

QUALITY OF LIFE AND HEART RATE VARIABILITY FOLLOWING ACUTE MYOCARDIAL INFARCTION

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Abstract

Objective : The aim of this study was to investigate whether cardiac autonomic function measured by heart rate variability (HRV) indices are related to quality of life (QOL) improvements in patients with acute myocardial infarction (AMI) treated by percutaneous coronary intervention.

Methods : We enrolled 20 consecutive patients with AMI. Measures of HRV, obtained from both frequency and time domain analyses using 24-h Holter monitoring before discharge, were as follows : low and high frequency (HF) domain measures, the square root of the mean squared differences of successive R-R intervals (rMSSD), and the percentage of differences between adjacent normal R-R intervals >50 ms for the whole analysis (pNN50). QOL was determined by physical and mental component summary (PCS and MCS, respectively) scores derived from the Japanese Medical Outcomes Study 36-item Short Form Health Survey before and 6 months after discharge.

Results : The subjects showed significant improvement in the MCS, but not the PCS score. There were also positive correlations between the parasympathetic parameters of HF, rMSSD, and pNN50 and the change in MCS score. In a multivariate analysis, rMSSD was found to be independently associated with the change in MCS score.

Conclusions : Parasympathetic tone, as measured by HRV, is independently associated with QOL, which emphasizes the role of cardiac autonomic function on QOL in patients with AMI.

Key words : acute myocardial infarction, heart rate variability, quality of life, SF-36

Introduction

Acute myocardial infarction (AMI) is a life-threatening cardiac event that affects both cardiac autonomic function and quality of life (QOL)^{1,2)}. In patients with AMI, sym-

pathetic hyperactivity occurs soon after onset³⁾. Heart rate variability (HRV), determined from continuous 24-h electrocardiographic recordings, is an established non-invasive marker of cardiac autonomic function in patients recovering from an AMI. Reduced HRV has been documented to be a marker of poor prognosis, and an independent predictor of sudden death in this population⁴⁾.

Reduced mortality and morbidity, as well as health-related QOL, are key goals for patients with coronary artery disease (CAD). Several studies have reported the beneficial effect of percutaneous coronary intervention (PCI) on QOL in patients with AMI^{5,6)}. Autonomic dys-

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function results in physiological functional impairments associated with behavioral responses, including a decreased QOL. Previous studies associated reduced HRV with depression, which has a greater impact on QOL outcomes in patients with AMI^{7,8)}. Carney *et al.*⁹⁾ reported that HRV was lower in depressed patients than in their non-depressed counterparts. A possible explanation is that autonomic dysfunction, characterized by reduced parasympathetic and increased sympathetic tone, might be directly associated with depressive symptoms.

The association between autonomic nervous system function and health-related QOL has been described in patients with various diseases¹⁰⁻¹³⁾. However, in patients with AMI, the association between cardiac autonomic function and QOL has not been well studied. Therefore, to examine the relationship between autonomic function and QOL outcomes, we prospectively examined whether HRV indices evaluated before discharge (baseline) are related to changes in QOL observed during the first 6 months post-PCI, hypothesizing that parasympathetic tone at baseline is associated with QOL improvements.

Materials and Methods

Study subjects

We prospectively enrolled 20 consecutive patients (mean age 65 years, 15 males) admitted to Akita University Hospital (Akita, Japan) or Hiraka General Hospital (Akita, Japan) for AMI and who underwent primary PCI of the culprit coronary artery within 12 h of symptom onset (mean 3.0 ± 2.0 h) between July 2012 and June 2013. AMI was diagnosed in patients presenting with typical chest pain lasting ≥ 30 min and associated with new ST-segment elevation ≥ 0.1 mV in ≥ 2 contiguous leads on an electrocardiogram, with a well-identified culprit artery upon coronary angiography. All patients underwent PCI using standard techniques. We excluded patients who had experienced a myocardial infarction < 6 months prior and patients with rhythm disturbances that could interfere with accurate HRV analysis such as atrial fibrillation or other significant arrhythmias. Additional exclusion criteria were any sign of neuropathy and congestive heart failure according to New York Heart Association class III or IV.

