Predictive Value of Heart Rate Variability Indexes for 2-year Prognosis of the Patients after Transcatheter Aortic Valve Replacement

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ABSTRACT

Objective: To explore the prognostic value of the heart rate variability (HRV) index in the patients undergoing transcatheter aortic valve replacement (TAVR).

Study Design: A cohort study.

Place and Duration of Study: Department of Cardiology, Subei people's Hospital, Yangzhou University, Yangzhou, Jiangsu Province, China, from April 2018 to April 2021.

Methodology: Patients with severe symptomatic aortic stenosis (AS), who were treated with TAVR, were enrolled. All the patients had completed a 24-hour ambulatory electrocardiogram (AECG), and detected HRV within one week before TAVR. All-time domain and frequency domain indexes were analysed. According to the standard deviation of NN intervals (SDNN), the patients were divided into the high HRV group (H-HRV), and the low HRV group (L-HRV). Postoperative cardiac function and major adverse cardiovascular events (MACEs) were observed on follow-up for 24 months.

Results: Compared with the H-HRV group, the L-HRV group had a lower preoperative left ventricular ejection fraction (LVEF) [49.0 (42.5, 60.0) *vs.* 59.5 (51.0, 62.3), p = 0.028] and higher preoperative cardiac troponin I (cTnI) [0.03(0.02, 0.10) *vs.* 0.02 (0.02, 0.02), p = 0.007]. The incidence of MACEs after TAVR in the L-HRV group was significantly higher than that in the H-HRV group (45.5% *vs.* 13.6%, p = 0.021). The results of the Kaplan-Meier survival curve also showed that the prognosis of the L-HRV group was worse than that of the H-HRV group (Log Rank = 4.975, p = 0.026). After adjusting for preoperative standard deviation of the average NN intervals (SDANN) or preoperative low-frequency (LF) domain / high-frequency (HF) domain (LF/HF), preoperative HRV still was an independent risk factor for MACEs in AS patients undergoing TAVR [HR 3.718, 95% CI (1.020, 13.548), p = 0.047]. The receiver operating characteristic (ROC) curve suggested that HRV <61.0ms may be a predictor of MACEs in AS patients undergoing TAVR. The sensitivity and specificity were 83.9% and 76.9%, respectively.

Conclusion: Preoperative HRV had a good short-term predictive value in AS patients undergoing TAVR.

Key Words: *Heart rate variability, Aortic stenosis, Transcatheter aortic valve replacement, Ambulatory electrocardiogram.*

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INTRODUCTION

Heart rate variability (HRV) was the variation in the time interval between consecutive heartbeats and had been extensively studied in the mammals.[1,2] By completing 24-hour ambulatory echocardiography (AECG) to get HRV data, HRV indexes usually included time domain indicators standard deviation of NN intervals (SDNN), standard deviation of the average NN intervals (SDANN), square root of the mean squared differences of successive NN intervals (RMSSD) and frequency domain indicators high-frequency (HF) domain, low-frequency (LF) domain, LF/HF.

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Among them, the time domain index SDNN was regarded as the best indicator and whole marker of HRV.[3] In recent years, changes in HRV had not only been shown to be associated with the occurrence of various arrhythmic events such as sinus arrhythmias, and ventricular fibrillation,[4,5] but also be predictive of major adverse cardiovascular events (MACEs) in the patients with acute myocardial infarction (AMI), undergoing percutaneous coronary intervention (PCI). The predictive value of MACEs after PCI in patients with AMI had been demonstrated.[6] The relative risk of death in the HRV <50ms group was 5.3 times higher than that in the HRV >100ms group.

Aortic valve stenosis (AS) was the most common form of heart valve disease in the adults and was the third leading cause of cardiovascular disease, after hypertension and coronary heart disease.[7] AS was usually caused by progressive calcification of the aortic valve. Due to the increase in life expectancy, this form of valvular heart disease is considered to be the future plague of the 21st century.[8] Since Alan Cribier performed the first transcatheter aortic valve replacement (TAVR) in 2002, more than 300,000 operations had been performed worldwide.[9,10] This number continued to rise as indications expand to low-risk patients, with the number of surgeries increasing sixfold from 2012 to 2015.[11] TAVR had become the first choice for severe and symptomatic AS patients. At present, there are still complications such as perivalvular leakage and cardiac block after TAVR.[12] In recent years, some studies had confirmed that high-sensitivity troponin T levels,[13] and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels were related to the mortality after TAVR,[14] but for the increasing number of TAVR, more comprehensive prognostic indicators were still needed. The purpose of this study was to compare the occurrence of MACEs within 2 years after TAVR in the patients with different HRV before operation and to explore the short-time prognostic value of HRV index before TAVR in patients with AS.

