

# Neurohormonal control of heart failure

## ■ ABSTRACT

For nearly three decades, starting in the early 1970s, the cardiology research laboratories at the University of Minnesota served as the focal point for the discovery and implementation of much of the information we now apply to the management of heart failure. Director Jay Cohn, building on his expertise in hypertension and hemodynamics, led many creative and committed investigators in the exploration of the mechanisms responsible for increased sensitivity to afterload in heart failure. The neurohormonal hypothesis of heart failure led to the development of several pharmacologic tools, such as angiotensin-converting enzyme inhibitors,  $\beta$ -adrenergic blockers, and, later, angiotensin-receptor blockers. By the late 1990s, it was understood that neurohormonal antagonists could prevent the progression of left ventricular remodeling and favorably influence the natural history of heart failure. Neurohormonal blockers are now considered standard therapy. Issues remain to be addressed, including early identification and treatment of patients at risk.

**W**e have known for more than 100 years that heart failure is characterized by excessive sympathetic nervous system (SNS) activity. Thanks to refinement of this concept in the 1980s and 1990s, we now have a good understanding of SNS activity in both experimental and clinical heart failure. During those two decades, we also realized the pathophysiologic importance of the renin-angiotensin-aldosterone system (RAAS) in patients with heart failure.<sup>1</sup> By 2000, it was obvious that heart failure was inextricably intertwined with excessive neurohormonal activity.<sup>2,3</sup> This understanding of the pathophysiology of heart failure took on greater importance with the ability to pharmacologically block these neurohormonal systems, thereby demonstrating the detrimental role of neurohormones in the onset and progression of heart failure.

Dr. Francis reported that he has served on advisory boards for Sanofi-Aventis and on data safety monitoring boards for Novartis and Corthera.

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This article is a brief historical and personal description of the study of neurohormonal control mechanisms as they relate to the clinical syndrome of heart failure. The article includes a personal account of how the story unfolded in the cardiology research laboratories at the University of Minnesota.

## ■ THE EARLY YEARS: NEUROHORMONAL HYPOTHESIS

A hypothesis emerged gradually in the 1980s suggesting that progression of heart failure was in part a product of excessive SNS and RAAS activity. Many believed that pharmacologic inhibition of these systems might mitigate against progressive cardiac remodeling and thereby reduce symptoms and extend life—the so called neurohormonal hypothesis.<sup>4</sup> SNS blockers and RAAS blockers are now widely used in tandem as first-line therapy to treat patients with heart failure,<sup>5–11</sup> but in 1980 we were just beginning to consider their therapeutic effects.

This major shift in thinking about neurohormonal systems and heart failure did not come about quickly. Early success was driven by the ability to quickly and precisely measure neurohormones in the laboratory coupled with the availability of drugs specifically designed to block the SNS and RAAS. It was also critically important to embrace the power of randomized controlled trials to test new therapies. Investigators, research nurses, and patients from many medical centers and laboratories should be credited with this astonishing success. I am proud to have been a part of this activity at the University of Minnesota.

## ■ THE COHN LABORATORY

Early work done in the 1960s by numerous investigators noted that the failing left ventricle (LV) was exquisitely sensitive to afterload conditions.<sup>12–15</sup> John Ross and Eugene Braunwald explored this observation in patients in 1964.<sup>15</sup> Jay Cohn, with his unique background in hypertension and hemodynamics, brought the concept back into the laboratory in the early 1970s, where he explored the mechanisms responsible for increased sensitivity to afterload in

patients with heart failure.<sup>16</sup>

I had the good fortune to join Cohn's laboratory in 1979, when this avenue of heart failure research was in full bloom. A team of investigators was gradually assembled that included Maria Teresa Olivari, who relocated from the Cardiovascular Research Institute in Milan, Italy, directed by Maurizio D. Guazzi. Also joining the group were T. Barry Levine from the University of Michigan, Ann Arbor; Steven Goldsmith from Ohio State University, Columbus; Susan Ziesche from the Minneapolis Veterans Affairs (VA) Medical Center; Thomas Rector, an expert statistician and pharmacologist at the University of Minnesota; and many research fellows, visitors, students, biochemists, statisticians, and research nurses. Joseph Franciosa joined the University of Minnesota group in 1974 and, after completing several important trials, left in 1979 to lead the cardiology group at the Philadelphia VA Medical Center.

