Journal of the American College of Cardiology
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 62, No. 6, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.04.070

STATE-OF-THE-ART PAPER

Abdominal Contributions to Cardiorenal Dysfunction in Congestive Heart Failure

Frederik H. Verbrugge, MD,*† Matthias Dupont, MD,* Paul Steels, MD,‡ Lars Grieten, PHD,*‡ Manu Malbrain, MD, PHD,§ W. H. Wilson Tang, MD,‖ Wilfried Mullens, MD, PHD*‡

Genk, Diepenbeek, and Antwerp, Belgium; and Cleveland, Ohio

Current pathophysiological models of congestive heart failure unsatisfactorily explain the detrimental link between congestion and cardiorenal function. Abdominal congestion (i.e., splanchnic venous and interstitial congestion) manifests in a substantial number of patients with advanced congestive heart failure, yet is poorly defined. Compromised capacitance function of the splanchnic vasculature and deficient abdominal lymph flow resulting in interstitial edema might both be implied in the occurrence of increased cardiac filling pressures and renal dysfunction. Indeed, increased intra-abdominal pressure, as an extreme marker of abdominal congestion, is correlated with renal dysfunction in advanced congestive heart failure. Intriguing findings provide preliminary evidence that alterations in the liver and spleen contribute to systemic congestion in heart failure. Finally, gut-derived hormones might influence sodium homeostasis, whereas entrance of bowel toxins into the circulatory system, as a result of impaired intestinal barrier function secondary to congestion, might further depress cardiac as well as renal function. Those toxins are mainly produced by micro-organisms in the gut lumen, with presumably important alterations in advanced heart failure, especially when renal function is depressed. Therefore, in this state-of-the-art review, we explore the crosstalk between the abdomen, heart, and kidneys in congestive heart failure. This might offer new diagnostic opportunities as well as treatment strategies to achieve decongestion in heart failure, especially when abdominal congestion is present. Among those currently under investigation are paracentesis, ultrafiltration, peritoneal dialysis, oral sodium binders, vasodilator therapy, renal sympathetic denervation and agents targeting the gut microbiota. (J Am Coll Cardiol 2013;62:485–95) © 2013 by the American College of Cardiology Foundation

The pathophysiology of advanced congestive heart failure (CHF) is complex and insufficiently elucidated. Historically, poor forward flow (i.e., low cardiac output), resulting in unrestrained neurohumoral up-regulation, has been considered the main culprit mechanism (1). However, growing evidence has emphasized the concurrent importance of backward failure (i.e., systemic congestion) in both in the pathophysiology and disease progression of CHF (2). Coexisting renal dysfunction often complicates the treatment of CHF and occurs more frequently in patients with increased cardiac filling pressures (3–8). Nevertheless, current pathophysiological models unsatisfactorily explain the detrimental link between congestion and cardiorenal function.

The abdominal compartment might contribute significantly to deranged cardiac as well as renal function in CHF. Abdominal symptoms of congestion are not uncommon in CHF, with constrictive pericarditis and restrictive cardiomyopathies being extreme examples in which splanchnic venous hypertension and the formation of ascites often occur. However, more subtle changes are generally overlooked and seldom recognized as potential drivers of disease progression. This review explores potential maladaptive derangements in the abdominal compartment that might affect cardiorenal efficiency in CHF. Further, emerging treatment strategies and potential new therapeutic targets, with a focus on the abdominal compartment, are discussed. A summary of the available evidence regarding this topic is provided in Table 1.

Components and Function of the Abdominal Compartment

The splanchnic vasculature: capacitance function and cardiac pre-load. Three splanchnic arteries (the celiac trunk and superior and inferior mesenteric arteries) supply all

From the *Department of Cardiology, Ziekenhuis Oost-Limburg, Genk, Belgium; †Doctoral School for Medicine and Life Sciences, Hasselt University, Diepenbeek, Belgium; ‡Biomedical Research Institute, Faculty of Medicine and Life Sciences, Hasselt University, Diepenbeek, Belgium; §Intensive Care and High Care Burn Unit, Ziekenhuis Netwerk Antwerpen, Campus St. Erasmus, Antwerp, Belgium; and the ‖Department of Cardiovascular Medicine, Heart and Vascular Institute, Cleveland Clinic, Cleveland, Ohio. Drs. Verbrugge, Grieten, and Mullens are researchers for the Limburg Clinical Research Program (LCRP) UHasselt-ZOL-Jessa, supported by the Foundation Limburg Sterk Merk (LSM), Hasselt University, Ziekenhuis Oost-Limburg and Jessa Hospital. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received January 20, 2013; revised manuscript received April 8, 2013, accepted April 17, 2013.

Abbreviations and Acronyms

ADHF = acute decompensated heart failure

ANP = atrial natriuretic peptide

cAMP = cyclic adenosine monophosphate

CHF = congestive heart failure

IAP = intra-abdominal pressure

abdominal organs with blood. Individual organ perfusion largely depends on pre-capillary arteriolar vascular tone. In contrast, post-capillary venules and veins all converge in the hepatic portal vein, which returns the blood to the effective circulatory volume after passage through the liver. In normal circumstances, splanchnic capacitance veins contain 25% of the total blood volume (9). As they pool and release blood in the face of a changing volume status, those veins play a crucial role in maintaining an optimal cardiac pre-load (10). Indeed, as much as 65% of blood volume added to an euvolemic circulatory system is buffered in the splanchnic vasculature without systemic hemodynamic effects (11). Under physiological circumstances, the transmural splanchnic venous pressure mimics changes in arterial blood flow (12). This means that if arterial flow decreases, elastic recoil of the veins mitigates the resulting decrease in pressure, and a driving force for expulsion into the systemic circulation is maintained (Fig. 1). Importantly, although splanchnic arterioles contain both α- and β_2-receptors that mediate vasoconstriction and vasodilation, respectively, the latter are not abundant in capacitance veins (13). Therefore, sympathetic stimulation through epinephrine and/or norepinephrine invariably causes venoconstriction, thereby reducing splanchnic capacitance and recruiting effective circulatory volume (10).

In CHF, because of backward failure and increased arteriolar vasoconstriction, a progressive shift of blood from the effective circulatory volume to splanchnic capacitance veins might be expected. Although this remains speculative, one could argue that splanchnic capacitance function ultimately becomes maladaptive in advanced CHF as a result of long-standing venous congestion and/or increased neurohumoral activation (14). Indeed, cardiac filling pressures generally start to increase ~5 days preceding an admission for acute decompensated heart failure (ADHF) (15,16). Although this can reflect a state of effective venous congestion as a result of the gradual build-up of volume, an equal proportion of patients gain <1 kg of weight during the week before admission (17). This suggests that transient venoconstriction, presumably because of increased sympathetic stimulation with redistribution of blood from (splanchnic) venous capacitance beds to the effective circulatory volume, is an alternative cause of increased cardiac filling pressures. Obviously, the relationship between intravascular pressure and volume is highly dynamic instead of simply linear, but the need for increased splanchnic congestion is a prerequisite before cardiac filling pressures start to increase.

The splanchnic microcirculation: lymph flow and interstitial edema. With few exceptions, Starling forces in the microcirculation favor continuous net filtration (18). Therefore, especially in the case of congestion with increased capillary hydrostatic pressure and resulting hyperfiltration, adequate lymph flow is key to preserve fluid homeostasis (Fig. 2, left). Physiologically, the interstitium exhibits low compliance, thereby driving excess fluid straight into the lymphatic system (19). Moreover, hydration of mucopolysaccharides in the interstitial matrix increases the hydraulic conductivity of the interstitium and expands the distribution volume of interstitial proteins, keeping their concentration low (20). As a result, hyperfiltration is met with increased lymph efflux. Importantly, because of solvent drag, lymph flow washes out interstitial proteins, which decreases interstitial colloid osmotic pressure and opposes increased filtration forces (18,21). Thus, a bidirectional interaction between net filtration rate and Starling forces is present.

However, once lymph efflux reaches a maximum rate, this delicate balance will change (Fig. 2, right). If the interstitial fluid with filtrated solutes is inadequately drained, protein-rich edema will form, expanding the interstitial compartment significantly (22). The interstitium now enters a high compliance state, which facilitates further edema accumulation (19).

