Relation Between Variability of Ventricular Response Intervals and Exercise Capacity in Patients With Non-Valvular Atrial Fibrillation

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Background Reduced variability of the ventricular response interval (VRI) has been reported to predict adverse prognosis in patients with atrial fibrillation (AF). To examine whether it could be related also to the quality of the daily life of patients with AF, the relationships between VRI variability and exercise tolerance, one of the markers for quality of life, were determined in patients with persistent AF.

Methods and Results Thirty-one patients with idiopathic AF were included in the present study. Holter monitoring results and symptom-limited treadmill exercise testing were correlated in these patients without medications for the rate control of AF. The VRI variability, both the SD of the mean R-R interval (SDNN) and the SD of the 5-min mean R-R interval (SDANN), showed significant positive correlation with the exercise capacity (r=0.583, p=0.0004, and r=0.543, p=0.0013, respectively), whereas age, left ventricular ejection fraction and body mass index did not have any significant relationships. Multiple regression analysis revealed that increased SDNN was the only independent predictor of good exercise capacity during the treadmill exercise testing.

Conclusions Increased VRI variability, independently of other clinical variables, can predict good exercise capacity in patients with idiopathic AF, thus being a new sensitive maker for quality of life in AF.

Key Words: Atrial fibrillation; Exercise capacity; Ventricular response interval variability

Atrial fibrillation (AF) is the most common arrhythmia, with a prevalence of 0.4–0.5% for the overall population, and is associated with increased mortality and morbidity. With regard to treatment, the heart rate control strategy is as effective as the rhythm control strategy, but the target heart rate in this strategy is as yet unclear, although the heart rate during AF may be related to the prognosis and/or the quality of the patient’s life. A heart rate less than 90 beats/min at rest and 115 beats/min during moderate exercise has been recommended, but is based on clinical experience.

In patients with sinus rhythm, heart rate variability has been used to evaluate the vagal and sympathetic influences on the heart and to identify patients at risk for a cardiovascular event or death. In patients with AF, recent studies have reported that reduced variability of the ventricular response interval (VRI) during AF might predict an adverse prognosis. VRI variability is known to be dependent on the increased parasympathetic tone in AF, as well as in sinus rhythm which may be related to an active life of AF patients. On the basis of these facts, we hypothesized that analysis of VRI variability during AF might be useful as an assessment of exercise capacity as a representative of quality of life in AF patients. To test this hypothesis, we examined whether or not VRI variability is related to exercise capacity in AF patients. If it holds true, it could be a new maker for the management of AF patients.

Methods

Study Patients Thirty-one patients with persistent AF for more than 6 months were included (29 men, 2 women; age 60±7.4 years; left ventricular ejection fraction (LVEF): 61.2±6.5%, left atrial dimension: 44.9±7.0 mm). None of the patients had structural heart disease or had been prescribed any drugs for the control of heart rate, including antiarrhythmic agents.

VRI Variability and Exercise Tolerance Twenty-four-h ambulatory electrocardiographic (ECG) recording was performed during the patients’ usual daily activities and the VRI variability was analyzed by the time domain method. Two parameters were adopted as the expression of total and 5 min-term VRI variability: the standard deviation of all the R-R intervals (SDNN) and the SD of the 5-min mean R-R interval (SDANN). To evaluate the exercise capacity of the patients, Bruce’s multi-stage maximal treadmill protocol was performed with 3-min periods to allow achievement of a steady state before workload was increased. Exercise was continued until the patients complained of shortness of breath, the endpoint of exercise in the present study. We determined the relation between the VRI variability during 24-h ambulatory ECG monitoring and exercise capacity in the treadmill exercise testing.

Statistical Analysis All values are expressed as mean±SD. Data were ana-
Correlations between exercise capacity, VRI variability, and the clinical variables of the patients were examined by Pearson's rank test. A p-value <0.05 was considered statistically significant. Multiple regression analysis was performed to determine the independent predictors for the exercise capacity.

Results

On the 24-h ambulatory ECG, patients had a mean SDNN of 184±46 ms, SDANN of 118±36 ms, and total heart beats of 124,874±25,031 during the recording period. Both SDNN and SDANN showed significant positive correlation with the exercise capacity (r=0.583, p=0.0004, and r=0.543, p=0.0013, respectively; Fig 1). Therefore, increased VRI would predict good exercise capacity in these patients.

