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The Role of Splanchnic Congestion and the Intestinal Microenvironment in the Pathogenesis of Advanced Heart Failure

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Abstract

Purpose of review: Right-sided heart failure (HF), which is often present in the setting of advanced HF, is associated with cardiac cachexia, the cardiorenal syndrome, and adverse outcomes. Improved understanding of venous congestion of the splanchnic circulation, which may play a key role in the pathogenesis of right-sided HF, could lead to novel therapeutics to ameliorate HF. Here we provide an overview of right-sided HF, splanchnic hemodynamics, fluid homeostasis, and the intestinal microenvironment. We review recent literature to describe pathophysiologic mechanisms and possible therapeutics.

Recent findings: Several possible mechanisms centered around upregulation of sodium-hydrogen exchanger-3 (NHE3) may form a causal link between right ventricular (RV) dysfunction, splanchnic congestion, and worsening HF. These include: (1) an anaerobic environment in enterocytes, resulting in reduced intracellular pH; (2) increased sodium absorption by the gut via NHE3; (3) decreased pH at the intestinal brush border thus altering the gut microbiome profile; (4) increased bacterial synthesis of trimethylamine N-oxide; and (5) decreased bacterial synthesis of short-chain fatty acids causing abnormal intestinal barrier function.

Summary: Splanchnic congestion in the setting of right-sided HF may serve an important role in the pathogenesis of advanced HF, and further exploration of these mechanisms may lead to new therapeutic advances.

Keywords

heart failure; right ventricle; NHE3; cardiorenal syndrome; splanchnic circulation

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Introduction

Multiple studies have demonstrated signs of right-sided heart failure (HF) such as right ventricular [RV] dysfunction, pulmonary hypertension, or central venous congestion are associated with cardiac cachexia, worsening renal function, and a poor prognosis in patients with HF [1, 2]. While it is apparent that RV failure and associated central venous congestion play an important role in the pathogenesis of HF, the exact mechanisms underlying the association of right-sided HF and poor outcomes are not clear. One specific organ system that may be central to the pathogenesis of right-sided HF is the gastrointestinal tract. Splanchnic venous congestion, precipitated by RV failure, may play a causal role in disease progression by: (1) altering the regulation of sodium absorption in the gut via the sodium-hydrogen exchanger-3 (NHE3); (2) reducing the intestinal barrier function, thus increasing systemic inflammation and predisposing to systemic infections; (3) changing the intestinal microenvironment to favor bacteria that are pro-inflammatory and reducing bacteria that secrete short chain fatty acids (SCFAs), which may be protective; and (4) altering phosphate homeostasis which has implications for cardiorenal interactions. Here we review the role of venous congestion, splanchnic hemodynamics, and the intestinal microenvironment in the setting of right-sided HF and discuss possible mechanisms of pathogenesis that may elucidate novel therapeutic targets for this high-risk patient population with few available treatment options.

The importance of venous congestion in heart failure

Venous congestion is considered a hallmark of HF, and diuretic therapy targeted to reduce venous congestion is a cornerstone of HF treatment. However, despite the knowledge that venous congestion is common in HF, it is relatively underappreciated as a key factor in the pathogenesis of HF. For example, systemic complications of advanced HF including renal failure and cardiac cachexia have historically been attributed to decreased arterial perfusion of relevant organs (due to low cardiac output), leading to ischemia and decreased organ function. However, the evidence for such an association is lacking. Data from multiple studies suggests that increased central venous pressure (i.e., venous congestion) is a major pathogenic factor in HF progression. By reducing the arterial-venous pressure gradient across multiple organs, venous congestion reduces perfusion and leads to organ dysfunction.

In a study to examine the association of various hemodynamic variables with worsening renal function (WRF) in the setting of acute decompensated HF (ADHF), Mullens et al. [3] prospectively enrolled 145 consecutive patients admitted for ADHF to an intensive care unit dedicated to HF. All patients (mean left ventricular ejection fraction [LVEF] $20 \pm 8\%$) underwent pulmonary artery (PA) catheter-guided therapy by an experienced HF cardiologist. The primary outcome, WRF, was defined as an increase of serum creatinine 0.3 mg/dL during the HF hospitalization. The authors compared those who developed WRF compared to those who did not and found that there were no differences were observed between groups in terms of B-natriuretic peptide level, heart rate, systolic blood pressure, PA systolic pressure, pulmonary capillary wedge pressure, or cardiac index ($p > 0.05$ for all comparisons). Of the hemodynamic variables, only elevated central venous pressure (CVP) at baseline ($p < 0.001$), and follow-up ($p = 0.04$), were observed to be associated with WRF

while reduced cardiac index was not. This study suggests there may be mechanisms of WRF directly related to venous congestion. Besides increasing afterload on the kidney, elevated renal venous pressure (due to high CVP) could lead to increased renal interstitial pressure, which may also compromise renal perfusion and renal function.

