The Neurohormonal Imbalance of Heart Failure: Recent Advances in Our Understanding of the Underlying Pathophysiology of Heart Failure

Narrator:
You are listening to ReachMD. Welcome to this medical industry feature entitled, The Neurohormonal Imbalance of Heart Failure: Recent Advances in Our Understanding of the Underlying Pathophysiology of Heart Failure, sponsored by Novartis Pharmaceuticals Corporation. This program is intended for physicians.

Dr. Mennen:
Increasing evidence suggests that neurohormones contribute to heart failure progression. Additional neurohormonal systems offset these deleterious effects, but less is known about these compensatory pathways. Today, we will be discussing what roles the natriuretic peptide system plays in modulating cardiac function.

I am your host, Dr. Barry Mennen, and I would like to welcome Dr. John Burnett, Jr. to the program. Dr. Burnett is a Professor of Medicine and Physiology and is the Marriott Family Cardiovascular Research Professor at the Mayo Clinic in Rochester, Minnesota.
Dr. Burnett, thank you for being here to share your insights on the role of the neurohormone systems in heart failure.

Dr. Burnett:
I'm delighted to be here, Barry, and I look forward to this session.

Dr. Mennen:
Let's begin your discussion today with a review of neurohormonal regulation of cardiac function. What are the key players in this regulation?

Dr. Burnett:
Well, this is a very interesting system that is very important in overall cardiovascular regulation, and I might say, as well, a very important part of it is the integration between the heart and the kidney, especially, as we’ll discuss, as it relates to heart failure. But these key players are the sympathetic nervous system, the renin-angiotensin-aldosterone system, and what we call the vasoactive but also natriuretic peptide, all of which interact to modulate myocardial function and also kidney function as well.

Dr. Mennen:
As we know, sympathetic activation in people without heart failure leads to increased heart rate, cardiac contractility, conduction speed, vasoconstriction, and coronary artery dilation. Activation of the renin-angiotensin-aldosterone system results in vasoconstriction, enhances sympathetic activity, and initiates cardiac and vascular hypertrophy among other actions.

Having set that stage, how does neurohormonal regulation change under pathophysiological conditions such as heart failure?

Dr. Burnett:
Well, very good question, and the question starts out by saying in people who are healthy and without heart failure or hypertension, these systems work together, and they work together to maintain our blood pressure at normal levels, maintain heart function, myocardial function under normal conditions, and they maintain salt and water balance through modulating the kidney. In heart failure, the first major step in deregulating this system is if the heart is injured in some way, either myocardial infarction or longstanding hypertension or even a hereditary cardiomyopathy. And as the pumping function of the heart is reduced, it really activates the sympathetic nervous system, because there are sensors that detect that there is not enough cardiac output and blood pressure to maintain normal sympathetic function, so that system is activated.

At the same time, the sympathetic nervous system can activate the renin-angiotensin-aldosterone
system either through sympathetic nerves or decreased blood pressure to the kidneys, and both of these systems will have their deleterious effects. At the same time, the natriuretic peptide system -- and keep in mind that these peptides ANP and BNP, which are part of the system, are made in the heart, and the heart tries to rescue itself with activation of this system that acts on the heart and the vasculature in the kidney, and interestingly, within the blood vessel wall, in the endothelium, there is CNP, which is a part of this system, and that plays a role in maintaining normal vascular function. So the way that this is really activated in terms of this sort of neurohumoral storm is the reduction in cardiac function with then activation of these systems.

Dr. Mennen:
That's right. And we know that patients with heart failure can remain asymptomatic or exhibit minimal symptoms for a period of time after an initial reduction in cardiac function. So Dr. Burnett, are the two systems you mentioned, the sympathetic nervous system and the renin-angiotensin-aldosterone system, beneficial or deleterious to a patient with heart failure?

Dr. Burnett:
Of course, under normal conditions, these two systems are important to maintain our physiologic normal-functioning cardiovascular system, but in heart failure they become overactivated, and when they're overactivated, they have very adverse effects. The sympathetic nervous system drives norepinephrine and adrenalin, and these hormones may affect the heart by increasing heart rate, which is not good in heart failure; it may induce injury to the myocyte causing myocardial cell death; it may have adverse effects on the fibroblast in the heart so that there is fibrosis; and all of that is only going to contribute to progression of heart failure.