METHODOLOGY

This was a prospective cohort study of 44 patients, who underwent TAVR surgery in the Department of Cardiology, Subei people's Hospital, Yangzhou University, from April 2018 to April 2021. Inclusion criteria were TAVR operation in the Hospital for the first time, femoral artery diameter, and AECG examination within one week before the operation. Exclusion criteria were previous valve replacement, conversion to surgical valve replacement, patients with chronic renal failure, use of Ia and III antiarrhythmic drugs 10-20 days before TAVR, and patients with chronic or persistent atrial fibrillation 10-20 days before TAVR. This study was approved by the Ethics Committee of Subei people's Hospital, and all the patients signed written informed consent.

The clinical treatment of patients' age, gender, body mass index (BMI), New York Heart Association (NYHA) cardiac function, and previous medical history were collected. Myocardial injury markers, NT-proBNP, and echocardiography were checked one week before and after the operation. All subjects had finished AECG measurement before the operation, and the time domain and frequency domain indexes of HRV: SDNN, SDANN, RMSSD, HF domain, LF domain, and LF/HF ratio were collected.

All the patients completed preoperative cardiac Doppler echocardiography. After evaluating the severity of AS, TAVR team considered that it was not suitable for surgical heart valve replacement, or the patients refused surgical valve surgery. The regional structure of the aortic valve root was evaluated by CT before operation. TAVR was performed in the hybrid operating room.

After general anesthesia, the arterial sheath tube was inserted through the femoral artery, and the common straight-head guide wire (Cordis, USA), was used to cross the aortic valve into the left ventricle, which was exchanged into Lunderquist super-hard guide wire (COOK, USA) to establish the track. Under the condition of rapid right ventricular pacing, the aortic valve was pre-dilated with a balloon. After the Venus-A valve (VENUSMEDTECH, China) was in place, the aortic root was accurately located by angiography, and the valve was released under temporary pacing. After withdrawing the release system, the valve position, function, and aortic regurgitation were evaluated by transesophageal echocardiography. The femoral artery was sutured at the end of the operation.

In antithrombotic strategy, patients were routinely given aspirin and clopidogrel for antiplatelet therapy. Aspirin 100mg and clopidogrel 75mg were given daily; 300mg load was applied for three consecutive days or before operation. Antiplatelet and anticoagulant drugs were adjusted according to the patient's past medical history, medication history, bleeding / thrombus risk, *etc*. After eliminating the obvious taboo after the operation, the patients were given aspirin 100mg combined with clopidogrel 75mg daily until 6 months after operation, and then long-term oral administration of the single antiplatelet drug.

All the patients were followed up through outpatient clinic, telephone, or hospitalisation in every 3 months after discharge to observe the occurrence of MACEs. The primary endpoint was postoperative all-cause death, and the secondary endpoints were postoperative stroke, massive gastrointestinal hemorrhage, permanent pacemaker implantation, and recurrence of severe heart failure (NYHA cardiac function grade ≥III).

All data were analysed by SPSS 26.0 statistical software. Analysis of data compliance with normal distribution using one-sample Kolmogorov-Smirnov test, continuous variables conforming to normal distribution were expressed as mean ± standard deviation, continuous variables not conforming to normal distribution were expressed as median (25^{th}, 75^{th}), and categorical variables were expressed as percentages. Comparisons between the low HRV group and high HRV group were made using the two independent samples t-test for the measures that conformed to a normal distribution, the Mann-Whitney U-test for measures that did not conform to a normal distribution, and the Chi-square test or Fisher's exact test for count data. In addition, univariate and multivariate COX regression analysis showed that all independent variables were classified according to the median. The results of the COX regression model are expressed by hazard ratio (HR), and 95% confidence interval (CI). Kaplan-Meier method was used to compare the survival time and draw the survival curve. The receiver operating characteristic (ROC) curve was used to evaluate the best cut-off point of HRV for predicting the occurrence of MACEs events in the patients with AS after TAVR, and the specificity and sensitivity of HRV $p < 0.05$ indicated that the difference is statistically significant.

