

Systolic HF Update



Heart Failure

Despite advances in diagnosis and treatment of heart failure (HF), it remains a growing disease state in the United States, annually affecting millions of people. It causes over one million hospitalizations, contributes to more than 50,000 deaths, and consumes billions of dollars in health care spending. This growing burden of HF is further amplified by the fact that the beneficial impact of new treatment advances and under-dosing of proven beneficial treatments have been limited by slow penetration of evidence-based therapy into clinical practice. This *Heartbeat* will outline pathophysiology, an optimal treatment program—proposing β -blockers first—and propose BNP testing to assist in obtaining the best outcomes.

By adjusting and intensifying treatment of patients at high risk for recurrent HF admission—based on brain natriuretic peptide levels (BNP)—HF outcomes can be improved and repeat admissions can be decreased, without increasing personal and financial resources. It may take a few extra visits with the HF specialist, but with significant savings overall by decreasing readmissions.

It's All About Neurohormonal Activation

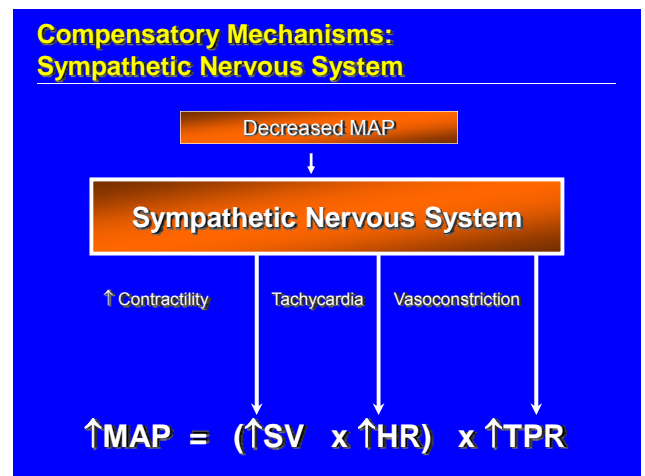
A review of the pathophysiologic mechanisms involved in HF and left ventricular remodeling are critical to understanding how treatment works.

Neurohormonal Activation:

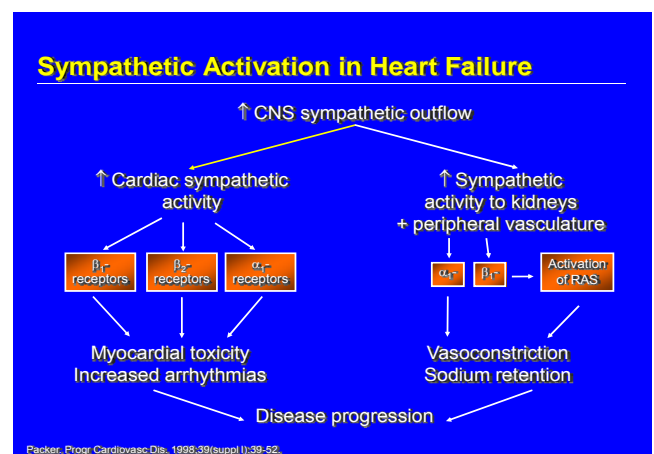
Many different hormone systems are involved in attempting to maintain normal cardiovascular homeostasis, in response to HF, including:

- Sympathetic nervous system (SNS)
- Renin-angiotensin-aldosterone system (RAAS)
- Vasopressin (a.k.a. antidiuretic hormone ADH)

The acute effects of neurohormonal stimulation are beneficial, but the long term or chronic activation of these mechanisms is detrimental.



The SNS is stimulated due to a decrease in mean arterial pressure (MAP) from HF. Sympathetic outflow is increased to the heart and the peripheral circulation causing an increase in the patient's heart rate and an increase in contractility. Vasoconstriction also occurs which increases the peripheral vascular resistance. Stroke volume (SV) is subsequently increased which in turn increases MAP.



