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EDITORIAL COMMENT

Unwinding the Interaction of Natriuretic Peptides and Neprilysin*

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Natriuretic peptides are an important aid for the diagnosis of heart failure (HF) and may allow for the monitoring of therapy in patients with HF over time. One view often taken to simplify their use is that elevated values reflect a more exuberant counterregulatory response to hemodynamic stress, such that these elevated levels are therefore indicative of the severity of HF and thus reflect prognosis.

However, it has been clear from a variety of studies that the natriuretic peptide system is far more complex. It is highly dysfunctional in HF; in many of these patients, it is difficult to detect significant quantities of bioactive B-type natriuretic peptide (BNP) 1-32 (1). Much of the BNP measured by contemporary assays is either nonprocessed proBNP or degradation products of BNP 1-32, such as BNP 3-32, BNP 5-32, and BNP 8-32 (1). The reasons for this have recently begun to be appreciated. ProBNP, which contains 108 amino acids, needs to be cleaved into constituents (a presumably inert N-terminal proBNP [NT-proBNP] fragment and active BNP 1-32), and that requires not only convertases such as corin (a transmembrane and soluble protease) and furin (an intercellular endopeptidase) but also the lack of glycosylation (or deglycosylation) of proBNP at amino acid 71 (threonine; i.e., T71). In the case of glycosylation at T71, it appears that proBNP processing is inhibited, and for that reason, more proBNP may be generated. ProBNP is much less potent in stimulating the second messengers responsible for the biological effects of natriuretic peptides. In acute HF, the greater plasma levels of natriuretic peptides are associated with a greater rate of deglycosylation, which leads to more effect of the natriuretic peptides. This may also be the reason values are more labile and increase and decrease more rapidly as the system adjusts. In more chronic HF, deglycosylation is less robust, and consequently, there is more proBNP and less BNP 1-32, and values, once elevated, take longer to become reduced in response to therapy (2).

Into this space come the recent provocative data regarding use of LCZ696, a combination neprilysin inhibitor and angiotensin receptor blocker. The PARADIGM-HF trial (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) demonstrated marked improvement in outcomes with LCZ696 compared with enalapril alone in patients with predominantly New York Heart Association functional class II HF (3). Because neprilysin is responsible, in part, for degrading natriuretic peptides, one view might be that by inhibiting natriuretic peptide degradation, one improves the level of BNP 1-32 and, by doing so, improves HF. But the realities of BNP processing presented as just discussed suggest that it is probably not that simple. Given the profound abnormalities of the natriuretic peptide system and its dependence on deglycosylation, it is likely that additional effects of neprilysin or angiotensin receptor blockers must be present to affect HF in any substantial way.

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The paper in this issue of the *Journal* from Bayés-Genís et al. (4) adds to our knowledge in this area. What they suggest is that measurement of neprilysin concentrations with an assay that appears reasonably specific holds prognostic importance. Specifically, this suggests that the neprilysin concentration in and of itself is an important prognostic factor.

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Levels manifested both incremental value and substantially improved calibration and reclassification. They maintained those attributes even when high-sensitivity cardiac troponin T, NT-proBNP, estimated glomerular filtration rate, and ST2 were added to the model. Unfortunately, this evaluation was based only on a single baseline sample, a common practice, but to this investigator a major limitation. Additionally, in a cohort designed to match the clinical characteristics of the PARADIGM-HF cohort, baseline neprilysin levels were significantly associated with the primary endpoint of cardiovascular death or HF hospitalization but not cardiovascular death alone or all-cause mortality. However, in patients who had more normal ejection fractions, recognizing that analyses of subsets induce smaller sample sizes, neprilysin concentration was associated with both the composite endpoint and HF hospitalizations, as well as cardiovascular death.

How might this all work? The simplistic view that by inhibiting neprilysin one is increasing BNP 1-32 may or may not be correct. Indeed, levels could go down because more functional natriuretic peptide is circulating. Perhaps neprilysin interacts with the deglycosylation process or changes the relative activity or efficacy of furin and corin, the convertases essential for cleaving proBNP into BNP 1-32 and the NT-proBNP fragment. On the other hand, BNP values also could diminish if other mechanisms of benefit, which could be independent of natriuretic peptides, lead to improvement in HF. It is known that neprilysin causes proteolysis not only of natriuretic peptides but also of a variety of components that are essential in the mechanisms of action for several other circulating hormones, such as adrenomedullin, atrial natriuretic peptide, bradykinins, angiotensin I, endothelin-1, and substance P (5). Any or all of these effects could modify HF severity and progression, and there may be other analytes that also are involved. Thus, it could be that neprilysin has a great deal to do with natriuretic peptide homeostasis or very little to do with natriuretic homeostasis as a primary mechanism of its effect.

Either way, a major paradigm shift has occurred in the cardiovascular realm. We now have a new agent in LCZ696 that is capable of reducing mortality and hospitalizations via mechanisms that are not yet totally understood. We already know that there are differences in the processing of natriuretic peptides between patients with acutely decompensated HF and those with chronic HF (2). Could it be that end-stage HF is different still? There are some suggestions that could be the case (6). If so, the impact of neprilysin on the natriuretic peptide system may vary by subset.

Nonetheless, the ability to add measurements of neprilysin concentrations to ongoing research efforts may enrich our understanding of these mechanisms and allow us to better leverage this approach to help patients with HF. At present, the assay used is not one that would be easy to implement clinically, and although it adds prognostic significance, it remains unclear whether the incremental value is robust enough to warrant routine use. Furthermore, it would be of interest to assess neprilysin activity, because it is known that the convertases can change activity without a recognizable change in mass concentration (2). In the interim, the proposition that neprilysin is important remains and suggests that for research studies, its inclusion in multivariate models that examine prognosis may be illuminating. The bigger hope is that future studies using serial samples will permit assessment of patient response to various treatments as part of efforts to improve our understanding of the basic mechanisms of neprilysin inhibition. In the long run, such understanding will allow further improvements in drug development based on this promising new therapy.

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