High Intraindividual Variation of B-Type Natriuretic Peptide (BNP) and Amino-Terminal proBNP in Patients with Stable Chronic Heart Failure

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Background: Plasma B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) are promising markers for heart failure diagnosis, prognosis, and treatment. Insufficient data on the intraindividual biological variation (CVi) of BNP and NT-proBNP hamper interpretation of changes in concentration on disease progression or treatment optimization. We therefore investigated CVi values in stable heart failure patients.

Methods: We recruited 43 patients with stable chronic heart failure living in Curacao (22 males, 21 females; median age, 63 years; range, 20–86 years; New York Heart Association classes I–III). Samples were collected for within-day CVi (n = 6; every 2 h starting at 0800), day-to-day CVi (n = 5; samples collected between 0800 and 1000 on 5 consecutive days), and week-to-week CVi (n = 6; samples collected between 0800 and 1000 on the same day of the week for 6 consecutive weeks). NT-proBNP (Roche) and BNP (Abbott) were measured by immunoassay.

Results: Median (range) concentrations were 134 (0–1630) ng/L (BNP) and 570 (17–5048) ng/L (NT-proBNP). Analytical variation, week-to-week CVi, and reference change values were 8.4%, 40%, and 113% (BNP), and 3.0%, 35%, and 98% (NT-proBNP). Week-to-week CVi values were inversely related to median BNP concentrations. BNP decreased between 0800 and 1000. Median NT-proBNP/BNP ratios were inversely related to median BNP concentrations.

Conclusions: The high CVi values hamper interpretation of changes in BNP and NT-proBNP concentrations and may partly explain their poor diagnostic values in chronic heart failure. Easily modifiable determinants to lower CVi have not been identified. The value of BNP and NT-proBNP for chronic heart failure diagnosis, and especially for follow-up and treatment optimization of individuals, remains largely to be established.

Plasma B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) are promising new markers for the diagnosis, prognosis, and treatment of patients with heart failure (1, 2). Measurement of BNP or NT-proBNP is of demonstrated value to rule-out acute heart failure in patients presenting with dyspnea in emergency departments (1). For this, a BNP cutoff value <100 ng/L has been advocated, as derived from the results of the Breathing Not Properly Multinational Study (4, 5). The value of BNP and NT-proBNP tests for the diagnosis of chronic heart failure, prognosis assessment, and tailored treatment is as yet unclear.

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6 Nonstandard abbreviations: BNP, B-type natriuretic peptide; NT-proBNP, N-terminal proBNP; CVi, intraindividual biological variation; NYHA, New York Heart Association; CVa, analytical variation; CVt, combined intraindividual and analytical variation; and RCV, reference change value.
(1, 6, 7). Studies on BNP and NT-proBNP have demonstrated that these peptides are effective markers in populations. However, the investigated study populations show sizeable overlaps, and it is consequently questionable whether these tests are useful for individual patients. There is notable lack of information on the intraindividual variation (CV). This information is necessary, e.g., for the correct interpretation of serial test results that are collected for follow-up or tailored treatment. Until now, CV has been studied in apparently healthy study populations, with observation periods ranging from 17 days (8) and 4 weeks (9) up to 8 weeks (10). The CVs for BNP and NT-proBNP in patients with stable heart failure or at high BNP or NT-proBNP concentrations are currently unknown; we therefore investigated the CVs of both BNP and NT-proBNP in patients with stable heart failure. We collected blood samples from these patients within a single day, within 1 week, and during 6 consecutive weeks.