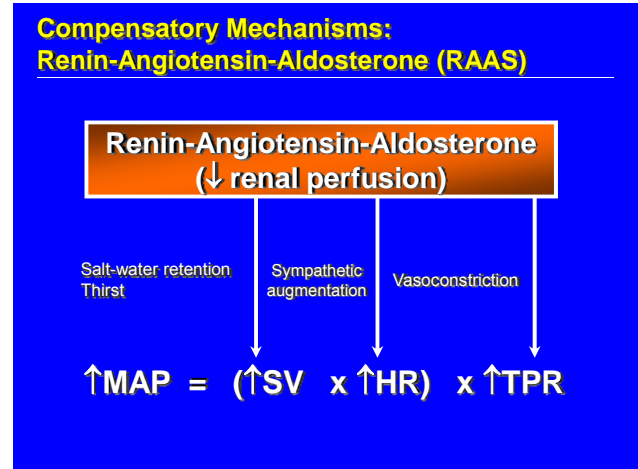
The SNS's goal is to increase cardiac sympathetic activity. This response is mediated through three receptors: Beta 1, Beta 2, and Alpha 1. In normal situations the Beta 1 receptor increases cardiac sympathetic activity. In HF patients, the Beta 1 and Beta 2 receptors are activated. Alpha receptors and their role are yet to be fully delineated.

Beta 1, Beta 2, and Alpha 1 receptors lead to myocardial toxicity in the ventricles. Myocardial toxicity leads to decreased ejection fraction, arrhythmias, and tachyarrhythmias caused by sympathetic activation.

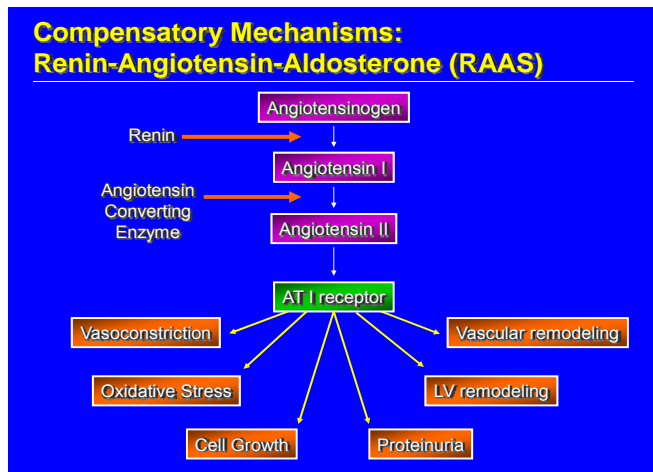
Increase in sympathetic activity also affects the kidneys and peripheral vasculature through the Beta 1 and Alpha 1 receptors. This mediates activation of the renin-angiotensin aldosterone system (RAAS), shown on the next slide, which causes vasoconstriction, sodium retention, and thirst. All of these responses cause the disease to progress.

Prolonged neurohormone release also has direct adverse effects on the heart tissue itself. Norepinephrine, for example, is known to be directly cardiotoxic. In fact, studies have established that in patients with HF, the probability of survival is markedly worse for those whose plasma norepinephrine levels are >400 pg/ml. vs <400 pg/ml.

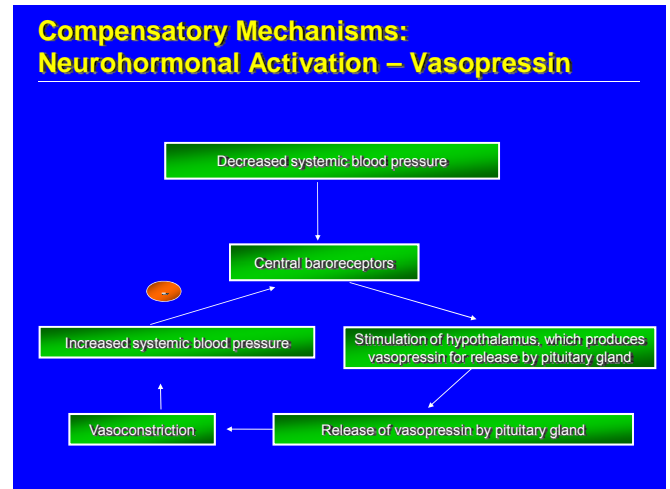
increase in aldosterone, facilitates the release of norepinephrine from the SNS, causes sodium reabsorption, stimulates vasopressin secretion from the brain, and increases contractility. **In a HF patient—NOT GOOD!!**



A decrease in the MAP causes decreased renal perfusion. The RAAS is stimulated, and the MAP is increased.

