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Preoperative Blood Pressure Complexity Indices as a Marker for Frailty in Patients Undergoing Cardiac Surgery

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Abstract

Objective—Frailty, a state of decreased physiological reserve increases the risk of adverse outcomes. There is no standard tool for frailty during perioperative period. Autonomic dysfunction, an underlying process in frailty could result in hemodynamic fluctuations. Complexity, the physiological adaptability of a system can quantify these fluctuations. We hypothesized complexity could be a marker for frailty and explored their relationship in cardiac surgical patients.

Design—Prospective, observational study

Setting—Single-center, teaching hospital.

Participants—364 adult patients undergoing cardiac surgery.

Intervention—none

Measurements and main results—Preoperative beat-to-beat systolic (SAP) and mean (MAP) arterial pressure time-series were obtained. Complexity indices were calculated using multiscale entropy (MSE) analysis. Frailty was assessed from: age > 70 years, BMI < 18.5, hematocrit < 35%, albumin < 3.4 g/dL, and creatinine >2.0 mg/dL. The association between complexity indices and frailty was explored by logistic regression and predictive ability by C-statistics. In total 190 (52%) patients had frailty. Complexity index (MSE_{Σ}) median (quartile1, quartile3) of SAP and MAP time series decreased significantly in frail patients [SAP: 8.32 (7.27, 9.24) vs 9.13 (8.00, 9.72), $P < 0.001$ and MAP: 8.56 (7.56; 9.27) vs 9.18 (8.26; 9.83), $P < 0.001$]. MSE_{Σ} demonstrated a fair predictive ability of frailty [C-statistic: SAP 0.62 and MAP 0.64].

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Conclusion—Preoperative BP complexity indices correlated and predicts frailty. Impaired autonomic control is the underlying mechanism to explain this finding. A simple automated measure of preoperative BP complexity in the surgeon's office has the potential to reliably assess frailty.

Keywords

Frailty; BP variability; complexity; cardiac surgeries; preoperative assessment

INTRODUCTION

It is estimated that one in every five US residents will be >65 years of age by 2030.[1] Increasing number of elderly patients at increased risk for perioperative adverse events are presenting for cardiac surgery. Frailty is a state of decreased physiological reserve and resistance to stressors.[2] It is a distinct concept of biological rather than chronological age and could explain the observed variations in outcomes that cannot be explained by chronological age alone. Moreover, the underlying mechanisms are different from ageing.[3]

Frailty, a better predictor of adverse outcomes than chronological age[4,5] has been shown to be significantly associated with adverse surgical outcomes.[6–8] However, there is no universally accepted tool to assess frailty especially in the perioperative period.[9] The precise mechanism behind frailty and complications remains less understood. Several underlying physiological processes result in frailty. A marker that influences or interacts with these mechanisms could better identify frailty. Autonomic dysfunction a distinct pathophysiological mechanism, when probed could better identify frailty.

Autonomic dysfunction measured by heart rate variability has been demonstrated as a better predictor of frailty and mortality in elderly patients.[10] Similarly, BP variability due to autonomic dysfunction has been proposed as a mediator of complications in frail patients.[11] Several methods were used to define BP variability.[12–14] However, none of them describe the temporal dynamics of BP changes. With advanced computational techniques, temporal dynamics of BP variability could be used to analyze complexity.[15] Complexity similar to frailty reflects the physiological adaptability of a system and decreases with ageing and underlying pathology. Studies have demonstrated significant association between BP complexity and standard risk prediction scores.[15–17]

We hypothesized autonomic dysfunction quantified by BP complexity indices as a marker of frailty. In this study, we explored the association between preoperative BP complexity indices[16] and frailty measured using a previously published score[11,18] in patients undergoing cardiac surgery.

