Original Article

Association of Preprocedural Ultrashort-Term Heart Rate Variability with Clinical Outcomes after Transcatheter Aortic Valve Replacement: A Nested, Case-Control, Pilot Study

Najla Beydoun[1,2], Sadeq A. Quraishi[1,2], Ebenezer Tolman[1], Wejdan Battarjee[1], Andrew Weintraub[2,3], Fredrick Cobey[1,2], Edward Hong[1]

[1]Department on Anesthesiology and Perioperative Medicine, [3]Divison for Cardiology, Department of Medicine, Tufts Medical Center, Boston, MA, [2]Department of Medicine, Tufts University School of Medicine, Boston, MA, United States

ABSTRACT

Background: Because heart rate variability (HRV) has been linked to important clinical outcomes in various cardiovascular disease states, we investigated whether preprocedural ultrashort-term HRV (UST-HRV) differs between 1-year survivors and nonsurvivors after transcatheter aortic valve replacement (TAVR).

Methods: In our single-center, retrospective, nested pilot study, we analyzed data from patients with severe aortic stenosis undergoing TAVR. All patients had preprocedural UST-HRV measured before the administration of any medications or any intervention. To investigate whether preprocedural HRV is associated with 1-year survival, we performed a logistic regression analysis controlling for Kansas City Cardiomyopathy Questionnaire 12 score.

Results: In our parent cohort of 100 patients, 42 patients (28 survivors and 14 nonsurvivors) were included for analysis. Root mean square of successive differences (RMSSD) and standard deviation of NN intervals (SDNN) were lower in patients who survived to 1-year post TAVR compared to nonsurvivors [10 (IQR 8–23) vs 23 (IQR 17–33), $P = 0.04$ and 10 (IQR 7–16) vs 17 (IQR 11–40), $P = 0.03$, respectively]. Logistic regression demonstrated a trend in the association of preprocedure RMSSD with 1-year mortality and a 5% higher risk of 1-year mortality with each unit increment in UST-HRV using SDNN (OR 1.05; 95%CI 1.01–1.09, $P = 0.02$).

Conclusion: Our data suggest an inverse relationship between preprocedural UST-HRV and 1-year survival post-TAVR. This finding highlights the potential complexity of HRV regulation in chronic vs acute illness. Prospective studies are needed to validate our findings and to determine whether UST-HRV can be used for risk stratification in patients with severe aortic stenosis.

Keywords: Aortic stenosis, heart rate variability, transcatheter aortic valve replacement

Address for correspondence: Dr. Edward Hong, Department of Anesthesiology and Perioperative Medicine, Tufts Medical Center, 800 Washington Street, Ziskind 6038, Boston, MA - 02118, United States.
E-mail: ehong1@tuftsmedicalcenter.org

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INTRODUCTION

The prevalence of aortic stenosis (AS) exceeds 12% in the general population of the United States.[1] Definitive management of severe AS was traditionally approached with open surgical valve replacement, which carries a

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high risk of intraoperative mortality and postoperative morbidity.[2] With the introduction of transcatheter aortic valve replacement (TAVR), many patients once deemed too complex to undergo surgery, are now being offered intervention.[3] However, the costs related to TAVR often parallel that of open surgical management, and 1-year mortality post-procedure is estimated to be as high as 15%.[4,5] As such, enhanced preprocedural risk stratification may help to identify patients with a lower risk of post-procedural morbidity and a greater likelihood of long-term survival.

Heart rate variability (HRV), which generally reflects the delicate balance between the parasympathetic and sympathetic nervous systems,[6] has been linked to important clinical outcomes in various cardiovascular disease states.[7-9] HRV is conventionally measured using a 24-h Holter monitor, which is often inconvenient and impractical.[10] As such, more recent studies have investigated the reliability of short term (5 min) and ultrashort term (<5 min) analysis of electrocardiographic (ECG) recordings for HRV assessment.[10,11] And while data supporting the clinical utility of these more abbreviated methods of assessing HRV in patients with cardiovascular diseases are growing,[12,13] their use in risk stratification for patients with severe AS remains underexplored. Therefore, our primary goal was to investigate whether preprocedural ultrashort-term HRV (UST-HRV) differs between 1-year survivors and nonsurvivors after TAVR. Our secondary goal was to investigate whether intensive care unit (ICU) length of stay (LOS) differs between 1-year survivors and nonsurvivors after TAVR.

