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Original Article

The Predictive Value of Heart Rate Variability for Long-Term Outcomes in Patients Undergoing Coronary Artery Bypass Grafting and ICU Referrals

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Abstract

Background: *Heart rate variability (HRV) is known to play a significant role in predicting poor prognosis after acute myocardial infarction. Nonetheless, its potential for predicting long-term adverse outcomes following revascularization procedures remains unclear. This study aims to elucidate this relationship.*

Methods: *This prospective cohort study included 258 consecutive patients undergoing elective isolated coronary artery bypass grafting (CABG). All patients required ICU referral before hospital discharge. A 3-week cardiac rehabilitation program with 24-hour ECG Holter monitoring was planned for all patients. HRV was analyzed by computer and manually over-read. During a follow-up period ranging from 1 to 3 years, patients were contacted via phone to assess long-term outcomes, including death and major adverse cardiovascular events (MACE), such as myocardial infarction, reoperation, or brain stroke.*

Results: *Out of 258 patients (177 males and 81 females) with an average age of 58.80±9.60 years, 4.3% of patients died due to cardiovascular events, and 15.1% experienced long-term MACE. A comparison of HRV indicators between the non-surviving and surviving subgroups revealed significantly lower mean RR, mean standard deviation of normal-to-normal HRV interval (SDNN), and low and high-frequency values in the former group. However, when comparing HRV indicators between the subgroups with and without long-term MACE, no significant differences were observed. Cox proportional hazard analysis demonstrated that decreased HRV (SDNN) effectively predicted long-term mortality in patients who underwent CABG.*

Conclusion: *Lower postoperative HRV serves as a valuable predictor of long-term mortality after CABG in ICU patients, with reduced SDNN values particularly relevant for anticipating long-term adverse events.*

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Introduction

The association between autonomic abnormalities and various pathological conditions, such as hypertension, hyperlipidemia, high body mass index, hyperglycemia, uncontrolled diabetes mellitus, and cardiovascular disorders, has been well-established.[1-5] Heart rate variability (HRV), a noninvasive measure of autonomic functional state, serves as a key indicator for autonomic dysfunction. Numerous studies have successfully demonstrated a significant association between HRV abnormalities and an increased risk of ischemic heart disease and its associated poorer outcomes.[6-8] It has been well-established that a decrease in the standard deviation of all normal-to-normal HRV intervals (SDNN) is associated with a 4-fold increased risk of cardiac ischemic events.[9] Furthermore, HRV and related indicators, such as SDNN, can be utilized effectively to stratify the risk of malignant arrhythmia, sudden death following myocardial infarction, and postoperative hemodynamic instability after cardiac surgeries.[10] Additionally, there is evidence of significantly reduced HRV following coronary revascularization, with recovery observed as patients' health status improves postoperatively.[11] It appears that variations in HRV following surgical interventions are influenced by factors such as anesthetic methods, surgical procedures, and the duration of cardioplegia.[12, 13] Still, evidence regarding the association between HRV changes and adverse outcomes following coronary artery bypass grafting (CABG), particularly in the long term, remains limited.

The objective of this study was to assess the predictive value of HRV for long-term postoperative adverse outcomes, including mortality and major adverse cardiovascular events (MACE) in patients undergoing CABG.

Methods

This prospective cohort study included 258 consecutive patients who underwent elective isolated CABG and were scheduled for the second phase of cardiac rehabilitation at our referral heart center between 2019 and 2021. All patients required ICU referral before hospital discharge, with a mean ICU stay of 3.2 days.

The study protocol received ethical approval from the Ethics Committee of Tehran University of Medical Sciences, and written informed consent was obtained from all participants after they had received comprehensive explanations regarding the study protocol and the safety of study-related interventions.

All included patients were aged 18 to 75 years and had normal sinus rhythm at the time of assessment. Patients with any ventricular ectopic activity, sinus sick syndrome, cardiac block, cardiac pacing, acute heart failure, or chronic conditions such as chronic renal insufficiency or hepatic disease that could potentially influence HRV were excluded from the study.

