Left ventricular (LV) remodeling is characterized by progressive LV dilatation, rearrangement of the wall structure, myocyte hypertrophy, and increasing muscle mass without an increase in wall thickness. Because LV remodeling strongly influences the prognosis of patients with acute myocardial infarction (AMI), it is currently a subject of intense investigation. Reduced heart rate variability (HRV) is also an important risk factor for mortality and life-threatening ventricular arrhythmias after AMI. Although HRV recovers during the healing stage of AMI, it may remain reduced in some patients, especially in those with severe LV dysfunction and subsequent LV remodeling. We hypothesized that inadequate improvement in HRV in the healing stage is related to postinfarction LV remodeling. In the present study, we sought to test this hypothesis AMI. To minimize confounding factors, such as previous MI, the site of the MI, and patency of the infarct-related artery, that can affect HRV as well as LV remodeling, we examined only patients with a first anterior wall AMI (≤24 h) who had successful primary coronary angioplasty with or without additional coronary stenting and no re-occlusion of the infarct-related artery during hospitalization, and Thrombolysis in Myocardial Infarction (TIMI) flow grade 3 at predischarge. We prospectively examined 20 patients (14 men, 6 women; mean age, 61±12 years) with an anterior wall AMI who were admitted within 24 h of the onset of symptoms and who met the following criteria: (1) typical chest pain lasting at least 30 min; (2) ST-segment elevation of at least 0.2 mV in at least 2 adjacent precordial leads on the admission electrocardiogram (ECG); (3) an increase in the serum creatine kinase concentration to more than twice the normal value; (4) no history of previous MI; (5) no other heart or lung diseases; (6) successful primary coronary angioplasty with or without additional coronary stenting; (7) no re-occlusion of the infarct-related artery during hospitalization, and TIMI flow grade 3 at predischarge; (8) sinus rhythm; and (9) adequate Holter ECG recordings for the analysis of HRV. The standard deviation of normal RR intervals (SDNN) was calculated from the 24-h ambulatory electrocardiogram recorded on day 3 of admission and at predischarge from the hospital. Left ventriculography was performed immediately after primary angioplasty and at predischarge. The change in SDNN (△SDNN) was compared with the change in the LV end-systolic volume index (△LVESVI), a parameter of LV remodeling. SDNN increased from 73±19 ms on day 3 to 109±35 ms at predischarge (p=0.0003). SDNN at predischarge and △SDNN correlated negatively with △LVESVI (r=−0.52, p=0.02, and r=−0.61, p=0.004, respectively), whereas SDNN on day 3 did not correlate with △LVESVI. Multiple regression analysis selected △LVESVI (p=0.02) as an independent factor of △SDNN. This study indicates that △SDNN and SDNN at predischarge are associated with △LVESVI in patients with a reperfused first anterior wall AMI, indicating that persistently reduced HRV is associated with postinfarction LV remodeling. (Circ J 2003; 67: 225–228)

Key Words: Acute myocardial infarction; Heart rate variability; Left ventricular remodeling

Methods

Study Patients

We prospectively examined 20 patients (14 men, 6 women; mean age, 61±12 years) with an anterior wall AMI who were admitted within 24 h of the onset of symptoms and who met the following criteria: (1) typical chest pain lasting at least 30 min; (2) ST-segment elevation of at least 0.2 mV in at least 2 adjacent precordial leads on the admission electrocardiogram (ECG); (3) an increase in the serum creatine kinase concentration to more than twice the normal value; (4) no history of previous MI; (5) no other heart or lung diseases; (6) successful primary coronary angioplasty with or without additional coronary stenting; (7) no re-occlusion of the infarct-related artery during hospitalization, and Thrombolysis in Myocardial Infarction (TIMI) flow grade 3 at predischarge; (8) sinus rhythm; and (9) adequate Holter ECG recordings for the analysis of HRV.

Emergency Cardiac Catheterization and Reperfusion Therapy

Emergency coronary arteriography was performed using either the Judkins or Amplatz technique. Multiple projections were recorded to ensure optimal visualization of the coronary vessels. The coronary flow in the left anterior descending coronary artery was graded according to the classification used in the TIMI trial. A proximal left anterior descending coronary artery occlusion was defined as an occlusion of the artery proximal to its first septal branch. The grade of collateral filling in the left anterior descending coronary artery was determined according to the criteria of Rentrop et al. Collateral circulation with a grade of 2 or 3 was defined as ‘good’. After angiographic confirmation of

(Circ J 2003; 67: 225–228)
Total or subtotal occlusion of the left anterior descending coronary artery, primary coronary angioplasty was performed. If an optimal result (residual stenosis <50%) could not be obtained, additional coronary stenting was performed (n=5). All patients had TIMI grade 3 flow in the left anterior descending coronary artery after primary coronary angioplasty with or without additional coronary stenting.

