Week-to-Week Biological Variation in the N-terminal Prohormone of Brain Natriuretic Peptide in Hemodialysis Patients and Healthy Individuals

To the Editor:

The concentration of the N-terminal prohormone of brain natriuretic peptide (NT-proBNP)\(^1\) is often increased in patients with a reduced renal function. The suggested diagnostic cutoffs in acute or subacute heart failure [e.g., 300 pg/mL (66 pmol/L) and 125 pg/mL (27 pmol/L), respectively] are therefore probably not applicable for hemodialysis (HD) patients. A better approach may be to diagnose patients according to changes from their baseline NT-proBNP concentrations. The changes in patients who experience a clinical event can be compared with the reference change value (RCV), which is based on the analytical CV (CVa) and the within-person biological variation (CVi). The within-person variation describes the natural fluctuations in the concentrations of constituents in a stable situation. This study reports the CVa, CVi, between-person biological variation (CVb), RCV, and index of individuality (II) in HD patients and healthy individuals.

The Regional Committee for Medical and Health Research Ethics approved the study. Informed written consent was obtained from 17 clinically stable patients who had been treated with HD at least twice weekly for ≥2 months. The patients had a median age of 71 years, and 4 of the patients were women. Twenty healthy individuals (50% women) with a median age of 61 years (range, 46–68 years) were included.

For the HD patients, 1 sample was collected before the midweek HD treatment for 10 consecutive weeks. For the healthy individuals, a weekly sample was collected (i.e., 7-day interval ± 1 day) for 10 consecutive weeks. Serum samples were frozen (−80 °C degrees) and stored until analyzed on a Modular E (Roche Diagnostics) in a single run with the Roche NT-proBNP assay.

The results of the Burnett test excluded 2 of the results as analytical outliers. Six healthy individuals and 1 patient were excluded because they had unmeasurable concentrations on >2 occasions. One healthy individual was excluded on the basis of the Reed criterion. The data for both HD patients and healthy individuals showed right-skewed distributions. After natural logarithmic transformation, the residuals of the data exhibited a gaussian distribution. The results of the Cochrane and Bartlett tests showed variance homogeneity for the analytical and within-person variances.

Two patients experienced exacerbation of heart failure during the study and were excluded from the calculations; patient 3 had a single episode of atrial fibrillation and dyspnea that led to admittance to the hospital; patient 13 had increasing hypertension and dyspnea that led to an increased dosage of antihypertensive and diuretic treatment and to changes in the HD prescription.

We included ln-transformed data from 13 healthy individuals and 14 HD patients in calculating CVa, CVi, and CVb via nested ANOVA with Excel software (version 2010; Microsoft). The RCV was calculated according to Fokkema et al. (1) \((95\% CI, \text{two-sided test})\) for ln-transformed data, and the II was calculated as the SD of the CVa and CVi divided by the SD of the CVb. Additionally, we calculated the RCV with a one-sided test to illustrate the situation in which patients experience (increasing) symptoms of heart failure.

Mean NT-proBNP concentrations, CVa, CVi, CVb, RCV, and II for healthy individuals and HD patients are shown in Table 1. The 2 patients who experienced clinical events both had NT-proBNP increases that were higher than the calculated RCV (102%). The NT-proBNP concentration increased in patients 3 and 13 by 545% and 151%, respectively, indicating that an unstable situation was present.

Table 1. Values for CVa, weekly CVi and CVb, RCV (two-sided test), and II for NT-proBNP, as measured in healthy individuals and HD patients.

<table>
<thead>
<tr>
<th></th>
<th>Healthy individuals</th>
<th>HD patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT-proBNP, pg/mL(^a)</td>
<td>42 (17–143)</td>
<td>10 427 (185–1 143)</td>
</tr>
<tr>
<td>CVa, %</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>CVi, %</td>
<td>60</td>
<td>26</td>
</tr>
<tr>
<td>CVb, %</td>
<td>70</td>
<td>310</td>
</tr>
<tr>
<td>RCV, %</td>
<td>For decrease −80</td>
<td>−51</td>
</tr>
<tr>
<td></td>
<td>For increase 389</td>
<td>102</td>
</tr>
<tr>
<td>II (95% CI)</td>
<td>0.84 (0.48–1.24)</td>
<td>0.17 (0.10–0.24)</td>
</tr>
</tbody>
</table>

\(^a\) NT-proBNP data are presented as the mean (range). To convert NT-proBNP data to picomoles per liter, please multiply by 0.118.

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\(^1\) Nonstandard abbreviations: NT-proBNP, N-terminal prohormone of brain natriuretic peptide; HD, hemodialysis; RCV, reference change value; CVa, analytical variation; CVi, within-person biological variation; CVb, between-person biological variation; II, index of individuality.

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A limitation of this study was the relatively small number of individuals included, although the numbers of individuals included and measurements made were sufficient for calculating the biological variation (2). A larger study that includes more patients with clinical events would be necessary to validate the use and sensitivity of RCV for diagnosing heart failure in HD patients.

Our study demonstrates that CVi values in stable HD patients (26%) were similar to those of patients with stable heart failure (3, 4). Specific diagnostic cutoffs are of little use if NT-proBNP is used for diagnosing heart failure in HD patients, but the low II for NT-proBNP indicates that applying Δ values could be a possible solution. One study showed that a 20% increase in NT-proBNP values had a sensitivity of 57% and a specificity of 77% in predicting a congestive heart failure event in HD patients (5). In the present study, a RCV (one-sided test) of +20% included 70% of the changes, yielding a specificity of 70%. At a specificity of 95%, the RCV (one-sided test, increasing values) is 80%. We conclude that clinical actions for HD patients could be based on a relatively small NT-proBNP change between 2 consecutive results, depending on the pretest probability of a congestive cardiac event.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

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References