Thus, venous congestion may not simply be a physical exam finding that denotes a high-risk patient; rather it may be integral in the pathogenesis of WRF and HF. Furthermore, these findings suggest that increased CVP may prove to be a pathogenic cause of other extra-cardiac organ dysfunction, such as the gastrointestinal tract, in patients with HF.

Sodium-hydrogen exchanger-3 (NHE3) and sodium balance

The gastrointestinal system was previously believed to be a bystander in patients with heart disease, but it is now known that the gut is likely involved in the pathogenesis of several cardiovascular syndromes, including HF. It is well known that deranged body fluid homeostasis is extremely important in HF, and a pathological driving mechanism to symptoms and disease progression related to fluid retention by the kidney. However, along with the kidney, the gastrointestinal system secretes and reabsorbs several liters of fluids on a daily basis, a process that is closely regulated by a series of ion channels and pumps elegantly regulated to maintain homeostasis. Perturbations in this homeostatic process, well observed in diarrheal illness, may cause severe fluid and electrolyte derangements in the setting of HF.

NHE3 has been identified as a major regulator of sodium and fluid balance in the intestines [4-6]. As a major regulator of fluid homeostasis in the gut, NHE3 is a closely regulated transporter. Several mechanisms of increased expression or activation have been identified, including factors known to be increased in HF such as aldosterone, angiotensin II, and catecholamines, but also glucocorticoids, and reduced intracellular pH [7-10]. Increased expression or activity of NHE3 may lead to at least two direct detrimental consequences related to HF progression. First, increased NHE3 expression and activity may cause an increase in sodium absorption by the gut, worsening the problem of sodium loading in HF. Second, as sodium absorption is increased, hydrogen ions are exchanged into the gut lumen, decreasing the local pH of the gut and altering the intestinal microenvironment, potentially resulting in shifts in the intestinal microbiome. These changes in the intestinal microenvironment may important implications for downstream cardiovascular and even non-cardiovascular risk, as summarized below.

Short-chain fatty acids (SCFAs), intestinal barrier function, and hemodynamics

Gut microbiota can interact with the host through different pathways, including the SCFA pathway and the trimethylamine N-oxide (TMAO) pathway. SCFAs, including butyrate, propionate, and acetate, are small molecules that are supplied by either a diet rich in fiber and leafy green vegetables, or actively synthesized and secreted by symbiotic bacteria living in the intestinal brush border [11]. Butyrate, which is known to be secreted by gut bacteria and absorbed by the intestinal epithelial cells, is thought to be the preferred metabolic

substrate for the gut epithelium [12]. An important mechanism relating gut barrier function and butyrate has been identified via a mechanism through hypoxia-inducible factor (HIF), a polypeptide signaling molecule that is required for the production and maintenance of several enterocyte barrier proteins [13]. Activation of HIF is modulated by two primary mechanisms: (1) normal blood circulation of each intestinal microvillus is structured as a plexus, and physiologic shunting occurs at the villus base causing a relative hypoxic microenvironment at the villus tip; and (2) butyrate, synthesized by bacteria or ingested, is absorbed by the enterocytes and enters the mitochondria and activates a mitochondrial pathway to lower the oxygen concentration in the cytoplasm, thereby also activating HIF, which regulates gene expression of important barrier proteins, including intercellular proteins and mucin production [14].

Although right-sided HF and splanchnic congestion may lead to increased hypoxia in the intestinal microvillus, thereby increasing activation of HIF, bacteria that generate SCFAs such as butyrate, may be downregulated by the increasingly acidic gut luminal microenvironment which leads to HIF destabilization and subsequent impairment of gut barrier function, leading to increased translocation of endotoxin and increased susceptibility to systemic infections.

SCFAs also have demonstrated a role in regulation of hemodynamics. Pluznick et al. identified two novel SFCA-associated receptors that altered blood pressure homeostasis, G protein coupled receptor 41 (Glf41), and olfactory receptor 78 (Olfr78) [15, 16]. These receptors, present on arteriolar smooth muscle cells, are directly activated by SCFAs circulating through the blood, and elicit smooth muscle relaxation. Moreover, Glf41 has also been identified within the juxtaglomerular apparatus, and may play an important role in the regulation of the renin-angiotensin-aldosterone system [15, 16]. Thus, a lack of SCFAs, which may be present in patients with right-sided HF, could lead to local vasoconstriction thereby exacerbating hemodynamic derangements in the setting of HF.