Cardio-Abdominal-Renal Interactions in Congestive Heart Failure

Increased intra-abdominal pressure as a marker of abdominal congestion. In advanced CHF, inefficient natriuresis with progressive volume overload may ultimately lead to a state of systemic congestion with increased intra-abdominal pressure (IAP) if capacitance function of the splanchnic vasculature is insufficient and the splanchnic microcirculation unable to cope with congestion. IAP can easily be measured through a bladder catheter connected to a pressure transducer (23). Depending on body mass index and body position, normal IAP measurements in healthy adults are between 5 and 7 mm Hg (24). However, in 60% of patients admitted with advanced CHF, IAP exceeds this value (23). Remarkably, frank ascites is found in only a small subset of these patients, suggesting the presence of splanchnic venous and/or interstitial congestion as the reason for increased IAP. In critically ill patients, intra-abdominal hypertension (IAP ≥12 mm Hg) is a common cause of organ dysfunction (25). In advanced CHF, already small increases in IAP, in the range of 8 to 12 mm Hg, are associated with impaired renal function (23). Importantly, reversing increased IAP by decongestive therapy ameliorates serum creatinine in this setting, presumably by alleviating abdominal congestion (23,26).

The liver in CHF. Hepatorenal syndrome is a well-known complication of chronic liver disease caused by overzealous vasodilation of the splanchnic circulation, resulting in arterial underfilling and intense renal vasoconstriction (27). Liver dysfunction is frequent in CHF, related to backward failure and characterized by a predominantly cholestatic enzyme profile associated with disease severity and prognosis (28,29).

Table 1 Review of the Literature on Abdominal Alterations Underlying Cardiorenal Dysfunction in Congestive Heart Failure

First Author, Year (Ref. #)	Study Design	Main Findings
Studies linking (abdominal) congestion to worsening renal function		
Mullens et al., 2008 (23)	Prospective observational study of 40 patients with advanced heart failure	Elevated intra-abdominal pressure is frequent in advanced heart failure and related to renal dysfunction
Mullens et al., 2008 (26)	Prospective observational study of 9 patients with advanced heart failure	Paracentesis- or ultrafiltration-related decreases of intra-abdominal pressure are correlated with improved renal function
Nohria et al., 2008 (3)	Prospective randomized study of 433 patients with hemodynamic-guided therapy vs. clinical assessment alone	Correlation between right atrial pressure and serum creatinine
Damman et al., 2009 (4)	Retrospective data review of 2,557 patients with right heart catheterization	Central venous pressure >6 mm Hg associated with steep decrease in renal function
Mullens et al., 2009 (5)	Prospective observational study of 145 patients with advanced heart failure	Worsening renal function showed a strong correlation with central venous pressure, and was independent of cardiac index
Testani et al., 2010 (6)	Retrospective review of 141 heart failure patients with congestion assessed by echocardiography	Right ventricular failure leads to venous congestion and the relief of congestion likely drives improvement in renal function
Verhaert et al., 2010 (7)	Prospective observational study of 62 patients with advanced heart failure	Patients with right ventricular dysfunction that improves after decongestive treatment have a better outcome
Guglin et al., 2011 (8)	Retrospective data review of 178 patients with right heart catheterization	Renal dysfunction relates to high cardiac filling pressures and lower renal perfusion pressure
Studies suggesting volume redistribution as a cause for elevated cardiac filling pressure		
Adamson et al., 2003 (15)	Prospective, observational study of 32 heart failure patients with an implantable hemodynamic monitor	Right-sided cardiac filling pressures start to increase ~5 days preceding an admission for acute decompensated heart failure
Chaudhry et al., 2007 (17)	Nested case-control study of 134 heart failure patients followed by telemonitoring	Only 46% of patients presenting with acute decompensated heart failure gain >2 lb in weight
Zile et al., 2008 (16)	Substudy of COMPASS-HF study (N = 274)	The transition from chronic to acute decompensated heart failure is associated with a progressive increase in cardiac filling pressures
Studies on cardiohepatic interactions in heart failure		
Ahloulay et al., 1996 (33)	Animal study (rats)	Hepatorenal pathway through extracellular cyclic adenosine monophosphate influences natriuresis in the presence of ascites
Ming et al., 2002 (30)	Animal study (rats)	Decreased portal blood flow triggers sodium and water retention
Poelzl et al., 2012 (28)	Prospective observational study of 1,032 heart failure patients	Liver dysfunction is frequent in patients with congestive heart failure and prognostically important
Poelzl et al., 2013 (29)	Prospective observational study of 1,290 heart failure patients, including invasive hemodynamics in 253 patients	Renal and liver dysfunction are independent negative predictors of worse outcome in heart failure and related to congestion rather than impaired cardiac output
Studies on cardiosplenic interactions in heart failure		
Sultanian et al., 2001 (39)	Animal study (rats)	Atrial natriuretic factor increases splenic microvascular pressure and fluid extravasation
Hamza et al., 2004 (42)	Animal study (rats)	Decreased splenic blood flow triggers sodium and water retention
Studies on gut-derived hormones in heart failure		
Carrithers et al., 2000 (45)	Case-control study with 16 heart failure patients and 53 healthy individuals	Heart failure patients have an increased uroguanylin excretion, which has natriuretic properties and is produced by the gut
Narayan et al., 2010 (46)	Case-control study with 243 heart failure patients and 53 healthy individuals	Prouroguanylin and proguanylin levels are increased in patients with heart failure, especially in severe heart failure with concomitant renal dysfunction
Studies on impaired intestinal barrier function in heart failure		
Sandek et al., 2007 (50)	Prospective observation study of 22 patients with heart failure	Intestinal morphology, permeability, and absorption are altered in heart failure
Arutyunov et al., 2008 (51)	Case-control study with 45 heart failure patients and 18 healthy individuals	Patients with heart failure demonstrate collagen accumulation and dysfunctional mucosal barrier of the small intestine

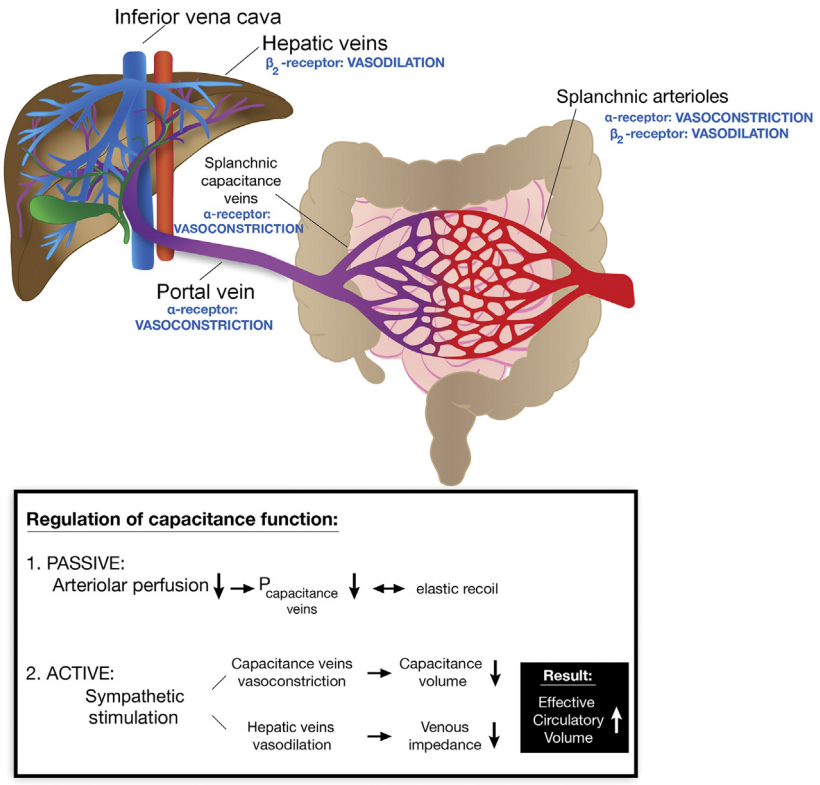

Figure 1 **The Splanchnic Vasculature: Capacitance Function and Cardiac Pre-load**

Splanchnic capacitance veins ensure a stable cardiac pre-load in the face of a changing volume status. First, if arteriolar perfusion drops, elastic recoil of the veins maintains a driving force for venous return. Second, sympathetic stimulation because of centrally perceived hypovolemia leads to α-mediated vasoconstriction of splanchnic capacitance veins, but β_2-mediated vasodilation of the hepatic veins. Consequently, autotransfusion from the splanchnic capacitance veins occur to increase the effective circulatory volume.

