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in this article, whereas pro-BNP1-108 is detected by this kit with slight less affinity (~70% to 80%) than BNP1-32 (unpublished data).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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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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