Although the aforementioned receptors could affect vascular smooth muscle in HF patients, they are not present in the heart. However, SCFAs may also directly affect the heart. Acetate, an SCFA produced by a high-fiber diet, was found in a small animal model of hypertension to significantly reduced blood pressure, cardiac fibrosis, left ventricular hypertrophy, and renal fibrosis when added as supplement to the diet [17]. In this study, acetate dietary supplementation led to downregulation of cardiac and renal *Egr1*, which is known to be involved in maladaptive cardiac hypertrophy and fibrosis, renal fibrosis, and inflammation, all of which are present in advanced HF [17]. In patients with right-sided HF, alteration of the gut microbiome due to changes in the gut lumen pH and microcirculation could lead to a loss of acetate production by gut microbiota, thereby worsening cardiac and renal fibrosis.

Trimethylamine-N-oxide (TMAO)

Trimethylamine-N-oxide (TMAO) is another small gut-derived biomolecule, generated from dietary nutrients that possess a TMA moiety (choline, phosphatidylcholine, N-carnitine). Several studies have found serum TMAO is associated with increased incidence of myocardial infarction, HF, and cardiovascular mortality [18-23]. Tang et al. recently showed

that increased circulating TMAO levels are associated with an increased rate of 5-year mortality in patients with HF [24]. Tang and colleagues have also demonstrated that plasma TMAO levels are elevated in patients with chronic kidney disease, and is associated with worse prognosis in these patients [22]. Thus, increased TMAO may be a major factor underlying progression of HF and the cardiorenal syndrome.

The mechanism that TMAO exerts its effects in humans has been partially described, and is recognized to function as a pro-thrombotic molecule [25, 26]. Organ and colleagues conducted a study in which they fed surgical aortic constriction pressure-overloaded mice a control, choline, or TMAO supplemented diet for 12 weeks found that the mice fed TMAO or choline had significantly worse pulmonary edema, LVEF, cardiac mass, and cardiac fibrosis when compared to controls [18]. These findings suggest that the TMAO pathway enhances HF susceptibility and may accelerate the progression of HF, through the development of adverse ventricular remodeling. In an animal model, chronic dietary-induced increases in TMAO were also associated with increased renal fibrosis [22]. Whether the gut luminal changes associated with splanchnic congestion leads to increased TMAO remains to be determined.

Bacterial invasion in the gut

The human gastrointestinal tract is an important component of host defenses. The gut is continuously exposed to potentially pathogenic bacteria, protozoa, and viral infectious agents which pass through its lumen. In advanced cirrhosis, portal venous pressures are increased due to an outlet obstruction imposed by a cirrhotic liver. Studies have demonstrated improved hemodynamics and reduced progression to cardiorenal syndrome in advanced cirrhosis when taking rifaximin, an oral non-absorbable antibiotic, believed to be secondary to the eradication of pathologic organisms in the gut lumen [27-29]. In HF, increased serum endotoxin concentrations have been observed [30]. It is believed in HF patients with liver dysfunction secondary to RV failure, venous congestion causes poor clearance of bacterial toxins and activation of the inflammatory cascade [31-33].

It is known that inflammation, as measured by high sensitivity c-reactive protein, is incrementally associated with increased risk of CVD, and reducing that risk with anti-inflammatory therapeutics improves mortality [34, 35]. GutHeart, a randomized, open-label, controlled trial is currently studying the potential benefits of rifaximin on stable HF patients with a left ventricular ejection fraction (LVEF) < 40%, compared to a probiotic, and to no treatment (control). The primary endpoint is baseline-adjusted LVEF as measured by echocardiography after 3 months [36]. Reducing the burden of inflammation by preventing bacterial translocation and gut inflammation may be a novel approach to reduce the onset of the inflammatory cascade, and this trial is likely to highlight the role of the gut microbiota in HF.

Splanchnic congestion and the intestinal microenvironment in heart failure

The detrimental effects of visceral congestion—particularly splanchnic congestion—in HF are poorly understood. Here we propose several potential mechanisms through which

splanchnic congestion may contribute to worsening HF, increased venous congestion, renal dysfunction, and ultimately, adverse outcomes (Figure 1). Elevated venous pressure reduces the arterial-venous pressure gradient across the intestinal capillary network. The microstructure of the intestinal villus forms a plexus, an ideal structure to optimize nutrient absorption, but also susceptible to shunting of oxygenated blood through the base of the villus, placing the villus tip at risk of a relative ischemia. This relative ischemia creates a unique microenvironment for the enterocyte in the setting of HF. First, the anaerobic conditions imposed by splanchnic congestion may produce an intracellular and regional acidosis. Intracellular acidosis is a known activator of NHE3, which, as noted above, is the major ion channel regulating sodium absorption in the intestines. Increased absorption of sodium would be counter-productive in the setting of HF, increasing volume overload, worsening venous congestion, and contributing to dysfunction of other organs such as the liver and kidney (and ultimately leading to adverse outcomes in HF).