The Cohn group developed a working hypothesis that activation of the SNS and RAAS in heart failure was most likely an adaptive mechanism intended for short-term circulatory support, such as in the setting of blood loss, dehydration, shock, volume depletion, or flight response. In patients with heart failure, according to the hypothesis, the SNS and RAAS activity persisted beyond that needed for adaptation, with chronic release of norepinephrine (NE), renin, angiotensin II, aldosterone, and other neurohormones. The neurohormones ultimately became "maladaptive." Thanks to the assaying skills of Ada Simon, we had the early advantage of precise and rapid radioenzyme measurement of plasma norepinephrine and renin activity in the blood of patients and animals.

We believed that neurohormonal activation contributed in part to the excessive afterload conditions observed in heart failure. We also thought that excessive neurohormonal activation directly impaired cardiac systolic function. The obvious next step was to explore whether neurohormonal antagonists would improve myocardial performance.

Under the leadership of Steven Goldsmith, many studies were performed to investigate reflex control mechanisms and their pathogenic role in patients with heart failure. The accumulating data suggested that persistent, excessive neurohormonal activity was characteristic of heart failure and that it was associated with a poor prognosis.<sup>17</sup> The precise mechanism that drives activation of the SNS remained elusive, however, and is poorly defined even today. In that era, when  $\beta$ -adrenergic blockers were believed to be

contraindicated, we inhibited the central SNS with bromocriptine, clonidine, and guanfacine with modestly favorable responses. We inhibited circulating arginine vasopressin antibody (thanks to Prof. Alan Cowley for noting an acute favorable response).

## ■ THE PHARMACOLOGIC ERA

The 1980s and 1990s saw the availability of several pharmacologic tools for assessing the roles of the SNS and RAAS in heart failure. The hypotensive effects of angiotensin-converting enzyme (ACE) inhibitors and, later, angiotensin-receptor blockers (ARBs) were sources of concern, since many patients with advanced heart failure had low- to normal-range blood pressures before they received RAAS blockers. However, our group as well as others observed that abrupt blood pressure reduction occurred primarily in patients with very hyperreninemic responses to intravenous diuretics (ie, volume-depleted patients). Eventually, we learned that low baseline blood pressure did not adversely affect outcomes when vasodilators were used in patients with heart failure,<sup>18,19</sup> leading us to titrate these drugs upward over days to weeks.

Several different combinations of vasodilators were used successfully to treat heart failure, including hydralazine, isosorbide dinitrate,<sup>20</sup> ACE inhibitors,<sup>21,22</sup> and ARBs.<sup>8,23-28</sup> Direct-acting calcium channel blocking vasodilators, such as amlodipine, did not improve survival in patients with systolic heart failure, although they appeared to be safe in this setting.<sup>29</sup> The aldosterone receptor blockers spironolactone<sup>30</sup> and eplerenone<sup>31</sup> were later demonstrated to improve survival of patients with advanced systolic heart failure when added to vasodilator therapy.

By the end of the 1990s, it was evident that drugs that blocked the SNS and RAAS were not just vasodilators or "afterload reducers," similar to  $\alpha$ -blockers, hydralazine, nitrates, and amlodipine. Neurohormonal blockers were doing something profoundly beneficial not observed with more direct-acting vasodilators.<sup>32-37</sup> Simple afterload reduction was not enough in patients with systolic heart failure.

Neurohormonal antagonists were acting more directly on the myocardium. They were preventing the progression of LV remodeling and, in some cases, promoting reverse remodeling, thus improving myocardial function and favorably influencing the natural history of heart failure.<sup>31-39</sup> We were astonished to discover that the failing, dilated heart could revert to normal size in response to neurohormone blockade with ACE inhibitors and  $\beta$ -adrenergic blockers; these findings were soon reported by other laboratories as well.

Contrary to our concept of heart failure in the 1970s, we now understood that the heart has inherent plasticity. It can dilate in response to abnormal loading conditions or myocardial injury, and it can restore itself to normal size when neurohormones are blocked and perverse loading conditions are improved. This reversal can occur spontaneously if an offending agent such as chronic alcohol use or inflammation is removed, but it is likely facilitated by SNS and RAAS blockers.

## ■ THE REMODELING ERA

Ken McDonald joined the University of Minnesota lab in 1989 as a research fellow. His skill in conducting both animal and clinical mechanistic studies was pivotal to our achieving our research goals. The inspired animal work by Boston-based Marc and Janice Pfeffer revealed the significance of the LV remodeling concept in the development of heart failure<sup>36</sup>; ventricular remodeling was a hallmark of systolic heart failure, and pharmacologic inhibition of LV remodeling by blocking neurohormones had profound clinical implications.