METHODS

Study population

Data for this prospective, observational, cohort study was collected from an observational study funded by the National Institute of Health (R01GM098406) conducted from January 2013 to June 2018. After obtaining Institutional Review Board (Beth Israel Deaconess

Medical Center, Boston, MA, USA) approval and informed verbal consent, we included adult patients undergoing elective cardiac surgery with cardiopulmonary bypass (CPB). This study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[19] Data related to patient characteristics, investigations, surgery, anesthesia, and hemodynamics were collected from institutional databases and Anesthesia Information Management System (AIMS; Philips Medical, Andover, MA) and were de-identified before analysis. Patients who experienced paroxysmal atrial flutter or atrial fibrillation were excluded from the analysis. Society of Thoracic Surgeons (STS) national database was used to obtain the STS Risk of Mortality and Morbidity Index. EuroSCORE II preoperative risk was calculated for all our patients.

Invasive arterial blood pressure waveforms

Before surgery, during the preoperative period, a 20-gauge catheter was inserted in the radial artery after midazolam sedation. Invasive BP measurements were obtained for a minimum of 15 minutes before induction. Extreme care was taken to prevent any external disturbances from the time of radial arterial catheter placement to the transfer into the operating room. The BP waveform recordings were sampled at a rate of 125 Hz with 12-bit amplitude resolution (Philips Medical, Andover, MA). The waveform signals were then transferred to a secure server within our hospital.

Blood pressure waveform Analysis

A custom-made software by PhysioNet[20] and Philips Health-care was used to convert the data to an open-source format (WFDB). Beat-to-beat systolic (SAP) and mean arterial pressure (MAP) were extracted using previously described software[21] as were characterized as maximum, minimum and mean BP values in each cardiac cycle, respectively. We then preprocessed the BP time-series for removing artefacts.[20,22,23]

Blood pressure Complexity measurement

The complexity of each of the detrended BP time-series was assessed using the multiscale entropy method (MSE) in conjunction with the sample entropy algorithm (SampEn)[24]. The MSE method quantifies the information content of a signal over multiple scales of time. Briefly, the method comprises of two steps: (1) the coarse-grained procedure creates one time-series for each scale (n = 1, 2, 3…) by averaging "*n*" consecutive data points of the original time-series, in non-overlapping windows; (2) quantification of the coarse-grained time-series complexity (entropy). The SampEn was calculated with parameters values $m = 2$ and $r = 0.15*SD$. Based on the curve of the entropy values as a function of the scale factor, three complexity indices were extracted: (1) MSE_{Σ}, the sum of entropy values from scales 1 to 5; (2) MSE_{slope}, the slope of linear regression line best fitting the entropy values over scales 1–5 and (3) the $MSE_{\Sigma \cdot slope}$, defined as the product of MSE_{Σ} and MSE_{slope}.[25,26] Each BP time-series were divided into non-overlapping windows of 750 data points and the complexity measures were computed for each of those segments. The computational steps have been previously published.[16]

Frailty measurement

Frailty was measured using a previously published chart derived frailty score based on preoperative patient characteristics.[11,18] It consists of 5 variables: age > 70, preoperative BMI < 18.5, hematocrit < 35%, albumin < 3.4 g/dL, and creatinine >2.0 mg/dL. A patient was considered to be frail when any one of the above five variables was present (Frailty: absent if score was 0, present if ≥ 1).

Statistical analysis

The complexity indices were summarized with median and quartiles, by frailty group due to their skewed distribution. The normality was visually accessed by the histogram and the QQ-plot. Wilcoxon test was used to compare the complexity between frail and not frail patients. The significance level was adjusted using the Hochberg sequential procedure, by ranking the original P values in descending order with a family-wise error rate at 5%.[27] The area under the receiver operating characteristic curve (C-statistic), as well as its 95% confidence interval, were also computed. The C-statistic, for binary outcomes, is a measure of discrimination of the logistic regression model. All analyses were performed using the statistical software R version (The R Foundation for Statistical Computing, Vienna, Austria) 3.5.0.[28]

Exploratory analysis

Current risk indices such as STS and EuroSCORE do not have a prediction model for ICU length of stay (LOS). Median ICU length of stay in our ICU was 30 hours with interquartile range of 28 to 56 hours. We chose 48 hours as cut off for short ICU length of stay. Total ICU length of stay was taken as the final outcome of interest. This includes both ICU readiness to discharge and readmissions to ICU.