METHODS

Following approval from our local Institutional Review Board, we performed a retrospective, nested, case-control study of patients who underwent TAVR at our institution between July 2012 and September 2015. All patients had preprocedural UST-HRV measured before the administration of any anesthetic medications for the procedure. Patients who were not in sinus rhythm and/or were pacemaker dependent on preprocedural ECG were excluded.

Patient characteristics

Baseline demographic information and clinical data for each patient were abstracted from the hospital electronic medical record (EMR) system and included: 1) age; 2) sex; 3) body mass index; 4) left ventricular ejection fraction (LVEF); 5) aortic valve area; 6) aortic mean gradient; 7) Charlson Comorbidity Index; 8) Kansas City Cardiomyopathy Questionnaire 12 (KCCQ12) score; 9) New York Heart Association (NYHA) classification; and 10) Society for Thoracic Surgery (STS) Adult Cardiac Surgery Risk score. Additionally, outcomes variables of interest abstracted from EMR system included: 1) ICU LOS; and 2) 1-year mortality after the TAVR procedure. Patients who were lost to follow-up and survival past 1-year post procedure could not be verified were excluded from analysis.

UST-HRV analysis

A 10-s, preprocedural ECG recording was obtained for each patient as part of large, prospective study cohort of outcomes after TAVR. Only ECGs with up to one ectopic beat and otherwise in sinus rhythm were considered for analysis. RR intervals prior to and following any ectopic beat were also excluded from UST-HRV calculation. RR intervals of sinus origin (also known as NN interval) were measured in lead II using a commercially available, digital caliper application (EP Studios, Inc., Louisville, KY) conjointly by two investigators (EH, ET). Root mean square of successive differences (RMSSD) and standard deviation of NN interval (SDNN) were then calculated using the RR intervals for time-domain metrics [Figure 1]. Frequency domain analysis was unable to be performed given the ultrashort duration of the ECG recordings.

Statistical analyses

Based on published literature and historical data from our institution, we assumed a 1-year mortality rate of 20%. To facilitate a 1:2 case-control matching, with 20% loss to follow-up or death within 24-h post-TAVR, and 20% of patients not falling within range for the matching variables, a cohort of 100 patients would be required. Patients in each group (1-year nonsurvivors vs survivors) were matched based on age, STS Adult Cardiac Surgery Risk score, NYHA classification, and preprocedural LVEF. For our analyses, we excluded all patients who died within 24 h of their TAVR procedure. All remaining patients who did not survive to 1 year were included in the analyses, while double the number of patients was randomly selected from the remaining patients until matching on the above 4 criteria was achieved. Bivariate data, stratified by 1-year nonsurvivors vs survivors, are presented as medians

$$*\text{RMSSD} = \sqrt{\frac{1}{N-1}\sum_{i=1}^{N-1}(RR_{i+1} - RR_i)^2}$$

$$\dagger\,\text{SDNN} = \sqrt{\frac{1}{N-1}\sum_{i=1}^{N}(RR_i - \overline{RR})^2} \quad (\overline{RR} = \text{mean of RR intervals})$$

Figure 1: Formula or RMSSD and SDNN

with interquartile ranges or proportions, and compared using either Mann–Whitney U tests or long-rank tests and Chi-square tests, respectively. Kaplan-Meier curves were generated to graphically represent the ICU LOS between 1-year nonsurvivors vs survivors. Furthermore, to investigate whether preprocedural HRV is associated with 1-year survival, we performed a logistic regression analysis controlling for KCCQ12 score. All analyses were performed using STATA v15 (StataCorp LLC, College Station, TX). All two-tailed *P* values < 0.05 and all odds ratios (ORs) with 95% confidence intervals (CIs) not spanning 1 were considered to be statistically significant.

RESULTS

In our parent cohort of 100 patients, 1-year mortality was 17%. We excluded 3 patients who died within 24 h of their TAVR procedure. Therefore, the analytic cohort was composed of 42 patients (14 nonsurvivors and 28 survivors) whose characteristics are presented in Table 1. Median UST-HRV calculated using RMSSD was 23 (IQR 17–33) vs 10 (IQR 8–23), *P* = 0.04 for 1-year nonsurvivors vs survivors, respectively. Median UST-HRV calculated using SDNN was 17 (IQR 11–40) vs 10 (IQR 7–16), *P* = 0.03, for 1-year nonsurvivors vs survivors, respectively. Kaplan-Meier curves demonstrated longer ICU LOS (log-rank test, *P* = 0.03) in 1-year nonsurvivors vs survivors [Figure 2]. Logistic regression analysis demonstrated a trend in the association of preprocedure RMSSD with 1-year mortality (OR 1.02; 95%CI 1.00–1.05, *P* = 0.09) and a 5% higher risk of 1-year mortality with each unit increment in UST-HRV using SDNN (OR 1.05; 95% CI 1.01–1.09, *P* = 0.02).

