The lognormal RCVs possess better biological plausibility. Paradoxical values of decreases greater than 100% are eliminated. However, in view of monitoring applications, these RCVs are still rather high. The corrected lognormal RCVs refer to the commonly used 5% bidirectional statistical error. This RCV setup implies that ~5% of clinically stable patients show changes greater than the RCV (false positives). However, for the treatment of heart failure, false negatives present the major risk, and it is imperative that deterioration in a patient’s clinical condition is not missed so that appropriate clinical intervention can be initiated (9). The common probability “insurance” of 95% against false positives could be too high, and another value, 80%, would be clinically more appropriate to lower the false-negative rate. When 80% is used in the construction of RCVs, then NT-proBNP week-to-week lognormal RCVs narrow to 85% for increases and to ~46% for decreases.

The important message we take from this analysis is that the skewness of the distribution requires adequate methods to deal with it to achieve clinically and biologically valid RCVs.

Reference

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Equimolar Ammonia Interference in Potassium Measurement on the Osmetech OPTI Critical Care Analyzer

To the Editor:
Ammonia is a toxic byproduct of amino acid metabolism, and increased blood concentrations of ammonia are associated with severe encephalopathy (1). In mammals, ammonia is detoxified in the liver via formation of urea (2). Hyperammonemia can result from hepatic failure, enzymatic deficiencies of the urea cycle or defects in ornithine transport [e.g., HHH syndrome (hyperornithinemia, hyperammonemia, hyperhomocitrullinuria)], or it may be secondary to other organic acidopathies (3). The hyperammonemia observed in methylmalonic acidemia is thought to arise because accumulated propionyl CoA interferes with formation of N-acetylglutamate, an obligatory activator of carbamyl phosphate synthase, the initial step in urea synthesis (4).

The Osmetech (Roswell, GA) OPTI Critical Care Analyzer (CCA) is a point-of-care instrument used to monitor electrolytes and blood gases; at our institution it is used to monitor critically ill patients during transport from outside facilities. The unique potassium (K+) sensor on this system consists of a macrocyclic ion-selective cryptand covalently coupled to an o-alkoxyaniline fluorophore. In the presence of K+, internal fluorescence quenching is reduced, and fluorescence emission is proportional to the K+ concentration in the specimen. The sensor displays negligible interference from pH, calcium, or sodium (5).

During the recent transport to our hospital of an infant with methylmalonic acidemia (mut5 subtype) and plasma ammonia >3000 μmol/L, apparent K+ concentrations were increased (>8 mmol/L) when measured by the OPTI CCA but were within reference values when measured in plasma by both direct and indirect ion-specific electrodes. We hypothesized that the increased K+ measurement observed on the OPTI CCA was the result of ammonia interference.

We obtained a plasma pool (endogenous ammonia = 150 μmol/L) and supplemented it with increasing concentrations of NH₄Cl and LiCl. Subsequent K+ measurements were performed on the OPTI CCA and on the following whole-blood direct ion-selective electrode platforms: ABL 735 (Radiometer), GEM Premier (Instrumentation Laboratories), and i-STAT (Abbott Point of Care). Potassium measurements were also performed with the Vitros 250 (Ortho Clinical Diagnostics). In the presence of increasing concentrations of ammonium chloride, we observed an equimolar increase in apparent K+ when measured on the OPTI CCA (Fig. 1). Ammonium chloride up to 5000 μmol/L had no effect on K+ measured with the Vitros 250, ABL 735, GEM, or i-STAT. LiCl had no impact on K+ measured with the
Fig. 1. Effect of ammonium on potassium measurements.

Plasma was supplemented with the indicated concentrations of NH₄Cl, and subsequent potassium measurements were performed on the OPTI CCA (●), Vitros 250 (▲), ABL 735 (●), ILGem (●), and i-STAT (●). Data shown are the means of 3 replicate measurements (respective SD is less than the size of the symbol for each point). Addition of NH₄Cl was 5% of the total sample volume at each concentration tested (data not shown).

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Usefulness of Longitudinal Measurements of β-Amyloid1–42 in Cerebrospinal Fluid of Patients with Various Cognitive and Neurologic Disorders

To the Editor:

Measuring protein concentrations in cerebrospinal fluid (CSF) has gained wide acceptance for the differential and early diagnosis of dementia (1–3). Longitudinal changes in CSF biomarkers such as β-amyloid1–42 (Aβ1–42) are of potential use for studying the disease course and the effects of treatment, but they have rarely been studied. We evaluated changes in Aβ1–42 concentrations with time and assessed the influence of assay variability and specimen storage on assay results.

At the Alzheimer Centre of the VU Medical Centre, 114 patients each underwent 2 lumbar punctures (LPs). Mean (SD) time between the first and second LP was 21 (9) months (i.e., follow-up time). CSF samples were collected in 12-mL polypropylene tubes, centrifuged within 2 h at 2100 × g for 10 min at 4 °C, aliquoted into 0.5- or 1-mL polypropylene tubes, and stored at −80 °C until further analysis. The study was approved by the ethics committee of the VU Medical Centre, and all participants gave informed consent.

Aβ1–42 was measured with a sandwich ELISA (Innotest β-amyloid1–42; Innogenetics) (4). Baseline samples were assayed twice: once shortly after the first LP (A1) and once, in a separately stored aliquot (A2), concomitant with the follow-up sample (B; note that storage time of the baseline sample equals follow-up time).

The intraassay CV [averaged (SD/mean) × 100%] was 2.8% for duplicate samples run in 4 different assays. The interassay CV was 6.9%–13% for 4 different quality-control samples run across 26 assays between January 2004 and December 2005. A paired-samples Student t-test was used to evaluate changes in Aβ1–42 concentrations. The CVs for baseline and follow-up sample pairs were calculated; CVs were then graphed in Bland–Altman plots and compared by use of the Pitman test (5).

The demographic characteristics of the study population are summarized in Table 1 of the Data Supplement that accompanies the online version of this letter at http://www.clinchem.org/content/vol52/issue8/.

The mean (SD) Aβ1–42 concentration in the baseline samples assayed shortly after collection (A1) was 485 (242) ng/L, and the mean con-