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Can Dysregulation in pro–B-type Natriuretic Peptide Glycosylation Explain Decreased B-type Natriuretic Peptide Concentrations in Obese Heart Failure Patients?

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Guest: Dr. Alexander Semenov, Project Manager in the R&D Department of the biotech company HyTest located in Turku, Finland and also from the School of Biology Lomonosov Moscow State University in Moscow, Russia.

Bob Barrett: This is a podcast from *Clinical Chemistry,* sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I am Bob Barrett.

B-type natriuretic peptide or BNP and N-terminal proBNP or NT-proBNP are peptides produced in the heart in response to increased wall stretch and volume overload. As their production and secretion increases in the heart with regression of heart failure, they have emerged as useful and cost-effective heart failure biomarkers. Since the discovery of BNPs in 1988, much effort has been made to precisely determine the BNP and NT-proBNP levels via immunoassays for reliable heart failure diagnostics. As a result, the measurements of these biomarkers is globally accepted and used as a tool by clinicians to diagnose acute and chronic heart failure, stratify risk, and monitor response to therapy.

Obesity is on the rise worldwide and it's a risk factor for systemic hypertension, hyperlipidemia, diabetes mellitus, and left ventricular hypertrophy, all of which are conditions associated with an increased prevalence of heart failure. However, the applications of BNP and NT-proBNP as biomarkers in obese patients are limited, as the relationship between their levels and myocardial stiffness is complex. An Editorial appearing in the September 2019 issue of *Clinical Chemistry* examines the interrelationship between obesity and BNP and NT-proBNP measurements. The authors of that Editorial are Alexander Semenov and Alexey Katrukha, both are from the biotech company HyTest located in Turku, Finland, and the School of Biology Lomonosov Moscow State University in Moscow, Russia. Dr. Semenov is our guest in this podcast. So, doctor, what are the relationships among B-type natriuretic peptide and NT-proBNP levels, body mass index, and heart failure?

Dr. Semenov: Well, obesity is a well-known risk factor for systemic hypertension, hyperlipidemia, diabetes, and left ventricular hypertrophy. These conditions, in turn, are associated with an increased prevalence of chronic heart failure and the proportion of heart failure patients with significant obesity

has increased dramatically, owing to the increase in obesity in the general population.

Notably, obese patients present unique challenges in the diagnosis of heart failure and particularly in the Emergency Department. Obesity may mask signs of edema during physical examination. Thus, the use of biomarkers to aid in the diagnosis and management of heart failure would be particularly valuable in obese patients. Natriuretic peptides, BNP and NT-proBNP are widely used nowadays to establish or exclude the diagnosis of heart failing patients with acute dyspnea. However, the use of these biomarkers is compromised in obese patients as the levels tend to be lower. Obese individuals have an impaired natriuretic peptide response, a so called natriuretic handicap.

Bob Barrett: So, since the relationship between BNP and NT-proBNP levels and myocardial stiffness is complex, do you agree that applications of BNP and NT-proBNP as biomarkers in obese patients are limited?

Dr. Semenov: Well, definitely. Considering that the established clinical thresholds are not relevant to distinguish heart failure from non-heart failure conditions among obese patients, the interpretation of results and clinical decisions are indeed rather complicated, and consequently, the applications of both BNP and NT-proBNP as biomarkers in obese patients are limited. Thus, a more precise understanding of the interrelationship between the BMI and natriuretic peptide measurement is of crucial importance, not only to accurately diagnose heart failure in obese patients, but also to formulate new therapeutic strategies.

Bob Barrett: What hypotheses had been proposed to explain the inverse relationship between obesity and circulating BNP and NT-proBNP concentrations?

Dr. Semenov: Actually, a number of hypotheses have been proposed to explain the inverse relationship between obesity and circulating concentrations of natriuretic peptides. The suggested mechanisms include altered renal clearance, altered activity or concentration of receptors responsible for clearance of natriuretic peptide's reduction, and stimulus from wall stretch caused by increased epicardial fat and altered activity of proteolytic enzymes. However, no conclusive evidence has yet been obtained in favor of any particular hypothesis.

Bob Barrett: Dr. Semenov, how do the results of the study by Lewis et al. recently published in *Clinical Chemistry* improved our current understanding of reduced circulating concentrations of both BNP and NT-proBNP in obese heart failure patients?

Dr. Semenov: The authors of the study explored this phenomenon from the viewpoint of in fact proBNP process in heart failure, both generally and particularly with respect to obesity. The appearance of BNP and the NT-proBNP in the blood is ultimately caused by proteolytic process which is a precursor proBNP. Glycosylation of the region close to the proBNP clearing site 30971, was shown to play a pivotal role in regulating the intermediate processing of proBNP. That also associated increased BMI with increased ratio of total proBNP to proBNP non-glycosylated at 30971 thereby suggesting a decrease in the production of potential source of BNP and NT-proBNP. A decreased proBNP process then could at least partially explain the lower NT-proBNP and BNP concentrations observed in obese individuals. This is a novel view on the complex interrelationship between obesity and natriuretic peptide concentration.

Bob Barrett: So, what differentiates the method used by the authors to detect different proBNP forms from previous studies?

Dr. Semenov: Well, glycosylation profile analysis of endogenous proteins is known to be a laborious process that requires complex methodological approach. For example, HPLC coupled to mass spectrometry base methods are known to have quite limited throughput. The authors used an alternative approach. They developed three immunoassays to distinguish between total proBNP, proBNP not glycosylated at 30971 and proBNP not glycosylated in the central region. These assays allow both directed and high throughput determination of the proBNP glycosylation profiles and facilitated glycosylation profile comparison in different subgroups of heart failure patients.

Bob Barrett: Do you think that this method can be used in other studies on the regulation of proBNP processing?

Dr. Semenov: Yes, definitely. By using antibodies of the highly specific and high affinity tool is principally possible to develop an assay for almost any particular form of BNP related peptide. I hope that these studies would encourage future research on the regulation of proBNP process in different subgroups of patients with different etiologies of heart failure. These studies might help to improve our understanding for heart failure development and the clinical significance of different forms of BNP related peptides.

Bob Barrett: Well, finally, Dr. Semenov, what limitations of the study by Lewis et al. do you think are to be considered while interpreting the results?

Dr. Semenov: I would imagine a few limitations of the study. First, total BNP concentrations were not evaluated in the analyzed

samples. Thus, it's not possible to estimate the ratio of the different proBNP forms in the total BNP pool and make a conclusion regarding alterations in BNP production in different subgroups of heart failure patients. Second, in key proBNP assay used to determine plasma proBNP concentrations was sensitive to NT-proBNP glycosylation. Consequently, the difference in NT-proBNP measurement in heart failure patients with and without obesity may be influenced by alterations in the glycosylation state in the central region of the NT-proBNP. And the validity of the conclusions that show a difference in NT-proBNP concentrations, in obese versus non-obese heart failure patients might be compromised because of the effects of glycosylation on antibody binding.

Bob Barrett: That was Dr. Alexander Semenov, Project Manager in the R&D Department of the biotech company HyTest located in Turku, Finland and also from the School of Biology Lomonosov Moscow State University in Moscow, Russia. He has been our guest in this podcast on the interrelationships between obesity and BNP and NT-proBNP measurements. His Editorial on that topic appears in the September 2019 issue of *Clinical Chemistry*. I'm Bob Barrett. Thanks for listening.