We also determined the relationships of other clinical variables to exercise capacity, including age, LVEF, body mass index (BMI), heart rate at rest and during moderate exercise of 5 Mets (3-min period at I stage of Bruce’s multi-stage maximal treadmill protocol) and total heart beats during 24-h ambulatory ECG. Of these, none of age, LVEF or BMI was significantly correlated with exercise capacity in our study population. Unfortunately, neither was heart rate at rest, which has been clinically used as a maker for AF management (Table 1). In contrast, both heart rate at moderate exercise and total heart beats during the 24h were negatively and significantly correlated with exercise capacity (r=−0.457, p=0.009, and r=−0.388, p=0.030, respectively).

The variables evaluated in the present study had some inter-relations; for example, SDNN was related to SDANN (r=0.869, p<0.0001), total heart beats during the 24h (r=−0.498, p=0.039), and heart rate during moderate exercise (r=−0.445, p=0.011). To ascertain the independent role of VRI in clinical situations involving these inter-relations, we carried out multiple regression analysis, which revealed that increased SDNN was the only independent predictor of good exercise capacity during treadmill exercise testing (r=0.709, p=0.046).

Discussion

Our study has revealed that VRI variability is a more sensitive indicator of exercise capacity than the commonly used variables such as heart rate at rest and during moderate exercise, and total heart beats during 24h. Patients with greater VRI variability during 24-h ambulatory ECG had better exercise capacity in the treadmill exercise test. Although heart rate during moderate exercise and total heart beats during the 24h were also related to the exercise capacity, the relationships were weaker in the present study.

In AF patients, VRI variability is closely related to vagal tone, because the parameters of VRI variability have been reported to increase after administration of propranolol and decrease after atropine. The principal determinant of ventricular rhythm in AF is the refractoriness of the atrioventricular node (AVN), which restricts the atrioventricular transmission of the atrial fibrillatory impulses. The irregularity of the ventricular rhythm is considered to be caused by varying degrees of penetration of the atrial impulses into the AVN, which is mainly dependent on vagal tone during usual activity. Therefore, our results would imply that AF patients with increased vagal tone have good exercise capacity.

Table 1  Correlations Between Clinical Variables and Exercise Capacity

<table>
<thead>
<tr>
<th>Variables</th>
<th>r</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>−0.089</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.024</td>
<td>NS</td>
</tr>
<tr>
<td>BMI</td>
<td>−0.240</td>
<td>NS</td>
</tr>
<tr>
<td>24-h ambulatory electrocardiographic monitorings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total heart beats</td>
<td>−0.388</td>
<td>0.030</td>
</tr>
<tr>
<td>SDNN</td>
<td>0.583</td>
<td>0.0004</td>
</tr>
<tr>
<td>SDANN</td>
<td>0.543</td>
<td>0.0013</td>
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<tr>
<td>Treadmill variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate at rest</td>
<td>−0.150</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate during moderate exercise (5 METs)</td>
<td>−0.457</td>
<td>0.009</td>
</tr>
</tbody>
</table>

LVEF, left ventricular ejection fraction; BMI, body mass index; SDNN, the standard deviation of all the R-R interval; SDANN, the standard deviation of the 5-min mean R-R interval.
There would be many mechanisms involved in the observed relation between VRI variability and exercise capacity. First, increased irregularity of VRI implies the existence of long ventricular intervals, which might contribute to the increased diastolic filling observed in AF. Therefore, patients with increased VRI could be capable of prolonged exercise because of this improved diastolic filling. Second, in AF patients with good exercise capacity, habitual exercise during daily life would possibly augment the parasympathetic tone, leading to the increased VRI variability. VRI variability might reflect the daily activity level of each patient, including at rest and during exercise. On this basis, increased VRI might not be causal, but the result of good exercise capacity. Though multifactorial and unknown in the present study, VRI variability could include more information than the commonly used clinical variables, thus being one of the sensitive markers for AF management.

There are some limitations, however, to using VRI variability in clinical situations. First, we studied only a small group of selected patients who did not require any drugs for the control of heart rate. Second, because atrioventricular dual pathways and the refractory period of the His bundle could affect VRI variability, these factors might have affected our results. Third, exercise capacity was evaluated by Bruce’s multi-stage maximal treadmill protocol in the present study. A more precise method that included cardiopulmonary exercise testing would be required to assess exercise capacity in detail. In addition, the observed relation between VRI variability and exercise capacity is restricted to patients without structural heart disease or on medication. Further investigations would be required to examine the effects of these 2 factors on the VRI variability in AF patients. Although limited, the present study suggests that a new sensitive tool for predicting the exercise capacity of AF patients can be obtained from 24-h ambulatory ECG and such noninvasive monitoring of AF patients could include more information than expected, and thus efforts to analyze them in detail would lead to better AF management of each patient.

References