of fully automated algorithms to correctly identify beat-to-beat

BP waveform maximum values in the presence of exaggerated anacrotic notches. The PP time series are expected to be the noisiest of the BP time series. Given that the PP is the difference between the diastolic and systolic pressures, noise in either one of these values, or in both, will likely "appear" in the PP time series. Mathematically, if $|s_i|$ and $|d_i|$ represent the magnitude of the error in the measurement of the systolic and diastolic BP at time t_i, respectively, then the error in the PP value, p_i, will be between $-|s_i - d_i|$ and $|s_i + d_i|$.

The modest-moderate correlations observed between the complexity of the preoperative BP time series and the two standard risk indices is of interest. If there were no correlations, the likelihood of a meaningful association between the complexity measures and clinical outcomes would be low. Conversely, if the correlations were very strong, then the complexity measures and the risk indices would likely be redundant. In this case, the probability that the complexity measures would be able to improve risk stratification would also be low.

Our results raise the possibility of being able to improve the predictive value of the STS and EuroSCORE indices by incorporating BP complexity measures. However, an evaluation of the additive value of complexity indices combined with the cardiac risk indices was deferred for a future study in which a sufficient sample size becomes available.

4.1 Limitations

Our study has several limitations. The preoperative BP recordings obtained during a relatively stable period may not reflect the actual resting BP. As a standard practice, patients received intravenous midazolam to facilitate arterial catheter insertion (MSE indices, $p > 0.08$, $n = 124$ with and $n = 23$ without midazolam). The shorter duration of BP recordings (range 10–70 min, mean 26 min.) limited the number of time scales we were able to analyze. BP signals can be subject to multiple sources of noise (instrumentation-related, fiducial point errors in the detection of the diastolic or systolic values of the waveform, and beat misclassification) [30]. While it is impossible to completely obviate all the confounding factors, cardiac surgery arguably provides among the most protocolized standards of acute interventional care. No other perturbations were knowingly allowed after the placement of arterial catheter until the patient was take inside the room. Despite these limitations, our results are encouraging in that they show that fluctuations in BP variables during sinus rhythm are not random and appear to contain information relevant to risk prediction. We did not use cardiac interbeat interval electrocardiogram (ECG) fluctuations. The loss of electrical function during bypass and the ubiquity of cardiac pacing afterward limit the use of ECG derived heart rate variability measures. Therefore, by design our main focus is on the BP complexity measures. Office based continuous noninvasive BP complexity data could provide earlier risk assessments and triaging opportunity, particularly in the elderly and other high risk patients [4].

5 Conclusions

Preoperative beat-to-beat BP dynamical complexity has an inverse correlation with risk prediction by the STS and EuroSCORE II indices, and that this information is independent of the SD of BP alone. These findings support further investigation of the utility of complexity measures and mean diastolic blood pressure as predictors of major adverse events among patients undergoing cardiac surgical procedures.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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