Using Homeostatic Peptides in Decompensated Heart Failure

A Reasonable Paradigm But a Flawed Practice?*

Marc A. Silver, MD, FACC,†
Clyde W. Yancy, MD, FACC‡

Oak Lawn, Illinois; and Dallas, Texas

The failing heart is not just an enlarged version of the normal heart.

Louis N. Katz (1)

In 1981, de Bold et al. (2) described a potent diuretic and natriuretic factor derived from the atrial extracts of rats. Subsequent research has led to the characterization of a family of peptides now known as natriuretic peptides. With the emerging understanding of the natriuretic peptide system has come the hope of enhanced diagnosis, more exact prognostication, and novel therapy for the heart failure syndrome (3,4). As with any “work in progress,” the status of each of these hopes waxes and wanes, but few new concepts or therapies have realized both the enthusiasm and the rancor experienced by natriuretic peptides.

Acute Decompensated Heart Failure

The primary therapeutic target for natriuretic peptides has been acute decompensated heart failure (ADHF), a relatively new addition to the vernacular of heart failure. We have come to define ADHF as new-onset heart failure or more likely worsening of a patient’s chronic, well-established heart failure that requires hospitalization or urgent care. Demographics have been described, and a natural history has been determined. But especially with regard to worsening of chronic heart failure, is this process truly an acute one or is it an expected consequence of the inexorable decline of a chronic insidious maladaptive state of delicate heart, kidney, and vascular interactions? Indeed, there are perturbations in cardiac function that trigger and propagate this “decompensated” state (e.g., ischemia, arrhythmia, dietary indiscretions). However, the corollary suggesting that there is a suddenness that could not have been anticipated has perhaps been overstated.

Nevertheless, patients hospitalized with heart failure are at increased risk for rehospitalization and near-term mortality and a compelling unmet clinical need emerges.

The fallacy in the sojourn to identify effective therapies for ADHF has been the presumption that short-term administration of any agent over hours to days would significantly affect longer-term outcomes over ensuing weeks, months, and years. Such an effect would require profound efficacy with minimal risk in a critically ill patient population. The recently reported EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study With Tolvaptan) studies (5,6) clearly demonstrate how difficult it is to impact death and rehospitalization after an episode of decompensated heart failure.

The Emergence of Natriuretic Peptides as Agents for ADHF

A consistent observation in heart failure has been that the level of endogenous natriuretic peptide synthesis and release parallels the severity of the heart failure syndrome. Despite a wide range of physiologic actions, including cardiac, renal, hemodynamic, antiremodeling, cytoprotective, and endocrinologic, a repeated observation has been that endogenous natriuretic peptides fail to fully ameliorate the overwhelming effects of adverse neurohormonal activation in heart failure. The therapeutic use of natriuretic peptides, as derived from recombinant technology, raised hope that exogenous administration might further augment natriuretic peptide activity and overcome the pathophysiological effects of neurohormonal activation in heart failure.

Limited moderate-sized randomized clinical trials demonstrating presumed safety and modest efficacy of nesiritide (B-type natriuretic peptide) led to Food and Drug Administration approval and introduction of nesiritide to the treatment armamentarium of acute decompensated heart failure. The primary clinical role of nesiritide has been as a vasodilator added to diuretic therapy for patients with decompensated heart failure with symptoms of dyspnea at rest in the absence of hypotension. Because of the adverse prognostic influence of concomitant renal disease in the setting of heart failure, it was hoped that nesiritide would be at least “friendly” to the kidney if not in fact renoprotective—this “wish” was in part responsible for the dramatic uptake of nesiritide after its approval.

However, the validity of the benefits of nesiritide was quickly called into question. In 2004, a small randomized, double-blind, crossover trial of nesiritide versus placebo in patients with ADHF found evidence of volume overload and recent worsened renal function failed to demonstrate improvement in renal function (7). Enthusiasm for nesiritide was further tempered after the emergence of a meta-analysis.
suggesting the possibility of worsening renal function in patients who had been exposed to nesiritide. This was impacted yet again by a second meta-analysis suggesting an increased risk of death 30 days after administration of natriuretic peptides for ADHF (8,9). What has been needed to corroborate or refute these concerns are prospective data that test the association of nesiritide use and the risk of worsening renal function in an “at-risk” population.

The BNP-CARDS (B-Type Natriuretic Peptide in Cardiorenal Decompensation Syndrome) trial is published in this issue of the Journal (10). This study was a small, single-center, randomized, placebo-controlled trial of 75 patients with baseline renal insufficiency and decompensated heart failure given fixed-dose nesiritide versus placebo over the course of 48 h with a primary end point of adverse change in renal function. The authors’ findings are noteworthy: “the main finding of this study was that in a cohort of patients with baseline renal insufficiency and ADHF, administration of nesiritide in addition to standard therapy did not result in worsened renal function. Importantly, administration of nesiritide did not protect against the development of renal dysfunction either.” It is important to note that the BNP-CARDS population was older, more likely to have preserved ejection fraction, and had lesser acuity than the earlier patient populations. Importantly, a bolus was not consistently used in the BNP-CARDS study. These data are provocative but not nearly definitive due to the small sample size, single-center experience, and lack of power to detect a change in important clinical outcomes.