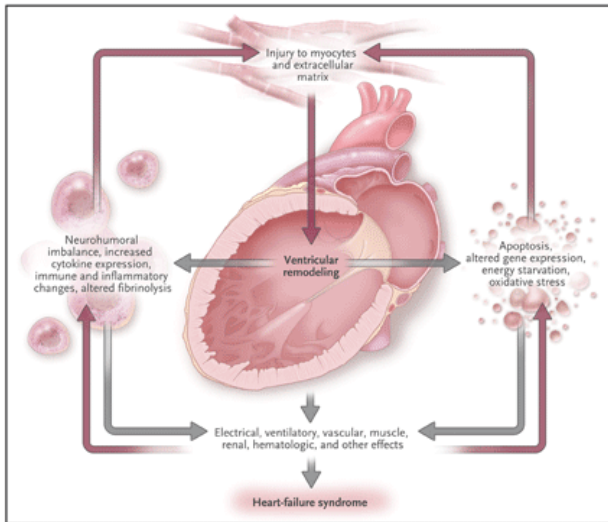


The other mechanism in the neurohumoral response to HF is the RAAS (slide above). In the RAAS, Renin (secreted by the kidney) acts on Angiotensinogen (secreted by the liver) to make Angiotensin I. The Angiotensin converting enzyme (secreted by the lungs) acts on Angiotensin I to make Angiotensin II. Angiotensin II in turn causes vasoconstriction, an



Another neurohormone, vasopressin—antidiuretic hormone (ADH) is involved in the regulation of blood pressure. Secretion of ADH from the pituitary is regulated by two different negative feedback loops shown in the slide above. When central baroreceptors detect decreased BP, fewer inhibitory impulses are sent to the hypothalamus. This stimulates the hypothalamus to produce ADH release by the pituitary. The ADH causes vasoconstriction, and thus increased BP. ADH causes the kidneys to retain water, which in turn, leads to decreased blood concentration (i.e. increased blood volume) which also increases BP.

Figure 1. Pathophysiology of Heart Failure.



Pharmacologic Therapy

Diuretics for Relief of Symptoms

Agents That Modify the Course of the Disease

Angiotensin-Converting-Enzyme (ACE) Inhibitors

Angiotensin-Receptor Blockers (ARBs)

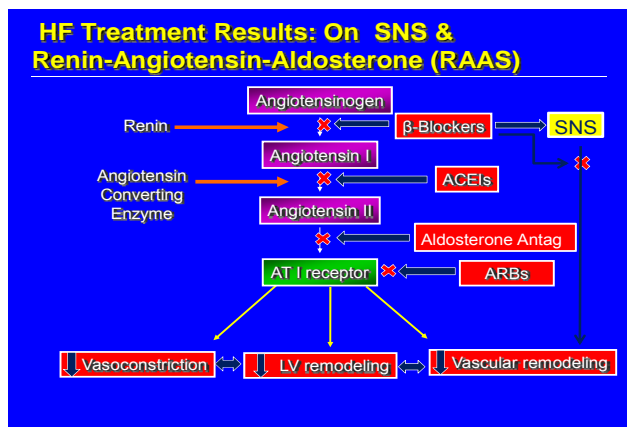
Beta-Blockers

Aldosterone Antagonists

Digoxin

Hydralazine and Isosorbide Dinitrate

All the agents listed above and part of the most recent HF guidelines¹, modify the course of the systolic HF by rebalancing the neurohumoral system in a positive manner to stop or reverse left ventricular remodeling as seen in Figure 1. The traditional "life-saving" drugs (β -blockers and ACE inhibitors or angiotensin receptor blockers, if ACE is not tolerated) we have used in HF direct their activity at reestablishing neurohormonal balance, namely by antagonizing an over-activated SNS and RAAS (slide below), thus stopping or reversing detrimental ventricular remodeling.



EVIDENCE BASED TREATMENT

1. ACE inhibitors: decrease mortality by > 20%.

	Start	Minimum	Goal
Captopril	6.25mg tid	50mg tid	100mg tid
Enalapril	2.5mg bid	10mg bid	20 mg bid
Lisinopril	2.5mg/day	20mg/day	40mg/day
Quinapril	5mg bid	10mg bid	20mg bid
Ramipril	2.5mg/day	5mg/day	10mg/day

Angiotensin-receptor blockers if ACEI intolerant.

	Start	Goal
Candesartan	4 mg/day	32mg/day
Valsartan	40mg/day	320mg/day
Losartan	50mg/day	150mg/day

2. β -blockers: decrease mortality by another 34% to 50 % on top of ACE inhibitors.