The following clinical and laboratory findings were determined for each subject: age, sex, body mass index (BMI), cardiovascular risk factors, site of infarction, time to PCI from symptom onset, peak creatine kinase (CK) value, and medications. The left ventricular ejection fraction (LVEF) was measured before discharge by echocardiography. Written informed consent was obtained from all study participants and the study protocol was approved by the Ethics Committees of Akita University School of Medicine and Hiraka General Hospital.

Health-related QOL

QOL was measured using the Japanese version of the Medical Outcomes Study 36-item Short Form Health Survey (SF-36), which has been validated for the general Japanese population^{14,15)}. The SF-36 is a widely used and thoroughly validated, standardized, generic health survey, consisting of eight subscales that measure physical functioning, body pain, role limitations due to physical or emotional problems, social role functions, as well as a sense of vitality and mental and general health. The scores for each subscale are normalized on a scale of 0-100, with lower scores representing a lower QOL. These scores were converted into a deviation score adjusted for age- and sex-based scores from the general Japanese population, calculated as a mean of 50 with a standard deviation (SD) of 10. The physical component summary (PCS) and mental component summary (MCS) scores derived from the SF-36 questionnaire were used as measures of the patients' perception of their physical and mental QOL, with a score > 50 representing better than average function and a score < 50 representing poorer than average function¹⁶⁾. We chose to focus on summary scores rather than the eight subscales because we were interested in overall physical and mental QOL. Patients were tested using the SF-36 questionnaire before and 6 months after discharge.

Cardiac autonomic function

Twenty-four-hour ambulatory electrocardiographic Holter monitoring was performed for all subjects using a Fukuda FM-180 two-channel recorder (Fukuda Denshi Co., Tokyo, Japan) before discharge (22 ± 6 days after the onset of AMI). HRV was assessed from records collated

from 24-h records, after extracting artefacts using the data analyzing system SCM-6600 (Fukuda Denshi Co.). HRV analysis is widely used for the indirect quantitative and non-invasive measurement of cardiac autonomic function. There are two main approaches to the analysis of HRV: time domain analysis and frequency domain analysis. For the purpose of our study, four different time domain HRV indices were measured, including the SD of all normal R-R intervals in the entire recording (SDNN), the SD of the average of R-R intervals in all 5-min segments of a 24-h recording (SDANN), the square root of the mean squared differences of successive R-R intervals (rMSSD), and the percentage of differences between adjacent normal RR intervals that were >50 ms for the whole analysis (pNN50). The SDNN reflects overall HRV and represents parasympathetic as well as sympathetic function, whereas rMSSD and pNN50 are more specific for parasympathetic function. In the frequency domain, the extent of low-frequency (LF) oscillations (LF: 0.04-0.15 Hz) and high-frequency (HF) oscillations (HF: 0.15-0.4 Hz) was quantified using the first Fourier transformation. The LF domain is mediated sympathetically and parasympathetically, whereas the HF domain represents primarily parasympathetically-mediated respiratory variation. The ratio of the LF to the HF domain (LF/HF) has been described as a marker of sympathetic to parasympathetic balance.

Statistical analysis

Continuous variables are expressed as means \pm SD and categorical variables are expressed as numbers (%). A paired *t*-test was used to compare changes in QOL variables at follow-up versus the pre-discharge values. Correlations between HRV parameters and QOL scores were determined using Pearson's correction. Because the distributions of frequency domain parameters (except the LF/HF ratio) are skewed, the data were transformed to their natural logarithms to achieve a normal distribution and permit parametric statistical comparisons. A multivariate analysis was performed to assess the independence of the associations between QOL and anthropometric characteristics (age, BMI), cardiac function parameter (LVEF), the degree of myocardial damage (peak CK), and cardiac autonomic modulation (rMSSD). A p-

value <0.05 was considered statistically significant. All data were analyzed using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA).