**Patients and Methods**

Adult patients with chronic heart failure were recruited from a cardiologist’s practice on the Caribbean island of Curaçao (The Netherlands Antilles). Patients were excluded if they had clinical signs of a change in heart function, had atrial fibrillation, or when their medication was altered within 2 months before the start of the study or during the study. A cardiologist blinded to the laboratory findings classified the patients according to blinded data available from files on New York Heart Association (NYHA) classification and recent history of clinical admission for heart failure. Admission had taken place at latest 2 months before inclusion in the study. The majority of the patients (n = 37; 86%) were considered as having systolic left ventricular failure, according to the criteria as stated in the American College of Cardiology/American Heart Association guidelines for the evaluation and management of chronic heart failure in the adult (11). These patients had a left ventricular ejection fraction <40%, measured by either echocardiography or gated scintigraphic left ventricular angiography. A small group (n = 6; 14%) was considered as having diastolic heart failure diagnosed by history of clinical symptoms and Doppler measurements of diastolic function according to American College of Cardiology/American Heart Association guidelines. All patients were treated for heart failure with standard drug regimens. Written informed consent was obtained from all participants before participation. The study protocol was approved by the medical ethics committee of the hospital and is in agreement with local ethical standards and the Helsinki Declaration of 1975, as revised in 2000.

The study duration was 6 weeks, during which each patient had 15 blood samples drawn. Within-day variation was calculated from six samples that were collected every 2 h starting at 0800. Day-to-day variation was calculated from five samples collected on consecutive days within 1 week between 0800 and 1000. Week-to-week variation was calculated from six samples taken on the same day of the week for 6 consecutive weeks between 0800 and 1000. Fasting was not a necessary prerequisite for sampling. The patients were interviewed at baseline about their regular drug intake (types of drugs).

EDTA-anticoagulated blood (10 mL) was collected by venous puncture during home visits. Blood samples were centrifuged within 2 h after sampling, and 30 µL of an aprotinin solution (protease inhibitor, 10 000 kIU/mL; Bayer, Germany) per milliliter of plasma was added to the samples before storage at −80 °C. NT-proBNP (electrochemiluminescence immunoassay; Roche Diagnostics) and BNP (microparticle enzyme immunoassay; Abbott Diagnostics) were measured within 6 months after collection. Samples from one person were analyzed in a single series to minimize the contribution of analytical variation (CVa). All collected samples were analyzed on 2 consecutive days. Serum creatinine was measured with a Vitros 950 chemistry analyzer (Ortho-Clinical Diagnostics).

The CVs for NT-proBNP and BNP were calculated from the results of five and three quality-control samples, respectively, that covered the usually encountered concentrations. Each of these was analyzed once after the analyses of 20 patient samples. Patient individual within-day, day-to-day, and week-to-week BNP and NT-proBNP CVs [CVtotal (CVt), representing the combination of CVi and CVa], and CVa provided the bases for the calculation of the within-day, day-to-day, and week-to-week CVi, according to the formula: $CV_i = (CV_i^2 - CV_a^2)^{1/2}$. From these we calculated the median CVi and CVi values for the entire group. Reference change values (RCVs) at a 95% confidence level were calculated from median CVi values, according to the formula: $RCV = Z \times 21/2 (CV_a^2/n_a + CV_i^2/n_i)^{1/2}$ (12), where $Z = 1.96$ (i.e., the Z-score for 95% confidence); $n_i$ is the number of replicate assays; and $n_i$ is the number of patient samples to estimate each of the two homeostatic setpoints. RCVs reflect the minimum percentage change in serial results that is, with 95% confidence, different from the combined analytical and biological variation. The significance of within-day, day-to-day, and week-to-week longitudinal changes in BNP and NT-proBNP concentrations were analyzed with the Wilcoxon rank test with a correction for type 1 errors according to Bonferroni at $P < 0.05/\text{number of tests}$. Spearman (non-linear) and Pearson (linear) correlation tests were used to investigate the relationships between (a) CVa and the mean BNP and NT-proBNP concentrations in quality-control samples, (b) BNP and NT-proBNP concentrations, (c) BNP (NT-proBNP) concentrations and the CV of BNP (NT-proBNP), and (d) BNP and NT-proBNP concentrations and the median and CV of the NT-proBNP/BNP ratio. The last ratio provides an idea of the regulation of plasma BNP and NT-proBNP concentrations.
Forty-three patients participated in our study. Age, gender, NYHA classification, medicine intake, and baseline BNP and NT-proBNP concentrations are shown in Table 1. Fifteen patients (35%) had serum creatinine concentrations that exceeded the upper reference limit (106-262 mol/L). There were no differences in BNP or NT-proBNP concentrations among the various NYHA classes, possibly because of low patient numbers. The study group was therefore not subdivided on the basis of NYHA class. BNP and NT-proBNP were highly related. The Pearson correlation coefficients were 0.957 (P < 0.0005) for the within-day medians, 0.960 (P < 0.0005) for day-to-day medians, and 0.935 (P < 0.0005) for week-to-week medians. Median week-to-week BNP and NT-proBNP concentrations did not correlate with NYHA class or age but were significantly related to serum creatinine [r = 0.381 (P = 0.018) for BNP; r = 0.381 (P = 0.018) for NT-proBNP]. Median concentrations were considered to reflect within-day, day-to-day, and week-to-week homeostatic setpoints.

