

hemodynamics. Clinicians should look at intraindividual variations in BNP as a mirror of variation in neuroendocrine network activity.

According to this hypothesis, we suggest that all changes in BNP concentration should potentially be considered as clinically relevant, even when they are narrower than the calculated intraindividual biological variation, because these variations reflect changes in activation of the neuroendocrine system as a result of specific pathophysiologic mechanisms. In other words, BNP variations should be interpreted and considered by physicians, in the same manner as variations in heart rate and blood pressure, by taking into account clinical history and examination, including response to specific treatments, as well as laboratory and instrumental test findings.

There is another important practical consequence of this approach. At an intraindividual biological variation of ~30%, the estimated imprecision goal for BNP immunoassays should be 15% (i.e., equal to one half of the intraindividual variation) (10, 11). On the contrary, we suggest that all measured variations of plasma BNP >3 times the analytical imprecision of the assay used (i.e., 3 SD of the assay variability) should potentially be considered as clinically relevant. According to this approach, the assay imprecision of BNP immunoassays should be as low as possible. A recent study from our laboratory evaluated the analytical imprecision of several commercial BNP immunoassays (12). On average, this study demonstrated that analytical performance, as well as reference and decision values, varied greatly among the BNP assay methods; in particular, the imprecision of these immunoassays varied, on average, from ~15% (the worst) to 5% (the best) (12). Evidently, the immunoassay with the best imprecision is able to detect significantly narrower changes in BNP concentrations (i.e., variations of ~15% for the method with the lowest imprecision).

We suggest that only clinical criteria should be used to evaluate the pathophysiologic relevance of the

measured variation in BNP concentration (defined as greater than 3 SD of assay variability) in an individual patient. Of course, the large number of pathophysiologic mechanisms affecting the CNH system may make it difficult for clinicians to recognize the cause(s) of variations in that system's activity. However, we believe that BNP assays should be considered as an intellectual stimulus in the search for explanations of the variations in hormone concentrations and their relationship to pathophysiologic stimuli and/or pharmacologic interventions. In this sense, assessment of the time course of BNP concentrations may be a novel, meaningful diagnostic tool for the follow-up of patients with cardiac diseases.

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N-Terminal pro-B-Type Natriuretic Peptide Concentrations in Mothers just before Delivery, in Cord Blood, and in Newborns

To the Editor:

The role of the heart as an endocrine organ was established in 1981 by de Bold et al. (1). Usually, in adults, atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) are secreted mainly by the cardiac atria and ventricles, respectively (2). Plasma concentrations of these peptides, particularly that of BNP, have been shown to reflect cardiac dysfunction and volume overload in adults and children (3–8).

There is evidence that these peptides have possible roles during fetal life in the regulation of organogenesis of the heart and the cardiovascular system, in the regulation of blood pressure and water balance in the developing embryo, and in the transition from fetal to extra-uterine life (9). BNP may also have an important role in the regulation of amniotic fluid volume (10).

Sparse data exist regarding N-terminal proBNP (NT-proBNP) concentrations in umbilical cord blood and in the newborn during the first days

of life (4, 11–13). In most of these studies, plasma concentrations of the peptide showed marked increases in the first day of life with a steady decrease during the first 5–7 days (4, 11–13).

Because NT-proBNP may be used as a marker for various pathologic conditions in perinatal medicine, we conducted a study to determine reference values for NT-proBNP in cord blood and in newborn blood compared with maternal blood.

EDTA-plasma NT-proBNP was measured in blood collected from 71 mothers just before delivery, from 122 umbilical cords, and from 33 full-term healthy newborns in the first days of life. Of 122 newborns enrolled in the study, 110 were delivered vaginally and 12 by cesarean section.

NT-proBNP was measured with an electrochemiluminescence immunoassay (Elecsys 1010/2010; Roche). The assay is unaffected by icterus (bilirubin <350 mg/L), hemolysis, or lipemia.

The mean (SD) NT-proBNP concentration in maternal blood (n = 71) was 88.5 (44.9) ng/L, the mean concentration in cord blood (n = 122) was 578.8 (351.3) ng/L, and the mean plasma NT-proBNP concentration in the newborns (n = 33) was 3042.4 (1783.2) ng/L. For paired samples, there was a significant difference between maternal predelivery NT-proBNP concentrations and umbilical cord NT-proBNP concentrations [89.7 (45.4) vs 612.2 (364.5) ng/L, respectively; $P < 0.0001$; n = 66]. We found no correlation between cord blood NT-proBNP concentrations and newborn weight loss.

There were no differences in NT-proBNP concentrations in cord blood and in newborns related to gender, gestational age, mode of delivery, duration of labor, or Apgar scores.

Because the reference values for the natriuretic peptides, including NT-proBNP, are assay specific (11, 14, 15), the use of different assays in the published studies makes it difficult to draw conclusions and relate to

the currently published baseline values (11–13).

Our report includes NT-proBNP concentrations for 71 mothers just before delivery, 122 umbilical cord blood samples, and 33 full-term newborns (ages, 1–4 days) measured by the Roche proBNP assay. In agreement with previous studies (11–13, 16), our study shows low NT-proBNP concentrations in prelabor maternal blood, intermediate concentrations in cord blood, and high concentrations in newborn blood in the first 4 days of life. Using the same assay, Bakker et al. (13) reported a mean umbilical cord NT-proBNP concentration of ~80 pmol/L (670 ng/L), which is comparable to our result of 600 ng/L (1 pmol/L = 8.47 ng/L).

Although this study was carried out on a relatively small population of newborns, the results of our study may be used as an additional reference baseline for comparing NT-proBNP concentrations in cord blood and plasma of neonates with heart disease, pulmonary problems, or with water and electrolyte disorders in which volume overload and cardiac dysfunction are involved. The results should be compared with regard to the assay used.

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