	Start	Goal
Carvedilol**	3.125mg bid	25-50mg bid
Metoprolol ER	12.5mg/day	150-200mg/day

** Beta blocker of choice

3. Aldosterone blockers: decrease mortality another 15% to 27% added to ACE inhibitor and beta-blocker benefits. Findings in a recent study suggest that the use of aldosterone antagonists for heart failure may be suboptimal.²

	Start	Goal
Spironolactone	25mg/day	50mg/day
Eplerenone	25mg/day	50mg/day

4. Digoxin: decreases morbidity (hospitalizations) and probably mortality at appropriate low doses.

	Start	Goal level
Digoxin	0.125mg/day	0.5 to 0.8 ng/ml

5. Hydralazine/isorbide dinitrate: An add-on in African-American patients—decreased mortality by > 40 % on top of standard therapy.³

	Start	Goal
Hydralazine	37.5mg/day	225mg/day
Isorbide dinitrate	20mg/day	120mg/day

β -blockers First: As new data emerge from clinical studies, it is crucial to update our clinical practices and treatment guidelines. ACEIs have long been recognized as the cornerstone in HF management, and as a result, these agents have typically been started before any other drugs—and are listed as the first agent in the HF guidelines (*They got here first*).

Today, many experienced HF specialists believe that if β -blockers had arrived at the scene first, ACEIs would now be viewed as second-line agents or as optional therapy, to be added on to the therapy of β -blockade, diuretic agents, spironolactone, and perhaps digoxin, with digoxin levels < 0.8 . In the past decade, our understanding of the role of β -blockers in the treatment of HF has made tremendous progress. These agents are now recognized as having the most impact on the number of lives saved and reduced hospitalizations. Studies have shown a more pronounced mortality reduction ($\sim 34\%$) on top of ACEI treatment whereas the ACEI mortality reduction ($\sim 20\%$) was without β -blockade.⁴ Previous concerns limiting their use in various patient subsets have been alleviated with recent evidence and experience.

In a scientifically humble, yet piercing report, β -blockers beat ACEIs in initial HF therapy. All of the measured end points (NYHA clinical classification, LV size and function, BNP and LVEF) were better in the 38 patient 'starting β -blockers first' group compared to the 40 patient 'starting ACEIs first' group.⁵ There are a number of possible scientific and theoretical reasons the results of this study make sense. β -blockade blunts the hyperactivation and effects of two major neuroendocrine forces in HF, namely the SNS and the RAAS, whereas ACE inhibitors mostly affect the latter. β -blockade reduces heart rate to far greater degree, with a consequent fall in myocardial O_2 consumption, while augmenting coronary perfusion by increasing diastolic filling-time. Additionally, β -blockade alone impedes the toxic effects of elevated circulating catecholamines on the myocardium in HF.

The question of starting β -blockers before ACEIs, or vice versa, has occurred to all clinicians treating a patient on neither. Because of the greater benefits and greater degree of difficulty in early upward dosage titration of β -blockers, our recommendation is that β -blockers be started first, provided the patient is deemed clinically stable with no volume overload. Similarly, β -blocker dosages should be titrated upward regardless of whether ACEIs have reached target doses.

Often, a patient may experience an exacerbation of HF despite optimal pharmacotherapy; however, it is strongly recommended that β -blockers not be discontinued. Rather, adjustment in treatment with diuretics or ACEIs should be considered first, with temporary decreases in β -blocker dosage, only if necessary. When patients become hypotensive, dosages

of diuretics should be reduced first (assuming patients are at dry weight and probably a little dehydrated), vasodilating agents should be reduced second if hypotension persists, with reductions in β -blocker dosages only as a last resort.

BNP Can Help

Despite advances in therapy, about 30% of chronic HF patients are readmitted within 60 to 90 days after a HF hospitalization, and about 10% die within this time span.⁶ Identifying useful strategies to facilitate HF monitoring and subsequent treatment is a very high priority, as the availability of multiple effective therapeutic interventions now creates a need for 'guides' that will let us know when patients are adequately or inadequately treated.

Brain-type natriuretic peptide (BNP) allows for direct assessment of ventricular wall stress. The measurement offers three diagnostic and treatment opportunities for the management of HF patients:

- 1) Global risk assessment at discharge which identifies the patients at highest risk for decompensation who should be followed closely and be treated more aggressively—a BNP at discharge < 350 predicts a 10% rate of death or readmission, and > 750 indicates an 80% chance of readmission.
- 2) Monitoring of short-term changes in wall stress, which allows for anticipation of cardiac decompensation and adjustment of medication in advance (goal < 100 if possible).
- 3) Reminder to optimize drug dosages when patients are feeling well.

