Heart rate recovery after exercise is associated with renal function in patients with a homogenous chronic renal disease

István Késői, Balázs Sági, Tibor Vas, Tibor Kovács, István Wittmann and Judit Nagy
Nephrology Center and 2nd Department of Internal Medicine, Medical Faculty, University of Pécs, Hungary

Correspondence and offprint requests to: Judit Nagy; E-mail: judit.nagy@aok.pte.hu

Abstract

Background. Attenuated heart rate recovery (HRR) is an independent predictor of cardiac and total mortality. Diminished renal function is a similar predictor. There are no data concerning the interaction between the two risk factors. We studied HRR in patients with a homogeneous renal disease, IgA nephropathy.

Methods. One hundred and seven patients with biopsy-proven chronic IgA nephropathy (71 males, 36 females aged 45 ± 11 years) performed a graded exercise treadmill stress test. HRR was measured as the heart rate difference between the peak value and the heart rate 1 min after exercise. The patients were divided into three groups based on estimated glomerular filtration rate (eGFR): CKD 1, eGFR ≥ 90 ml/min (n = 46); CKD 2, eGFR 60–89 ml/min (n = 38), CKD 3–4, eGFR 15–59 ml/min (n = 23). We compared these data with 29 normal controls (aged 46 ± 14 years).

Results. HRR values corresponded to eGFR as follows: 29.9 ± 8.8 bpm normal controls, 27.8 ± 9.2 bpm CKD 1, 24.5 ± 10.5 bpm CKD 2 and 16.3 ± 9.3 bpm CKD 3–4. The latter differed from the other groups significantly (P < 0.05). Metabolic syndrome was common in IgA nephropathy patients (27%). Metabolic syndrome patients had a HRR of 19.6 ± 10.1 bpm, compared to 25.8 ± 10.4 bpm in patients without metabolic syndrome (P = 0.007). Nevertheless, a multivariate regression analysis accepted only eGFR as an independent predictor of HRR.

Conclusion. eGFR predicts HRR in patients with a homogenous renal disease. Metabolic syndrome influences HRR, albeit not independently in this cohort.

Keywords: cardiovascular risk; chronic kidney disease; heart rate recovery; IgA nephropathy; metabolic syndrome

Introduction

Graded exercise testing is a tool to predict cardiovascular risk in any given subject, generally based on the electrocardiogram and exercise capacity [1,2]. However, heart rate recovery (HRR) after exercise, which is related to the balance of sympathetic and parasympathetic tone, is also a predictor of cardiovascular risk [3–5]. HRR at 1 or 2 min detected during treadmill stress test exercise has been established as a validated method [6]. Earlier studies have evaluated the prognostic significance of HRR in patients with different cardiac diseases. Attenuated HRR has been described as a predictor of total mortality and sudden cardiac death in coronary artery disease, heart failure, left ventricular dysfunction, and after coronary artery revascularization [7–12]. Cardiovascular risk is increased with any decrease in kidney function [13,14]. However, any relationship between HRR and renal function is unexplored. We have focused our attention on patients with IgA nephropathy, a
condition thought to be relatively benign, but nonetheless a common cause of decreased renal function [15]. Patients with IgA nephropathy have a relatively homogeneous form of renal disease. As is common in chronic renal disease of any cause, these patients are subject to develop insulin resistance, dyslipidaemia, hypertension and other features of the metabolic syndrome, a condition also associated with decreased HRR in an earlier study [16]. We tested the effect of diminished renal function on HRR in IgA nephropathy patients and examined any possible confounding effects of the metabolic syndrome.

Patients and methods

We studied 107 biopsy-verified IgA nephropathy patients, who did not have known heart failure, although treated coronary artery disease (CAD) was accepted. Left bundle branch block on ECG was an exclusion criterion because in that case it is impossible to analyse the ST segment changes during the stress test. Patients with manifest symptoms of heart failure (NYHA III-IV) were also excluded, as well as patients with atrial fibrillation or severe hypertension (≥180/110 mm Hg). All patients that we included were able to perform exercise testing. The cohort included 71 men and 36 women aged 45 ± 11 years. Written informed consent was obtained in all participants after the University ethical committee had approved the study. As is routine in our department, the patients had been instructed to be on a low sodium diet (100 mmol/day), protein reduction to 0.6–0.8 g/kg/day, they had been advised not to smoke and to exercise regularly.

