Beat-to-Beat Blood Pressure Variability for Long-Term Risk Assessment

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Abstract

Previous studies investigated the use of Heart Rate Variability (HRV) from electrocardiogram waveforms for risk stratification, as embedded temporal features may associate with post-operative complications and mortality. We aim to test whether beat-to-beat Blood Pressure Variability (BPV) can predict one-year mortality in Transcatheter Aortic Valve Implantation (TAVI) patients, and if so, which aspects can improve mortality prediction.

High frequency, 500 Hz, blood pressure waveforms of 385 consecutive patients undergoing TAVI were identified and recorded. Of the 385 patients 357 had mortality outcomes up to one-year, of which 49 were deceased. We compared select linear and non-linear beat-to-beat variability metrics with one-year mortality as the performance metric. Statistical differences between the populations were verified using Wilcoxon Rank Sum Test.

Analysis of HRV showed high frequency power percent $p < 0.05$; density $p < 0.05$; and local dynamic score $p < 0.01$. Non-linear Systolic Multiscale Entropy Average, Slope and Average x slope of systolic BPV were significant $p < 0.001$. We did not find any statistical difference between the diastolic metrics. Beat-to-beat analysis of temporal dynamics showed that high resolution blood pressure waveforms predicted one year mortality.

1. Introduction

Previous studies investigated heart rate variability (HRV) from high frequency electrocardiogram (ECG) waveforms for frailty assessment and post-surgical risk stratification of Transcatheter Aortic Valve Implantation (TAVI)cohorts, as embedded temporal features in the sequence of R-R intervals of the QRS complex may be a useful biomarker for autonomic nervous system (ANS) tone, associated with post-operative complications and mortality [1]. Many surgical procedures generate high frequency blood pressure (BP) waveforms for patient monitoring, which waveform data may also contain temporal dynamics information that can be retrospectively assayed for relative frailty and risk [2]. This study aims to test whether invasive beat-to-beat blood pressure variability (BPV) is associated with one-year mortality in TAVI patients, and if so, which aspects can improve mortality prediction. We also compared beat-to-beat HRV versus BPV metrics in both linear and nonlinear forms to test which kinds of measures might best assess patients' frailty and long-term risk.

2. Methods

2.1. Patient Population

After Institutional Review Board approval, high frequency femoral artery BP and ECG tracings from 362 contiguous patients undergoing TAVI procedures at Tufts Medical Center (Boston MA) were de-identified, transferred from local perioperative servers (Merge Hemo, Merge Healthcare Incorporated, Hartland WI, USA) and stored in a central archive for retrospective analysis. On the Society of Thoracic Surgeons and American College of Cardiology Transcatheter Valve Therapy Registry, 357 subjects had one-year outcomes recorded, of which 46 (12.9%) were deceased within one year. As shown in Figure 1, four patient data sets were not available and 12 did not support the subsequent analysis due to persistent waveform instability.

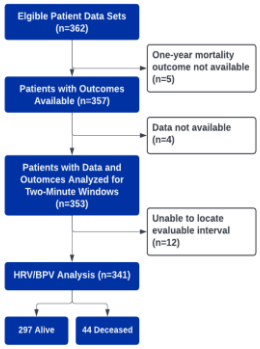

Figure 1. Patient waveform selection and processing for final cohort n numbers.

2.3. Waveform Processing

During TAVI procedures, the BP waveform is subject to significant disruption and interference due to the ongoing surgical perturbation of the cardiovascular system which includes tunneling (catheter threading), flushing (with liquid) and valve deployment. To address this, we implemented an optimization strategy to identify multiple two-minute segments of stable BP waveforms before and after the intervention. Stability was ensured by requiring that each identified ECG QRS complex was paired with a detected BP peak. The selected time periods were further qualified based upon timing and we prioritized segments according to the number of identified non-arrhythmic matched ECG and BP beats.

Processing of ECG and BP waveforms began with the qualification of each signal based upon predefined amplitude ranges followed by the identification of individuals beats. The ECG R-wave was detected from the lead II waveform using a first difference algorithm [11-12] and was followed by identification and removal of ectopic beats based upon peak width and the local beat-to-beat interval.

Blood pressure waveforms were band-pass filtered between 0.1 and 25 Hz and subject to a loose peak detection algorithm to identify each beat. Fiducial points associated with peak amplitudes that were beyond five standard deviations of the median value were removed.