The Systolic Heart Failure Treatment Supported by BNP (**STARS-BNP**) trial suggested that the biomarker-guided approach with BNP was a good complement to traditional clinically driven management and led to greater use of evidence-based medications (at higher, more beneficial doses) and fewer clinical events.⁷ Clinicians prescribed more diuretics and especially ACE inhibitors (ACEI's) and β -blockers when they aimed dosage adjustments at the achievement of plasma (BNP) levels of < 100 pg/mL, compared with guidance solely by clinical signs and symptoms. In addition, patients on BNP-guided management showed a significant decrease in the primary end point of death or unplanned hospitalization due to HF, fewer HF-related hospitalizations, and better event-free survival. There

were no significant differences in all-cause mortality or all-cause hospitalization.

Another recent study (measuring NT-proBNP) proves the concept of applying intensified treatment to patients at high risk for cardiac decompensation selected via BNP levels and of adjusting medical treatment in advance according to short-term changes in BNP levels.⁸ The first HF rehospitalization and the combined end point of death or HF rehospitalization were lower in those with BNP guided treatment. Death rate was the same.

Conclusions:

- Targeting the abnormal biology of HF—the counter-productive neurohormonal response—is crucial to reduce the considerable risk that we see with this disease.
- A diuretic will quickly alleviate the patient's initial HF symptomatology, but it is insufficient therapy alone and has no long term benefits.
- Both a β -blocker and an ACE inhibitor should be prescribed at doses outlined above—shown in evidence-based randomized trials to be effective (*our preference is β -blocker first*); if symptoms persist, we recommend adding an aldosterone antagonist, carefully monitoring potassium levels and renal function along with BNP. Digoxin would be our fourth ad-on.
- Although not endorsed by the HF guidelines—or ready for prime-time, BNP can be used *to help* with diagnosis, prognosis and as a guide to optimizing multiple neurohormonal strategies in concert with instituting more aggressive intervention. Careful up-titration is especially necessary in the elderly ≥ 75 and we believe the benefits are worth the additional effort. Some studies suggest mortality benefit. It is especially useful in higher-risk patients but can be used judiciously in all systolic HF patients to prevent recurrent HF and to assist in getting to optimal dose levels of these life prolonging-therapies.
- With these treatments, the patient's ejection fraction is expected to improve over the course of 3 to 6 months, but if it remains at 35% or below, an implantable cardioverter-defibrillator (ICD) should be considered. If the patient's 12-lead electrocardiogram shows QRS prolongation, consider a device that provides both cardiac-

resynchronization therapy (CRT) and ICD instead, especially if the patient continues to have functional limitations owing to his/her symptoms.

- Consideration for evaluation for a ventricular assist device, transplantation or destination therapy should be earlier rather than later.

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Heartbeats online: www.sjhg.org

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¹ Hunt SA, et al. 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation* April 14 2009; 119(14): e391-e479.

² Albert NM, Fonarow GC, et al. Use of aldosterone antagonists in heart failure. *JAMA* Oct 21 2009; 302:1658-1665.

³ Taylor AL et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure (A-HeFT). *N Engl J Med* November 11 2004; 351: 2049-2057.

⁴ McMurray JVC. Systolic heart failure. *N Engl J Med* January 21 2010; 362: 228-238.

⁵ Sliwa K, et al. Impact of initiating carvedilol before angiotensin-converting enzyme inhibitor therapy on cardiac function in newly diagnosed heart failure. *J Am Coll Cardiol* November 2 2004; 44: 1825-1830.

⁶ Fonarow GC, et al. Association between performance measures and clinical outcomes for patients hospitalized with heart failure. *JAMA* January 3 2007; 297: 61-70.

⁷ Jourdain P, et al. Plasma brain natriuretic peptide-guided therapy to improve outcome in Heart Failure: The STARS-BNP multicenter study. *J Am Coll Cardiol* April 24 2007; 49: 1733-1739.

⁸ Berger R, et al. N-Terminal Pro-B-Type Natriuretic Peptide-Guided, Intensive Patient Management in Addition to Multidisciplinary Care in Chronic Heart Failure. *J Am Coll Cardiol* February 16, 2010:645-653