Table 1: Characteristics of study cohort (*n*=42)

	1-year survivors (*n*=28)	1-year nonsurvivors (*n*=14)	*P*
Age (years)	80 (70-85)	79 (73-83)	0.78
Sex (%)			0.83
Female	46	50	
Male	54	50	
BMI (kg/m^2)	27 (24-20)	27 (26-32)	0.47
CCI	4 (3-5)	4 (3-5)	0.89
STS Risk score	8 (7-10)	8 (6-11)	0.58
AVA (cm^2)	0.72 (0.70-0.73)	0.72 (0.70-0.73)	0.93
AMG (mm Hg)	38 (30-50)	41 (24-50)	0.77
LVEF (%)	55 (52-65)	55 (39-60)	0.32
NYHA Classification	3 (3-3)	3 (3-3)	0.91
KCCQ12	50 (31-65)	34 (19-61)	0.19
RMSSD	10 (8-23)	23 (17-33)	0.04
SDNN	10 (7-16)	17 (11-40)	0.03
ICU LOS (hours)	52 (30-79)	103 (45-191)	0.03

BMI=Body mass index; CCI=Charlson Comorbidity Index; STS=Society of Thoracic Surgeons; AVA=Aortic Valve Area; AMG=Aortic Valve Mean Gradient; LVEF=Left Ventricular Ejection Fraction; NYHA=New York Heart Association; KCCQ12=Kansas City Cardiomyopathy Questionnaire 12; RMSSD=Root Mean Square of Successive Differences; SDNN=Standard Deviation of NN Intervals; ICU LOS=Intensive Care Unit Length of Stay. Aggregate data are presented as either median (interquartile range) or proportions, and compared using Mann–Whitney *U* tests or log rank tests and Chi-square tests, respectively.

DISCUSSION

In this retrospective, nested, case-control, pilot study, we demonstrate an inverse relationship between preprocedural UST-HRV, as expressed by SDNN, and survival at 1-year post-TAVR. Moreover, our data suggest that ICU LOS is longer in patients who do not survive to 1-year post TAVR compared to those who do survive. These preliminary findings suggest that UST-HRV data may have clinical relevance in patients with severe AS.

Traditional HRV measurements have used 24-h or 5-min recordings for time-domain or power spectral analysis.[10] Time-domain indices quantify the amount of HRV observed over the monitoring period ranging from less than 1 min to greater than 24 h, whereas frequency domain measurements are derived by Fast Fourier Transformation that separates HRV into different frequency ranges.[14] In recent years, UST-HRV has gained attention as a potential substitute for longer measurements. Indeed, Nussinovitch *et al*.[11] demonstrated a strong correlation between the 5-min and 10-s calculations of RMSSD (intraclass correlation 0.9; 95%CI 0.85–0.94, *P* < 0.05) in healthy adults (*n* = 70). Similarly, in a retrospective analysis of data from a large prospective cohorts of adults (*n* = 3387), Munoz *et al*.[15] demonstrated a substantial agreement between the 5-min and 10-s recordings for both RMSSD (r = 0.85; 95%CI 0.84–0.86, *P* < 0.05) and SDNN (r = 0.76; 95%CI 0.74–0.77, *P* < 0.05). Moreover, in a retrospective study of post ST-elevation myocardial infarction (STEMI) patients (*n* = 196), Karp *et al*.[12] demonstrated that 2-year mortality risk in patients with UST-HRV (using SDNN

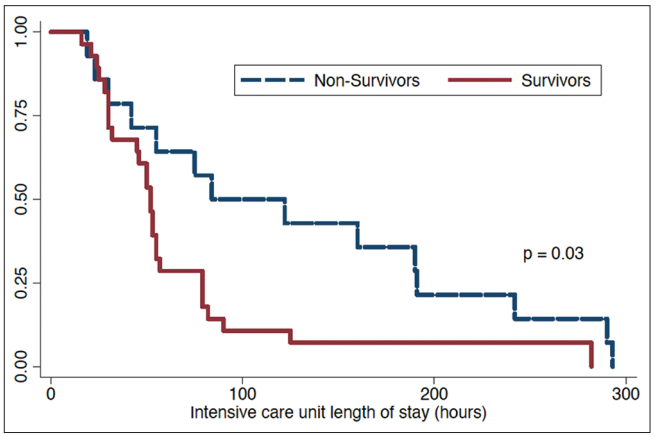

Figure 2: Kaplan-Meier curve demonstrating intensive care unit length of stay between 1-year survivors and nonsurvivors post-TAVR (*n* = 42). Time between groups was compared using log-rank test