2.4. Interval Selection

Having determined estimates of ECG and BP fiduciary points, we qualified the beat detections using the Pulse Transit Time (PTT), calculated as the time interval between each R-wave location and the closest subsequent BP peak waveform. Extra ECG and BP beats were detected and removed as were intervals associated with PTT values beyond the 0.1 to 0.5 second interval.

Within each two-minute interval, we required at least 60 valid matched ECG and BP beats. Given the full set of two-minute segments, we selected 20 intervals based upon the highest number of matched and validated beats waveforms.

2.5. Heart Rate Variability

The R-R intervals were calculated within each selected two-minute segment. Intervals less than 0.2 seconds or greater than 2 seconds were discarded. Within each two-minute segment the remaining series of R-R intervals were normalized to the intersegment median and statistical, frequency domain, geometric and nonlinear HRV metrics were calculated [13-18]. For geometric methods we used the ratio of SD1/SD2 from the Poincaré plot.

Frequency domain metrics were derived from an estimate of the power spectral density (PSD) of the time series of R-R intervals using the Lomb-Scargle method [17-18]. Frequency domain metrics were determined through a box-car integration over the published ranges low and high frequency and then evaluated as a percentage of total power. Composite HRV metrics for each patient were calculated as the median value over the 20 segments.

2.5. Blood Pressure Variability

The diastolic and systolic blood pressures associated with each beat were determined and the beat-to-beat linear and nonlinear variation were evaluated using statistical and complexity measures, respectively. Linear measures included the mean, the coefficient of variation, the average real variation, the root-mean-square of the first difference and the standard deviation. The complexity of each diastolic and systolic two-minute time series was assessed through the multiscale entropy (MSE) [17] by applying the sample entropy [18] over multiple time scales. Using the computed entropy values as a function of scale factor, we computed additional complexity indices including the sum of entropy values from scales 1-5, the slope of the first five entropy and the product of the sum and slope as describe by Rangasamy [19].

Composite linear and nonlinear BPV metrics for each patient were calculated as the median value over the 20 segments.

2.6. Statistical Analysis

Statistical differences in the computed HRV and BPV metrics between the two populations were evaluated using a Wilcoxson Rank Sum Test and visualized the results using box plots. Significant (<0.01) HRV metrics included High frequency power percent, Local Dynamic score, Density Score, and the ratio of SD1/SD2 (PoincarSD2dSD1). Linear systolic BPV average variance was associated with mortality (p value <0.01) but differed with Wilcoxson Rank sum analysis (>0.05). There was no significance in diastolic pressure dynamics between the two cohorts.

3. Tables

Table 1. Patient Demographics

Average (SD) or n/N (%)	Alive at 1 year	Deceased at 1 year	P Value (T Test)
Age	82 (±8.55)	79 (±10.14)	0.102
≤69	40/297 (13.5)	5/44 (11.4)	0.169
70-89	236/297 (79.5)	28/44 (63.6)	0.905
≥90	30/297 (10.1)	10/44 (22.7)	0.532

Gender, male	162/297 (54.5)	24/44 (54.5)	0.823

IRB only allowed for limited demographics to be collected. As shown in Table 1, the alive versus deceased populations were not biased by age or sex.

Table 2. HRV Metrics

HRV Metric	P Value (Wilcoxson Rank Sum Test)
High Frequency Power Percentage (%)	0.003
Low Frequency/High Frequency	0.017
Local Dynamic Score	0.013
Density Score	0.014
Poincare SD2/SD1	0.003

Heart Rate Variability Metrics showed significant difference when analysed following normalization between the cohorts. The results show that within our cohorts there is a significant difference in the HRV metrics.

Table 3. Systolic BPV Metrics

Systolic Multiscale Entropy Metric	P Value (Wilcoxson Rank Sum Test)
Average	0.007
Slope	0.003
Product	0.004
CV	0.003

All systolic MSE (Scales 1-5) metrics were significantly different in a frail cohort.

Table 4. Diastolic BPV Metrics

Diastolic Multiscale Entropy Metrics	P Value (Wilcoxson Rank Sum Test)
Average	0.031
Slope	0.670
Product	0.734
CV	0.643

Diastolic BPV metrics were overall insignificant except for the average which is (<0.05). In this cohort of frail patients systolic BPV findings are overall more significant.

