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B-Type Natriuretic Peptide Is Associated with Indices of Left Ventricular Dysfunction in Healthy Subjects from the General Population: The Akershus Cardiac Examination 1950 Study

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Guest: Dr. Magnus Lyngbakken is in the Cardiovascular Research Group in the University of Oslo and the Akershus University Hospital in Norway.

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.

Measurement of natriuretic peptides is fundamental in diagnosing heart failure, as higher concentrations of these peptides in plasma are strongly associated with risk of incident cardiovascular disease.

Increased concentrations of natriuretic peptides are positively associated with left ventricular mass and inversely associated with left ventricular ejection, but can measuring the natriuretic peptides be useful in assessing heart health in healthy subjects from the general population? A paper that appears in the January 2021 issue of *Clinical Chemistry* looks at that very issue. That study from researchers in Norway examined B-type natriuretic peptide concentrations in over 3,400 women and men free from known coronary heart disease.

Dr. Magnus Lyngbakken is the lead author of that study. He is in the Cardiovascular Research Group in the University of Oslo and the Akershus University Hospital in Norway. Dr. Lyngbakken is our guest in this podcast. First doctor, so all of our listeners are on the same page, what are the main biological actions of natriuretic peptides?

Magnus Lyngbakken: The natriuretic peptides are inherently cardioprotective hormones, and their effects includes vasodilation, natriuresis, and they inhibit the renin-angiotensin-aldosterone system, and accordingly the long-term regulation of sodium and water balance, and blood volume, and, ultimately, blood pressure. These hormones are released into the circulation as a response to both atrial and ventricular stress or just tension, as well as sympathetic activation. And all the latter are commonly seen in heart failure, where we see left ventricular overload and also neurohormonal dysregulation.

Bob Barrett: Natriuretic peptides are considered to have beneficial biological actions; can you please explain why high concentrations still seem to be associated with poor outcome? This seems paradoxical.

Magnus Lyngbakken: Well, it's true that the natriuretic peptides are associated with inferior outcomes, both in patients with established cardiovascular disease such as heart failure, and in presumably healthy community dwellers.

In our patients with asymptomatic heart failure, the concentrations of natriuretic peptides are commonly elevated far beyond the reference range and they are strongly associated with the left ventricular function usually quantified by left ventricular ejection fraction. So, the lower the left ventricular ejection fraction, the worse the heart function, the higher the concentrations of natriuretic peptides are expected. And this also associated with the severity of heart failure in our patients, and also, the symptoms of heart failure and ultimately, inferior prognosis. In the heart failure patients, the higher concentrations of natriuretic peptides that we see is a physiological response to the systemic stress that we call syndrome or heart failure.

This is why the higher concentrations are indeed associated with poor outcomes. In healthy subjects, in subjects with no cardiovascular disease with no heart failure, what we call the community dwellers, the associations with outcomes are not as straight forward as for the heart failure patients. And what we know is that the association of natriuretic peptides with outcomes are largely non-linear and there appears to be a threshold effect. And as long as your natriuretic peptides are low or at least within the normal reference range, your cardiovascular risk is probably going to be really low. But as soon as the concentrations start to increase and close in on the upper reference limit, the cardiovascular risk also increases quite exponentially.

Bob Barrett: Measurement of natriuretic peptides such as B-type natriuretic peptide is a cornerstone in the diagnostic workup of patients with suspected heart failure. What is known about natriuretic peptides and subjects outside the emergency room setting?

Magnus Lyngbakken: Well, as I pointed out previously, the natriuretic peptide is associated with cardiovascular risk in community dwellers but not in a strictly linear fashion. Previous studies have also documented associations of natriuretic peptides with left ventricular function in subjects from the general population. The associations with outcomes are, however, not as strong as, for instance, for the cardiac components but I believe that most investigators view natriuretic

peptides as a possibly valuable tool in cardiovascular risk prediction also outside the emergency room setting.

Bob Barrett: So, it seems like higher concentrations of natriuretic peptides are indeed associated with inferior prognosis in both subjects with established cardiovascular disease and presumably, healthy community dwellers. So how did these associations influence the hypotheses of your current investigation?