derived from 10-s ECG recordings) values <9.5 was 3-fold higher than in patients with UST-HRV >9.5 (OR 2.90; 95%CI 1.12–7.56, $P = 0.03$). Our study builds on these findings and offers potentially novel insights on UST-HRV due to its seemingly contradictory results.

HRV represents the balance of parasympathetic and sympathetic input to the cardiac electrical system and is shown to decrease under situations of stress where the sympathetic tone dominates.[10] Low HRV in the setting of acute processes such as myocardial infarction carries a predictive value concerning outcomes as it may represent the inability of a host to compensate in the face of physiologic stress without an exaggerated activation of the sympathetic nervous system.[10] Similarly, longitudinal studies in patients with chronic diseases such as congestive heart failure demonstrate that lower HRV (presumably from chronic sympathetic nervous system over activation) is associated with worse outcomes.[8,9] AS is usually an indolent process and as such, we hypothesize that lower preprocedural UST-HRV in our patients represents not only the chronicity of disease but also the degree of physiologic impact; i.e., low UST-HRV identifies patients with the least reserve and who are most likely to benefit from rapid resolution of their stenotic lesion. For example, in early acute stenosis, due to upregulation of sympathetic responses and hence more physiologic reserve, HRV is likely to be higher. As the disease progresses and patients are chronically ill over long periods of time, their ability to mount a sympathetic response to stress decreases significantly, as represented by a low HRV. It is also important to mention that in both groups of patients in our study, HRV parameters were quite low compared to the general population, where SDNN values below 50 are considered "unhealthy."[14] Nonetheless, our findings are in line with those of Karp *et al*.,[12] where HRV thresholds in STEMI patients were around 10. As such, patients with well-compensated chronic disease may still have lower than "normal" HRV values. Accordingly, thresholds for asymptomatic vs symptomatic disease may need to be defined for individual chronic diseases to better risk-stratify patients.

While our results are intriguing, it is important to discuss the potential limitations of our study. Due to the retrospective nature of our study, a causal a relationship between UST-HRV and clinical outcomes cannot be established. Although we attempted to control for differences between groups (nonsurvivors vs survivors) in our analyses, there may be residual confounding that we were unable to control for. It is also important to emphasize the limited sample size of this pilot study, which further limits our ability to control multiple factors that may influence the relationship between UST-HRV and ICU LOS as well as all-cause 1-year mortality post-TAVR. Additionally, the patients in our study were all enrolled at a single teaching hospital that is a referral center for highly complex patients and, therefore, our results may not be generalizable to centers where less morbid patients may undergo TAVR procedures. Moreover, TAVR procedures were performed by 1 of 3 primary interventional cardiologists and given our small sample size, we are unable to adequately adjust for this, thereby further potentially reducing the generalizability of our findings. We also used the shortest duration of validated UST-HRV measurements (10-s ECG recordings), and while there is strong agreement between these measures and longer assessments of HRV, more recent data suggest that 120-s recordings might be the best reflection of traditional HRV measures.[15] Moreover, we only assess UST-HRV at a single time point, which was immediately before the TAVR. It is unclear how UST-HRV may change immediately post-procedure as well as over the following days and weeks after TAVR. And finally, while medical management post TAVR is standardized within our institution, adherence to medical therapy could not be validated fully. In future prospective studies, medication adherence will need to be carefully controlled as it could play a role in patient survival. Indeed, data regarding short- and long-term changes in UST-HRV in this patient cohort may informative. These and other issues will need to be addressed in future studies.

CONCLUSION

In this pilot, nested, case-control study of TAVR patients, we demonstrate an inverse relationship between preprocedural time-domain UST-HRV using SDNN and 1-year survival. This observation, which seems contradictory to the existing literature on HRV and health outcomes, likely highlights the complexity of HRV analysis in patients with acute vs chronic illnesses and their ability to compensate during physiologic stress. Further studies are needed to validate our findings in larger cohorts of patients and to determine whether preprocedural UST-HRV can be used as a risk stratification tool in potential TAVR candidates.

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Conflicts of interest
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