Results

The baseline characteristics of the 20 patients with AMI are presented in Table 1. Most patients were male and the mean age was 65 years (range, 28-81 years). The mean BMI was 24 kg/m². The global LVEF was within the normal range. Anterior and non-anterior lesions were localized proportionally amongst the subjects. All patients were medicated with statins at the time of study registration. Angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), and beta-blockers were prescribed at discharge in 95 and 75% of patients, respectively.

Changes in QOL

All patients completed the SF-36 questionnaire, in full, before and 6 months after discharge. The changes in eight subscale and two summary scores are shown in Table 2. The body pain and social functioning subscale scores were significantly improved after 6 months. The subjects also exhibited significant improvement in their MCS scores, but not in their PCS scores.

Relationship between QOL and cardiac autonomic function

Based on the high statistical significance, we chose the change in MCS score as a parameter for the change in QOL. There was a significant positive correlation between HF and the change in MCS score. Furthermore, correlations were found between rMSSD, pNN50, and the change in MCS score. A negative correlation was found between the LF/HF ratio and the change in MCS score (Fig. 1). There was no significant correlation between MCS score and SDNN.

Predictor of QOL improvement

We analyzed which clinical and HRV parameters were independently associated with the change in MCS score by including age, BMI, LVEF, and peak CK value in a multivariate regression model. The results indepen-

Table 1. Baseline characteristics of the study population

Characteristics	Mean or Number
Age (years)	65±11
Gender (M/F)	15/5
BMI (kg/m ²)	23.9±2.3
HR (beats/min)	72±10
Peak CK (U/l)	2,483±2,042
LVEF (%)	63±14
Infarct site (anterior : non-anterior)	11 : 9 (55 : 45)
<u>Risk factors</u>	
Hypertension	14 (70)
Diabetes mellitus	7 (35)
Dyslipidemia	17 (85)
Smoking	12 (60)
<u>Medications</u>	
ACE inhibitor or ARB	19 (95)
Beta-blocker	15 (75)
Diuretics	1 (5)
Statin	20 (100)
<u>HRV parameters</u>	
HF [ln (ms ²)]	5.37±1.11
LF [ln (ms ²)]	5.81±0.87
LF/HF	1.66±0.91
SDNN (ms)	111.2±28.7
SDANN (ms)	92.8±27.0
rMSSD (ms)	35.7±29.9
pNN50 (%)	5.98±9.76

All values are expressed as means±SD or a number (%). ACE, angiotensin converting enzyme ; ARB, angiotensin receptor blocker ; BMI, body mass index ; CK, creatine kinase ; HR, heart rate ; HRV, heart rate variability ; LF, low-frequency oscillations ; LVEF, left ventricular ejection fraction ; pNN50, the percentage of differences between adjacent normal R-R intervals that were >50 ms ; rMSSD, the square root of the mean squared differences of successive R-R intervals ; SDNN, the standard deviation of all normal R-R intervals ; SDANN, the standard deviation of the average of normal R-R intervals in all 5-min segments.

dently associated BMI and rMSSD with the change in MCS score, but not with age, LVEF, or peak CK value (Table 3).

Discussion

This study assessed the relationship between cardiac

autonomic function determined by HRV and the change in QOL assessed using the SF-36 questionnaire in patients with AMI treated by primary PCI. We found that parasympathetic tone (rMSSD) before discharge was independently associated with an improved mental QOL (MCS score) after correction for parameters reflecting age, body composition, left ventricular function, and the degree of myocardial damage. This result underlines the predominant role of cardiac autonomic function in QOL in patients with AMI. During the 6-month follow-up period, the mental component of QOL improved significantly while the physical component of QOL did not. These changes in mental and physical health are similar to those demonstrated in previous studies¹⁷⁻¹⁹.