As advanced liver dysfunction negatively affects cardiorenal function, a vicious cycle might be created. In addition, it is notable that the portal vein contains α-adrenergic receptors but not β_2-receptors, whereas the latter are abundant in hepatic veins (13). As a result, sympathetic stimulation might be expected to decrease post-hepatic vascular resistance and shift blood to augment cardiac pre-load, which could be harmful in ADHF (Fig. 1). Moreover, data from animal studies show that decreased intrahepatic blood flow, as caused by α-adrenergic–mediated portal vasoconstriction, leads to accumulation of intrahepatic adenosine, which is produced by the metabolism of hepatocytes and leaves the liver through the lymphatic and venous systems (Fig. 3). Increasing local adenosine stimulates hepatic afferent nerve activity in rats, triggering a hepatorenal reflex as hepatic afferent nerves synapse on renal efferent nerves (30). This results in renal vasoconstriction, whereas sodium retention is promoted. Finally, some intriguing animal data from a rat model of ascites link cyclic adenosine monophosphate (cAMP) production by the liver to renal sodium homeostasis (31). cAMP, widely known as a second messenger, also acts as a distant messenger produced by the liver and regulating sodium reabsorption in the proximal renal tubules. Indeed, extracellular cAMP produced by hepatocytes in response to glucagon increases natriuresis and phosphate excretion in a dose-dependent manner in humans (32). Remarkably, this response is blunted in rats that have cirrhosis with ascites, possibly because of liver dysfunction (33). Therefore, liver congestion in CHF might directly contribute to a state of impaired natriuresis.

The spleen in CHF. The spleen, which constitutes an integral part of the splanchnic vasculature, receives ~5% of the cardiac output, making it a perfectly placed organ to regulate intravascular volume (34,35). The splenic vein joins the superior mesenteric vein to form the hepatic portal vein, allowing splenic hemodynamics to modulate splanchnic congestion. It has been shown that after volume expansion, fluid is accumulating in the gel-like lymphatic matrix within connective tissues surrounding the splenic vascular arcade (36). Importantly, fluid from this splenic lymphatic reservoir has the same protein content as splenic venous blood, which suggests that splenic capillaries are freely permeable to plasma proteins (36). Thus, intrasplenic extravasation of iso-oncotic fluid is directly dependent on intraluminal hydrostatic pressure and consequently related to congestion in the splanchnic vasculature (Fig. 4). Interestingly, atrial

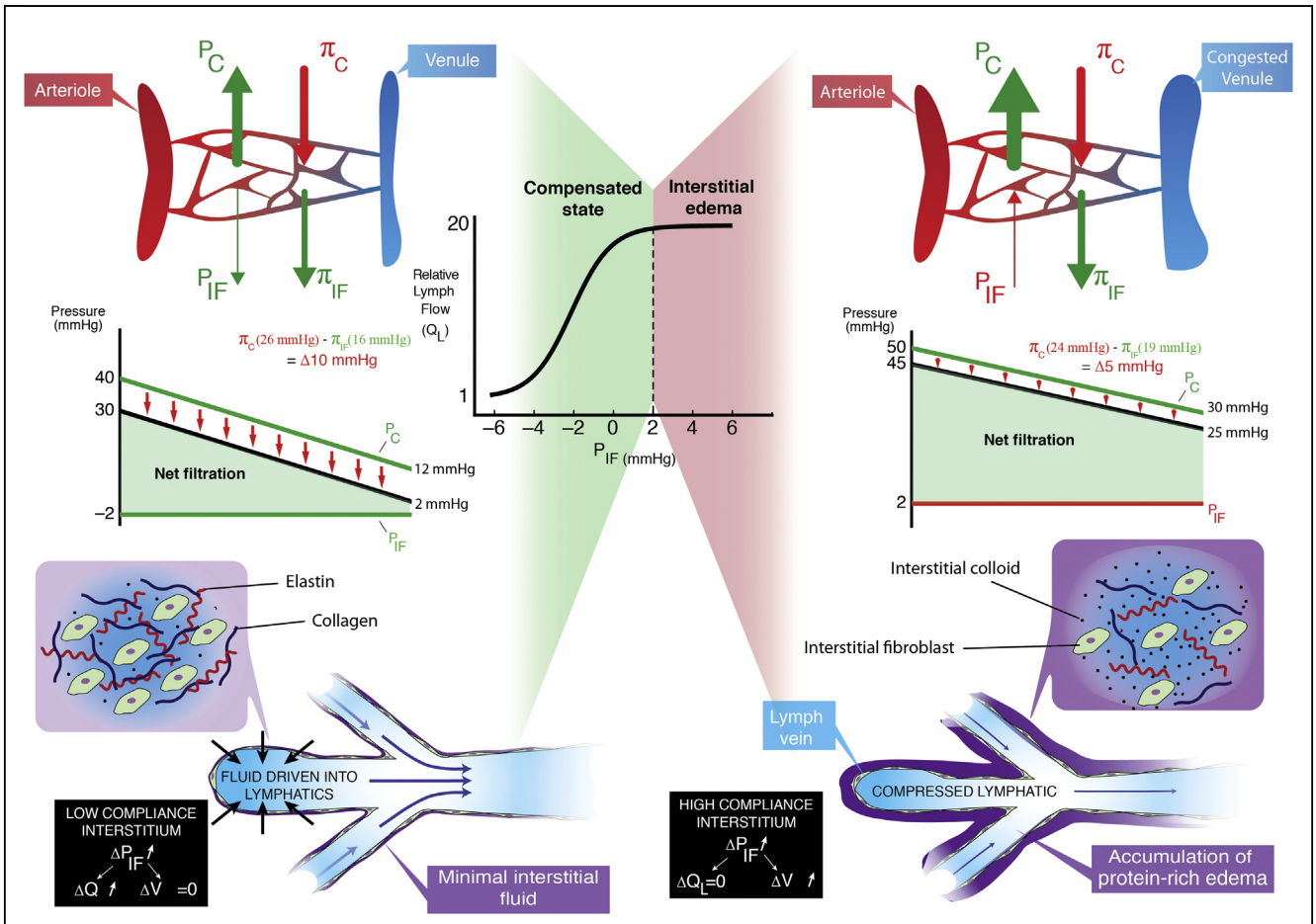

Figure 2 **The Splanchnic Microcirculation: Lymph Flow and Interstitial Edema**

Net filtration rate in the splanchnic microcirculation is determined by Starling forces: $(P_C - P_{IF}) - (\pi_C - \pi_{IF})$. P_C = capillary hydrostatic pressure; P_{IF} = interstitial fluid hydrostatic pressure; π_C = capillary oncotic pressure; π_{IF} = interstitial fluid oncotic pressure. **(Left, compensated state)**: P_C (35 to 45 mm Hg arteriolar to 12 to 15 mm Hg venular), P_{IF} (−2 mm Hg) and π_{IF} (16 mm Hg) all favor filtration **(green arrows)**, whereas π_C (25 to 28 mm Hg) opposes filtration **(red arrows)**. Therefore, net filtration prevails over the entire length of the splanchnic capillary with net filtration pressure decreasing from 32 mm Hg (arteriolar side) to 4 mm Hg (venular side). In case of congestion with increased P_C, net filtration pressure is even higher. Therefore, abdominal lymph flow (Q_L) is important to drain fluid and solutes. Normally, the interstitium exhibits low compliance. Thus, excess filtrated fluid is drained straight into lymphatic capillaries, allowing only a limited build-up of interstitial fluid volume (V_{IF}). Consequently, Q_L can increase as much as 20 times its normal value (22). Importantly, increased Q_L washes out interstitial proteins, which decreases π_{IF}, opposing filtration. In this state of compensated splanchnic congestion, increased net filtration because of increased P_C is met by enhanced Q_L, thereby preventing the accumulation of interstitial fluid. **(Right, interstitial edema)**: Once a critical flow is reached, Q_L cannot increase further. In addition, from a P_{IF} of ~2 mm Hg, the interstitium enters a high compliance state (19). Both lead to V_{IF} expansion. As lymph flow is now deficient in washing out interstitial proteins, protein-rich edema arises and compresses lymphatics, impeding lymph flow and promoting edema formation even further.