The CVa values of the BNP quality-control samples were 11% at 112 ng/L, 6.6% at 527 ng/L, and 7.4% at 1986 ng/L. The CVa of the NT-proBNP quality-control samples were 3.5% at 140 ng/L, 2.2% at 191 ng/L, 3.1% at 2426 ng/L, 2.2% at 5029 ng/L, and 3.5% at 9702 ng/L. Because CVa was not significantly related to BNP and NT-proBNP concentrations, we decided to use the CVa of all samples for the calculations. These amounted to 8.4% for BNP and 3.0% for NT-proBNP (Table 2.). The within-day (41 patients; 10 of 246 samples missing), day-to-day (35 patients; 3 of 175 samples missing), and week-to-week (43 patients; 6 of 258 samples missing) values for CVa, CVr, and RCV are shown in Table 2. The influence of taking multiple samples from a patient and analyzing each in singleton or triplicate on the RCV for week-to-week BNP and NT-proBNP is shown in Fig. 1. The week-to-week RCV decreased from 113% to 68% for BNP and from 98% to 57% for NT-proBNP when the number of patient samples was increased from one to three for the estimation of the homeostatic setpoints of two serial results. BNP RCVs were lowest for BNP concentrations between 346 ng/L (see Fig. 1 and below). In this BNP range, RCVs decreased from 87% to 54% on triplicate sampling.

### Results

The within-day changes in plasma BNP and NT-proBNP concentrations are shown in Fig. 2. BNP increased significantly during the day from 0800–1000 (P < 0.0005), 1000–1200 (P < 0.003), and 1600–1800 (P < 0.005) at a significance level of P < 0.01. NT-proBNP increased significantly from 1000–1200 (P < 0.0005) and remained stable afterward. The within-day CVr was not related to median BNP or NT-proBNP concentrations.

### Table 1. Patient characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>43</td>
</tr>
<tr>
<td>Median (range) age, years</td>
<td>63 (20–86)</td>
</tr>
<tr>
<td>Gender (M/F), n</td>
<td>22/21</td>
</tr>
<tr>
<td>NYHA classification, n</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>3</td>
</tr>
<tr>
<td>II</td>
<td>30</td>
</tr>
<tr>
<td>III</td>
<td>10</td>
</tr>
<tr>
<td>Medication, n</td>
<td></td>
</tr>
<tr>
<td>β-Blocker</td>
<td>29</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>34</td>
</tr>
<tr>
<td>Diuretics</td>
<td>35</td>
</tr>
<tr>
<td>Digoxin</td>
<td>12</td>
</tr>
<tr>
<td>Median (range) creatinine, μmol/L</td>
<td>89 (58–219)</td>
</tr>
<tr>
<td>Median (range) BNP, ng/L</td>
<td>134 (0–1630)</td>
</tr>
<tr>
<td>Median (range) NT-proBNP, ng/L</td>
<td>570 (17–5048)</td>
</tr>
</tbody>
</table>

