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EDITORIAL COMMENT

(Re)Discovering the Neurohormonal and Hemodynamic Duality of Heart Failure*

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"Coming together is a beginning; keeping together is progress; working together is success."
—Henry Ford (1)

The last 3 decades have seen enormous progress in the management of heart failure with reduced ejection fraction (HFrEF), from largely a pure symptomatic approach using diuretic agents and digoxin, to a full neurohormonal blockade with angiotensin receptor-neprilysin inhibitors, beta-blockers, and mineralocorticoid receptor antagonists, supplemented by cardiac resynchronization therapy in selected patients. The combination of these therapies has improved the 1-year mortality rates from 50% (2) to below 10% (3), along with marked improvements in symptoms, quality of life, and functional status, and reduction in heart failure hospitalizations. Despite these advances, the morbidity of the heart failure syndrome remains high, with >1 million annual hospitalizations in the United States, a sobering figure that has not changed over the last decade. These episodes of acute exacerbation requiring treatment with intravenous rescue therapies (in the outpatient clinic or in a hospital setting) are associated with increased mortality (4); hence, numerous attempts have been made to prevent disease worsening and thus the much-feared hospitalizations by enhancing the use of guideline-directed medical therapy (GDMT). There is a strong belief in the practicing heart failure community that maximizing the background GDMT in patients with HFrEF lowers the risk for disease progression, so that other strategies to prevent hospitalizations are rarely needed. In fact, both the American and European heart failure guidelines recommend that recently hospitalized patients in the post-discharge phase should be seen in the office within 1 to 2 weeks, be enrolled in multidisciplinary heart failure disease management programs, receive volume status and blood pressure monitoring, and have GDMT implemented or maximized (5,6). Despite these intensive efforts, recent randomized clinical trials have shown that such strategies, using either state-of-the-art intensive home telemonitoring (7) or natriuretic peptide-guided therapy optimization (8), fail to improve the post-discharge outcomes, with rehospitalization rates close to 50% over 6 months.

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The major reason for this unacceptably high event rate is our failure to understand and recognize the dissociation between clinical congestion and hemodynamic congestion and that persistent hemodynamic congestion has a direct link not only to hospitalizations, but also to mortality (9). In addition, it is possible that during different phases of the heart failure syndrome, the hemodynamic congestion in HFrEF is somewhat independent of an adequate neurohormonal blockade and appropriate use of GDMT, and that addressing the hemodynamic congestion might have a synergistic beneficial effect to the neurohormonal blockade. In the first study to shed light on this concept, in this issue of the *Journal*, Givertz et al. (10) elegantly described how pharmacological interventions tailored to intracardiac hemodynamics were responsible for successful outcomes in HFrEF patients enrolled in the CHAMPION-HF (CardioMEMS Heart sensor Allows Monitoring of Pressure to Improve Outcomes

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in Class III Heart Failure) study. There is still a lot of skepticism of whether the knowledge of hemodynamics could have led to such marked improvement in outcomes in the CHAMPION-HF trial (11), but this result was due to the carefully designed and implemented medication titration algorithm used in the study. The stepped-up pharmacological approach recommended the use of sequential doses of diuretic agents and nitrates to bring down and maintain the pulmonary artery diastolic pressure below 20 mm Hg over the long term while maximizing the GDMT in patients with HFrEF. The present analysis in a subset of 456 patients who had an ejection fraction below 40% showed that the HFrEF patients had a 28% lower heart failure hospitalization rate if they were treated according to their hemodynamics compared with a standard of care symptoms-based approach (10). Importantly, when the authors examined the overall survival, taking into account the dose changes in GDMT or vasodilators over the blinded period of the trial (6 months), the mortality was similarly 30% lower in the hemodynamically treated group, suggesting an equal and potentially additive beneficial effect of both of these types of therapies (10).

Several important findings of this analysis require highlighting. First, the baseline treatment of HFrEF patients was excellent: 74% were on dual GDMT and 45% on triple GDMT at adequate dosing of angiotensin-converting enzyme inhibitors/receptor blockers, beta-blockers, and mineralocorticoid receptor antagonists; this is very similar to recently published landmark trials (3). The HFrEF patients in the hemodynamically treated group had a significant increase (~22 mg daily) in their nitrate dosing from baseline to 6 months, compared with little change (~3 mg daily increase) in the standard of care group (10). Because the hemodynamically treated patients had only a minimal dose increase in GDMT from baseline to 6 months compared with the standard of care group, it is clear that the beneficial effects on heart failure rehospitalization and overall survival were due to the appropriate management of hemodynamic congestion. Indeed, the overall CHAMPION-HF study showed that the hemodynamic-guided approach resulted in the preservation of baseline pulmonary artery diastolic pressures (median reduction −3.0 mm Hg-days), while the filling pressures increased significantly over the 6-month follow-up in the standard of care group (median increase of 98 mm Hg-days) (11). Second, the current analysis showed that the ability to reach maximal neurohormonal blockade has an additional beneficial effect. The reduction in heart failure hospitalizations and mortality in the hemodynamically treated group compared with the standard of care HFrEF groups was larger (43% vs. 33% for hospitalizations; 57% vs. 37% for total mortality) in the group that achieved dual GDMT compared with those who achieved single GDMT, despite changes of similar magnitude in vasodilator doses over time (10). Third, this study highlights the importance of tailored therapy to improve hemodynamic congestion even in patients who are able to tolerate maximal GDMT (10), as opposed to other strategies of using clinical parameters (7) or biomarkers (8) to change outcomes. Last, we must understand the meaning of this analysis from the perspective of other recent clinical trials. In recently hospitalized HFrEF patients with persistent New York Heart Association (NYHA) functional class III symptoms adequately treated with dual GDMT (of which 50% were also taking mineralocorticoid receptor antagonists), a hemodynamically tailored approach that improved hemodynamic congestion lowered the total 1-year mortality rate to 6.7%. By comparison, our best pharmacological approach with angiotensin receptor blockers–neprilysin inhibitors in a study of mostly NYHA functional class II HFrEF patients yielded a total 1-year mortality rate of 7.5% (3). The same hemodynamic-guided management can also lower the 1-year heart failure hospitalization rate to just <40%, compared to >60% found in similar studies of hospitalized HFrEF patients with NYHA functional class III symptoms using telemonitoring (7) or natriuretic peptide-guided therapy (8).

Reading the paper by Givertz et al. (10) caused me to pause and reflect on a brilliantly written piece, 25 years ago to date in this *Journal*: "Based on the studies cited in this review, can we conclude that there is sufficient evidence to accept the neurohormonal hypothesis and reject the hemodynamic hypothesis of heart failure?... It is the interplay of these neurohormonal and hemodynamic forces that defines the syndrome of heart failure" (12).

Only when we are truly ready to (re)discover and finally accept that treating both the neurohormonal abnormalities and the hemodynamic derangements in HFrEF is what leads to successful outcomes for our patients, can we hope to embrace Henry Ford's words: *"Coming together is a beginning; keeping together is progress; working together is success"* (1).

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