Cardiac Catheterization at Predischarge

Left ventriculography was performed immediately after revascularization therapy and at predischarge. Left ventriculograms in the 30° right anterior oblique projection were analyzed for LV volume by an experienced cardiologist who was unaware of the patients’ data. LV volume was calculated by the area–length method.19 The changes in LV end-systolic volume index (LVESVI) between the acute phase and predischARGE were obtained (ΔLVESVI) and used as an index of postinfarction LV remodeling.

Analysis of HRV

All patients underwent 24-h Holter recording using 2-channel real-time tape recorders (DMC-3253, Nihonkoden Co, Tokyo, Japan) on day 3 and at predischarge. None of the patients studied showed any evidence of ischemic ST-T change on the Holter ECG recordings. The magnetic tapes were analyzed using a commercially available computerized system (MemCalc/CHIRAM GMS Co, Tokyo, Japan). The intervals that differed by more than 20% from previous intervals were weeded out from the RR data to avoid the influence of those related to premature beats or artifacts. The RR sequence was subsequently visually inspected and corrected manually, if necessary. In our study, recordings with less than 18 h of data or less than 80% of the qualified beats were not included. The SD of all the normal RR intervals (SDNN), one of the time-domain parameters, was obtained, as were the changes in SDNN between day 3 and predischarge (ΔSDNN).

Table 1  Patient Characteristics

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61±12</td>
</tr>
<tr>
<td>Male</td>
<td>14 (70%)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24±2</td>
</tr>
<tr>
<td>Time from the onset to admission (min)</td>
<td>370±400</td>
</tr>
<tr>
<td>Preinfarction angina</td>
<td>8 (40%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12 (60%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>8 (40%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>12 (60%)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>14 (70%)</td>
</tr>
<tr>
<td>Emergency coronary angiographic findings</td>
<td></td>
</tr>
<tr>
<td>TIMI flow grade</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>12 (60%)</td>
</tr>
<tr>
<td>2</td>
<td>5 (25%)</td>
</tr>
<tr>
<td>3</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>Proximal LAD occlusion</td>
<td>11 (55%)</td>
</tr>
<tr>
<td>Good collateral circulation</td>
<td>8 (40%)</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>6 (30%)</td>
</tr>
<tr>
<td>Additional coronary stenting</td>
<td>5 (25%)</td>
</tr>
<tr>
<td>LVEF immediately after emergency PCI (%)</td>
<td>54±10</td>
</tr>
<tr>
<td>LVEF at predischarge (%)</td>
<td>58±11</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>12 (60%)</td>
</tr>
<tr>
<td>Angiotensin II type 1 receptor antagonists</td>
<td>5 (25%)</td>
</tr>
<tr>
<td>β-blockers</td>
<td>6 (30%)</td>
</tr>
</tbody>
</table>

Angiotensin II type 1 receptor antagonists 5 (25%)

Angiotensin-converting enzyme inhibitors 12 (60%)

Hypertension 12 (60%)

Smoking 12 (60%)

Preinfarction angina 8 (40%)

Electrocardiographic criteria for ischemia were the presence of ST-segment depression >1 mm or T-wave inversion >1 mm in any of the limb or precordial leads. No patient was found to have any evidence of ST-segment depression or T-wave inversion >1 mm in any of the limb or precordial leads. The patients studied showed any evidence of ischemic ST-T change on the Holter ECG recordings. The magnetic tapes in the 30° right anterior oblique projection were analyzed for LV volume by an experienced cardiologist who was unaware of the patients’ data. LV volume was calculated by the area–length method.19 The changes in LV end-systolic volume index (LVESVI) between the acute phase and predischARGE were obtained (ΔLVESVI) and used as an index of postinfarction LV remodeling.

Statistical Analysis

Data are expressed as the means±SD or as a proportion (percent). Continuous variables were analyzed by the unpaired or paired t-test. Pearson’s correlation analysis was performed to estimate correlations between variables. Multivariate regression analysis was used to determine independent factors for ΔSDNN. A p<0.05 was considered statistically significant.

Results

Patient characteristics are shown in Table 1. There were histories of smoking, hypertension, and diabetes mellitus in 12 (60%), 12 (60%), and 8 patients (40%), respectively. Angiotensin-converting enzyme inhibitors, angiotensin II type 1 receptor antagonists, and β-blockers were administered during hospitalization in 12 (60%), 5 (25%), and 6 patients (30%), respectively.

SDNN increased from 73±19 ms on day 3 to 109±35 ms at predischarge from hospital (p=0.003). SDNN on day 3 did not correlate with ΔLVESVI (Fig 1); however, at predischarge it correlated negatively with ΔLVESVI (r=–0.52, p=0.02) (Fig 2). ΔSDNN also correlated negatively with ΔLVESVI (r=–0.61, p=0.004) (Fig 3).