Magnus Lyngbakken: Well, we now know that the natriuretic peptides are associated with both cardiovascular outcomes and cardiac function. In the later years, however, we have developed more sensitive measurements of cardiac function: such as global longitudinal strain, abbreviated GLS, which has increased sensitivity compared to left ventricular ejection fraction, which is the measurement that is routinely used today.

And we accordingly hypothesize that natriuretic peptides would be associated with both GLS and several other echocardiographic measurements that reflect both cardiac function and cardiac structure. And that mildly elevated concentrations would associate with cardiac dysfunction and possibly left ventricular hypertrophy.

Bob Barrett: What were the novel findings of your study? And what were some explanations of these results?

Magnus Lyngbakken: In our study, we found that B-type natriuretic peptides, or BNP as abbreviated, was independently associated with left ventricular systolic function that we quantified by GLS and also by left ventricular ejection fraction. To my knowledge, this is one of the largest studies to this day that have investigated the associations of natriuretic peptides with GLS. As I said it's a more sensitive and more novel index of a cardiac function compared to left ventricular ejection fraction.

But more interestingly, the associations that we found were non-linear in nature, and we observed the most favorable cardiac function in the medium reference range. And the subjects in our study that had either very low or very high concentrations of the BMP actually had worse cardiac function. And this is actually in accordance with recent literature, in a document what we call natriuretic peptide deficiency and as we discussed previously. The natriuretic peptides are inherently beneficial, and subjects that for some reason had attenuated natriuretic peptides release will accordingly miss this beneficial effect.

And we know that there are several factors that may contribute to natriuretic peptides deficiency, such as obesity

and male sex. And there are several other studies that have documented this U-shaped association of natriuretic peptides with outcomes. So that subject with either very low or very high concentrations of natriuretic peptides are at increased cardiovascular risk compared to subjects with concentrations that are within the medium normal reference range.

Bob Barrett: What is known about genetic determinants of circulating BNP concentrations. How did these observations fit with your findings?

Magnus Lyngbakken: That's actually a very interesting question and one that could actually help us explain parts of this natriuretic peptides' conundrum. As we have previously discussed, natriuretic peptides promote vasodilation and by this, they decrease blood pressure which we know to be beneficial.

In several genetic variants of natriuretic peptides, observed both in European and American populations, have been shown to associate with both elevated concentrations and lower blood pressure and decreased risk of clinical hypertension. And what's even more interesting is that the specific genetic variants of BNP that associate with increased concentrations of natriuretic peptides are also associated with reduced cardiovascular mortality and this is very much in accordance with the findings of our study. I believe it further supports this notion that natriuretic peptides are beneficial and promote both better cardiac function and reduce overall cardiovascular risk.

Bob Barrett: Well finally doctor, what are the possible clinical implications of these findings?

Magnus Lyngbakken: Well, in subjects that has established heart failure, lower concentrations of natriuretic peptides are associated with inferior outcomes compared to subjects with moderately increased concentrations of natriuretic peptides. And these observations are in accordance to our findings with inferior cardiac function in both the lower and the higher reference range of BNP. From this, we would assume that patients with heart failure and just apparently a lower concentration of natriuretic peptides are actually at higher cardiovascular risk that would be expected from the natriuretic peptide values themselves and this might actually be surprising to many clinicians as we commonly interpret natriuretic peptides on a linear scale; with increasing risk associated with increasing concentrations.

And I believe that clinicians dealing with heart failure patients need to acknowledge this discrepancy, and at least not underestimate the residual cardiovascular risk in heart failure patients that have low concentrations of natriuretic

peptides. And with regard to risk prediction in the general population, the sentiment actually remains the same; and we should interpret both especially low and especially high concentrations of natriuretic peptides as a signal of dysregulation and possibly increased cardiovascular risk.

Bob Barrett: That was Dr. Magnus Lyngbakken from the Cardiovascular Research Group at the University of Oslo and the Akershus University Hospital in Norway. He is the lead author of a study examining b-type natriuretic peptide measured in healthy subjects from the general population. That study appears in the January 2021 issue of *Clinical Chemistry*. I am Bob Barrett, thanks for listening.