Do Commercially Available Assay Kits for B-Type Natriuretic Peptide Measure Pro-BNP1-108, as Well as BNP1-32?

To the Editor:

We read with great interest the recent article by Heublein et al\(^1\) on plasma pro-BNP1-108 measurement with commercially available assay kits and the effect of pro-BNP1-108 on cGMP levels. They demonstrated that Shionogi’s or Biosite’s triage assay kit did not cross-react with pro-BNP1-108 and that pro-BNP1-108 did not increase intracellular cGMP levels in cardiac myocytes or fibroblasts.

Shionogi’s immunoradiometric assay kit uses 2 monoclonal antibodies: one recognizes the ring portion and the other recognizes the C-terminal tail. Therefore, this assay kit measures B-type natriuretic peptide independent of the length of the N-terminal extension from the ring structure. Indeed, Heublein et al\(^1\) reported that this assay kit measured BNP3-32, BNP5-32, and BNP1-32, but it did not measure C-terminal deletion forms of B-type natriuretic peptide, such as BNP1-30 and BNP1-28.\(^2\)

Namely, this assay kit does not measure B-type natriuretic peptide lacking the ring portion or C-terminal tail. Thus, an N-terminal peptide pro-BNP1-76 lacking the ring portion cannot be recognized by the Shionogi’s immunoradiometric assay kit as shown in this article, whereas pro-BNP1-108 is detected by this kit with slight less affinity (≈70% to 80%) than BNP1-32 (unpublished data). In fact, using Shionogi’s immunoradiometric assay kit, we detected and measured immunoreactivity corresponding with pro-BNP1-108, as well as BNP1-32, after gel filtration of human plasma.\(^2\)

In the study by Heublein et al,\(^1\) moreover, pro-BNP1-108 did not increase intracellular cGMP levels in myocytes or fibroblasts. As for the activity of the natriuretic peptide, the studies of the structure-activity relationship demonstrated that the ring structure and the C-terminal tail are essential for eliciting the biological activity, whereas the N-terminal extension from the ring structure confirmed to be not essential.\(^3,4\)

Indeed, Kangawa et al\(^5\) demonstrated previously that pro-atrial natriuretic peptide induced diuresis, natriuresis, and potassium excretion in the rat, although it was less potent than ANP1-28. BNP1-32 and pro-BNP1-108 act on the same natriuretic peptide receptor-A.

Taken together, available evidence suggests that Shionogi’s immunoradiometric assay kit measures pro-BNP1-108, as well as BNP1-32, and both of them are deduced to have the cGMP elevating activity. We do not know the reason why pro-BNP1-108 was not measured by Shionogi’s immunoradiometric assay kit or why pro-BNP did not increase the intracellular cGMP levels of cardiac myocytes and fibroblasts in the study by Heublein et al.\(^1\) It is reasonable to consider that the same reason diminished the antigenicity, as well as the biological activity, of the pro-BNP1-108 used in their experiment, although they did not precisely describe how they confirmed the structure of the recombinant pro-BNP1-108.

We agree with the notion by Heublein et al\(^1\) that clarifying the molecular form of BNP in plasma and its physiological action in heart failure are of importance. We believe that a better understanding of the structure, biological activity, and plasma concentrations of endogenously present natriuretic peptides, especially BNP, provides useful information in clinical medicine.

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Disclosures

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Toshio Nishikimi
Department of Hypertension and Cardiorenal Medicine
Dokkyo Medical University
Tochigi, Japan

Naoto Minamino
Department of Pharmacology
National Cardiovascular Center, Research Institute
Osaka, Japan

Kazukiyo Horii
Diagnostics Department
Shionogi & Co, Ltd
Osaka, Japan

Hiroaki Matsuoka
Department of Hypertension and Cardiorenal Medicine
Dokkyo Medical University
Tochigi, Japan


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Toshio Nishikimi, Naoto Minamino, Kazukiyo Horii and Hiroaki Matsuoka

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