Reduced Baroreflex Effectiveness Index in Hypertensive Patients With Chronic Renal Failure

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Background: Impaired arterial baroreflex function has been associated with an increased risk of ventricular arrhythmia and sudden death. This has also been suggested for patients with chronic renal failure (CRF) who are at high risk for cardiovascular morbidity. The aim of this study was to investigate the arterial baroreflex function in CRF patients with emphasis on analyzing the time during which the arterial baroreflex is active, the baroreflex effectiveness index (BEI).

Methods: Beat-to-beat blood pressure (measured with Portapres) and electrocardiography were continuously registered during 30 min rest in 216 hypertensive CRF patients on hemodialysis (n = 95), continuous ambulatory peritoneal dialysis (n = 59), or conservative treatment (n = 59). The spontaneous sequence method was used to calculate BRS and BEI. Age-matched healthy subjects (n = 43) were examined for comparison.

Results: The BRS was reduced by 51% and the BEI by 49% in CRF patients compared with healthy subjects (P < .001 for both). In addition, CRF patients with diabetes showed further reductions compared with patients without diabetes (15% reduction of BRS and 44% of BEI, P < .01 for both). The treatment modality for renal failure had no effect on BRS or BEI. In a multivariate linear regression analysis, age, body mass index, and systolic blood pressure were independent predictors of BRS, whereas age and diabetes were independent predictors of BEI in patients with CRF.

Conclusions: We conclude that BEI, which is markedly reduced in hypertensive patients with CRF, may convey information on arterial baroreflex function that is complementary to BRS. Am J Hypertens 2005;18:995–1000 © 2005 American Journal of Hypertension, Ltd.

Key Words: Baroreflex, effectiveness index, renal failure.
Inclusion criteria were chronic renal failure and were recruited from eight hospitals in the western region of Sweden. Patients with CRF were on conservative treatment, hemodialysis, or continuous ambulatory peritoneal dialysis (CAPD). In addition to BRS, the numbers of baroreflex-mediated sequences may be assessed when the spontaneous sequence method is used. In healthy subjects, progressive beat-to-beat increases or decreases in systolic BP ramps are not always accompanied by baroreflex-driven lengthening or shortening in pulse interval (PI) ramps, respectively. In ambulatory healthy subjects, a proper baroreflex response is elicited in only 25% of all systolic BP (SBP) ramps during daytime, possibly because of central inhibitory influences because of interferences at sinus node level by nonbaroreflex mechanisms. This relation can be described using the baroreflex effectiveness index (BEI), defined as the ratio between the number of SBP ramps followed by proper concordant PI interval ramps, and the total number of SBP ramps observed in a given time window have been suggested to provide information that is complementary to BRS. Few previous studies have focused on assessing the arterial baroreflex function and BEI in a population at high risk for cardiovascular disease. Hence, the primary aim of the present study was to assess the BEI in adjunct to BRS using the spontaneous sequence method in a large group of patients with CRF and in age-matched healthy subjects. Because concomitant diabetes is associated with a worse prognosis among CRF patients, a subgroup analysis of this population was planned in advance. Furthermore, because there is also uncertainty as to the influence of the treatment modality for renal failure on the arterial baroreflex function, we aimed to compare these subgroups in terms of BRS and BEI.

Methods

The local ethical committee at Sahlgrenska University Hospital approved the study, and all subjects gave their informed consent to participate.