The patients underwent a 75 g glucose tolerance test. Impaired glucose tolerance (IGT) was defined as a 2-h glucose level between 7.8–11.1 mmol/L. If it was above 11.1 mmol/L, diabetes mellitus (DM) was diagnosed. Impaired fasting glucose was established if the fasting glucose value was between 6.0 and 6.9 mmol/L. If any of them was detected, carbohydrate (CH) metabolic disorder was diagnosed. Dyslipidaemia was defined as a triglyceride level >1.7 mmol/l or high-density cholesterol (HDL) <0.9 mmol/l for men or <1.0 mmol/l for women. Ambulatory blood pressure measurement (ABPM) over 24 h was measured oscillometrically. BMI was determined by the standard method [17]. We estimated the glomerular filtration rate (eGFR; ml/min/1.73 m²) with the Cockcroft–Gault formula. We classified the degree of renal insufficiency according to the Clinical Practice Guidelines for Chronic Kidney Diseases from the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative Group for CKD [18] as follows: CKD 1 group, (eGFR ≥ 90 ml/min, n = 46), CKD 2 group (eGFR: 60–89 ml/min, n = 38), CKD 3–4 group (eGFR: 15–59 ml/min, n = 23).

To assess the left ventricular systolic condition we performed echocardiography on every patient before the stress test. Left ventricular systolic function was characterized by ejection fraction (LVEF). It was calculated by the two-dimensional-directed M-mode method, using the Quinones formula. Patients with severe left ventricular systolic dysfunction (LVEF <35%) were not included in this study. The patients underwent a symptom-limited graded exercise treadmill test according to the standard Bruce protocol with a goal of achieving the maximum predicted heart rate (220 minus age) [19]. All examinations were performed in the late morning. The patients were instructed not to smoke and fast at least 2 h before the exercise, but to take their regular medications. Beta-blockers and nitrates were stopped at least for 48 h before the examination. Continuous 12-lead electrocardiographic (ECG) monitoring was performed throughout testing. ECG samples were recorded and printed every minute during the examination including the whole recovery. Exercise capacity was expressed in seconds and was measured from the zero second of the first step to the termination moment at peak exercise. The termination was followed by at least 1-min cool-down period with a treadmill speed of 1.6 km per hour. The value for HRR was defined as the difference between the heart rate from peak exercise to 1 min after the peak. Analyses were performed off-line on printed formats. Diagnosis of CAD was established if horizontal or down-sloping ST depression of ≥1 mm was found for at least 1 min in two or more coherent leads.

Twenty-nine patients with normal renal function and without any renal disease formed the control group. The indication of a cardiac stress test for all patients was to determine the exercise capacity and to verify the suspected diagnosis of CAD.

Statistical analysis

All results were presented as mean value ± SD unless indicated otherwise. The difference between the clinical parameters of the groups was investigated by ANOVA. The Pearson chi-square or Fisher’s exact test was applied to analyse categorical variables. Correlation analysis was performed to determine the association between renal function and HRR. Univariate and multivariate linear regression analyses were used to identify independent risk factors associated with HRR. A value of $P < 0.05$ was considered statistically significant. Data analysis was performed using the SPSS software program version 13.0 (SPSS Inc., Chicago, IL, USA).