### Table 2. Analytical and biological variation of BNP and NT-proBNP.

<table>
<thead>
<tr>
<th></th>
<th>Within-day</th>
<th>Day-to-day</th>
<th>Week-to-week</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP</td>
<td>CVa, %</td>
<td>CVr, %</td>
<td>RCV, %</td>
</tr>
<tr>
<td>≤350 ng/L</td>
<td>8.2 (0.0–173)</td>
<td>25 (0.0–223)</td>
<td>40 (0.0–232)</td>
</tr>
<tr>
<td>&gt;350 ng/L</td>
<td>12 (0.0–174)</td>
<td>27 (4.6–224)</td>
<td>41 (4.1–232)</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>CVa, %</td>
<td>CVr, %</td>
<td>RCV, %</td>
</tr>
<tr>
<td>≤350 ng/L</td>
<td>3.0</td>
<td>20 (3.1–80)</td>
<td>35 (7.6–103)</td>
</tr>
<tr>
<td>&gt;350 ng/L</td>
<td>8.6 (0.0–20)</td>
<td>25 (4.3–80)</td>
<td>35 (8.2–103)</td>
</tr>
</tbody>
</table>

CVa, CVr, and RCV are given as the median (range). Week-to-week CVr was inversely related to median week-to-week BNP concentrations, with constant CVr from a BNP of ~350 ng/L (Fig. 3). Therefore, we also calculated week-to-week CVr for BNP ≤350 ng/L and BNP >350 ng/L separately.

**Fig. 1. Influence of multiple sampling on BNP and NT-proBNP RCVs.**
Fig. 2. Changes in plasma BNP and NT-proBNP concentrations during the day.

<, significant changes (P < 0.01; i.e., 0.05/5) between sampling intervals.

WEEK-TO-WEEK

We observed no significant changes in BNP and NT-proBNP from day to day or from week to week. Week-to-week BNP CV values were inversely related to the median week-to-week BNP concentrations (n = 41; r = −0.434; P = 0.005; Fig. 3A). On the basis of this relationship, we decided to calculate separately the week-to-week median (range) CVs and RCVs for BNP concentrations up to 350 ng/L and for BNP concentrations >350 ng/L (Table 2 and Fig. 1). There was no significant relationship between CV and median week-to-week NT-proBNP concentrations (Fig. 3B).

NT-proBNP/BNP RATIO

Median NT-proBNP/BNP ratios were significantly related to median BNP concentrations. The Spearman correlation coefficients were −0.331 (P < 0.0005; Fig. 3C) for all data combined (i.e., those of the within-day, day-to-day, plus week-to-week medians) and −0.332 (P = 0.034; Fig. 3C, inset) for week-to-week data only. The NT-proBNP/BNP ratio did not correlate with NT-proBNP concentrations (Fig. 3D). The median NT-proBNP/BNP ratio was not related to serum creatinine concentrations for all data combined (within-day, day-to-day, plus week-to-week medians) or for the week-to-week data only.

Discussion

We investigated the within-day, day-to-day, and week-to-week total and biological variation of BNP and NT-proBNP in patients with stable heart failure who were treated with standard drug regimens. Any influences deriving from physical exercise and emotional stress, if any, were minimized by taking blood samples during regular visits at the patients’ homes. With respect to the aim of the present study, the study of an untreated group was considered unethical (drug withdrawal), confined to NYHA class 1 (recruitment of asymptomatic individuals from screening programs), or to provide unrealistic data (measurements immediately after first event). Biological variation data deriving from treated patients are more realistic for judging the value of BNP and NT-proBNP in heart failure progression and tailored treatment in daily practice. At present, the data on the latter derive predominantly from a controlled trial reported by Troughton et al. (13), who randomized 69 patients to either clinically guided or BNP-guided treatments. It appears that their patients were treated for heart failure at study entry, which implies that we are dealing with guided therapy adjustment rather than with guided therapy.