In our limited sample size, we explored the ability of following indices to predict short ICU length of stay, a) complexity index MSE_{Σ}, b) Frailty index, c) Predicted STS short LOS, d) STS combined with complexity indices. This prediction was expressed as AUC values with confidence intervals after adjustment for age and gender.

RESULTS

In total, 364 patients were included in the final analysis. Baseline characteristics of the patients were presented in Table 1. The median age was 67 years and 261 (72%) patients were male. The study population had a mean (SD) BMI of 29.2 (5.5) and hematocrit 38.6 (5.1) %. The median (IQR) serum levels of creatinine and albumin were 1 (0.5, 8.4) mg/dl and 4.1 (1.8, 5.1) gm/dl respectively. Coronary artery bypass grafting surgery (CABG) was done in 184 (51%) patients, isolated valve surgeries in 93 (25%), combined CABG with valve surgeries in 76 (21%) and 11 (3%) patients underwent aortic surgeries. The median (IQR) STS score was 12.98 (3.5, 70) % and EuroSCORE II was 1.79 (0.6, 43) % for our patients.

Frailty computation

Frailty was present in 190 (52%) patients varying from 0 to 3. Frailty score of 3 was seen in 11, 2 in 56 patients, and 1 in 123 patients. Association between BP complexity indices and frailty is shown in Table 2. The complexity measures for systolic and mean arterial pressure time series significantly decreased in patients with frailty.

Frailty and complexity measures

The values of all three complexity indices for SAP and MAP stratified by frailty is presented in Table 2. After performing Hochberg sequential procedure, all *P* values were significant. Complexity index [MSE_{Σ}, median (quartile1, quartile3)] significantly decreased in patients with frailty as compared to those without frailty. MSE_{Σ} for SAP [8.32 (7.27, 9.24) vs 9.13 (8.00, 9.72); P <0.001] and MAP [8.56 (7.56; 9.27) vs 9.18 (8.26; 9.83); P <0.001].

Other complexity measures of SAP: MSE_{slope} [−0.03 (−0.09; 0.03) vs 0.03 (−0.06; 0.11), P <0.001], $MSE_{\Sigma.slope}$ [−0.25 (−0.74; 0.29) vs 0.25 (−0.45; 1.00), P <0.001] and MAP: MSE_{slope} [0.02 (−0.06; 0.08) vs 0.05 (−0.04; 0.11), $P = 0.007$], $MSE_{\Sigma.slope}$ [0.14 (−0.42; 0.71) vs 0.42 (−0.25; 1.07), $P = 0.003$] were significantly decreased in patients with frailty (Table 2).

Prediction of frailty

The ability of BP complexity measures to predict frailty was explored using area under the receiver operating characteristic curve (AUC) (Table 3). Complexity index (MSE_{Σ}) of SAP and MAP time series demonstrated fair predictive ability for frailty [C-statistic (95% confidence intervals): SAP 0.62 (0.56, 0.67), MAP 0.64 (0.58, 0.70)]. Similar results were observed for other complexity measures from SAP [MSE_{slope} 0.65 (0.59, 0.71), $MSE_{\Sigma.slope}$ 0.65 (0.59, 0.71)] and MAP [MSE_{slope} 0.56 (0.50, 0.62), $MSE_{\Sigma.slope}$ 0.54 (0.48, 0.60)] time series.

Exploratory analysis

a) Other Blood Pressure Time series—As an exploratory analysis, we computed complexity measures from preoperative diastolic (DAP) and pulse pressure (PP) time series and studied their correlation with frailty. Similar to the primary analysis, the complexity measures were significantly decreased in frail patients.

b) Association with outcomes—Table 3 presents the results of predictive ability of BP complexity measures, frailty, STS risk index alone and in combination with complexity measures towards the outcome, 48 hour intensive care unit (ICU) length of stay (LOS). Complexity index alone predicted 48-hour ICU LOS when adjusted for age and gender similar to that observed with frailty and STS. Addition of the complexity score did not increase the ability of STS prediction. A sensitivity analysis to initial ICU readiness to discharge at 48 hours and 60 hours as outcome of interest showed similar AUC values for all parameters of interest.