The finding that high body weight evaluated by BMI was identified as a predictor of improved mental QOL was interesting. Previous studies demonstrated that BMI was inversely associated with physical function and the overall QOL in CAD patients, especially in patients with severe obesity^{20,21}. A high BMI is a predominant risk factor, however, given the apparent 'obesity paradox' in patients with CAD ; future studies should be conducted to clarify the relationship between BMI and QOL in patients with AMI.

There is increasing awareness of the importance of QOL, and it has become a major end-point in clinical trials. QOL is a multidimensional construct that reflects health, happiness, and well-being, which are influenced by internal and external environmental factors. Internal factors include psycho-emotional factors as well as biological characteristics of the individual, such as emotional health and autonomic modulation. Autonomic dysfunction results in a multitude of unbearable complications that reflect altered biological function and create emotional distress to potentially lower one's QOL. In patients with myocardial infarction, cardiac autonomic dysfunction, as assessed by reduced HRV, may account for a substantial part of the risk associated with stress, anxiety, and depression^{8,9}. Furthermore, there is evidence that in patients with psychiatric disorders anxiety and depression are directly related to autonomic dysfunction²², and that treatment for depression improves HRV in patients with CAD²³.

Measures reflecting the parasympathetic modulation of

Table 2. Changes in quality of life parameters before and 6 months after discharge

Variable	Baseline	6 months after	<i>p</i> value
<u>SF-36 subscales</u>			
Physical functioning	46.4±14.8	43.5±15.1	0.22
Role physical	43.2±14.3	39.6±14.2	0.28
Body pain	46.5±9.3	54.9±8.3	0.01
General health	42.1±6.2	44.3±6.6	0.09
Vitality	50.5±9.8	52.9±8.3	0.32
Social functioning	44.8±11.1	50.9±6.3	0.04
Role emotional	45.5±13.6	44.0±14.9	0.64
Mental health	48.2±8.4	53.4±8.2	0.05
<u>SF-36 summary scores</u>			
PCS	46.0±9.9	45.9±6.7	0.97
MCS	46.3±5.5	50.1±4.3	0.01

All values are expressed as means±SD.

MCS, mental component summary ; PCS, physical component summary.

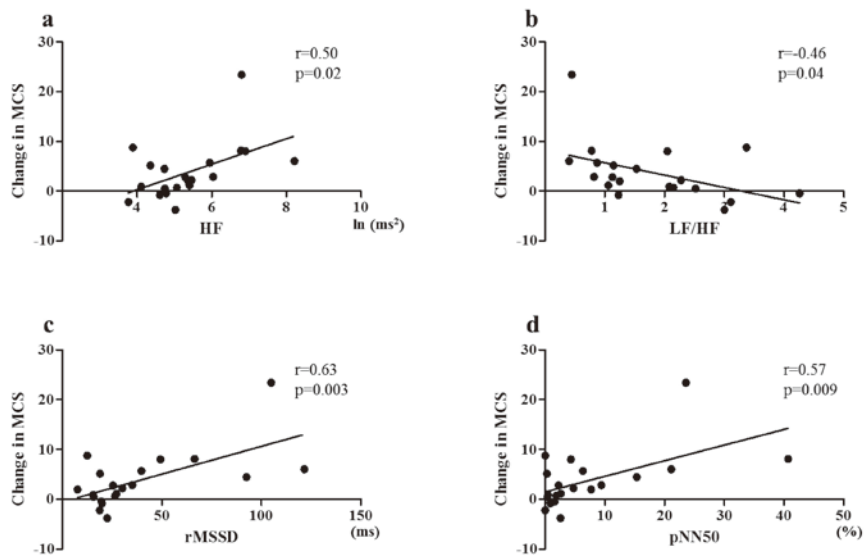


Fig. 1. Relationship between heart rate variability (HRV) parameters and changes in the mental component summary (MCS) score.

