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EDITORIAL COMMENT

Natriuretic Peptides and Metabolic Hypertension

A Match Made in Heaven?*

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Cardiac natriuretic peptides have become a biochemical mainstay in the assessment of chronic heart failure. Plasma measurement is now implemented in guidelines from both Europe and the United States, and their diagnostic role can, to some extent, be compared to the role of troponin measurement in acute myocardial infraction. Thus, molecules released by cardiomyocytes have key roles in our diagnostic approach to cardiovascular disease, whether it be cell death and necrosis or dynamic regulation and release.

Natriuretic peptides are potent hormones that lower blood pressure and reduce body fluids by stimulating renal excretion of sodium and water.[1] In this regard, early research focused on their potential as therapy in diseases like essential hypertension. However, natriuretic peptides are peptides that require infusion or injection as human therapy, which may at that time have dampened the overall enthusiasm for developing natriuretic peptide therapy for common hypertension. To that end, the short half-life in circulation for the active peptides also challenges their pharmacodynamic profile. Finally, natriuretic peptides, when infused, are highly potent, which could be perceived as a problem in terms of patient safety. In this issue of *JACC: Basic to Translational Science*, Ma et al[2] report from a phase I trial for the cardiovascular peptide MANP, a modified form of atrial natriuretic peptide. In this trial, MANP was administered once subcutaneously in patients (n = 17) with hypertension as part of the metabolic syndrome; the outcome was defined as safety, tolerability, and cyclic guanosine monophosphate activation. The results were compared with 5 matched patients receiving placebo. Overall, there were no major adverse events in either group. Two patients receiving MANP experienced orthostatic hypotension. Blood pressure was borderline lower in the MANP group 6 hours after injection with no effect on heart rate. In addition, biochemical measures related to insulin sensitivity were in favor of MANP with small reductions in blood glucose and a favorable change in HOMA2–insulin sensitivity. Taken together, the drug was well-tolerated and showed a promising profile in terms of blood pressure lowering as well as indications of a beneficial effect on glucose metabolism.

So far, atrial natriuretic peptide (ANP) or brain natriuretic peptide as therapy has not been a success in fighting hypertension. Like insulin, the peptides cause a marked effect that can trigger adverse effects; for insulin, hypoglycemia and coma, and for ANP, hypotension and syncope. Both side effects should be regarded as a major obstacle in terms of daily use. In parallel with modified insulin, however, changing the molecular form of ANP toward a peptide with a prolonged metabolic clearance seems to be the way to go. For MANP, the chemical modification consists of a duodecapeptide located at the N terminus.[3] This form has its inspiration from a genetic variant first identified in patients with familial atrial fibrillation.[4] The modified peptide has a much longer half-life in circulation and is, therefore, a relevant candidate for therapeutic purposes. The current trial supports that this modified ANP form is meaningful as a potential drug, as no serious adverse effects were recorded

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from 1 injection. For administration, there will still be a need for subcutaneous injections. However, as other peptides have gained momentum in, for instance, diabetes and obesity treatment, this obstacle seems of lesser concern anno 2023. Many patients are already used to weekly injections, and the modern pen formulation for peptide injection should not pose a drawback for an effective and safe treatment.

Besides treating hypertension, ANP and MANP have effects beyond blood pressure. As patients with obesity and/or the metabolic syndrome are prone to hypertension, it is of major relevance that natriuretic peptides also have effects on glucose metabolism. Although the current study only looked at short-term effects of a singular treatment, the data point toward a beneficial effect on glucose concentrations and insulin sensitivity. If future clinical studies can substantiate this effect over time, MANP treatment may be particularly relevant in patients with the metabolic syndrome alongside with hypertension. This patient group is growing in the world, and a prospect may even be that MANP could be a first-choice treatment before overt diabetes precipitates—with the hope that overt diabetes does then not precipitate. One major contender is off course incretion-based therapy, which right now is flooding internal medicine and endocrinology. In time, we may even see a combination of the two with smaller doses and, thus, fewer side effects and better safety.

Treatment of human disease using peptides goes back to the discovery of insulin. Since then, tremendous progress has been achieved for patients lacking insulin in terms of a plethora of various insulin formulations. For patients in whom the lack of peptide is relative, progress has also been made within metabolic disease. Besides the effects of the peptide in question on the central phenotype, cardiovascular protection is emerging as a relatively new facet, which only will become more needed in the coming decades, as we continue to strive for a longer life for us all. This aspect will, per definition, be hard to explore for natriuretic peptides, but basic and experimental studies strongly suggest that the natriuretic peptides also possess such an element. To this end, what patients are likely to benefit most from MANP? The choice of patients with obesity and the metabolic syndrome seems obvious. But even this can be more precise: perhaps, patients with obesity and a relative deficiency in endogenous natriuretic peptides would be the prime patient group. Notably, this type of precision medicine is already possible, as natriuretic peptide deficiency can easily be identified in terms of measuring low natriuretic peptides; and this "endotype" is not uncommon: a recent report suggests that in the United States alone, 8 to 10 million people have this endotype.[5] Although the phenomenon of low natriuretic peptides as an actual cause of disease still needs more exploration, the prospect of true precision medicine is highly appealing. Moreover, patients with the metabolic syndrome, obesity, or type 2 diabetes are also at substantial risk of developing or already having heart failure with preserved ejection fraction. This type of heart failure will only become more prevalent and could soon prove to be the number 1 issue for patients with hypertension and metabolic disturbances. It will be interesting to see whether MANP could be a potential drug for these patients, as the use of neprilysin inhibition does point to such an effect. The so-called ARNI treatment regimen (angiotensin receptor and neprilysin inhibition) seems to increase endogenous natriuretic peptides, which a classic substitution-based therapy with modified ANP may be the most direct way to achieve. Other types of antihypertensive treatment options should of course also be explored further in terms of which patients may benefit the most beyond using only blood pressure as the final measure of effect. After all, lowering blood pressure is not our final target in human medicine—whereas an increase in quality of life and life expectancy is.

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