natriuretic peptide (ANP) infusions in rats cause hemoconcentration and a reduction in plasma volume that is not entirely explained by urinary losses alone (37). This observation, however, is virtually abolished in animals previously splenectomized (38). The reason for this phenomenon is that ANP alters splenic hemodynamics (i.e., increases intrasplenic pressure) by specific and direct actions on the splenic microvasculature (39). Although evidence is only preliminary, this might have important pathophysiological implications in CHF (Fig. 4). One could speculate that, initially, increased fluid efflux through the spleen into the lymphatic vasculature might help to reduce splanchnic congestion. However, in a more advanced state, especially when high ANP is present, a paradoxical reduction in effective arterial blood volume might develop, as continuous fluid efflux out of the intravascular space might exacerbate perceived central hypovolemia. At the same time, as splanchnic congestion worsens, intrasplenic microvascular pressure remains increased and fluid efflux out of the spleen continues in a vicious cycle, overloading the lymphatic system and leading to an accumulation of excess fluid in the perivascular third spaces. Indeed, CHF is the fourth most common cause of splenomegaly after hepatic disease, hematological disorders, and infection (40,41). Moreover, in this context, a splenorenal reflex, similar to the hepatorenal reflex, has been demonstrated (42).

Gut-derived hormones in CHF. Further supporting a role of the abdominal compartment in renal sodium handling and volume homeostasis are the peptides uroguanylin and guanylin. Both are involved in the regulation of water and electrolyte

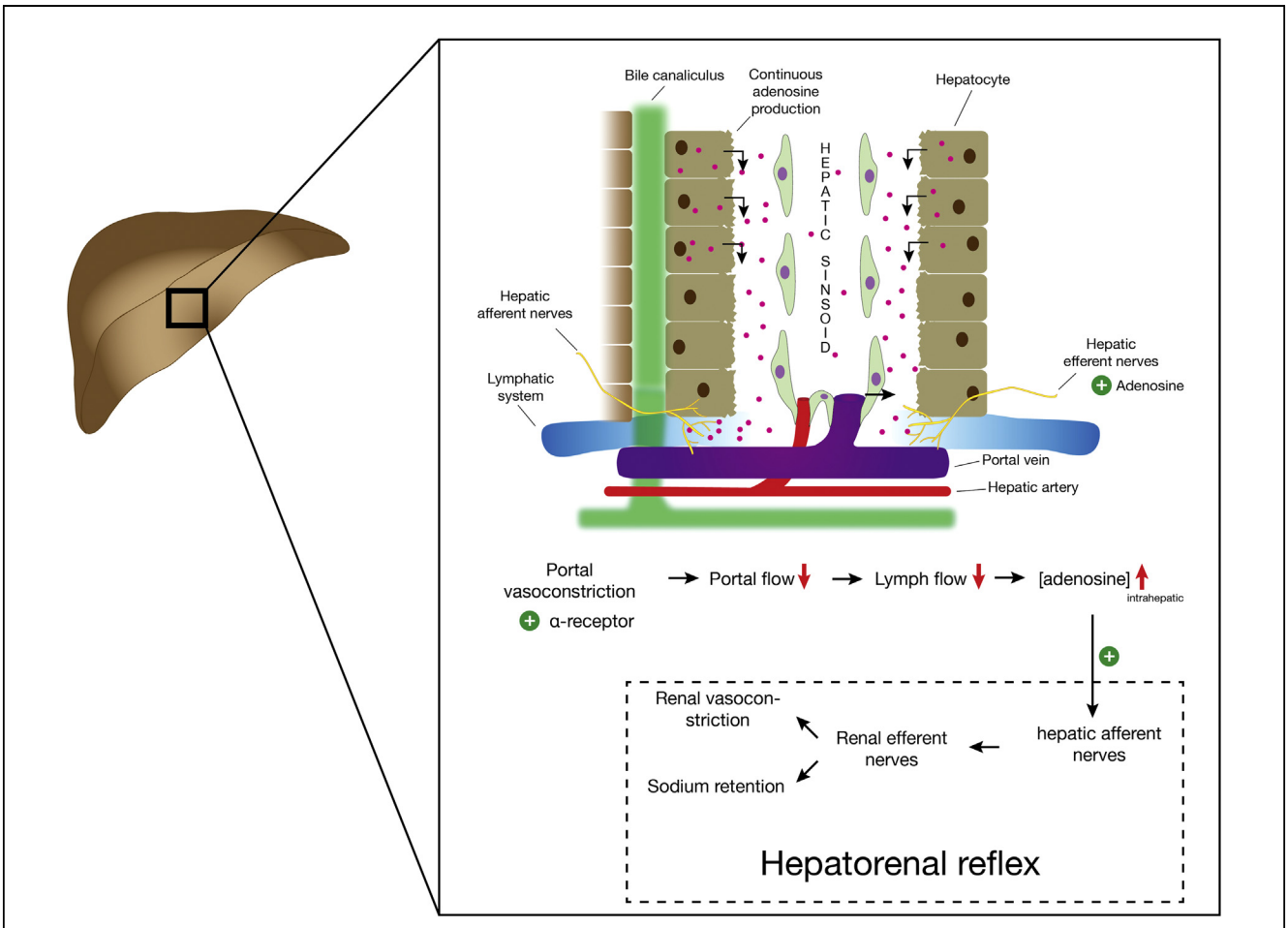

Figure 3 **The Liver in Congestive Heart Failure: Hepatorenal Reflex**

Hepatocytes continuously produce adenosine as a byproduct from the breakdown of adenosine triphosphate. Adenosine accumulates in the perisinusoidal space, which is drained by the lymphatic system. When portal blood flow is reduced because of α-receptor–mediated vasoconstriction, lymph flow will decrease and intrahepatic concentrations of adenosine increase. As a result, hepatic afferent nerves are stimulated, which subsequently synapse on renal efferent nerves. Consequently, renal vasoconstriction and sodium retention are promoted.

transport in the gut and share natriuretic properties mediated by a cyclic guanosine monophosphate–dependent mechanism (43). Their role in regulating the sodium balance via an intestinal-renal pathway has been demonstrated, as it is observed that an oral sodium intake evokes more rapid natriuresis than an equivalent intravenous load (44). Urinary excretion of uroguanylin is increased in patients with CHF, whereas increased plasma levels of the precursor proteins proguanylin and prouroguanylin are correlated with the severity of CHF symptoms assessed by New York Heart Association functional class (45,46). Thus, analogous to the congested heart producing ANP and B-type natriuretic peptide, there seems to be an intestinal natriuretic peptide that is increased in patients with CHF who presumably have abdominal congestion. Yet, the exact pathophysiological role of uroguanylin and guanylin in CHF remains to be determined.