Results

The baseline characteristics of patients are shown in Table 1. No significant gender differences were seen. The blood pressure did not differ significantly among groups; the values were well controlled (average BP on ABPM < 130/80 mmHg). Medication distribution of angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), calcium channel blockers (CCB), beta-blockers (BBL) and statins is given. Heart rate and exercise capacity calculated by the stress test time were also similar amongst the groups. The occurrence of CAD did not differ across the groups. LVEF of the CKD2 group was slightly but significantly higher than in the other groups. HRR values in the CKD 3–4 group (16.3 bpm) were significantly lower compared to the patients of the CKD 2 group (24.5 bpm, $P = 0.015$) or the CKD 1 group (27.8 bpm, $P < 0.001$) and the control group (29.9 bpm, $P < 0.001$), respectively (Figure 1). There was no difference in HRR between the control group, the CKD 1 and CKD 2 groups. HRR reduction (Figure 2) showed significant correlation with decreased eGFR ($r = 0.422$ $P < 0.001$). To assess the occurrence of metabolic syndrome, we used the World Health Organization criteria. We found that 29 (27%) of the 107 renal patients had complete metabolic syndrome; there was no statistically significant difference in the occurrence of metabolic syndrome among groups. The HRR of metabolic patients was significantly lower than in patients without the metabolic syndrome (19.6 ± 10.1 bpm versus 25.8 ± 10.4 bpm, $P = 0.007$). Univariate linear regression analysis was performed in renal patients including 23 confounding variables: gender, age, exercise capacity, CAD, metabolic syndrome, hypertension in history, systolic and diastolic BP, systolic and diastolic diurnal index on ABPM, pulse pressure, heart rate, BMI, dyslipidaemia, carbohydrate metabolic disorder, LVEF, smoking habit, haemoglobin level, eGFR and medical treatment (ACEi/ARB, Ca-antagonists, beta-blockers and statins). The factors associated with HRR were age, metabolic syndrome, systolic 24 h BP, systolic diurnal index on ABPM, pulse pressure, BMI, dyslipidaemia, CH
Table 1. Baseline characteristics of the CKD and control groups

<table>
<thead>
<tr>
<th></th>
<th>CKD1 group (n = 46)</th>
<th>CKD2 group (n = 38)</th>
<th>CKD3–4 group (n = 23)</th>
<th>Control (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male n (%)</td>
<td>30 (65)</td>
<td>25 (66)</td>
<td>16 (70)</td>
<td>16 (55)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>38 ± 11</td>
<td>48 ± 10</td>
<td>51 ± 12</td>
<td>46 ± 14</td>
</tr>
<tr>
<td>Exercise capacity (s)</td>
<td>605 ± 192</td>
<td>560 ± 143</td>
<td>483 ± 230</td>
<td>601 ± 218</td>
</tr>
<tr>
<td>CAD (positive stress test), n (%)</td>
<td>7 (16)</td>
<td>8 (21)</td>
<td>4 (19)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>11 (24)</td>
<td>11 (29)</td>
<td>7 (30)</td>
<td>6 (21)</td>
</tr>
<tr>
<td>Hypertension n (%)</td>
<td>25 (56)</td>
<td>29 (78)</td>
<td>21 (91)</td>
<td>18 (62)</td>
</tr>
<tr>
<td>Systolic BP (mmHg, ABPM)</td>
<td>120.0 ± 6.9</td>
<td>125.0 ± 8.7</td>
<td>127.0 ± 8.5</td>
<td>124.0 ± 13.0</td>
</tr>
<tr>
<td>Diastolic BP (mmHg, ABPM)</td>
<td>72.0 ± 9</td>
<td>75.0 ± 8.0</td>
<td>76.0 ± 8.0</td>
<td>74.0 ± 10.0</td>
</tr>
<tr>
<td>Diastolic diurnal index (%)</td>
<td>14.6 ± 9.6</td>
<td>13.0 ± 6.0</td>
<td>12.8 ± 5.7</td>
<td>10.2 ± 8.6</td>
</tr>
<tr>
<td>Pulse pressure (mmHg)</td>
<td>48.2 ± 6.8</td>
<td>50.0 ± 9.1</td>
<td>51.2 ± 14.7</td>
<td>50.1 ± 7.0</td>
</tr>
<tr>
<td>Obesity: BMI (kg/m²)</td>
<td>26.5 ± 5.0</td>
<td>26.6 ± 4.5</td>
<td>27.6 ± 8.7</td>
<td>27.0 ± 5.6</td>
</tr>
<tr>
<td>Dyslipidaemia n (%)</td>
<td>17 (37)</td>
<td>18 (47)</td>
<td>14 (61)</td>
<td>7 (24)</td>
</tr>
<tr>
<td>CH metabolic disorders n (%)</td>
<td>11 (24)</td>
<td>12 (32)</td>
<td>7 (30)</td>
<td>6 (21)</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>61.3 ± 6.1</td>
<td>65.0 ± 6.1</td>
<td>61.3 ± 6.9</td>
<td>61.1 ± 5.9</td>
</tr>
<tr>
<td>Current smokers n (%)</td>
<td>6 (13)</td>
<td>6 (16)</td>
<td>5 (22)</td>
<td>4 (14)</td>
</tr>
<tr>
<td>Haemoglobin (g/l)</td>
<td>14.3 ± 1.4</td>
<td>13.6 ± 1.4</td>
<td>12.6 ± 1.8</td>
<td>14.2 ± 1.4</td>
</tr>
<tr>
<td>eGFR (ml/min)</td>
<td>116 ± 18</td>
<td>74 ± 9</td>
<td>39 ± 17</td>
<td>102 ± 18</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On ACEi/ARB n (%)</td>
<td>32 (70)</td>
<td>34 (89)</td>
<td>21 (91)</td>
<td>12 (41)</td>
</tr>
<tr>
<td>On Ca-antagonists n (%)</td>
<td>5 (11)</td>
<td>14 (37)</td>
<td>8 (35)</td>
<td>8 (28)</td>
</tr>
<tr>
<td>On beta-blockers n (%)</td>
<td>10 (22)</td>
<td>9 (24)</td>
<td>10 (43)</td>
<td>8 (28)</td>
</tr>
<tr>
<td>On statin n (%)</td>
<td>9 (20)</td>
<td>12 (32)</td>
<td>12 (52)</td>
<td>2 (7)</td>
</tr>
</tbody>
</table>