RESULTS

During the specified study period, 46 TAVR operations were completed. One case was excluded through the subclavian artery, while another case for having converted to surgical thoracotomy during operation. The forty four patients who met the criteria were enrolled at last. The range of SDNN was 67.5 (53.0, 98.5) ms, with a median of 67.5 ms. According to the median of SDNN, all the patients were divided into low the HRV group (L-HRV, n = 22, 76.9 ± 4.7 years, 12 males, 10 females) and the high HRV group (H-HRV, n = 22, 75.5 ± 4.8 years, 14 males, 8 females).

The baseline data of the two groups were shown in Table I. There were no significant differences in age, gender, BMI, smoking, and previous medical history of hypertension and diabetes between the two groups (all p >0.05). Preoperative examination index: Compared with the H-HRV group, the L-HRV group had a lower left ventricular ejection fraction (LVEF) [49.0 (42.5,60.0) *vs.* 59.5 (51.0, 62.3), p = 0.028], and higher cardiac troponin I (cTnI) [0.03 (0.02,0.10) *vs.* 0.02 (0.02,0.02), p = 0.007], while there were no significant differences in CK-MB, NT-proBNP and, preoperative NYHA cardiac function between the groups (all p >0.05).

Table I: Baseline characteristics of all enrolled patients.

Project	L- HRV Group (n = 22)	H-HRV Group (n = 22)	p
Age (years)	76.9±4.7	75.5±4.8	0.334
Male [male n (%)]	12(54.5)	14(63.6)	0.540
BMI	21.0(19.0,23.0)	20.0(20.0,22.3)	0.952
NYHA III grade or above [*n* (%)]	12(54.5)	13(59.1)	0.761
Smoking [*n* (%)]	2(9.1)	0(0.0)	0.488
Hypertension [*n* (%)]	2(9.1)	0(0.0)	0.488
Diabetes [*n* (%)]	3(13.6)	2(9.1)	1.000
Lab tests			
LVEF (%)	49.0(42.5,60.0)	59.5(51.0,62.3)	0.028
cTnI (ng/ml)	0.03(0.02,0.10)	0.02(0.02,0.02)	0.007
CK-MB)ng/ml)	1.2(1.0,2.8)	1.7(0.9,2.0)	0.531
NT-proBNP (pg/ml)	2305(1658,6470)	2360(1763,2618)	0.611

BMI: Body mass index, NYHA: New York Heart Association, LVEF: Left ventricular ejection fraction, cTnI: Cardiac troponin I, CK-MB: Creatine kinase MB, NT-proBNP: N terminal pro B type natriuretic peptide.

Table II: Adverse events during follow-up [n (%)].

	Group L-HRV (*n*=22)	Group H-HRV (*n*=22)	p
Primary endpoint			
Death	2(9.1)	1(4.5)	1.000
Secondary endpoint			
Stroke	1(4.5)	0(0.0)	1.000
Gastrointestinal bleeding	1(4.5)	0(0.0)	1.000
Pacemaker implantation	4(18.2)	1(4.5)	0.345
Recurrent heart failure	2(9.1)	1(4.5)	1.000
Total	10(45.5)	3(13.6)	0.021

All the patients successfully completed the TAVR operation through the femoral artery. The average follow-up time was 24 months. There were 13 cases of MACEs, including 3 cases of all cause death (two cases of cardiogenic death and one case of respiratory failure), 5 cases of new conduction block implantation of a permanent pacemaker, three cases of recurrent NYHA cardiac function of III grade or above, and two cases of postoperative bleeding (Table II).

There were 10 cases of MACEs (2 cases of all-cause death) in the L-HRV group and 3 cases of MACEs (1 case of all-cause death) in the H-HRV group. The differences between the groups were statistically significant (45.5% *vs.* 13.6%, p = 0.021). The results of the Kaplan-Meier survival curve also showed that the prognosis of L-HRV group was worse than that of H-HRV group, and the difference was statistically significant (Log Rank = 4.975, p = 0.026) (Figure 1). Except SDNN (HRV), other factors could not enter the regression equation, and there was no statistical significance (p >0.05). After adjusting SDANN or LF/HF, preoperative HRV was still an independent risk factor for MACEs in AS patients, who were treated with TAVR [*HR*3.718, 95% CI (1.020, 13.548), p = 0.047].