Our data indicate that both BNP and NT-proBNP have high CVs and therefore high RCVs of 113% and 98%, respectively. High RCVs in patients, especially for BNP, are in line with previous findings in apparently healthy persons. The 8-week RCVs were 130% for BNP and 90% for NT-proBNP in the study of Wu et al. (10), whereas Pagani et al. (9) reported a 4-week NT-proBNP RCV of 99%. Unfortunately, the 17-day NT-proBNP RCV of 26% reported by Melzi d’Eril et al. (8) was calculated based on log-transformed data and cannot therefore be compared with previous data. High CVs for BNP and NT-proBNP increase the chance of false-positive and false-negative test results and may, next to a sizeable interindividual variation (see, for example, the ranges in Table 1), be the major reason for overlapping patient populations (6). The high CVs and the resulting high RCVs also hamper interpretation of analyte changes with disease progression and therapy adjustment for optimized treatment. Only BNP changes >113% and NT-proBNP changes >98% may be considered to have overcome the combined analytical and biological variation with 95% certainty. These results might render BNP or NT-proBNP monitoring unfit for tailored treatment because the expected reductions in BNP with therapy are below these RCVs. Standard chronic heart failure treatments have been shown to reduce BNP and NT-proBNP by no more than 45–55% (14–16) and 35% (13), respectively, with large interindividual differences. These reductions are similar to those found in placebo-controlled trials, in which plasma BNP decreased with treatment with angiotensin-converting enzyme inhibitors [5–40% (17–19)], angiotensin II antagonists [10% (20)], and aldosterone antagonists [23–55% (21, 22)] and prolonged treatment with β-blockers [54–60% (23, 24)]. No placebo-controlled studies in which NT-proBNP was monitored are as yet available, but taking the simultaneous release of BNP and NT-proBNP into account, one might expect decreases in NT-proBNP during therapy to be on the same order of magnitude. Although subject to large interindividual differences in response, previously conducted small studies indicated that BNP- or NT-proBNP-guided treatment might be superior to treatment based on clinical judgments (13, 17). Moreover, BNP was related to the clinical picture during treatment, which implies that BNP concentrations decreased in those who responded to treatment, whereas those who did not respond had unchanged or increasing BNP concentrations (14). As a consequence of...
the present, somewhat disappointing, findings, it might, however, still be worthwhile to investigate whether treatment monitoring can be based on BNP or NT-proBNP if a patient’s own CVi is known.

It seems that unrestricted use of BNP and NT-proBNP for accurate diagnosis and especially treatment optimization necessitates implementation of procedures to lower the contribution of CVi, or more specifically of CVt (i.e., the combination of CVi and CVa). One option for monitoring of therapy when confronted with high RCVs is to increase the number of patient samples to reach a better estimate of a patient’s homeostatic setpoint. We found that the RCVs decreased to 68% (BNP) and 57% (NT-proBNP) when data were based on three patient samples. This option is not only costly and impractical, but unfortunately also causes the RCVs to drop to values that are still too high when compared with the decreases that can be achieved with medical treatments. Another possibility is to decrease the CVi itself. Increasing the number of replicate assays (see the formula for calculating RCV) may lower the contribution of CVi. It is, however, unlikely that relevant reductions in CVi can be achieved by reducing CVs because the CVs was 21% of the CVi for BNP and 9% of the CVi for NT-proBNP, both fulfilling the CVs < 0.5 × CVi criterion that is generally accepted in laboratory medicine (12).

To achieve relevant reductions in CVi, it seems necessary to gain more insight into the determinants that govern the encountered high CVi values. These determinants are as yet largely unknown. Exercise, fluid intake, and fluid infusion affect plasma BNP and NT-proBNP concentrations to some extent. Exercise increased plasma BNP concentrations by 10–30% in a short time period in heart failure patients (25, 26), but this increase does not seem to occur in healthy individuals (25–27). Saline infusions increase plasma NT-proBNP, and possibly also

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**Fig. 3. Influences of BNP (A and C) and NT-proBNP (B and D) concentrations on CVi and the NT-proBNP/BNP ratio.**