Study Population

Patients With CRF A total of 216 patients with CRF were recruited from eight hospitals in the western region of Sweden. Inclusion criteria were chronic renal failure and glomerular filtration rate <35 mL/min/1.73 m². Exclusion criteria were atrial fibrillation, permanent pacemaker, myocardial infarction, or stroke within the preceding 3 months. Three patients were excluded because of inadequate BP signals, leaving 213 patients with CRF included in the study. Clinical information provided by the responsible nephrologists, antihypertensive medication used, and laboratory data are given in Table 1. Of the CRF patients, 90% were hypertensive or were receiving antihypertensive treatment, and 25% had a history of coronary artery disease including previous myocardial infarction, coronary bypass operation, percutaneous coronary angioplasty, or angina pectoris. Almost one third (31%) of the CRF population had diabetes with an average duration of 24 years (range 2 months to 50 years). Signs of peripheral neuropathy (paresthesia or reduced perception of touch) were reported in 18% of CRF patients (90% had diabetes). The cause of renal failure was diabetes mellitus (26%), glomerulonephritis (23%), hypertension (10%), polycystic kidney disease (6%), and miscellaneous or unknown causes (35%). Patients on hemodialysis treatment (n = 95) were treated in hospital three times per week and the fractional urea clearance (Kt/Vurea) was 1.5 ± 0.5. Likewise, patients on CAPD (n = 59) or conservative treatment (n = 59) received standard treatment regimens. The average treatment duration for patients on dialysis was 2.0 ± 2.0 years. The glomerular filtration rate for CRF patients on conservative treatment was on average 12 mL/min/1.73 m² (range 7 to 34 mL/min/1.73 m²).

Healthy Subjects A total of 43 healthy control subjects similar in age and body mass index (BMI, weight/height²) to the CRF patients were recruited from the staff at Sahlgrenska University Hospital and by advertisement in a local newspaper (Table 2). All healthy subjects were non-smokers, had no significant past medical history, and were not taking any regular medication. All were normotensive with normal electrocardiography (ECG) results.

Data Acquisition and Calculations

All subjects refrained from consuming caffeine-containing beverages for at least 12 h before the investigations. Patients on hemodialysis treatment were investigated on the day when they did not receive dialysis treatment. On arrival at the laboratory, subjects

Table 1. Clinical variables, antihypertensive medication, and laboratory data in patients with chronic renal failure (n = 213)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoker</td>
<td>24</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>90</td>
</tr>
<tr>
<td>Coronary artery disease†</td>
<td>25</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>15</td>
</tr>
<tr>
<td>Stroke</td>
<td>9</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>8</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>4</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>31</td>
</tr>
<tr>
<td>β-Receptor blocker</td>
<td>57</td>
</tr>
<tr>
<td>Angiotensin converting enzyme inhibitor</td>
<td>19</td>
</tr>
<tr>
<td>Angiotensin II receptor antagonist</td>
<td>29</td>
</tr>
<tr>
<td>Calcium antagonist</td>
<td>41</td>
</tr>
<tr>
<td>Diuretic agent</td>
<td>64</td>
</tr>
<tr>
<td>α-Receptor blocker</td>
<td>10</td>
</tr>
</tbody>
</table>

* Blood pressure >140/90 mm Hg or antihypertensive treatment; † History of angina pectoris, coronary artery bypass grafting operation, or percutaneous transluminal coronary angioplasty.
rested supine in a quiet room for 10 min. After the resting period, simultaneous surface ECG (lead II) and beat-to-beat BP signals measured by the Portapres device (TNO Biomedical Instrumentation, Amsterdam, The Netherlands) were acquired for 30 min in CRF patients and 20 min in healthy subjects. Registrations were recorded at a sampling frequency of 1000 Hz and stored on a personal computer. The recordings were inspected off-line for removal of artifactual segments and sequences containing nonsinus beats. Ectopic beats were corrected by interpolation.

The time series of SBP and PI interval from the entire recording period were scanned to identify baroreflex sequences, which were defined as three or more consecutive beats in which successive SBP and PI intervals concurrently increased or decreased, with the threshold set at 1.0 mm Hg and 5.0 msec, respectively, and a shift of +1 between the BP pulse and the PI interval that we have previously used.