DISCUSSION

In this cohort of patients undergoing cardiac surgery, we found a significant correlation between preoperative frailty assessment and blood pressure complexity measured by MSE analysis. We observed a significant decrease in BP complexity measures among patients with frailty. Our results were similar to previous studies that showed a similar decrease in complexity measures in patients with adverse outcomes after cardiac surgery.[15] A decrease in physiological adaptiveness and functional integrity has been hypothesized as a possible reason for the observed reduction in complexity of hemodynamic signals. Several other studies have demonstrated a decrease in complexity due to aging and underlying pathological conditions.[29–31] These factors may explain the relatively good correlation between complexity and frailty observed in this study.

Autonomic dysfunction quantified by beat-to-beat variability of physiological signals has been demonstrated to predict organ damage and adverse outcomes.[32] In a study among elderly patients, spectral heart rate variability measures, from continuous ECG recordings over 2–3 hours during standardized clinical assessments, were found significantly associated with frailty.[10] We found a similar correlation between complexity measured from BP variability and frailty, using BP time series, with at least 15 min, from the perioperative setting. Moreover, we chose to study BP instead of heart rate fluctuations for a couple of reasons: 1) BP regulation determines organ perfusion than heart rate and 2) a significant number of cardiac surgical patients have electronically paced rhythms, limiting the utility of heart rate time series.

James et al[11] demonstrated associations between BP variability and frailty related postoperative mortality in noncardiac surgical patients. They used MAP lability, a relative change of ≥15% from the previous interval. Our study showed a similar relation between complexity indices computed from BP variability and frailty. However, we studied in cardiac surgical patients and measured complexity[15,16,25] using beat-to-beat BP signals that has high data resolution compared to wider measurement intervals in other studies.

Frailty is a state of decreased capacity in adaptive mechanisms to respond to stressors and has been significantly associated with adverse postoperative outcomes.[6–8] However, a routine assessment is often not considered in perioperative settings which led to the researchers even referring frailty as “elephant in the operating room: easy to spot but often ignored”.[33]

Deterioration of underlying homeostatic mechanisms results in frailty and a marker interacting with these mechanisms could better identify frailty. Impaired autonomic control results in loss of complexity,[10] which is the physiological adaptability of the system in response to stressors.

Multiple model and indices for frailty assessment exits in literature.[34] However, they remain complex, needs specialized testing, consumes time, require patient participation and may not be feasible in perioperative settings.[35] Methods that are simple, doesn’t need patient participation or laboratory work and place minimal burden on perioperative physicians is desirable. Our complexity measures assessed from continuous invasive or noninvasive BP signals that can be obtained from surgeon's office has a potential to be routinely incorporated for frailty assessment by itself or in combination with existing frailty indices.

Due to the limitation of sample size, we resorted to test the frailty score, complexity score, and STS short length of stay prediction in their ability to predict 48-hour ICU length of stay. The AUC C-statistic though was modest, their individual ability to predict this was similar to that of the complex STS score. STS scores have done reliably well for morbidity and mortality prediction in a given population. Therefore, the ability of this complexity index that can be derived from a non-invasive monitor to predict ICU length of stay needs to be tested in a larger database.

Our study has several limitations. First, we didn't explore the relationship with postoperative adverse outcomes. We acknowledge that while an association was not explored, identifying a marker for frailty that would be feasible during perioperative setting would be a major initial step. Second, as with any observational study identifying a causative link for associations is a challenge. Third, we didn't use the traditional indices of frailty rather used a recently published chart derived frailty score. However, this tool utilizes preoperative variables avoiding intense workload associated with formal instruments. We studied our BP complexity indices with laboratory based frailty index which may not be accurate. Association with other frailty indices may provide better provide ability but will need prospective data collection. Fourth, outcome analysis was done in a small sample size that precludes definitive conclusions. The small sample size also had limited outcomes (less than 5% of patients had a major adverse postoperative outcome). Therefore, we chose ICU length of stay as outcome of interest. However, the ability of complexity score to fair as good as the STS score in this small database warrants testing in larger populations. There are several strengths in our study. While other studies used static indices to measure BP variability, we used MSE that gives importance to the temporal significance of beat-to-beat BP change. Moreover, beat by beat BP fluctuations were analyzed compared to other studies that used non-invasive BP and wider measurement time interval.