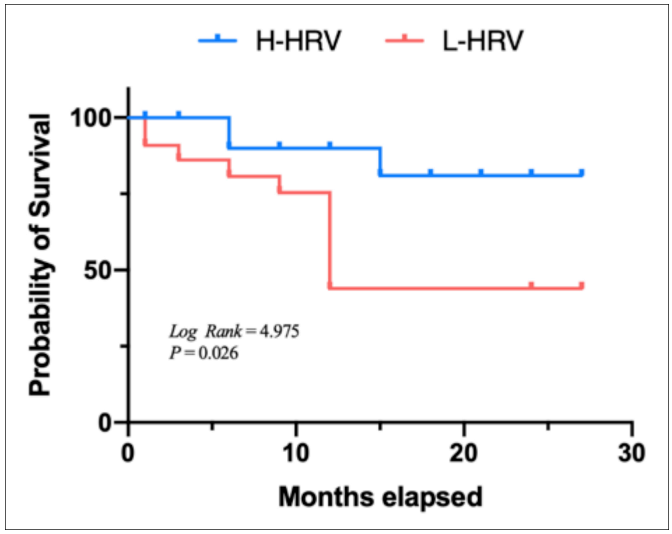

Figure 1: Kaplan-Meier survival curve on the HRV and MACEs in AS patients receiving TAVR.

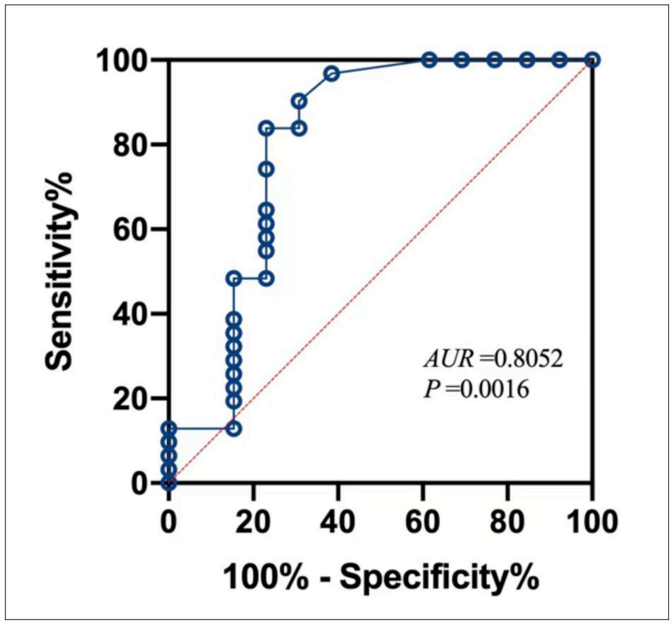

Figure 2: Prognostic value of HRV in AS patients receiving TAVR by *ROC curve* (cut-off value: 61.0ms, sensitivity = 83.9%, specificity = 76.9%).

By taking the postoperative MACEs as the dependent variable and HRV as the independent variable, the ROC curve was drawn. As shown in Figure 2, the area under the curve was 0.805 (95% CI 0.627, 0.984, p<0.05). The cut-off value was 6.0ms, meanwhile, the sensitivity and specificity were 83.9% and 76.9%, respectively.

DISCUSSION

The results showed that the preoperative high HRV had a higher incidence of postoperative MACEs, and it is also probable to be an independent risk factor for MACEs in the patients treated with TAVR. Patients with HRV greater than 61.0ms after TAVR may have a better prognosis (sensitivity: 83.9%, specificity: 76.9%).

Generally speaking, when the SDNN value was less than 50ms, the HRV in patients was significantly decreased. The lower HRV, which reflected the excessive sympathetic activity or the weak vagus' activity, can predict the mortality of AMI patients after PCI.[6] HRV included time- domain variables and frequency domain variables. The time-domain variable SDNN represented the mixed variable of sympathetic nerve and vagus nerve.[15,16] The overall marker of HRV, SDNN represented HRV in this study, while the frequency domain variable LF/HF meant the tension of the sympathetic nerve. The power of each frequency band in the frequency domain had a corresponding variable in the time domain, and there was a strong correlation between the time domain variable and the frequency domain variable.[17,18] Therefore, after analysis of calibration, it was concluded that preoperative HRV was an independent risk factor for the occurrence of MACES in AS patients receiving TAVR.