Linear regression was applied to each sequence, and only those with the squared correlation coefficient ($r^2$) $>0.85$ were accepted for further analysis. The arterial baroreflex function was estimated by calculating the following: 1) the spontaneous BRS was calculated, reflecting the average regression slope for all the linear regressions plotted for accepted baroreflex sequences within the whole time frame; 2) the numbers of sequences were calculated per 1000 heart beats; and 3) the baroreflex effectiveness index (BEI), defined as the ratio between the number of SBP ramps followed by the respective reflex PI interval ramps that fulfilled the BRS criteria and the total number of SBP ramps calculated during the recording period. For each BP ramp the overall BP change was calculated and the slope of the ramp was estimated by the maximum of the first derivative of the BP signal within the time interval of the ramp (max dP/dt).

**Table 2.** Demographic data, body mass index, blood pressure, and heart rate in patients with chronic renal failure (CRF) and in healthy subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Healthy Subjects ($n = 43$)</th>
<th>CRF Patients ($n = 213$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>59 ± 11</td>
<td>59 ± 13</td>
</tr>
<tr>
<td>Gender (female/male)</td>
<td>20/23</td>
<td>76/137</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24 ± 2</td>
<td>25 ± 5</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)*</td>
<td>120 ± 12</td>
<td>141 ± 24†</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)*</td>
<td>74 ± 6</td>
<td>78 ± 9‡</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>62 ± 7</td>
<td>71 ± 11†</td>
</tr>
</tbody>
</table>

Values represent number in each group or mean value ± SD. * Blood pressure measured by sphygmomanometer; † Statistically significant difference, $P < .0001$; ‡ Statistically significant difference, $P < .05$.

**Statistical Analysis**

Numerical distributions are presented as means ± SD. Student $t$ tests for unpaired and paired comparisons were used for continuous data with a normal distribution. The number of sequences and BEI showed a non-normal distribution and hence the Mann-Whitney $U$ test and Wilcoxon sign rank test for unpaired and paired comparisons were used. The $\chi^2$ test was used for binomial data. The relationship between two variables was assessed from bivariate scatter plots, and calculation of the rank correlation coefficient was performed according to Spearman. Multiple forward stepwise linear regression analysis was performed with BRS and BEI as the dependent variables. All variables with significant univariate association to BRS or BEI were added to the two models. Statistical significance was defined as $P < .05$.

**Results**

The BRS, numbers of sequences per 1000 beats, and BEI did not differ among subgroups of patients receiving hemodialysis, CAPD, or conservative treatment. There were no differences regarding BRS, the number of sequences per 1000 beats, or BEI between patients on versus off treatment with an angiotensin-converting enzyme inhibitor (ACE-I), angiotensin II receptor blocker (ARB), $\beta$-receptor blocker, or diuretics. Hence, all CRF patients were pooled and represented one group that was compared with the group of healthy subjects.

There were no differences regarding age, gender, and BMI between CRF patients and healthy subjects (Table 2). The mean heart rate, SBP, and diastolic BP (DBP) were elevated in CRF patients compared with healthy subjects ($P < .05$ for all) (Table 1). Patients with diabetes had elevated SBP compared with the other CRF patients (148 ± 25 v 138 ± 24 mm Hg, $P < .01$), whereas DBP and heart rate did not differ. The BRS, number of sequences per 1000 heart beats, and BEI were all reduced in patients with CRF compared with healthy subjects with further reductions among patients with diabetes ($P < .01$ for all) (Table 3). The average BP change of the BP ramps did not differ between CRF patients and healthy subjects (5.7 ± 3.0 v 5.7 ± 1.4 mm Hg for healthy subjects). In addition, the average maximum of the first derivative of the BP signal within the time interval of the BP ramps did not differ between the groups (3.1 ± 1.9 v 2.7 ± 0.8 mm Hg/sec for healthy subjects).