Postoperatively, all patients were scheduled for a 3-week cardiac rehabilitation program that included 24-hour ECG Holter monitoring. HRV was analyzed by computer and manually over-read. Algorithms for arrhythmia analysis labeled each Q wave, R wave, and S wave (QRS) complex. Under the supervision of a cardiologist, an operator removed artifacts from the recordings, reviewed beats, and made modifications as necessary. Only recordings with fewer than 15% ectopic beats were utilized. The periods with the highest and lowest average R-R intervals, identified from R-R interval histograms, were consistently validated. The corrected data were processed, and HRV was computed. Time domain analysis consisted of the following parameters:

a) Mean of R-R intervals for normal beats,
b) SDNN,
c) Standard deviation of the 5-minute means of R-R intervals (SDANN),
d) Mean of the 5-minute standard deviations of RR intervals (SDNN-i),
e) Square root of the mean of the squared successive differences in R-R intervals (RMSSD),
f) Percentage of R-R intervals that are at least 50 milliseconds different from the previous interval (pNN50),
g) Total power (0.0–0.5 Hz) (TP),
h) Very low frequency (0.003–0.04 Hz) (VLF),
i) Low frequency (0.04–0.15 Hz) (LF),
j) High frequency (0.15–0.4 Hz) (HF), and
k) Low to high-frequency ratio (LF/HF).[14]

In addition to Holter monitoring, participants underwent echocardiography and exercise testing at the end of the rehabilitation program. During a follow-up period ranging from 1 to 3 years, with a mean of 2.8 years, patients were contacted via phone to assess long-term outcomes, including mortality and MACE, such as myocardial infarction, reoperation, and brain stroke.

Data were analyzed using SPSS software, version 21. Quantitative variables were reported as mean ± SD, while qualitative variables were expressed as percentages and frequencies. Comparisons between quantitative variables for 2 groups were performed using the t-test or the Mann-Whitney test, while comparisons between qualitative variables utilized the χ^2 or Fisher exact test. The Cox proportional hazard model was employed to evaluate the predictive value of HRV for long-term outcomes, taking into account baseline parameters. A P value equal to or less than 0.05 was considered statistically significant. Receiver operating characteristic (ROC) curve analysis was conducted to determine the optimal cutoff points for HRV and related indicators, as well as their specificity and sensitivity in predicting outcomes.

Results

A total of 258 patients who underwent CABG were included in the study. The mean age of the participants was 58.80±9.60 years, ranging from 46 to 72 years, and 68.6% were men. Regarding the cardiovascular risk profile, 33.3% had hypertension, 30.2% had diabetes, 12.4% were current smokers, and 32.4% had a history of hyperlipidemia. Additionally, 25.6% had a family history of coronary artery disease. Multi-vessel coronary involvement was observed in 86.8% of the patients. The mean left ventricular ejection fraction was 42.61±4.50 (Table 1).

During the long-term follow-up period with a mean duration of 2.8 years (range =1–3 y), 11 patients (4.3%) passed away due to cardiovascular events, and 39 patients (15.1%) experienced long-term MACE. A comparison of HRV indicators between the non-surviving and surviving subgroups (Table 2) revealed significantly lower mean RR (786.24±99.26 ms vs 826.2±100.9 ms; *P*=0.026), SDNN (95.21±22.12 ms vs 127.25±32.20 ms; *P*=0.039), LF (339.23±46.35 ms^2 vs 386.26±52.52 ms^2; *P*=0.022), and HF (225.24±64.60 ms^2 vs 252.46±72.21 ms^2; *P*=0.036) in the non-surviving group. However, the comparison of HRV between the subgroups with and without long-term

Table 1. Baseline characteristics of the study population (n=258)*

Characteristics	Percentages
Male sex, (%)	177 (68.6)
Age (y)	58.80±9.60
Body mass index (kg/m^2)	25.40±2.20
History of hypertension (%)	86 (33.3)
History of diabetes mellitus (%)	78 (30.2)
History of hyperlipidemia (%)	84 (32.4)
History of smoking (%)	32 (12.4)
Family history of coronary disease %)	66 (25.6)
Multi-vessel involvement (%)	224 (86.8)
Mean left ventricular ejection fraction (%)	42.60±4.50
History of aspirin use (%)	189 (73.2)
History of diuretic use (%)	146 (56.6)
History of β-blocker use (%)	177 (68.6)
History of calcium-blocker use (%)	46 (17.8)
History of ACE-inhibitor use (%)	59 (22.8)
History of statin use (%)	72 (27.9)
Serum WBC count (/mm^3)	7800.23±789.23
Serum hemoglobin level (g/dL)	12.56±1.20
Platelet count (/mm^3)	244.22±12.26
Serum triglyceride level (mg/dL)	178.42±10.23
Total cholesterol level (mg/dL)	156.6±8.56
Low-density lipoprotein level (mg/dL)	88.55±4.50
High-density lipoprotein level (mg/dL)	36.81±2.50
ICU stay (d)	3.22±0.89

*Data are presented as mean±SD or n (%).
ACE, Angiotensin-converting enzyme; WBC, White blood cell

Table 2. Heart rate variability indices in the non-surviving and surviving groups