There was a significant positive correlation between high-frequency (HF) oscillations and the change in MCS score (a). Furthermore, correlations were found between the square root of the mean squared differences of successive R-R intervals (rMSSD), the percentage of differences between adjacent normal R-R intervals that were >50 ms (pNN50), and the change in MCS score (c and d). A negative correlation was found between the low-frequency (LF)/HF ratio and the change in MCS score (b).

Table 3. Multivariate regression analysis : an analysis of predictors of the MCS score

Variables	Coefficient β	<i>t</i> value	<i>p</i> value
Age (year)	-0.1	-0.71	0.48
BMI (kg/m ²)	0.49	2.73	0.02
LVEF (%)	0.01	0.08	0.93
Peak CK (U/l)	-0.04	-0.21	0.83
rMSSD (ms)	0.66	3.71	0.002

BMI, body mass index ; CK, creatine kinase ; LVEF, left ventricular ejection fraction ; MCS, mental component summary ; rMSSD, the square root of the mean squared differences of successive R-R intervals.

heart rate (HF, rMSSD, and pNN50) were significantly associated with the mental component of QOL, while the LF/HF ratio, a marker of sympathetic to parasympathetic balance, showed a significant negative association with it. Moreover, we found that rMSSD appeared to be independently associated with the mental component of QOL after correcting for variables reflecting pathophysiologic features of AMI. The strongest correlations in AMI patients occurred between time domain measures of HRV and MCS score in QOL. These findings suggest that time domain measures may be more sensitive indicators of HRV for AMI patients. Our study suggests that patients with AMI have an overall shift in their autonomic balance towards sympathetic predominance, and that the resulting parasympathetic tone is directly linked to the patients' perceived QOL. The mechanism of these findings remains speculative.

In this study, we showed that before discharge was the best time to assess HRV in our patients. Our study is in disagreement with a recent report that suggested a higher predictive value for HRV assessed 12 weeks after AMI²⁴), but it is in agreement with the high prognostic value of early HRV assessment reported in other studies^{4,25}). The reasons for these discordant results are unclear, but differences in patient selection and treatment, as well as in clinical characteristics and outcomes, might have played a role.

Taken together, cardiac autonomic function, particularly better parasympathetic modulation, was predictive of an improved QOL, particularly the mental component. Our findings suggest that if autonomic modulation

could be enhanced during the early period after PCI, associated improvements in QOL may occur. Cardiac autonomic function, therefore, should be added as a target for therapeutic intervention.

This study must be regarded as a pilot study due to the small number of patients and because there was no control group. Therefore, one should interpret our results with caution. Most of the patients were on medication such as ACE inhibitors, ARBs, and beta-blockers during Holter monitoring, which possibly influenced their HRV. Furthermore, as patients with conditions known to have an adverse effect on HRV (e.g., diabetes and renal dysfunction) were included in this study, we are unable to fully account for the significant association in the observed data. In our study, psycho-emotional factors such as depression, anger, and anxiety were not determined by means of specific questionnaires such as the 'Beck Depression Inventory' and 'Hospital Anxiety and Depression Scale'. The parameters obtained from these instruments would provide useful information about the correlation between cardiac autonomic function and psycho-emotional status related with QOL. Finally, because of the small sample size we could not perform a sub-analysis of the localization of coronary lesions that affect HRV. Previous studies reported that HRV was lower in patients with anterior AMI compared with non-anterior AMI^{26,27}). Parasympathetic predominance, possibly due to greater activity of vagal afferents, has been proposed in cases of non-anterior AMI²⁸). Accordingly, further study is needed to assess the dependency of cardiac autonomic function on the infarct area.

In conclusion, our study shows that HRV assessed before discharge is an independent predictor of the change in QOL 6 months later in patients with AMI treated by primary PCI. The data demonstrate that increased parasympathetic tone, indicated by HRV, was significantly associated with improved health-related QOL, emphasizing the important role of cardiac autonomic function in the QOL for patients with AMI. Modification of cardiac autonomic dysfunction could be beneficial in the treatment of AMI patients.

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