Second, acidotic conditions within the enterocytes are extended to the intestinal brush border through normal mechanisms of homeostasis via NHE3-induced shifting of hydrogen ion load to the gut lumen. The reduced pH in the gut may alter the bacterial flora of the brush border in a way that is deleterious to SCFA-producing bacteria, and promote the growth of species which secrete TMAO. The shift in these novel regulatory biomolecules may prove deleterious to the decompensated HF patient. TMAO has been shown to be increased in patients with worsening HF, and has been shown to be associated with a pro-atherosclerotic state. Moreover, SCFAs have recently been demonstrated to function as vasodilators and reduce peripheral vascular resistance. Reduction in serum SCFA is associated with worsening HF and elevated blood pressure in non-HF patients. Diets high in fiber, promoting SCFAs production, have proved to lower the risk of both all-cause deaths, and cardiovascular deaths [37]. Identifying the how these patients become predisposed to these adverse biochemical profiles may help slow the progression of HF in patients with severe HF, RV dysfunction, and venous congestion.

Third, both ischemia and relative depletion of SCFAs can destabilize HIF, an enterocyte regulatory protein which promotes normal barrier function of the gut. Loss of the gut-blood barrier allows gut-derived bacterial endotoxins to enter the blood, triggering a pro-inflammatory state which has been observed in acute HF patients [38], and endotoxemia and sub-clinical septic hemodynamic vasodilation which has been observed in acute decompensated HF. This period of vasodilation may actually improve the patient in the short term, however once the gut recovers and the vasodilatory proteins clear, a rebound vasoconstriction can occur, increasing late-systolic pulse-wave reflections and further cardiac compromise.

Furthermore, some studies have found increased levels of bacterial endotoxins within the blood of patients in ADHF, and may function as a causal factor for worsening renal function in these patients. In addition, some studies have shown that lipopolysaccharide (LPS) can directly regulate proteins in epithelial cells, including NHE3, and NHE8, a basolateral exchange protein involved in pH and Na⁺ balance [9].

Conclusions

Right-sided HF with resultant venous congestion is a common problem in advanced HF that is associated with cardiac cachexia, the cardiorenal syndrome, and adverse outcomes. Detrimental effects of increased venous pressure and splanchnic congestion in relation to the gut include: (1) relative ischemia on the intestinal microvillus, leaving enterocytes at the villus tip susceptible to ischemic injury, acidosis, and increased sodium absorption via NHE3, (2) gut environmental alterations predisposing the host to colonization with deleterious TMAO-producing bacteria instead of protective SCFA-producing bacteria; and (3) reduced gut barrier function and translocation of potentially pathogenic microorganisms and bacterial endotoxin. Taken together, these conditions may play an important role in the progression of HF that warrants further investigation.

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KEY POINTS

- Key point #1: Venous congestion—an important pathophysiologic determinant of outcomes in advanced heart failure—has been relatively underexplored compared to low cardiac output, but is likely critical in the development of cardiac cachexia, renal dysfunction, and adverse outcomes.
- Key point #2: Splanchnic congestion may be a key factor in the pathogenesis of advanced heart failure by leading to changes in the gut microenvironment that increase sodium-hydrogen exchanger-3 (NHE3) expression, thereby leading to increased sodium and fluid absorption and reduced pH of the gut lumen.
- Key point #3: Changes in the gut lumen induced by enhanced NHE3 on the surface of enterocytes lining the gut may result in changes in the gut microbiome, shifting the balance from protective bacteria that produce short chain fatty acids to deleterious bacteria that produce trimethylamine N-oxide, causing increased vasoconstriction and inflammation.

Figure 1. Conceptual Diagram of the Relationship Between Right-Sided Heart Failure, Splanchnic Congestion, the Intestinal Microenvironment and Adverse Outcomes, including Cachexia, Worsening Renal Failure, and Progression of Heart Failure

It is well known that right-sided HF and venous congestion is associated with increased risk of renal failure and death, however the exact mechanisms between these observations are less well known. Here we propose a potential pathophysiological mechanism to explain these associations. Right-sided heart failure causes venous congestion, which leads to splanchnic congestion. Venous congestion of the splanchnic vasculature causes reduced blood flow to the gut enterocytes, causing hypoxia and anaerobic metabolism in these cells. These conditions induce upregulation and increased activation of NHE3, inducing increased sodium absorption and decreased luminal pH at the brush border resulting in worsened volume overload, and a microbial dysbiosis. Microbial dysbiosis may result in an increased bacterial secretion of TMAO, reduced production of SCFAs, and worsening of systemic inflammation.