Indices	Non-Surviving Group	Surviving Group	P	
			Non-adjusted	Adjusted**
Mean RR (ms)	786.24±99.26	826.24±100.89	0.026	0.039
SDNN (ms)	95.20±22.10	127.20±32.20	0.039	0.046
SDNN-i (ms)	36.23±18.10	48.54±22.12	0.123	0.224
SDANN-i (ms)	89.25±25.82	92.12±28.56	0.224	0.625
rMSSD (ms)	24.23±14.20	26.44±12.79	0.589	0.797
pNN50 (%)		4.91±0.72	0.556	0.645
TP (ms^2)	2236±1678	2254±1444	0.789	0.895
VLF (ms^2)	1361±249	1129±234	0.097	0.123
LF (ms^2)	339.23±46.35	386.26±52.52	0.022	0.026
HF (ms^2)	225.2±64.6	252.4±72.2	0.036	0.042
LF/HF	1.5±0.7	1.5±0.7	0.778	0.889

*Data are presented as mean±SD.
**Adjusted for age and CAD RF
Mean RR, Mean of the R-R interval; SDNN, Standard deviation of normal-to-normal HRV intervals; SDNN-i, Mean of the 5-minute standard deviations of RR intervals; RMSSD, Square root of the mean of the squared successive differences in R–R intervals; pNN50, Percentage of R–R intervals that are at least 50 milliseconds different from the previous interval; TP, Total power; VLF, Very low frequency; LF, Low frequency; HF, High frequency; LF/HF, Low frequency/High frequency

MACE (Table 3) showed no significant differences in HRV indicators. Using Cox proportional hazard analysis, adjusting for baseline parameters (Table 4), we found that a decrease in HRV (SDNN) was an effective predictor of long-term mortality in patients who underwent CABG (OR, 0.3; 95% CI, 0.12 to 0.889; *P*=0.032). According to the receiver operating characteristic (ROC) curve analysis (Figure 1), mean RR (area under the curve [AUC]=0.951) and SDNN (AUC=0.842) measurements were found to predict long-term mortality effectively. The best cutoff value for mean RR in predicting long-term mortality was 790, with a sensitivity of 92.3% and a specificity of 72.0%. Additionally, the optimal cutoff point for SDNN in predicting this outcome was 98.0, with a sensitivity of 84.6% and a specificity of 56.0%.

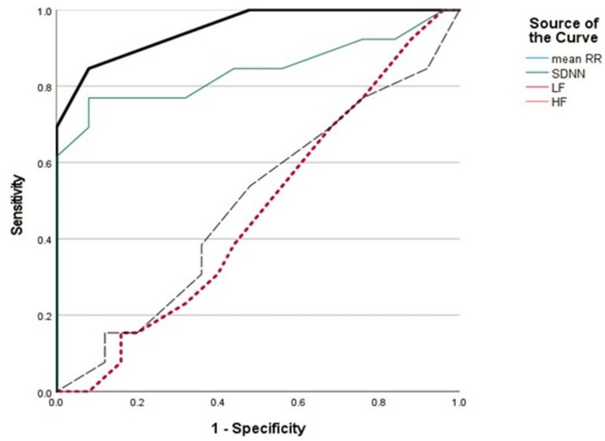

Figure 1. The image showcases the receiver operating characteristic curve analysis to determine the predictive value of HRV indicators for long-term mortality.

HRV, Heart rate variability; SDNN, Standard deviation of normal-to-normal HRV intervals; LF, Low frequency; HF, High frequency

Table 3. HRV indices in groups with and without MACE*

Indices	MACE (+)	MACE (−)	P	
			Non-adjusted	Adjusted**
Mean RR (ms)	814.12±56.30	829.26±95.51	0.122	0.259
SDNN (ms)	102.12±19.26	119.51±34.54	0.336	0.426
SDNN-i (ms)	38.40±20.11	42.26±22.16	0.546	0.644
SDANN-i (ms)	88.21±19.18	89.43±20.12	0.875	0.879
rMSSD (ms)	25.14±14.04	26.54±8.86	0.842	0.926
pNN50 (%)	5.30±0.70	5.40±0.40	0.926	0.999
TP (ms^2)	2275.00±1426.00	2246.00±1440.00	0.225	0.378
VLF (ms^2)	1289.00±282.00	1236.00±119.00	0.451	0.654
LF (ms^2)	352.20±45.32	374.18±42.26	0.249	0.324
HF (ms^2)	254.41±62.36	248.36±70.24	0.654	0.725
LF/HF	1.51±0.26	1.52±0.22	0.897	0.902

*Data are presented as mean±SD.