Factors Affecting ΔSDNN

The association of ΔSDNN with the selected variables (ie, age, gender, time to admission, preinfarction angina, hypertension, diabetes mellitus, proximal left anterior descending coronary artery occlusion, good collaterals to the left anterior descending coronary artery, multivessel disease, peak creatine kinase concentration and the use of angiotensin-converting enzyme inhibitors, angiotensin II type 1 receptor antagonists or β-blockers) was analyzed by univariate analysis. Patients with diabetes mellitus tended to have a greater ΔSDNN than those without (48±28 vs 27±24 ms, p=0.09). ΔSDNN did not differ significantly between patients with or without angiotensin-converting enzyme inhibitors or angiotensin II type 1 receptor antagonists (37±28 vs 32±30 ms, p=0.77), or between patients with or without β-blockers (48±27 vs 32±27 ms, p=0.23). Peak creatine kinase concentration did not correlate with ΔSDNN (r=–0.13, p=0.60).

ΔSDNN and a variable with a value of p<0.2 on univariate analysis (diabetes mellitus) were used for multivariate regression analysis. Multivariate regression analysis selected ΔLVESVI (p=0.02) as an independent factor of ΔSDNN.

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**Fig 1.** Relationship between SD of the all normal RR intervals (SDNN) on day 3 and Δ left ventricular end-systolic volume index (ΔLVESVI).
HRV and LV Remodeling in Anterior Wall AMI

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Discussion

In the present study, SDNN was independently associated with LVESVI in patients successfully treated by primary coronary angioplasty for a first anterior wall AMI. Furthermore, SDNN at predischarge also correlated negatively with LVESVI. These results indicate that persistently reduced HRV is related to postinfarction LV remodeling. SDNN on day 3 did not correlate with LVESVI. This lack of correlation might be because a large extent of dysfunctional but viable myocardium as well as a larger extent of necrotic myocardium reduce HRV. Patients with a large extent of dysfunctional but viable myocardium would be expected to show an improvement in HRV and less subsequent postinfarction LV remodeling.

Mechanisms by Which LV Remodeling Affects HRV in AMI

Postinfarction LV remodeling is divided into early and late phases. Infarct expansion occurring within hours of the onset of AMI results from the degradation of the intermyocyte collagen struts by serine proteases and the activation of matrix metalloproteases released from activated neutrophils. Infarct expansion results in wall thinning and ventricular dilatation and increases diastolic and systolic wall stress. Myocardial stretch, caused by the increased wall stress, can lead to mechanical distortion of the sensory endings of sympathetic afferent nerves to local tissue angiotensin II release at the infarct zone and remote sites and, finally, to the activation of the sympathetic nervous system. Furthermore, disturbances in circulatory hemodynamics also trigger the sympathetic adrenergic system. An increase in afferent sympathetic activity would cause reflex inhibition of vagal fibers to the sinus node and stimulation of sympathetic activity directed to the heart. The autonomic alteration consequent to these reflex mechanisms can result in depressed HRV. Late LV remodeling occurs beyond 72 h of the onset of AMI and involves myocyte hypertrophy and alterations in ventricular architecture, causing further increased wall stress, which also results in a reduction in HRV. Thus, postinfarct LV remodeling can cause persistently reduced HRV.

Clinical Implications

It is recommended that HRV should be assessed approximately 1 week after AMI; it remains unclear whether the assessment of HRV in the early phase (ie, on day 2 or 3) of AMI has important clinical implications. Clinical usefulness of the assessment of HRV in the early phase was demonstrated by our result that the assessment of HRV both in the early phase and at predischarge can offer important information on postinfarction LV remodeling. In an animal experiment, it was shown that the speed of HRV recovery after AMI correlates with subsequent risk. Further investigations are needed to clarify whether the assessment of HRV both in the early phase and at predischarge is useful in identifying patients with poor outcomes after AMI.

Study Limitations

First, we studied only a small group of selected patients that did not include patients with severe complications such as death, severe pump failure, or severe arrhythmias who would be expected to have reduced HRV or subsequent LV remodeling. In addition, because HRV is affected by various factors such as age, diabetes mellitus, the use of angiotensin-converting enzyme inhibitors and ß-blockers, these factors might have affected our results. Further studies with a large population will be needed to confirm our results. Second, our study did not include patients with inferior or posterior wall AMI. HRV has been reported to differ between anterior and non-anterior wall AMI. It needs to be clarified whether our results can be applied to patients with non-anterior wall AMI. Third, we investigated the relationship between HRV and LV remodeling within 1 month after the onset of AMI, but postinfarction LV remodeling lasts for months or years. Therefore, further studies will be needed to clarify the relationship between HRV and LV remodeling in the long term.

Conclusions

The present results indicate that SDNN at predischarge and SDNN are associated with LVESVI in patients with a reperfused first anterior wall AMI, indicating that persistently reduced HRV is associated with postinfarction...
LV remodeling.

References