4. Results

Nonlinear BPV metrics were derived from Multiscale Entropy (MSE) Scales 1-5 (see table 3). We found statistical significance in all systolic metric values. Differences related to diastolic BPV were not found to be significant except for the average with a significance <0.05 (See table 4).

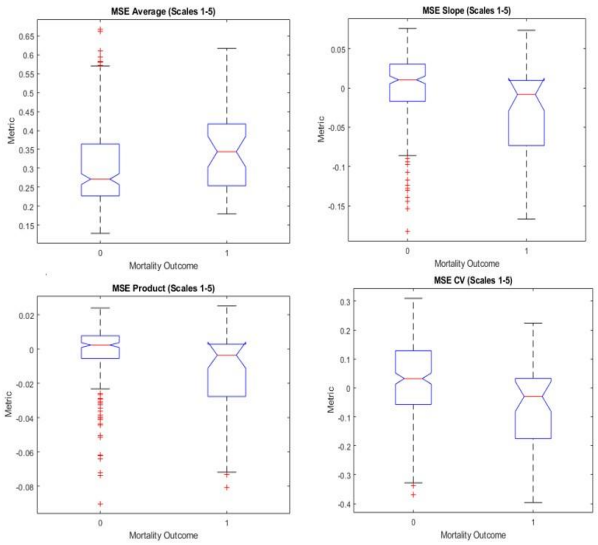

Figure 2. The longer tails present in the mortality cohorts boxplots allow for greater complexity in terms of the mean. This finding means that systolic BPV metrics contribute to prediction of morality.

5. Discussion

Complex autoregulation may allow mammalian cardiovascular systems to respond effectively to changing external conditions while maintaining stable internal perfusion and self-care [3]. This complexity of regulatory dynamics reduces with aging, as the body's ability to maintain reciprocating nonlinear feedback loops is diminished [4, 5]. However, there is uncertainty whether diminished HRV has clinical utility in assessing post-operative risk in cohorts with compromised cardiovascular function [6]. A difficulty of HRV as a reproducible biomarker for long-term risk is that the ANS as an information conduit is delicately sensitive to stimuli and is therefore inherently unstable. Methods of nonlinear time series analysis assume stability as a prerequisite of determining signal complexity [7]. Meanwhile, nonlinear BPV may also show frailty and risk [8]. For example, Lee et al showed that BP complexity fell consistently across age quintiles [9]. However, often BPV studies use non-invasive finger cuff or low-frequency sampling, limiting the ability to understand risk from short time series [7].

It is noted that as in [10], discussions of physiological oscillations equate beat-to-beat 'chaotic' or 'complex' signals as intrinsic to biological processes and looked for increased nonlinear 'variability' as indicators of health. In study of BPV, however, this narrative faltered, as extended (day-to-night, week-to-week, visit-to-visit) low frequency 'variability' came to indicate linear variance or spread of

the signal, and therefore increased variance came with frailty, pathology, and poor outcomes. But the same word - variability - was used for studies of both phenomena, leading to confusion and hindering clinical applications.

The HRV is measure of the neurological signal quality, where irregularity or aperiodicity as a marker of information content indicates a healthy feedback loop, while BPV is the outcome of signal quality, where increased spread of data values results from information loss, thermodynamic inefficiency, and therefore an increased risk of hypotension or hypertension. Our results showed increased 'linear variability' in BPV as a significant predictor of risk, and scales of 'complex' or 'nonlinear variability' at MSE-5 also associated with outcomes as there may be a regulatory harmonic oscillation within the BP waveform.

The most accurate picture of relative frailty, pathology and risk in an older cohort may be a combined index of linear and nonlinear measures of pressure and shape, rather than one single metric. As interdependent feedback loops (pressure, biochemical, neurohumoral) operate at different dynamic tempos, it may take an ensemble of time series approaches using multimodal high frequency waveform data to best characterize the physiological state. Further study will be needed to test this.

6. Conclusion

Beat-to-beat analysis of temporal dynamics showed that high-resolution BP waveforms predicted 1 year mortality. Our study highlights the potential of incorporating temporal dynamics of physiological waveforms to assess the risk of adverse outcomes after treatment. Validation is needed using larger datasets.

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