*P < 0.05; †P < 0.01 CKD1 versus the CKD2 and CKD3–4 groups; ‡P < 0.05 CKD2 versus all other groups; §P < 0.01 CKD3–4 versus the CKD1 group and the control group; #P < 0.01 between groups, except CKD1 versus the control group.

Fig. 1. Heart rate recovery in the different groups.

Fig. 2. Correlation between heart rate recovery and renal function.

Discussion

The important finding in our study is the demonstration of an independent association between attenuated HRR and eGFR in a homogenous group of CKD patients with IgA nephropathy. Previous data suggest that decreased HRR has prognostic significance in CAD and heart failure. We found that IgA nephropathy patients with CKD 3–4 (eGFR < 60 ml/min) have significantly lower HRR than those with greater eGFR. Furthermore, we demonstrate a robust inverse correlation between eGFR and HRR. Autonomic imbalance characterized by HRR may represent one of the most important markers of cardiovascular risk and may predict total and cardiac mortality in patients with heart disease. Observations suggest that autonomic dysfunction has at least the same importance on the cardiovascular outcome as the presence of advanced CAD per se in cardiac patients [9,10].

McManus et al. investigated renal function and HRR in a cardiac population [20]. They found that the increased...
concentration of circulating cystatin C, which is a marker of decreased renal function, showed a nearly linear association with poor exercise capacity and HRR. Our data generalize these findings to patients with CKD.

Both increased sympathetic and decreased parasympathetic activity may contribute to autonomic imbalance. Evidence suggests that sympathetic hyperactivity is present in CKD patients. Increased sympathetic activity has been established not only in end-stage renal disease, but also in patients with polycystic kidney disease with partially preserved renal function, as well as in patients after renal transplantation [21–23]. Campese et al. used a rat model to show that renal afferent impulses in chronic kidney failure cause sympathetic hyperactivity and hypertension [24]. Converse et al. demonstrated the important effect of kidney damage on sympathetic overdrive [21]. In their study, the blood pressure of CKD patients decreased after bilateral concomitant nephrectomy with lower vascular resistance and reduced sympathetic nerve firing. In CKD, the effect of the damaged kidney itself on sympathetic nerve activity seems to be more important than putative uraemic toxins per se. Hausberg et al. failed to find any difference in sympathetic nerve activity between renal transplant patient with excellent graft function and uraemic patients on maintained haemodialysis [23].