Under the direction of Wenda Carlyle, a molecular biology laboratory was established at the University of Minnesota whose work was dedicated solely to exploration of remodeling at a very basic level. Alan Hirsch was recruited from Victor Dzau's laboratory at Brigham and Women's Hospital in Boston to extend our efforts to understand the molecular basis of cardiac remodeling. Ken McDonald guided the use of magnetic resonance imaging to study remodeling in dogs.

The late 1970s saw the initiation and eventual execution of several important clinical trials, including the Vasodilator Heart Failure Trials (V-HeFT I and V-HeFT II)<sup>40,41</sup> under our leadership, and Studies of Left Ventricular Dysfunction (SOLVD)<sup>5,6</sup> under the leadership of Salim Yusuf and others at the National Heart Lung and Blood Institute (NHLBI). Many neurohormonal and remodeling substudies sprang from these large clinical trials. Spencer Kubo joined our group from the Medical College of Cornell University in the mid-1980s, and he immediately demonstrated his prowess in clinical research. He also recruited Alan Bank to study the endothelium in both experimental and human heart failure.

Integrating the molecular, animal, and clinical laboratories allowed us to pursue many mechanistic studies. Laboratory meetings, often held on Saturday mornings, generated ideas for program projects that were subsequently funded by NHLBI. Birthday parties and other social events with laboratory staff and

their families were part of our fabric. Late-night trips to the Post Office to send off abstracts for national meetings before the midnight deadline were a regular feature.

Our coordination of and participation in the large clinical trials allowed us to meet frequently in Bethesda with colleagues from other major centers, fostering many collaborations and friendships that continue to thrive. Susan Ziesche deserves much of the credit for coordinating many groups that were part of these large, complex trials. Cheryl Yano, our administrator, also played a key role. All National Institutes of Health (NIH) grants passed through Cheryl, and she worked tirelessly to ensure that the proposals were in the best possible shape before we submitted them. Inder Anand joined our group in the early 1990s and became a major analytical force. Jay Cohn was the intellectual leader of the group, as well as our soul and inspiration. People worked hard for him, and he taught us much in a setting that valued creativity and new ideas above all.

## ■ THE LATER YEARS

By 1997, the face of heart failure had changed. New treatments were effective, but there were new challenges to face. I moved that year to the Cleveland Clinic, where I spent 11 enjoyable and productive years. I returned to Minnesota in 2008 to help build a new cardiovascular division.

It is gratifying to look back and see what has become of the "neurohormonal hypothesis." Today, nearly all major medical centers have heart failure programs, and certification in advanced heart failure/heart transplantation is a reality. Training programs in advanced heart failure and heart transplant are common. The Heart Failure Society of America sprang up in the early 1990s, dedicated to patients with heart failure. Jay Cohn founded the *Journal of Cardiac Failure*, which flourished under his leadership. Neurohormonal blockers are now considered standard, conventional therapy and are widely used throughout the world.

## ■ CONCLUSIONS

Still, there is much work to do. An increasing number of devices are being developed, largely for patients with more advanced heart failure, but attention is also being directed to prevention of heart failure. Identification and possible treatment of patients at risk for the development of heart failure, and identification of those who already have some early structural and functional perturbation without advanced symptoms,

are critically important. Since event rates are so low in these patients, we need to create new strategies for studying interventions. In the long term, the best treatment for nearly any condition is early diagnosis and perhaps early treatment with a goal of prevention.

One consequence of our progress over the years may be that heart failure now primarily affects a more elderly group—patients who often have many associated comorbidities. The consequences include more frequent readmissions, large numbers of patients with intractable signs and symptoms, and the emergence of difficult end-of-life decisions. If we could truly prevent heart failure rather than forestall its emergence to a later point in life, perhaps we could do more good.

For me, the study of neurohormonal mechanisms in the setting of heart failure was the centerpiece of my early career. Jay Cohn had asked several of us early in our laboratory experience to choose a neurohormonal system and learn about it in great depth and detail. My assignment was the SNS. Since then, I have never tired of learning about its control mechanisms, how it achieves circulatory homeostasis, how its excess quantities can be directly toxic to the heart, and the variety of pharmacologic ways that we can control it. I am indeed fortunate to have been part of this amazing study group.

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**Correspondence:** Gary S. Francis, MD, University of Minnesota Medical School, 284 VCRC, 420 Delaware Street SE, MMC 508, Minneapolis, MN 55455; franc354@umn.edu.