Our results demonstrate a significant relationship between complexity and frailty probably due to underlying impaired autonomic control. Complexity measures of BP variability could serve as a potential marker of frailty, with an ability to discriminate subtle changes in an individual's physiological reserve. We conclude that, preoperative BP complexity by itself or in addition with frailty indices could accurately quantify frailty.

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Table 1.

Baseline patient and surgical characteristics

Variables	All patients (N = 364)
Age (years)†	67 [24, 92]
Gender (male)‡	261 (72)
Body Mass Index§	29.20 (5.53)
HCT§	38.59 (5.11)
Creatinine†	1.00 [0.50, 8.40]
Albumin†	4.10 [1.80, 5.10]
STS (%)†	12.98 [3.46, 69.50]
EuroSCORE II (%)†	1.79 [0.55, 42.91]
Surgery Type‡	
CABG	184 (51)
CABG + Valve	76 (21)
Valve	93 (25)
Aortic Surgeries	11 (3)

† median [quartile 1, quartile 3],

‡ number (percentage),

§ mean ± SD.

SD = standard deviation; STS = Society of Thoracic Surgeons risk score; EuroSCORE II = European System for Cardiac Operative Risk Evaluation; CABG = Coronary Artery Bypass Grafting

Table 2.

Blood pressure complexity measures stratified by frailty and predictive ability from area under the receiver operating characteristic curve (C-statistic)

Complexity Measures[†]	No Frailty	Frailty	*P* value[*]	C-statistic[‡]
Systolic Arterial Pressure				
MSE_{Σ}	9.13 [8.00; 9.72]	8.32 [7.27; 9.24]	<0.001	0.62 [0.56, 0.67]
MSE_{slope}	0.03 [−0.06; 0.11]	−0.03 [−0.09; 0.03]	<0.001	0.65 [0.59, 0.71]
$MSE_{\Sigma \cdot slope}$	0.25 [−0.45; 1.00]	−0.25 [−0.74; 0.29]	<0.001	0.65 [0.59, 0.71]
Mean Arterial Pressure				
MSE_{Σ}	9.18 [8.26; 9.83]	8.56 [7.56; 9.27]	<0.001	0.64 [0.58, 0.70]
MSE_{slope}	0.05 [−0.04; 0.11]	0.02 [−0.06; 0.08]	0.007	0.56 [0.50, 0.62]
$MSE_{\Sigma \cdot slope}$	0.42 [−0.25; 1.07]	0.14 [−0.42; 0.71]	0.003	0.54 [0.48, 0.60]

[*]Level of significance was adjusted using Hochberg sequential procedure

[†]Blood pressure complexity measures are presented as median [quartile 1; quartile 3].

MSEΣ = complexity index, the sum of entropy values from scales 1 to 5;

MSEslope = slope of linear regression line best fitting the entropy values over scales 1 to 5;

MSEΣ.slope = product of MSEΣ and MSEslope

[‡]C-statistic = Concordance statistic values and their corresponding 95% confidence intervals.

Table 3.

Predictive ability complexity index, frailty, STS risk score and complexity index combined with STS risk score towards of 48 hour ICU length of stay

Indices	C-statistic*
MSE_{Σ}- SAP	0.61 [0.55,0.68]
MSE_{Σ}- MAP	0.59 [0.53,0.65]
Frailty Score	0.59 [0.54,0.64]
STS	0.64 [0.58, 0.70]
STS + MSE_{Σ} - SAP	0.65 [0.58, 0.71]
STS + MSE_{Σ} - MAP	0.64. [0.58,0.71]

*C-statistic, concordance statistic values with 95% confidence intervals, adjusted for age and gender

MSEΣ = complexity index, the sum of entropy values from scales 1 to 5;

SAP = systolic arterial pressure; MAP = mean arterial pressure; STS = society of thoracic surgeons