Nevertheless, we believe that these observations, when added to other recent data, serve to mute, but not resolve, concerns regarding renal insufficiency related to the use of natriuretic peptides. This quelling of our angst began with the earlier report of the NAPA (Nesiritide Administered Peri-Anesthesia in Patients Undergoing Cardiac Surgery) trial, where nesiritide given to patients with left ventricular dysfunction demonstrated attenuation of renal dysfunction commonly found after cardiopulmonary bypass (11). More recently, the preliminary results of the FUSION II (Follow-Up Serial Infusions of Nesiritide in Advanced Heart Failure) study, a trial testing the safety and efficacy of serial outpatient administration of nesiritide to patients with advanced heart failure, likewise failed to reveal evidence of renal harm (12).

So, how do we synthesize the information before us? The paradigm of natriuretic peptides remains provocative and continues to offer both diagnostic and therapeutic promise. However, the natriuretic peptide system as intended in nature is a homeostatic system operating at very low levels of synthesis and release. In patients with advanced heart failure, the natriuretic peptide system is exaggerated and may even be dysfunctional. Efforts to restore natriuretic peptide homeostasis with exogenous administration of nesiritide are reasonable, although counterintuitive, to the usual paradigm of neurohormonal antagonism and with the awareness that unintended consequences of exogenous administration might occur. Clearly, the administration of natriuretic peptides must be carefully considered, and it is possible that our early forays into the therapeutic application of natriuretic peptides may have been flawed and should be revisited.

Nesiritide was originally tested at greater doses than are currently used, given consistently with a bolus and with much less regard for the adverse implications of hypotension, concomitant high dose diuretic therapy, and dynamic changes in renal function in the setting of decompensated heart failure. It is likely perhaps that the earlier concerns of renal harm reflect those incipient or flawed practices and are not now duplicated in contemporary datasets with carefully managed patient populations. Certainly, the questions regarding nesiritide are far from resolved and the large ASCEND HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure) trial needs to proceed. However, pending new information, the current data make sense.

Patients with heart failure exist at the edge of a compensated state, and minimal perturbations can result in “decompensation.” It is not implausible for acute therapies to lack a dramatic effect on outcomes, nor is it impossible to observe adverse outcomes temporally related to an acute therapy and to ascribe morbidity/mortality risks to that intervention. It is also quite possible that even naturally occurring compounds, if used at nonphysiological doses, may provoke harm. Clinical trials frequently resolve these issues, but the significant patient heterogeneity in the population of patients with ADHF has limited the generation of clear signals. Especially with regards to nesiritide, there have been important background changes in the global management of decompensated heart failure and in a better understanding of the natriuretic peptide paradigm; thus, the practice has indeed changed. The more recent prospective, randomized, double-blind studies now being completed and reported, including NAPA, BNP-CARDS, and FUSION II, have assuaged some of our concerns of renal harm and refocused the question on efficacy. We must however continue to resolve the questions of safety while also continuing to pursue the precise clinical role, ideal patient phenotype, and reasonable expectation of drug effect. Perhaps we have set our expectations too high; there is a progression of disease along the continuum of heart failure that is irreversible. That point may, in fact, be the true “ADHF” phenotype (i.e., “advanced” rather than “acute” decompensated heart failure). If that is true, then our task at hand is earlier identification and treatment of the heart failure patient before the downward spiral begins.

May we suggest revisiting a lesson from Louis N. Katz (13): “the patient with heart failure does not just have an enlarged version of the normal heart but rather a radically deranged milieu which borders most of the time on the edge of depleted reserves.” We ought not to expect most therapies, even aggressive ones, to work all of the time, reverse target organ damage in most, or provide a “cure” to even a few. Certainly we should not apply this standard to a
peptide system designed for homeostasis. As we do more trials to further investigate natriuretic peptides, we must resolve to better address the earlier stages of the heart failure syndrome unravel the pathophysiology of decompensation, and study the role of earlier intervention with these peptides in a more physiologic way. We should not yet dismiss the natriuretic paradigm until we resolve the best practice.

Reprint requests and correspondence: Dr. Marc A. Silver, Department of Medicine, Director, Heart Failure Institute, Advocate Christ Medical Center, 4440 West 95th Street, Suite NO 131, Oak Lawn, Illinois 60453. E-mail: Marc.Silver@Advocatehealth.com.

REFERENCES