The gut in CHF: the intestinal barrier function, gut microbiota, and uremic toxicity. Arterioles, capillaries, and venules have a peculiar organization in the intestinal microcirculation, forming a countercurrent system that strongly resembles the vasa recta of the renal medulla (Fig. 5A) (47). As a result, the intestinal villus can build up an interstitial concentration gradient with the highest osmolality at its tip, which is needed for continuous fluid absorption. However, a drawback of this system is that arteriolar oxygen short circuits to venules before reaching the villus tip, making this place particularly susceptible to anoxic damage (47). Because of low perfusion (i.e., low cardiac output), congestion (i.e., increased central venous pressure), and increased sympathetic vasoconstriction, CHF patients are at risk of nonocclusive bowel ischemia (Fig. 5B) (48). Importantly, the combination of hypoxia and local production of lipopolysaccharides by gram-negative bacteria residing in the gut lumen causes an increase in the paracellular permeability of the intestinal wall (49). Indeed, it has been shown that the intestinal morphology, permeability, and function are substantially altered in CHF, especially in advanced states with cardiac cachexia (50,51). Moreover,

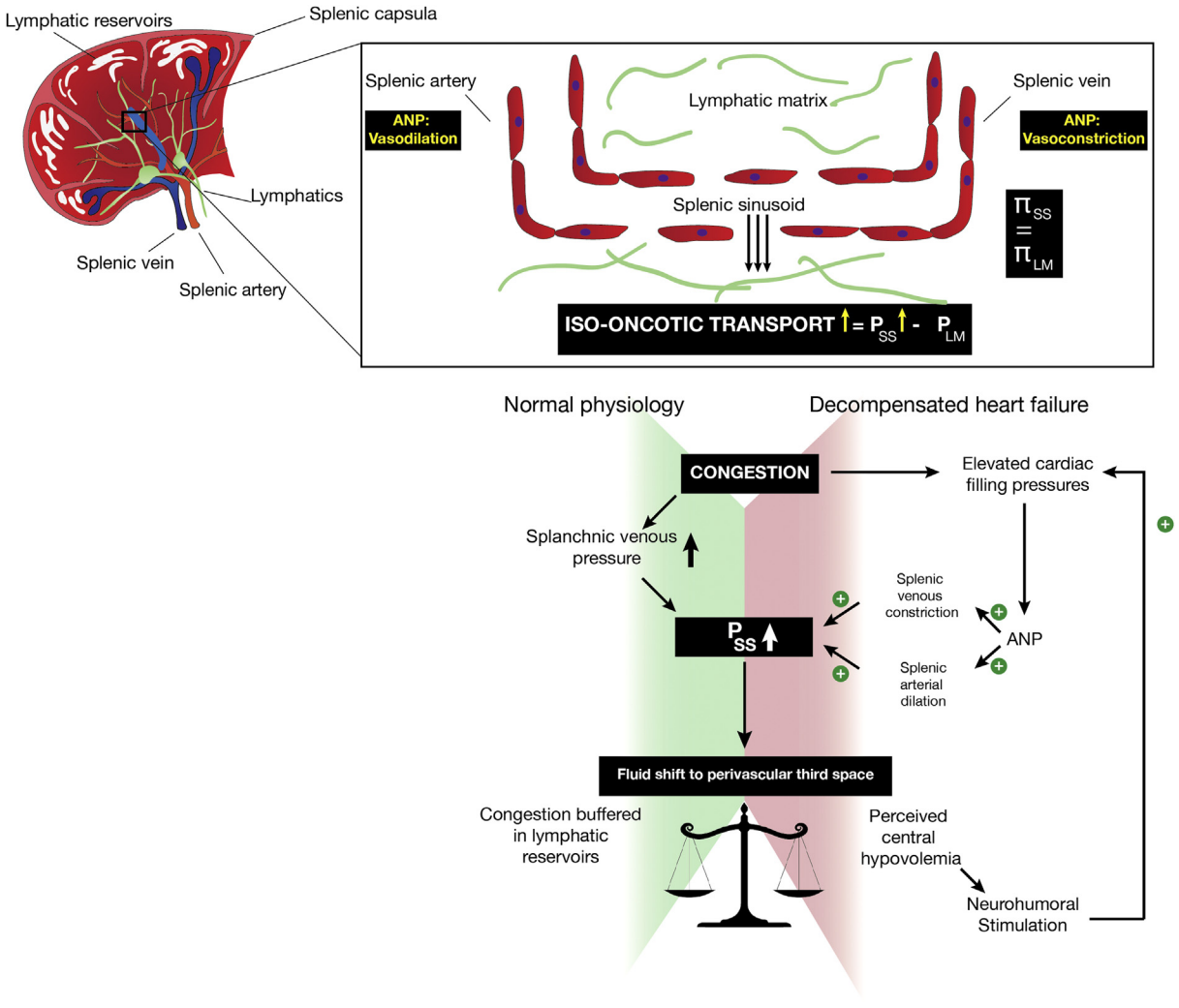

Figure 4 **The Spleen in Congestive Heart Failure: A Regulator of Intravascular Volume**

Splenic sinusoids are freely permeable to plasma proteins. As a result, the colloid osmotic pressure inside the splenic sinusoids is the same as in the surrounding lymphatic matrix, and fluid transport between the 2 spaces is determined by differences in hydrostatic pressure. Transient congestion of the splanchnic venous system results in an increased hydrostatic pressure inside the splenic sinusoids. Therefore, more fluid is drained to the lymphatic matrix and buffered inside the lymphatic reservoirs of the spleen. However, especially in the presence of increased cardiac filling pressures and resulting atrial natriuretic peptide (ANP) production, splenic arterial vasodilation, and venous vasoconstriction greatly enhance the fluid shift to the perivascular third space inside the spleen. This might lead to perceived central hypovolemia, exacerbating neurohumoral stimulation and creating a vicious cycle. Moreover, the lymphatic system becomes overloaded, which results in interstitial edema. P_{LM} = lymphatic matrix hydrostatic pressure; P_{SS} = splenic sinusoidal hydrostatic pressure; π_{LM} = lymphatic matrix colloid osmotic pressure; π_{SS} = splenic sinusoidal colloid osmotic pressure.

concomitant uremia caused by renal dysfunction alters the bacterial colonization of the gut and may also contribute to increased intestinal permeability (52,53). It has been demonstrated that microbiota are the cause of fermentation processes in the gut, which produce protein-bound uremic toxins that are ineffectively cleared from the circulation in cases of renal dysfunction (54,55). Moreover, lipopolysaccharide in the circulation triggers systemic inflammation and cytokine generation (i.e., tumor necrosis factor-α, interleukin-6), which results in depression of excitation-contraction coupling, decreased peak velocity of cardiomyocyte shortening, disturbed mitochondrial respiration, and impaired substrate metabolism in cardiomyocytes (56–58).

New Diagnostic Opportunities

From a clinical point of view, it is obvious that despite aggressive diuretic therapy and treatment with neurohumoral blockers, a subset of patients present with persistent signs and symptoms of congestion. Although the presence of frank ascites clearly represents the most extreme side of a spectrum, abdominal congestion remains difficult to evaluate at the bedside. As explained, IAP is potentially a useful surrogate marker for abdominal congestion and can easily be measured via a bladder catheter connected to a pressure transducer (23). Noninvasive alternatives for patients without a bladder catheter have emerged in the field of laparoscopic surgery, but