Our data suggest that IgA nephropathy patients with decreased renal function (CKD 3–4) have autonomic imbalance. Furthermore, the effect of kidney damage on increased sympathetic activity seems to be more important than other classic cardiovascular risk factors. We considered many factors that may have influence on the cardiovascular status of IgA nephropathy patients. We found that all classic metabolic risk factors (i.e. high blood pressure, CH metabolic disorders, lipid alterations and obesity) have an influence on HRR. IgA nephropathy patients with the metabolic syndrome had significantly lower HRR values than patients without it. This finding is similar to the results of Spies et al. who investigated the association of metabolic syndrome, exercise capacity and HRR in their CAD patients [16]. The appearance of metabolic syndrome components resulted in a larger decline of HRR in the longitudinal investigation of Kizilbash et al. [25]. However, we could not find an independent relationship between metabolic syndrome and HRR. It may be due to the confounder effect of chronic kidney failure. Our finding suggests a more important role for decreased GFR in the development of sympathetic hyperactivity in IgA nephropathy patients than diabetes or other established risk factors.

The question arises how this sympathetic hyperactivity could be best influenced. Theoretically, the use of renin–angiotensin–aldosterone system inhibitors and the use of sympathetic adrenergic blocking agents should be beneficial. Klein et al. found that enalapril and losartan may decrease the sympathetic hyperactivity in CKD patients [26]. We cannot answer the question about the influence of different treatments on the autonomic dysfunction of CKD patients on the basis of this cross-sectional study.

Our study necessarily has limitations. Although the treadmill stress test is a simply, widely used method for measuring HRR, there are considerable differences in threshold limits of HRR values in the literature. The protocols also varied in terms of cool-down period length. We did not perform coronary angiography as diagnostic criteria for CAD. This fact may decrease the sensitivity and specificity of the CAD diagnosis. We could not find a significant relationship between CAD, exercise capacity and HRR in IgA nephropathy, which may be due to the relatively small numbers and to the high standard deviation of the exercise capacity in the different CKD groups. Our study was cross-sectional. We cannot draw conclusions about the effect of decreased HRR on mortality in CKD 3–4 patients. Our use of eGFR could be criticized. We studied only one type of renal disease. However, we believe this state-of-affairs is a strength since our patient population was homogenous.

Our study suggests that reduced eGFR is a strong independent risk factor for reduced HRR, a well-accepted risk factor for cardiovascular death. HRR may be a marker and a prognostic factor of cardiovascular morbidity and mortality in CKD patients; however, longitudinal studies will be needed to verify the casual connection. Further investigations may clarify whether or not any specific drug therapy could influence HRR and reduce cardiovascular risk in these patients.

Conflict of interest statement. None declared.

References

Impairment of endogenous melatonin rhythm is related to the degree of chronic kidney disease (CREAM study)

Birgit C. P. Koch1, Karien van der Putten2, Eus J. W. Van Someren3,4, Jos P. M. Wielanders5, Piet M. ter Wee6, J. Elsbeth Nagtegaal1 and Carlo A. J. M. Gaillard2

1Department of Clinical Pharmacy, 2Department of Internal Medicine, Meander MC, Amersfoort, 3Netherlands Institute for Neuroscience, 4Departments of Neurology, Clinical Neurophysiology and Medical Psychology, VU University Medical Center, Amsterdam, 5Department of Clinical Chemistry, Meander MC, Amersfoort and 6Department of Nephrology, VU University Medical Center, Amsterdam, The Netherlands

Correspondence and offprint requests to: Birgit C. P. Koch; E-mail: B.Koch@vumc.nl

Abstract

Background. The nocturnal endogenous melatonin rise, which is associated with the onset of sleep propensity, is absent in haemodialysis patients. Information on melatonin rhythms in chronic kidney disease (CKD) is limited. Clear relationships exist between melatonin, core body temperature and cortisol in healthy subjects. In CKD, no data are available on these relationships. The objective of the study

References


Received for publication: 8.3.09; Accepted in revised form: 31.8.09

doi: 10.1093/ndt/gfp493
Advance Access publication 19 September 2009