When analyzing all subjects together, there were positive relationships between BRS and the numbers of sequences per 1000 beats ($r = 0.44, P < .001$), between BRS and BEI ($r = 0.35, P < .001$) and between numbers of sequences/1000 beats and BEI ($r = 0.85 P < .001$). There were no significant relationships between BRS, number of sequences, or BEI and the duration of the dialysis, the fractional urea clearance (Kt/V urea), serum phosphate, or parathyroid hormone levels.
The relation between BRS, the number of sequences per 1000 beats, and BEI and the following factors were analyzed among CRF patients using simple regression. Age, SBP, and BMI were analyzed as continuous variables. Gender, smoking habit, coronary artery disease, peripheral arterial disease, congestive heart failure, chronic obstructive disease, stroke, signs of neuropathy, and diabetes mellitus were analyzed as binary variables with values of 0 or 1 for each individual. Using univariate regression analysis, age, BMI, and SBP were significantly associated with BRS and were thus tested in the multivariate model. Age, systolic BP, peripheral artery disease, signs of neuropathy, and diabetes were significantly associated with BEI and were included in the multivariate analysis. Forward stepwise multiple regression analyses were then performed. The SBP (regression coefficient B = −0.053, standard error of the mean, SE(b) = 0.010), age (B = −0.083, SE(b) = 0.019), and BMI (B = −0.153, SE (b) = 0.055) were independent predictors of BRS (multiple \( r = 0.46, r^2 = 0.22, P < .001, \) intercept 23). Diabetes (B = −0.112, SE(b) = 0.022) and age (B = −0.003, SE(b) = 0.001) were independent predictors of BEI (\( P < .01 \) for all, multiple \( r = 0.41, r^2 = 0.17, P < .001, \) intercept 0.44). Similar results of the multivariate analysis as for BEI with diabetes and age being independent predictors were obtained when the number of sequences was the dependent variable.

### Discussion

Apart from estimating BRS, the spontaneous sequence method provides information about the time that the arterial baroreflex actively modulates heart rate in response to BP fluctuations. The novel finding of this study was a reduced BEI in CRF patients, reflecting the number of times the arterial baroreflex is active in driving the sinus node in response to BP fluctuations. Di Rienzo et al reported that sino-aortic denervation in cats reduced BEI to a value near zero, supporting the contention that BEI was related to arterial baroreflex function.6 The finding of reduced BEI in CRF patients suggests that the arterial baroreflex is less effective in overcoming nonbaroreflex influences on BP and heart rate. There are a variety of mechanisms that could be responsible for the reduced BEI in CRF patients. First, we cannot conclude that reduced BEI is a consequence of CRF per se, as we did not examine a control group matched for BP, concomitant diseases, and medication, which all may affect the arterial baroreflex function. A larger magnitude of the BP changes of the individual ramps or steeper slopes of the BP ramps or both have been associated with higher BEI values.6 However, in the current study there were no differences between CRF patients and healthy subjects regarding these variables. Although positive relationships have been reported between BRS and left ventricular mass and carotid artery distensibility, there are no published data regarding the relationships to BEI.8,9 One may speculate that reduced arterial distensibility leading to increased threshold values for the BP fluctuations to activate the baroreceptors could have contributed to the reduced BEI in CRF patients. The further reduction of BEI in CRF patients with diabetes mellitus corroborates previous data showing reduced number of baroreflex sequences in patients with diabetes.10 Moreover, in the multivariate analysis performed in the present study, diabetes was the strongest predictor of BEI. The link between diabetes and BEI could be due either to neuropathy of the autonomic peripheral nerves or to increased central inhibitory influences. In patients with diabetes, the unmyelinated C- and deltafibers of the autonomic nervous system are the first to be involved when neuropathy occurs.11 The baroreflex is modulated centrally and electrophysiologic studies have provided evidence that cardiac vagal motoneurons are affected by areas located in the prefrontal cortex and the insular cortex.12 Under normal circumstances, it seems that the role of the insular cortex is to enhance BRS, whereas the effect on BEI remains elusive. One may speculate, however, that the number of times the baroreflex is being active is modulated by cortical areas. Clinically silent lacunar cerebral infarctions are prevalent both in CRF and in diabetes.13,14 Thus, ischemic changes affecting cortical areas critical for cardiovascular control could have contributed to the reduced BEI in CRF patients.
A recent publication showed that alteration of the SBP or PI interval thresholds affected both the number of valid sequences and the value of BRS in congestive heart failure patients and in healthy subjects. In addition, the shift between the SBP and PI intervals also affected the number of sequences. We calculated BEI using the threshold values suggested by Davies et al for arterial systolic blood fluctuations of 0.5 mm Hg, and fluctuations of the PI intervals of 1 msec to calculate BRS in addition to 0 shift between the SBP and PI intervals, to optimize the numbers of sequences detected in patients with reduced BRS. Although BEI increased when the shift 0 low threshold values were used, the differences between the study groups remained unchanged.

