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Which Signaling Pathways Are Disrupted During a Worsening Heart Failure Event?

Announcer: This is ReachMD. Welcome to *Spotlight on Worsening Heart Failure Events*. This program, titled "Which Signaling Pathways Are Disrupted During a Worsening Heart Failure Event?," is brought to you by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., and is intended for health care professionals in the United States. Here is your host, Dr. Javed Butler.

Moderator (Dr. Javed Butler): Hello, and welcome to the part 3 of our podcast series *Spotlight on Worsening Heart Failure Events.* I am **Dr. Javed Butler** from the University of Mississippi, and I am joined by **Dr. Robert Mentz** from Duke University and **Dr. Bill Colucci** from Boston University. Today, we will take a close look at the signaling pathways that are disrupted in worsening heart failure events. **Rob**, what do we know about the underlying pathophysiology of worsening heart failure events?

Dr. Robert Mentz: So, I'd like to first ground us all in the physiology of heart failure. Heart failure is characterized by systemic and renal vasoconstriction, as well as myocardial remodeling.[3] So, myocardial dysfunction results in decreased left ventricular pump function, which reduces cardiac output.[4] When this happens, the body compensates by activating neurohormonal systems, initially the sympathetic nervous system, or SNS, and the renin-angiotensin-aldosterone system, or RAAS, in order to restore cardiac output and supply enough oxygen to meet the increasing demands.[4,5] So, the SNS is a compensatory mechanism that stimulates beta-adrenergic receptors and funny channel activity in the sinoatrial node. So, this increases heart rate, contractility, and vasoconstriction.[6,7] An increased activity in the SNS, it contributes to the pathophysiology of heart failure through various mechanisms involving the cardiac, renal, and the vascular systems.[5] So, in the heart itself, this increased SNS activity leads to myocyte hypertrophy, necrosis, apoptosis, and fibrosis.[5,6] And in the kidneys, you will see vasoconstriction, activation of the RAAS, increase in salt and water retention, and an attenuated response to natriuretic peptides.[5,6]

Moderator (Dr. Javed Butler): Thank you, **Rob**, for this explanation. **Bill**, can you elaborate further on the activity of the renin-angiotensin-aldosterone system during a worsening heart failure event?

Dr. Wilson Colucci: Certainly. As **Rob** mentioned, the RAAS is a system that plays a central role in worsening heart failure events.[3] Activation of the RAAS increases the production of renin, angiotensin II, and aldosterone, which leads to vasoconstriction, sodium reabsorption, and fluid retention.[6,8] Angiotensin II, as the main product of the RAAS, is involved in regulating fluid volume and electrolytes, both of which have important consequences for the pathophysiology of heart failure.[4] While stimulation of the RAAS may be of value during an acute response, the chronic activation of this system is maladaptive.[3,9] In this scenario, the circulatory system is subjected to excessive vasoconstriction in the setting of increased blood volume. The resulting increase in vascular load puts additional strain on the patient's heart.[4,5]

Moderator (Dr. Javed Butler): It's a terrible cascade of events. **Rob**, you briefly mentioned natriuretic peptides previously. Could you explain the role of natriuretic peptide system, or NPS, in worsening heart failure events?

Dr. Robert Mentz: Sure, **Javed**. There are a number of feedback mechanisms that become activated in heart failure in order to offset the deterioration caused by chronic activation of the SNS and RAAS.[3,5] The natriuretic peptide system, or NPS, is one counterregulatory neurohormonal mechanism. So, under physiologic conditions, natriuretic peptides are released in response to an increase in atrial and myocardial stretching.[3,5] And once released, these peptides act on the kidneys and on the peripheral circulation to decrease the cardiac load by increasing excretion of sodium and water through peripheral vasodilation.[5,6] There is a loss of response in the NPS over

time, and it's this loss of response that results in ongoing vasoconstriction and fluid retention.[3,5]

Dr. Wilson Colucci: I would like to add that the impairment of the NPS also leads to lower production of the secondary messenger cyclic guanosine monophosphate, or cGMP, which is a regulator of cardiac and vascular tissue function.[5,10] Another source of cGMP is the activation by nitric oxide of the enzyme soluble guanylate cyclase, or sGC. During heart failure, low levels of nitric oxide reduce the activity of sGC, which then contributes to cGMP deficiency.[10,11] This disruption in the nitric oxide–soluble guanylate cyclase–cGMP pathway may contribute to adverse ventricular remodeling, as well as vascular and myocardial dysfunction.[3,11]

Moderator (Dr. Javed Butler): Thank you for the interesting discussion, Doctors Mentz and Bill Colucci. And we will leave it at that. To quickly summarize our discussion: today, we learned about the relevant pathways that may be involved in worsening heart failure events, in particular the activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system, which are normally counteracted by the NPS or natriuretic peptides.[3,5] As heart failure worsens, the activity of the NPS is blunted, resulting in vasoconstriction and fluid retention.[3,5] In addition, we learned that the NO-sGC-cGMP pathway can lead to further progression and worsening of heart failure events and lead to decreased cGMP synthesis, resulting in progression and worsening of chronic heart failure.[11] If you haven't done so, please make sure to listen to our two previous episodes in this series, where we discuss the importance of identifying patients with chronic HFrEF, who are at risk of experiencing worsening heart failure events, and the poor outcomes associated with this progression. Thank you for tuning in.

Announcer: This program was brought to you by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. If you missed any part of this discussion or to find others in this series, visit ReachMD.com/HFEvents. This is ReachMD. Be part of the knowledge.

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