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References


5. Nakanshi K, Sakiyama T, Imamura K. On the adsorption of proteins on solid surfaces, a consensus protocol that specifically links cutoff values to given sampling tubes and handling/analytical protocols.


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Diurnal Plasma Concentrations of Natriuretic Peptides in Healthy Young Males

To the Editor:

Natriuretic peptides are a family of structurally related hormones encoded by genes for atrial natriuretic peptide (ANP),1 B-type natriuretic peptide (BNP), and C-type natriuretic peptide (CNP). Although the bioactive peptides are related, their tissue and receptor specificities differ. Natriuretic peptide production can also be assessed by measuring the N-terminal fragments from their prohormones in plasma, because these fragments constitute stable markers in vitro and in vivo. The molecular heterogeneity of the propeptides has proved to be complex, and cardiac biosynthesis involves both endoproteolytic cleavage and posttranslational modification (1). The BNP precursor, for instance, is a glycosylated polypeptide and variably matures to the C-terminal, bioactive BNP hormone. The CNP products

1 Nonstandard abbreviations: ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; CNP, C-type natriuretic peptide; MR-proANP, midregional proANP; NT-proBNP, N-terminal proBNP.

Letters to the Editor

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encoded by the NPPC (natriuretic peptide C) gene have been difficult to measure accurately because their plasma concentrations are considerably lower than for the ANP and BNP peptides.

Diurnal hormone production is a hallmark of many endocrine systems. In mouse models, expression of the genes encoding ANP and BNP has been shown to be regulated in a circadian manner by clock genes. We recently reported that BNP mRNA contents, but not ANP mRNA contents, are produced in a circadian manner in the ventricles of wild-type mice and that the production pattern reflects the local expression of the central clock genes Per1 [period homolog 1 (Drosophila)] and Bmal1 [officially known as Arntl (aryl hydrocarbon receptor nuclear translocator-like)] (2). In the present study, we included 24 healthy Caucasian male volunteers (mean age, 26 years). The study was approved by the local ethics committee, and the demographic data of the volunteers and the study setup have previously been reported (3).

For proANP measurement, we used 2 immunoassays. The first assay measures midregional proANP (MR-proANP) on the Kryptor platform (BRAHMS). The assay sensitivity is 6 pmol/L with an interassay CV of 20% at 18 pmol/L and 10% at 65 pmol/L (4). In addition, we used a newly developed assay for quantifying "total" proANP in plasma. In brief, this assay uses a preanalytical step with proteolytic cleavage, which releases an N-terminal 1–16 fragment from proANP. The 1–16 fragment is then quantified with an RIA directed against the C terminus (5). The interassay CV is 11.0% at 240 pmol/L and 6.0% at 2468 pmol/L; the limit of detection is 34 pmol/L. N-terminal proBNP (NT-proBNP) was analyzed on a Modular E system (Roche Diagnostics); the level of detection is 0.6 pmol/L with an interassay CV of 6.0% at 10.2 pmol/L and 5.0% at 45 pmol/L. The functional sensitivity was 4.9 pmol/L with a CV of 20%. Finally, total proCNP was measured with an in-house assay. The analytical sensitivity was 3.2 pmol/L, and the interassay CV was 12.9% at 8 pmol/L and 6.1% at 40 pmol/L. The time-related data for all volunteers were analyzed for the presence of diurnal changes with the methods for cosinor rhythmometry for groups, as described previously (3). Results are presented as the mean (SD) after normal distribution of the data was verified with the D’Agostino–Pearson omnibus and Shapiro–Wilk normality tests.

The variation in the plasma melatonin concentration validated the regular routine of diurnal activity and nocturnal sleep, with concentrations showing the expected 24-h pattern for the group. Concentrations were lowest in the afternoon and increased gradually to peak concentrations at 0334 h (P < 0.0001). There was a distinct diurnal pattern for MR-proANP and “total” proANP plasma concentrations (Fig. 1), with the lowest concentrations occurring during late afternoon [mean MR-proANP at 1800 h, 30.4 (2.3) pmol/L] and the highest concentrations occurring at night [mean MR-proANP at 0300 h, 43.5 (2.9) pmol/L]. The proANP plasma profile thus mimicked the melatonin profile. In contrast, no significant change over a 24-h period could be established for plasma NT-proBNP and total proCNP concentrations [mean NT-proBNP, 1.8 (0.1) pmol/L; mean total proCNP, 46.2 (0.3) pmol/L; n = 216 for both].