JACC Vol. 62, No. 6, 2013
August 6, 2013:485–95

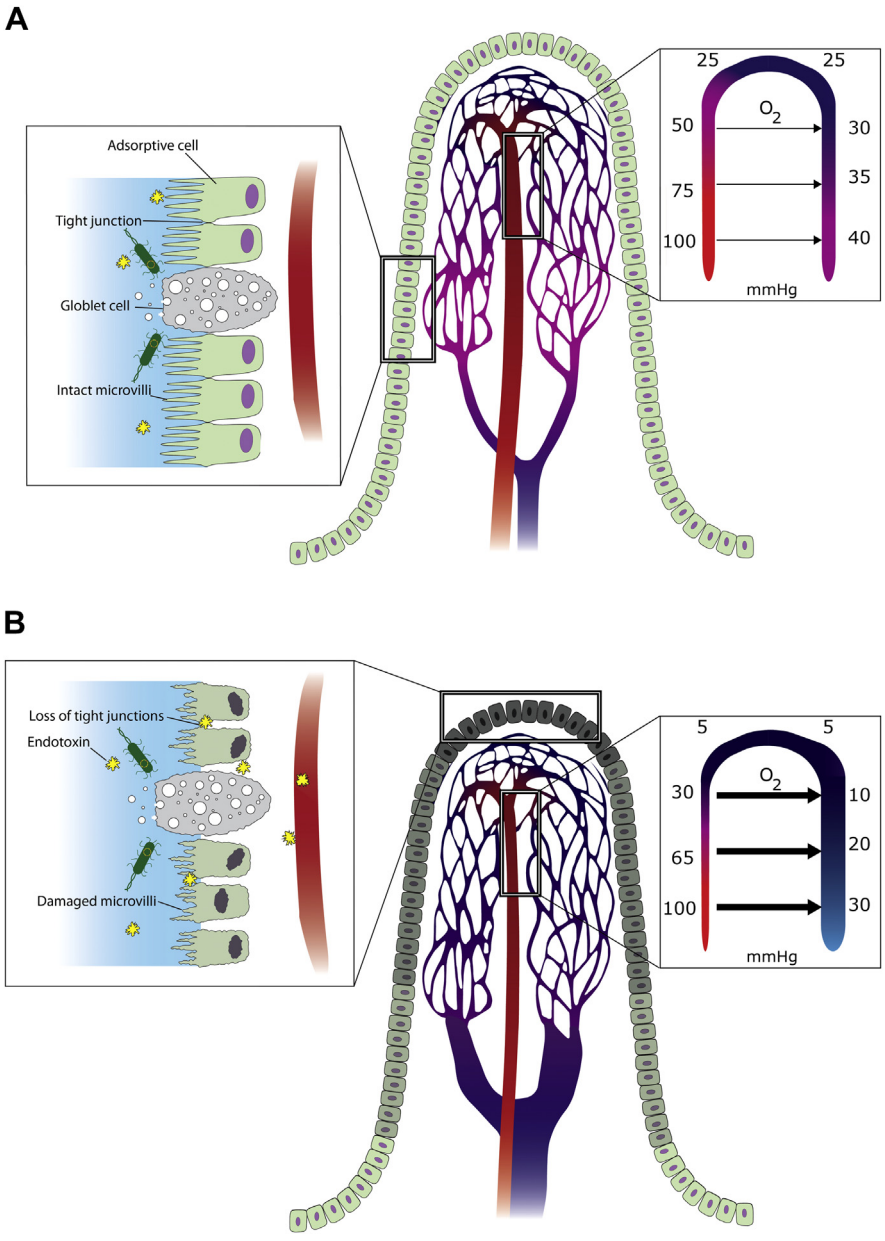

Figure 5 The Gut in Congestive Heart Failure: The Intestinal Barrier Function

(A) The countercurrent system of the intestinal microcirculation makes extensive exchange possible between arterioles and venules. As a result, oxygen (O_2) short circuits from arterioles to venules, creating a gradient with the lowest partial O_2 pressure at the villus tip. **(B)** In congestive heart failure, there is a low-flow state in the splanchnic microcirculation because of low perfusion, increased venous stasis, and sympathetically mediated arteriolar vasoconstriction, which stimulates O_2 exchange between arterioles and venules, exaggerating the gradient between the villus base and tip. This causes nonocclusive ischemia, resulting in dysfunctional epithelial cells and loss of intestinal barrier function. As a result, lipopolysaccharide or endotoxin, produced by gram-negative bacteria residing in the gut lumen, enter the circulatory system.

are currently not sensitive enough to evaluate small changes in the range described in CHF patients (59). Therefore, an interesting alternative would be to visualize the microcirculation directly. As such, new evolving techniques such as orthogonal polarized spectral and side-stream dark field allow assessment of alterations in the microcirculation of the patient at the bedside (60). Moreover, a better evaluation of renal, hepatic, and splenic hemodynamics might improve the phenotyping of patients presenting with acute decompensated heart failure. Noninvasive echocardiography measurements or even measuring the portal "wedge" pressure during right-sided heart catheterization might offer ample new diagnostic opportunities (61–63). Obviously, better insight into cardio-abdominal-renal interactions with regard to different heart failure phenotypes (i.e., heart failure with reduced versus preserved ejection fraction, left- versus right-

sided heart failure) is needed and an area of future research. Importantly, because congestion is a characteristic feature in each of these conditions, abdominal contributions to pathophysiology might be a major focus of interest.

New Treatment Strategies and Therapeutic Targets

Relieving abdominal congestion. In advanced CHF with increased IAP and ascites, paracentesis might be useful to correct fluid loss in the perivascular third spaces and to improve renal function (26). In addition, it has been shown that mechanical fluid removal through ultrafiltration removes more sodium in the same amount of water compared with diuretics (64). Therefore, ultrafiltration has the potential to reduce interstitial edema more efficiently in CHF. However, as was recently demonstrated in the CARRESS-HF (Cardiorenal Rescue Study in Acute Decompensated Heart Failure) study, the need for central venous access is associated with potential complications, and a strategy with diuretics if titrated to urinary output and including combination therapy, is generally successful in achieving decongestion (65). Therefore, we would recommend ultrafiltration only in the case of clear systemic congestion refractory to combination therapy with diuretics and with the ultrafiltration rate guided by central hemodynamics to avoid intravascular volume depletion. However, prognosis is often sobering in such cases with high mortality, and often a need for continued renal replacement therapy (66).

Continuous ambulatory peritoneal dialysis offers a (physiological) therapeutic alternative in patients with CHF and concomitant renal dysfunction. Recently, 2 studies reported improvements in symptoms, physical performance, quality of life, and biochemical profile after initiation of peritoneal dialysis in a pooled cohort of 143 patients with advanced CHF, impaired renal function, and persistent congestion despite therapy with high-dose loop diuretics (67,68). As peritoneal dialysis provides continuous slow ultrafiltration, it has a minimal impact on hemodynamics and consequently neurohumoral stimulation (69). In addition, sodium and potassium are effectively removed, potentially allowing better up-titration of neurohumoral blockers (69). Finally, although speculative, providing a permanent outlet of the abdominal cavity might reduce IAP, which has been demonstrated to improve renal function in CHF (26,69). Nevertheless, current evidence from observational, small, single-center studies should be considered hypothesis-generating, requiring confirmation by a randomized clinical trial.

Targeting maladaptive responses in the abdominal compartment. SODIUM AVIDITY AND ORAL SODIUM BINDERS. As already explained by the neurohumoral model, impaired natriuresis is a typical finding in CHF (1). Remarkably, early in the disease process, before emerging symptoms or impaired central hemodynamics, sodium avidity is present, which initially can be overcome with the administration of exogenous natriuretic peptides (70). However, in more advanced CHF, high concentrations of natriuretic peptides might be insufficient to prevent systemic congestion and could even contribute to perceived central hypovolemia and fluid accumulation in perivascular third spaces. Indeed, this explains the overall neutral results and high incidence of hypotension with nesiritide (a synthetic analog of human B-type natriuretic peptide) in the ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure) study in a population with advanced CHF admitted with ADHF (71). Hypothetically, using natriuretic peptides earlier in the disease process to counter sodium avidity might be more physiologically reasonable.

Despite typical recommendations of salt restriction, diuretics are usually needed to achieve a neutral sodium balance in CHF. Although bias by indication almost certainly plays a role, the correlation between a higher dose of loop diuretics and adverse outcome in CHF remains a concern (72). Oral sodium binders target sodium absorption in the gut and are an emerging therapeutic strategy in CHF (73). Because they prevent sodium and fluid accumulation without influencing hemodynamics, they have the benefit of not causing further maladaptive neurohumoral stimulation.

VASODILATOR THERAPY. Vasodilator therapy in addition to neurohumoral blockers to recruit venous capacitance veins is an appealing strategy to treat misdistribution of blood volume. Venous vasodilation might temporarily improve the buffer capacity of the splanchnic vasculature, whereas arteriolar vasodilation increases the effective circulatory volume on which the kidneys exert their regulating function. Moreover, left ventricular wall tension and afterload will be reduced as well, which improves hemodynamics and organ perfusion, especially when cardiac output is impaired (74,75). Interestingly, targeting cardiac filling pressures primarily by adding vasodilator therapy reduced admissions for ADHF by >30% in the CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients) trial, with similar benefits in both patients with reduced and preserved ejection fraction (76). Indeed, a lower dose of diuretics is needed for the same amount of decongestion when vasodilators are added (77). Specific data regarding the role of vasodilators to improve renal function in patients with cardiorenal syndrome are lacking, but low-dose dopamine and nesiritide, both sharing renal vasodilator properties, are currently under investigation in the ROSE AHF (Renal Optimization Strategies Evaluation in Acute Heart Failure) trial (NCT01132846).