**Adjusted for age and CAD RF

HRV, Heart rate variability; Mean RR, Mean of the R-R interval; SDNN, Standard deviation of normal-to-normal HRV intervals; SDNN-I, Mean of the 5-minute standard deviations of RR intervals; RMSSD, Square root of the mean of the squared successive differences in R–R intervals; pNN50, Percentage of R–R intervals that are at least 50 milliseconds different from the previous interval; TP, Total power; VLF, Very low frequency; LF, Low frequency; HF, High frequency; LF/HF, Low frequency/High frequency

Table 4. The Cox proportional hazard model for assessing the predictive value of HRV (SDNN) for long-term mortality*

Variables	P	Hazard Ratio	95% CI for Hazard Ratio	
			Lower limit	Upper limit
HRV (SDNN)	0.032	0.32	0.12	0.88
Male sex	0.012	2.21	1.49	3.25
Age (y)	0.008	1.78	1.22	2.13
Body mass index	0.089	0.88	0.74	1.00
History of hypertension	0.002	1.89	1.21	3.41
History of diabetes mellitus	0.001	2.21	1.49	4.22
History of hyperlipidemia	0.123	1.72	0.52	1.21
History of smoking	0.452	1.78	0.56	1.45
Family history of coronary disease	0.234	1.25	0.24	1.47
Multi-vessel involvement	0.002	2.45	1.73	4.58
Mean left ventricular ejection fraction	0.008	0.23	0.09	0.48
History of aspirin use	0.018	0.42	0.22	0.52
History of diuretics use	0.456	0.42	0.24	1.66
History of β-blocker use	0.223	0.75	0.22	1.75
History of calcium-blocker use	0.452	0.45	0.12	1.45
History of ACE-inhibitor use	0.212	0.78	0.42	1.47
History of statin use	0.097	0.25	0.12	1.48

HRV, Heart rate variability; ACE, Angiotensin-converting enzyme; SDNN, Standard deviation of normal-to-normal HRV intervals

Discussion

Indubitably, changes in HRV indices, particularly in patients admitted to the ICU, are recognized as significant prognostic markers for predicting arrhythmic disorders and subsequent mortality. Nevertheless, their value in predicting long-term outcomes after cardiac surgeries remains unclear. Our study demonstrated the high predictive value of this parameter for long-term mortality after CABG, although we could not confirm its predictive value for long-term cardiovascular events in this study.

In a 2013 study by Lakusic et al,[15] similar to our results, a decrease in HRV (<97 ms) was identified as an independent predictor of long-term mortality in CABG patients. Nonetheless, in contrast to our findings, a 2004 study by Milicevic et al[16] found no significant difference in HRV between survivors and non-survivors in the CABG group, although this index could predict long-term mortality in patients experiencing a myocardial infarction. Huikuri et al[17] also demonstrated that a drop in HRV could signify the substantial progression of coronary atherosclerosis. In this context, SDNN was low, and minimum HR was fast in patients with marked progression compared with those with regression of focal coronary atherosclerosis. The multiple regression analysis revealed that the progression of focal coronary atherosclerosis was independently predicted by SDNN. Rich et al[18] also suggested that reduced HRV and ejection fraction were the strongest predictors of mortality, with HRV contributing independently of ejection fraction, the extent of coronary artery disease, and other variables. It appears that HRV possesses a strong predictive capacity for both in-hospital and long-term mortality following CABG, as well as in patients experiencing a myocardial infarction, with this prognostic value being entirely independent of the underlying risk factors for heart diseases.

From a pathophysiological standpoint, HR within sinus rhythm is a consequence of parasympathetic and sympathetic nervous system modulation. It is important to note that considerable HRV can occur in healthy individuals, but deviations outside the normal range are a key indicator of arrhythmia. This event may be attributed to a decrease in vagal cardiac tone and/or diminished adrenergic responsiveness.[19] These alterations can become more prominent following cardiac surgeries involving invasive manipulation of heart tissue, potentially resulting in adverse long-term outcomes.[20] In other words, HRV reduction following cardiac surgery, even within a rehabilitation program, may serve as a robust indicator of long-term mortality. Notably, changes in HRV can also be a significant predictor of cardiac-related sudden death and progression to heart failure in individuals without substantial heart disease.[21–24]

Consequently, it can be concluded that, irrespective of whether the patient has undergone CABG or experienced an acute coronary syndrome, the development of any HRV disturbance following the procedure or after a primary heart attack can potentially elevate the risk of mortality, even in the long term.

Conclusion

HRV measurement following CABG can assist in predicting long-term death. Among different indices of HRV, reduced SDNN and mean RR have a higher value for predicting long-term MACE in this surgical procedure.

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