Our results of diurnally varying proANP plasma concentrations but nondiurnal NT-proBNP plasma concentrations in healthy individuals seem to conflict with previous findings regarding the production of mRNA in mouse hearts (2). That study noted a circadian production of BNP mRNA in the cardiac ventricles but little response for the ANP mRNA content in the cardiac atria. This discrepancy may partially be explained by differences between mice and humans in gene expression, given that normal ventricular expression of the gene encoding BNP is mostly a rodent phenomenon. Moreover, the differences suggest that mRNA data and plasma concentrations may not always be correlated and that the cellular pattern of secretion from cardiomyocytes should also be considered. Finally, rodents are not subjected to hemodynamic changes related to sleeping, whereas humans go from an upright to a horizontal position, thereby increasing venous return.

We studied the diurnal plasma profile of the entire natriuretic propeptide family. By measuring unique epitopes in the precursor structures, we show that proANP, but not NT-proBNP and total proCNP, circulates in a diurnal manner, which suggests that the circadian sodium homeostasis reported in healthy individuals may partly be regulated by cardiac ANP production (6). A diurnal variation could have implications with respect to the clinical use of MR-proANP measurement in population studies and/or for diagnosis/risk assessment in healthy individuals. Our findings also suggest that the biological variation for proANP may relate to diurnal production to some extent, whereas the biological variation in NT-proBNP plasma concentration seems caused by other stimuli.

2 Genes: NPPC, natriuretic peptide C; Mus musculus gene Per1, period homolog 1 (Drosophila); Mus musculus gene Bmal1, officially known as Arntl (aryl hydrocarbon receptor nuclear translocator-like).
Fig. 1. Plasma profiles for MR-proANP and processing-independent (PIA) (or “total”) proANP (A), NT-proBNP (B), and total proCNP (C) over a 24-h period in 24 healthy young males. Shaded area represents the nighttime/early-morning period.
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References

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Assessing Pneumatic Tube Systems with Patient-Specific Populations and Laboratory-Derived Criteria

To the Editor:

The October 2011 issue of Clinical Chemistry highlights the importance of monitoring pneumatic tube systems (PTSs) to control pre-analytical factors that may affect laboratory results (1, 2). Two important themes emerge: (a) the possible requirement of more frequent monitoring if the PTS produces changes in the 3-axis acceleration (i.e., forces) and (b) consideration for specific populations of patients (i.e., hematology and/or oncology patients) whose blood samples may be more susceptible to PTS. As Felder noted, the work by Streichert et al. may usher in a new practice for monitoring PTS by means of data loggers (1, 2); however, in the interim, laboratories will be required to monitor PTSs with split-sample testing. In this regard, the number of studies and approaches that have assessed the impact of PTSs on the quality of samples has been surprisingly limited (3). Moreover, the available guidelines have mainly suggested that PTSs be evaluated and that certain analytes may be affected by the automated system (e.g., lactate dehydrogenase), whereas others (e.g., aspartate aminotransferase) may not (4). Additional questions arising from the study of Streichert et al. are whether samples from healthy volunteers are the most appropriate to test in PTSs and what criteria should be used to evaluate the acceptability of samples subjected to PTSs. While implementing a new PTS in our hospital, we wanted to determine if patient-specific attributes and laboratory-defined criteria could be used to assess the performance of the new PTS.

Given that patients may be relocated to different hospital locations/wards, one of our goals was to evaluate the new PTS by using available leftover blood samples in the core laboratory that had been obtained from the different locations. For this evaluation, we randomly selected and resuspended lithium heparin blood samples (4-mL green-top Vacutainers; BD) from 5 different patients in each of 4 different hospital locations: the emergency department, the intensive care unit, surgical oncology, and orthopedics, and hematology/oncology. We pooled samples from each location and aliquoted them uniformly (1 mL) into 5 tubes (groups A–E) that were to be sent from the same station (the hematology/oncology ward) via PTS and tested with different interventions. The groups were as follows: group A, control (no PTS); group B, PTS (no intervention); group C, PTS and foam liner in tube only; group D, PTS and no foam, but tube caught at end destination without impact; and group E, PTS and foam with tube caught at end destination. The analytes chosen for this experiment were those that Streichert et al. found to produce different results when the PTS was used (potassium, lactate dehydrogenase, aspartate aminotransfer-