Attenuated baroreflex sensitivity in CRF patients corroborates previous studies using the invasive technique where phenylephrine was infused and the heart rate response measured. The present study group is, however, larger and comprises patients receiving hemodialysis, CAPD, or conservative treatment. Although all CRF patients showed reduced BRS compared with healthy subjects, patients with diabetes mellitus had a further reduction in BRS compared to CRF patients without diabetes. In the present study, the treatment modality for renal failure did not affect BRS. Agarwal et al found that BRS measured by the phenylephrine method was reduced in CRF patients on conservative treatment and was not affected by short- or long-term hemodialysis, whereas Pickering et al reported improved BRS after long-term hemodialysis. There are several possible explanations for the reduced BRS in CRF patients. The majority (approximately 90%) of the CRF population were hypertensive or on antihypertensive treatment. Hypertension causes cardiovascular hypertrophy and reduced arterial distensibility, which could reduce the BRS. The other independent predictors of BRS, namely BMI and age, are also linked to cardiovascular hypertrophy. An activated renin–angiotensin system, which often prevails in CRF, could have contributed to the observed impairment of BRS by promoting vascular hypertrophy or by exerting effects directly within the central nervous system.

Ambulatory invasive BP recordings in humans have shown that the variation of BRS and BEI during day and night show a different pattern. During the night time, BEI was lower compared with daytime (0.25 during the day and 0.15 during the night), whereas the BRS showed the opposite pattern with lower values during the night. The current study showed a positive relationship between BRS and BEI. However, the relationship was weak, implying that only about 10% of the variability in one of the variables could be explained by variability in the other. Moreover, in the multivariate analysis, diabetes and age were independent predictors of BEI in CRF patients; in contrast, SBP, age, and BMI were independent predictors of BRS, supporting the notion that these variables provide different information on the arterial baroreflex function. Regarding the functional importance of BEI, we have recently found that never-treated patients with borderline hypertension and patients with severe renovascular hypertension both had reduced BRS, whereas BEI did not differ compared with healthy subjects (Myredal et al, submitted for publication). This discrepant behavior of BRS and BEI suggests that the two variables may convey information about the arterial baroreflex function that is complementary. In the present study, signs of neuropathy were associated with lower BEI, whereas no association was found for BRS. One may speculate that neuropathy of the autonomic nervous system or central nervous effects or both mainly impair BEI, whereas vascular hypertrophy resulting from hypertension mainly affects the BRS. Therefore, one may speculate that a reduced BEI, reflecting autonomic neuropathy, could predict susceptibility for hypertension during hemodialysis treatment.

**Study Limitations**

Antihypertensive drug therapy, including β-blocker, ACE-I, or ARB treatment, is known to interfere with cardiovascular autonomic control. However, there were no differences regarding BRS, number of sequences per 1000 beats, or BEI between CRF patients who were on β-blockers, ACE-I, or ARB compared with patients who were not receiving therapy. Despite this, a drug influence on these variables cannot be ruled out, although a major effect seems unlikely.

In summary, the present study demonstrated reduced BRS and BEI in CRF patients receiving hemodialysis, CAPD, or conservative treatment, with the greatest reduction in values observed in the diabetic subgroup of patients. Both BRS and BEI appear to provide complementary information about arterial baroreflex function. Future studies are needed to establish whether these measurements convey prognostic information in CRF patients.

**Acknowledgments**

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**References**