Understanding the mechanism of HRV was helpful for the authors to analyse the prognostic value in AS patients receiving TAVR. HRV was mainly determined by the two mechanisms: one was the autonomic nervous system (ANS).[5,19] It through two signal pathways to control the sinoatrial node to affect HRV (sinoatrial node was a special area of cardiomyocytes that can beat spontaneously and constituted the main pacing area of the heart): sympathetic nerve stimulation and vagal nerve stimulation, sympathetic nerve stimulation reduced HRV, vagal nerve stimulation increased HRV. Previous studies focused on the relation between AMI and HRV had shown that elevated sympathetic activity during ischemia/infarction increased the incidence of ventricular fibrillation.[20,21] On the contrary, elevated vagus nerve' activity or decreased sympathetic nerve activity can reduce the susceptibility of ischemia to ventricular fibrillation, which confirmed ANS affects HRV and the prognosis of patients through the regulation of sympathetic nerve and vagal nerve. Another mechanism that affected HRV was the intercellular mechanism of the sinoatrial node itself, called the coupled-clock system.[22] This system consisted of the sum of the stimulated ion channels on the surface of sinoatrial node cells and the vibration caused by the rhythmic uptake and release of calcium ions in the sarcoplasmic reticulum of sinoatrial node cells. These two mechanisms were found to have their own division of labor on the composition of HRV, and the regulation of the intercellular mechanism of sinoatrial node was complex and long-term, while ANS mainly implemented short-term periodic regulation.[23] Therefore, low HRV before operation meant that the activity of the sympathetic nerve was stronger than that of the vagal nerve, which may be the cause of short-term heart failure or even sudden death after the operation.

An elevated myocardial zymogram after TAVR had been found to be an appropriate short-term prognostic indicator. Some earlier small sample studies suggested that elevated myocardial zymogram after TAVR may be a predictor of poor prognosis.[24] In 2012, the definition of myocardial injury after TAVR as the outcome of TAVR clinical study was published by the Valve Academic Research Consortium (VARC).[12] Jean-Michel showed that the increase of cTnI was associated with a high frequency of 30-days all-cause mortality and cardiovascular mortality after femoral artery approach TAVR.[25,26] A large increase in CK-MB was associated with an increase in 30-days and 1-year all-cause mortality and cardiovascular mortality. In this study, there was a correlation between HRV and myocardial zymogram after TAVR. All the 44 patients that authors included had varying degrees of increase in myocardial zymogram after the operation. The degree of increase in myocardial zymogram in the L-HRV group was generally higher than that in the H-HRV group, although there was no statistically significant difference probably due to the small sample size of this study, but attention should be paid to it. The predictive value of preoperative HRV on the elevation of myocardial zymogram in patients after TAVR remained to be further studied.

At present, there are no relevant studies on preoperative HRV in predicting MACEs in the patients with AS after TAVR. This study also have several limitations. Some patients might take drugs that potentially affect HRV before the operation, such as beta-blockers. Diabetic patients, who are known to have adverse effects on HRV, were also included in the study, which may affect the results, even if the multivariate analysis does not show any significant effects. The sample size of this study was so small that some factors cannot be included in *COX* regression analysis.

CONCLUSION

This study suggested that AS patients with lower HRV had lower vagus nerve tension or higher sympathetic nerve tension, which played a positive role in predicting the occurrence of MACEs in patients after TAVR. Medicines that inactivate sympathetic effects such as beta-blockers or that promote vagal effects such as low-dose atropine may have therapeutic value in reducing MACEs after TAVR, especially in patients with lower HRV. In addition, the prognostic information related to HRV had no additional cost for HRV measurement. Therefore, the simplicity and low cost of measuring HRV can become important progress in risk stratification before TAVR.

ETHICAL APPROVAL:
The study protocol was approved by the Ethics Committee of the Northern Jiangsu People's Hospital in accordance with the Declaration of Helsinki.

PATIENTS' CONSENT:
Written informed consent was obtained from all study participants.

COMPETING INTERESTS:
The authors declared no competing interests.

AUTHORS' CONTRIBUTIONS:
JZ: Interpretation of data for the work; drafting the work.
YL: Revised the work critically for important intellectual content.
JJ: Interpretation of data for the work.
SC: Analysis, critical revision.
JZ: Patient selection, data acquisition.
SH: Contributed to concept and design, and agreed to be accountable for all aspects of the work.
All authors approved the final version of the manuscript to be published.

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