(A and B), individual week-to-week CVi values plotted vs the individual median week-to-week concentrations for BNP (n = 41) and NT-proBNP (n = 42), respectively. (C and D), individual median within-day, day-to-day, and week-to-week NT-proBNP/BNP ratios plotted vs the individual median within-day, day-to-day, and week-to-week concentrations of BNP (n = 112) and NT-proBNP (n = 112), respectively. The inset in panel C illustrates the relationship for the week-to-week BNP data only. Three ratios >20 g/g and BNP < 5 ng/L or NT-proBNP < 130 ng/L (three patients) are not depicted but were included for statistical analysis.
BNP (28), by >200% in a delayed fashion after a few hours (29). Water consumption during exercise in the heat, i.e., with dehydration, also increased BNP by >400% (27), but the effects of typical daily beverage consumption on BNP are unknown. We found that plasma BNP, and to a lesser extent plasma NT-proBNP, concentrations increase during the day and reach stable values in the afternoon. These observations are in agreement with the NT-proBNP day-curve of the control group reported by Heringlake et al. (29). BNP and NT-proBNP changes during the day follow the circadian rhythmicity of hemodynamic indices, probably as a consequence of increasing blood pressure and heart rate during the day (30). Standardization of physical activity, fluid intake, or sampling at preset clock times may be indicated, but these measures are unlikely to reduce CVi to a sufficient extent. The observed within-day variation, including the variation caused by daily beverage consumption and exercise, amounted to no more than 8.5% for both BNP and NT-proBNP, which is considerably less than the week-to-week CVi s of ~40%. Until relevant and easily modifiable determinants of CVi are identified, CVi remains an important source of BNP and NT-proBNP total biological variation. More studies and cost–benefit analyses are necessary to establish the added value of serial BNP and NT-proBNP tests.

One interesting finding was the inverse relationship between the week-to-week CVi and the median week-to-week BNP concentration. CVi values for BNP concentrations above ~350 ng/L appeared lower than CVi values below ~350 ng/L (Fig. 3A), but this was not the case for NT-proBNP. The reason for the observed relationship is unknown, but we speculate that the encountered high CVi at relatively low BNP concentrations reflects the normal release of BNP, which seems to occur with a pulsatile pattern with intervals of ~48 min (31). It is likely that episodes of increased BNP secretion follow short-term increases in transmural cardiac pressure. In this context, a high CVi for BNP could be explained by the short BNP half-life of ~20 min (32), whereas the stability of in vivo plasma NT-proBNP [half-life ~120 min (32)] predicts the absence of such a relationship for NT-proBNP. Pulsatile releases and half-life differences may also be the basis of the encountered high NT-proBNP/BNP ratio at low BNP concentrations and the low NT-proBNP/BNP ratio at high BNP concentrations (Fig. 3C). Constant release of BNP at conditions of continuous myocyte stretch, such as in chronic heart failure, seems to cause a stable high plasma BNP plateau with a relatively low CVi and a RCV of 87% (Figs. 2 and 3). The idea of continuous BNP release is supported by our finding that both NT-proBNP/BNP ratios and CVi s were low in patients with high plasma BNP concentrations (>350 ng/L). It is in this respects interesting to note that several authors suggested the use of a BNP cutoff of >400 ng/L to rule-in patients with heart failure (6). The high diagnostic value at this cutoff supports the idea of continuous BNP release during prolonged myocyte stretch. The implications of these findings are unknown, but the lower RCV of 87% (i.e., 54% with triplicate sampling) that applies for BNP concentrations >350 ng/L (Fig. 1) might be of practical value for tailored treatment of patients with BNP concentrations above this cutoff.

In conclusion, both BNP and NT-proBNP have high CVi s and, consequently, high RCVs. High CVi s may to a certain extent explain the poor diagnostic value of these markers in chronic heart failure. Most importantly, they hamper interpretation of changes in plasma BNP and NT-proBNP concentrations for detection of disease progression or their use in BNP- or NT-proBNP-guided treatment. Taking multiple samples from a patient does not lower the contribution of CVi to a relevant extent, and easily modifiable determinants to lower CVi have not yet been identified. An exception might be for BNP concentrations >350 ng/L. These give RCVs that are in the same order of magnitude as the BNP changes that might be expected on institution of therapy, provided that these changes derive from triplicate sampling both before and after institution of therapy. The value of BNP and NT-proBNP for chronic heart failure diagnosis, and especially for follow-up and treatment optimization of individuals, remains largely to be established.

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