And the renin-angiotensin system is much like the sympathetic nervous system in these adverse effects, but they work through different receptor systems, particularly, angiotensin II working through the angiotensin type 1 receptor and aldosterone through the mineralocorticoid receptor. They contribute as well to hypertrophy, fibrosis, and what we're learning a lot is inflammation, and this inflammation and activation of one's own immune system further contributes to remodeling of the heart.

Now, these two systems and the hormones that we just talked about target the vasculature to induce vasoconstriction and endothelial dysfunction, and also, the kidney is a major component to this deleterious action inducing sodium and water retention. All of this contributes, again, to symptoms and to progression of heart failure.

Dr. Mennen:
If you are just tuning in, you are listening to ReachMD. I am your host, Dr. Barry Mennen, and I have the pleasure of speaking with cardiologist, Dr. John Burnett, Jr., on the topic of the role of
We were just discussing the fact that enhanced neurohormonal activation in patients with heart failure becomes deleterious over time, leading to end-organ changes such as left ventricular remodeling. Are there any neurohormonal systems that provide beneficial compensatory effects in patients experiencing heart failure?

Dr. Burnett:
Well, another great question, and we've learned a lot in the last few years about the heart being an endocrine organ, and it produces beneficial hormones like ANP and BNP, which are part of the natriuretic peptide system and activate a molecule called cyclic GMP.

As these hormones are released from the heart, they really have a wonderful beneficial effect -- again under physiologic conditions maintaining blood pressure, renal function, vascular function -- but in the very earliest stages of damage to the heart, early asymptomatic heart failure, the heart releases these peptides, which really help maintain patients being asymptomatic. We've learned that they help maintain sodium balance, they help preserve heart function, they fight off hypertrophy and fibrosis. And so, these are very favorable hormones, ANP, BNP, and CNP, which is a part of this, as I said, coming from the endothelium.

A bradykinin is another important vasoactive peptide that's a vasodilator and works on the vascular wall in the endothelium to mediate vasodilation, and we've learned that adrenomedullin is also activated in heart failure and contributes to vasodilation. So, these three, the natriuretic peptide system, bradykinin, adrenomedullin, can be looked at as beneficial compensatory mechanisms in heart failure.

Now, what happens in progressive heart failure is that there is activation, as we said, of the sympathetic nervous system and also of the renin-angiotensin-aldosterone system, and they counteract, they fight against these beneficial hormones, so there becomes a pathologic imbalance.

Dr. Mennen:
As we know, a number of counterregulatory neurohormonal systems become activated in heart failure to blunt the vasoconstricting neurohormones. These include vasodilatory prostaglandin E2, prostacyclin, and the natriuretic peptides. Can you talk a bit about how the natriuretic peptides are activated?

Dr. Burnett:
These vasoactive peptides are activated primarily from a mechanical stimulation. So, in the heart, as the heart begins to fail in heart failure and there's increased pressure in the heart, the heart muscle is
stretched. And these hormones are made in the heart muscle or the myocyte, and when the myocyte is stretched, it activates the production and the release of ANP and BNP.

Dr. Mennen:
We are nearing the end of our time, but do you have any closing thoughts, summaries, or comments for the audience?

Dr. Burnett:
Yes, I do. I think that I'd like to just close by saying we've learned a lot about neurohormonal systems in heart failure, particularly the deleterious systems such as the sympathetic nervous system and the renin-angiotensin-aldosterone system. On the other hand, we've learned the beneficial and protective roles of the natriuretic peptide system and other vasoactive peptides like adrenomedullin and bradykinin.

Dr. Mennen:
Dr. Burnett, thank you so much for speaking with me today.

Dr. Burnett:
You're welcome.

Narrator:
You've been listening to ReachMD. This segment entitled, The Neurohormonal Imbalance of Heart Failure: Recent Advances in Our Understanding of the Underlying Pathophysiology of Heart Failure is sponsored by Novartis Pharmaceuticals Corporation. The views expressed in this interview reflect the views of Dr. Burnett. If you missed any part of this discussion, please visit ReachMD.com/neurohormonal. That's ReachMD.com/neurohormonal. Thank you for listening.

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