RENAL SYMPATHETIC DENERVATION. Unrestrained sympathetic up-regulation is one of the many factors driving sodium avidity in CHF (1). Moreover, because of the abundance of α-receptors in the splanchnic vasculature, it might cause venoconstriction, thereby increasing the effective circulatory volume (13). Furthermore, animal experiments have demonstrated the existence of both a hepatorenal

and splenorenal reflex, mediated by renal efferent nerves and causing renal vasoconstriction with consequently low renal blood flow that might impair renal function (30,42). Finally, sympathetic stimulation presumably contributes to non-occlusive bowel ischemia through arteriolar vasoconstriction in CHF. Because all these effects are mediated by α-receptors and thus not targeted by β-blocker therapy, renal sympathetic denervation might be an appealing strategy to lower sympathetic drive in general and target both afferent and efferent sympathetic nerves (78).

Altering gut microbiota and preserving the intestinal barrier function. Although interesting from a pathophysiological point of view, there really is a lack of knowledge about how to exploit the symbiosis of the human body with gut microbiota. Current CHF therapies like β-blockers and angiotensin-converting enzyme inhibitors probably have beneficial effects, whereas the value of probiotics, selective bowel decontamination, endotoxin immunoadsorption, *N*-acetylcysteine, and other immunomodulators have yet to be elucidated (48). Rifaximin, a virtually unabsorbable antibiotic with broad-spectrum activity against both gram-negative and -positive, has recently shown some promising results in this respect. In patients with decompensated liver cirrhosis and ascites, it improved systemic hemodynamics and renal function, presumably by inhibiting gut inflammation, resulting in toxin entrance into the circulatory system (79).

Conclusions

Although patients frequently present with abdominal symptoms, especially when they have marked signs and symptoms of congestion, the abdomen remains largely understudied in CHF. Although not always easy to evaluate at the bedside, cardio-abdominal-renal interactions most probably play an important role in the development of persistent systemic congestion despite adequately dosed diuretic therapy. Better insight into these interactions by understanding the capacitance function of splanchnic blood vessels, the splanchnic organs, and the microcirculation might offer a venue for new diagnostic and therapeutic strategies in CHF.

Reprint requests and correspondence: Dr. Wilfried Mullens, Department of Cardiology, Ziekenhuis Oost-Limburg, Schiepse Bos 6, 3600 Genk, Belgium. E-mail: wilfried.mullens@zol.be.

REFERENCES

1. Schrier RW, Abraham WT. Hormones and hemodynamics in heart failure. N Engl J Med 1999;341:577–85.
2. Dupont M, Mullens W, Tang WH. Impact of systemic venous congestion in heart failure. Curr Heart Fail Rep 2011;8:233–41.
3. Nohria A, Hasselblad V, Stebbins A, et al. Cardiorenal interactions: insights from the ESCAPE trial. J Am Coll Cardiol 2008;51:1268–74.
4. Damman K, van Deursen VM, Navis G, Voors AA, van Veldhuisen DJ, Hillege HL. Increased central venous pressure is associated with impaired renal function and mortality in a broad spectrum of patients with cardiovascular disease. J Am Coll Cardiol 2009;53:582–8.
5. Mullens W, Abrahams Z, Francis GS, et al. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. J Am Coll Cardiol 2009;53:589–96.
6. Testani JM, Khera AV, St John Sutton MG, et al. Effect of right ventricular function and venous congestion on cardiorenal interactions during the treatment of decompensated heart failure. Am J Cardiol 2010;105:511–6.
7. Verhaert D, Mullens W, Borowski A, et al. Right ventricular response to intensive medical therapy in advanced decompensated heart failure. Circ Heart Fail 2010;3:340–6.
8. Guglin M, Rivero A, Matar F, Garcia M. Renal dysfunction in heart failure is due to congestion but not low output. Clin Cardiol 2011;34:113–6.
9. Greenway CV, Lister GE. Capacitance effects and blood reservoir function in the splanchnic vascular bed during non-hypotensive haemorrhage and blood volume expansion in anaesthetized cats. J Physiol 1974;237:279–94.
10. Gelman S, Mushlin PS. Catecholamine-induced changes in the splanchnic circulation affecting systemic hemodynamics. Anesthesiology 2004;100:434–9.
11. Greenway CV. Role of splanchnic venous system in overall cardiovascular homeostasis. Fed Proc 1983;42:1678–84.
12. Greenway CV, Seaman KL, Innes IR. Norepinephrine on venous compliance and unstressed volume in cat liver. Am J Physiol 1985;248:H468–76.
13. Patel P, Bose D, Greenway C. Effects of prazosin and phenoxybenzamine on alpha- and beta-receptor-mediated responses in intestinal resistance and capacitance vessels. J Cardiovasc Pharmacol 1981;3:1050–9.
14. Fallick C, Sobotka PA, Dunlap ME. Sympathetically mediated changes in capacitance: redistribution of the venous reservoir as a cause of decompensation. Circ Heart Fail 2011;4:669–75.
15. Adamson PB, Magalski A, Braunschweig F, et al. Ongoing right ventricular hemodynamics in heart failure: clinical value of measurements derived from an implantable monitoring system. J Am Coll Cardiol 2003;41:565–71.
16. Zile MR, Bennett TD, St John Sutton M, et al. Transition from chronic compensated to acute decompensated heart failure: pathophysiological insights obtained from continuous monitoring of intracardiac pressures. Circulation 2008;118:1433–41.
17. Chaudhry SI, Wang Y, Concato J, Gill TM, Krumholz HM. Patterns of weight change preceding hospitalization for heart failure. Circulation 2007;116:1549–54.
18. Levick JR, Michel CC. Microvascular fluid exchange and the revised Starling principle. Cardiovasc Res 2010;87:198–210.
19. Guyton AC. Interstitial fluid pressure. II. Pressure-volume curves of interstitial space. Circ Res 1965;16:452–60.
20. Granger DN, Mortillaro NA, Kvietys PR, Rutili G, Parker JC, Taylor AE. Role of the interstitial matrix during intestinal volume absorption. Am J Physiol 1980;238:G183–9.
21. Renkin EM, Joyner WL, Sloop CH, Watson PD. Influence of venous pressure on plasma-lymph transport in the dog's paw: convective and dissipative mechanisms. Microvasc Res 1977;14:191–204.
22. Aukland K, Reed RK. Interstitial-lymphatic mechanisms in the control of extracellular fluid volume. Physiol Rev 1993;73:1–78.
23. Mullens W, Abrahams Z, Skouri HN, et al. Elevated intra-abdominal pressure in acute decompensated heart failure: a potential contributor to worsening renal function? J Am Coll Cardiol 2008;51:300–6.
24. Malbrain ML, Cheatham ML, Kirkpatrick A, et al. Results from the international conference of experts on intra-abdominal hypertension and abdominal compartment syndrome. I. Definitions. Intensive Care Med 2006;32:1722–32.
25. Malbrain ML, Chiumello D, Pelosi P, et al. Prevalence of intra-abdominal hypertension in critically ill patients: a multicentre epidemiological study. Intensive Care Med 2004;30:822–9.
26. Mullens W, Abrahams Z, Francis GS, Taylor DO, Starling RC, Tang WH. Prompt reduction in intra-abdominal pressure following large-volume mechanical fluid removal improves renal insufficiency in refractory decompensated heart failure. J Card Fail 2008;14:508–14.
27. Hasper D, Jorres A. New insights into the management of hepato-renal syndrome. Liver Int 2011;31 Suppl 3:27–30.
28. Poelzl G, Ess M, Mussner-Seeber C, Pachinger O, Frick M, Ulmer H. Liver dysfunction in chronic heart failure: prevalence, characteristics and prognostic significance. Eur J Clin Invest 2012;42:153–63.
29. Poelzl G, Ess M, Von der Heidt A, Rudnicki M, Frick M, Ulmer H. Concomitant renal and hepatic dysfunctions in chronic heart failure:

clinical implications and prognostic significance. Eur J Intern Med 2013;24:177–82.
30. Ming Z, Smyth DD, Lautt WW. Decreases in portal flow trigger a hepatorenal reflex to inhibit renal sodium and water excretion in rats: role of adenosine. Hepatology 2002;35:167–75.
31. Bankir L, Ahloulay M, Devreotes PN, Parent CA. Extracellular cAMP inhibits proximal reabsorption: are plasma membrane cAMP receptors involved? Am J Physiol Renal Physiol 2002;282:F376–92.
32. Hendy GN, Tomlinson S, O'Riordan JL. Impaired responsiveness to the effect of glucagon on plasma adenosine 3':5'-cyclic monophosphate in normal man. Eur J Clin Invest 1977;7:155–60.
33. Ahloulay M, Dechaux M, Hassler C, Bouby N, Bankir L. Cyclic AMP is a hepatorenal link influencing natriuresis and contributing to glucagon-induced hyperfiltration in rats. J Clin Invest 1996;98:2251–8.
34. Huchzermeyer H, Schmitz-Feuerhake I, Reblin T. Determination of splenic blood flow by inhalation of radioactive rare gases. Eur J Clin Invest 1977;7:345–9.
35. Garnett ES, Goddard BA, Markby D, Webber CE. The spleen as an arteriovenous shunt. Lancet 1969;1:386–8.
36. Kaufman S, Deng Y. Splenic control of intravascular volume in the rat. J Physiol 1993;468:557–65.
37. de Bold AJ, Borenstein HB, Veress AT, Sonnenberg H. A rapid and potent natriuretic response to intravenous injection of atrial myocardial extract in rats. Life Sci 1981;28:89–94.
38. Kaufman S. Role of spleen in ANF-induced reduction in plasma volume. Can J Physiol Pharmacol 1992;70:1104–8.
39. Sultanian R, Deng Y, Kaufman S. Atrial natriuretic factor increases splenic microvascular pressure and fluid extravasation in the rat. J Physiol 2001;533:273–80.
40. O'Reilly RA. Splenomegaly in 2,505 patients in a large university medical center from 1913 to 1995. 1913 to 1962: 2,056 patients. West J Med 1998;169:78–87.
41. O'Reilly RA. Splenomegaly in 2,505 patients at a large university medical center from 1913 to 1995. 1963 to 1995: 449 patients. West J Med 1998;169:88–97.
42. Hamza SM, Kaufman S. Splenorenal reflex modulates renal blood flow in the rat. J Physiol 2004;558:277–82.
43. Beltowski J. Guanylin and related peptides. J Physiol Pharmacol 2001; 52:351–75.
44. Forte LR. A novel role for uroguanylin in the regulation of sodium balance. J Clin Invest 2003;112:1138–41.
45. Carrithers SL, Eber SL, Forte LR, Greenberg RN. Increased urinary excretion of uroguanylin in patients with congestive heart failure. Am J Physiol Heart Circ Physiol 2000;278:H538–47.
46. Narayan H, Mohammed N, Quinn PA, Squire IB, Davies JE, Ng LL. Activation of a novel natriuretic endocrine system in humans with heart failure. Clin Sci 2010;118:367–74.
47. Takala J. Determinants of splanchnic blood flow. Br J Anaesth 1996; 77:50–8.
48. Sandek A, Rauchhaus M, Anker SD, von Haehling S. The emerging role of the gut in chronic heart failure. Curr Opin Clin Nutr Metab Care 2008;11:632–9.
49. Ding J, Magnotti LJ, Huang Q_, Xu DZ, Condon MR, Deitch EA. Hypoxia combined with *Escherichia coli* produces irreversible gut mucosal injury characterized by increased intestinal cytokine production and DNA degradation. Shock 2001;16:189–95.
50. Sandek A, Bauditz J, Swidsinski A, et al. Altered intestinal function in patients with chronic heart failure. J Am Coll Cardiol 2007;50:1561–9.
51. Arutyunov GP, Kostyukevich OI, Serov RA, Rylova NV, Bylova NA. Collagen accumulation and dysfunctional mucosal barrier of the small intestine in patients with chronic heart failure. Int J Cardiol 2008;125:240–5.
52. Simenhoff ML, Saukkonen JJ, Burke JF, Wesson LG Jr., Schaedler RW, Gordon SJ. Bacterial populations of the small intestine in uremia. Nephron 1978;22:63–8.
53. Magnusson M, Magnusson KE, Denneberg T. Impaired gut barrier in experimental chronic uremic rats. Miner Electrolyte Metab 1992;18:288–92.
54. Evenepoel P, Meijers BK, Bammens BR, Verbeke K. Uremic toxins originating from colonic microbial metabolism. Kidney Int Suppl 2009:S12–9.
55. Vanholder R, De Smet R, Glorieux G, et al. Review on uremic toxins: classification, concentration, and interindividual variability. Kidney Int 2003;63:1934–43.
56. Kumar A, Brar R, Wang P, et al. Role of nitric oxide and cGMP in human septic serum-induced depression of cardiac myocyte contractility. Am J Physiol 1999;276:R265–76.
57. Zhu X, Bernecker OY, Manohar NS, et al. Increased leakage of sarcoplasmic reticulum Ca2+ contributes to abnormal myocyte Ca2+ handling and shortening in sepsis. Crit Care Med 2005;33:598–604.
58. Charalambous BM, Stephens RC, Feavers IM, Montgomery HE. Role of bacterial endotoxin in chronic heart failure: the gut of the matter. Shock 2007;28:15–23.
59. van Ramshorst GH, Salih M, Hop WC, et al. Noninvasive assessment of intra-abdominal pressure by measurement of abdominal wall tension. J Surg Res 2011;171:240–4.
60. Piagnerelli M, Ince C, Dubin A. Microcirculation. Crit Care Res Pract 2012;2012:867176.
61. Shih CY, Yang SS, Hu JT, Lin CL, Lai YC, Chang CW. Portal vein pulsatility index is a more important indicator than congestion index in the clinical evaluation of right heart function. World J Gastroenterol 2006;12:768–71.
62. Bolognesi M, Quaglio C, Bombonato G, et al. Splenic Doppler impedance indices estimate splenic congestion in patients with right-sided or congestive heart failure. Ultrasound Med Biol 2012;38:21–7.
63. Wei K, Lindner J. Contrast ultrasound in the assessment of patients presenting with suspected cardiac ischemia. Crit Care Med 2007;35: S280–9.
64. Ali SS, Olinger CC, Sobotka PA, et al. Loop diuretics can cause clinical natriuretic failure: a prescription for volume expansion. Congest Heart Fail 2009;15:1–4.
65. Bart BA, Goldsmith SR, Lee KL, et al. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. N Engl J Med 2012; 367:296–304.
66. Patarroyo M, Wehbe E, Hanna M, et al. Cardiorenal outcomes after slow continuous ultrafiltration therapy in refractory patients with advanced decompensated heart failure. J Am Coll Cardiol 2012;60:1906–12.
67. Koch M, Haastert B, Kohnle M, et al. Peritoneal dialysis relieves clinical symptoms and is well tolerated in patients with refractory heart failure and chronic kidney disease. Eur J Heart Fail 2012;14:530–9.
68. Nunez J, Gonzalez M, Minana G, et al. Continuous ambulatory peritoneal dialysis as a therapeutic alternative in patients with advanced congestive heart failure. Eur J Heart Fail 2012;14:540–8.
69. Courivaud C, Kazory A. Can we treat fluid overload with fluid? Role of peritoneal dialysis in management of heart failure. Eur J Heart Fail 2012;14:461–3.
70. McKie PM, Schirger JA, Costello-Boerrigter LC, et al. Impaired natriuretic and renal endocrine response to acute volume expansion in pre-clinical systolic and diastolic dysfunction. J Am Coll Cardiol 2011; 58:2095–103.
71. O'Connor CM, Starling RC, Hernandez AF, et al. Effect of nesiritide in patients with acute decompensated heart failure. N Engl J Med 2011;365:32–43.
72. Hasselblad V, Gattis Stough W, Shah MR, et al. Relation between dose of loop diuretics and outcomes in a heart failure population: results of the ESCAPE trial. Eur J Heart Fail 2007;9:1064–9.
73. Costanzo MR, Heywood JT, Massie BM, et al. A double-blind, randomized, parallel, placebo-controlled study examining the effect of cross-linked polyelectrolyte in heart failure patients with chronic kidney disease. Eur J Heart Fail 2012;14:922–30.
74. Mullens W, Abrahams Z, Francis GS, et al. Sodium nitroprusside for advanced low-output heart failure. J Am Coll Cardiol 2008;52:200–7.
75. Mullens W, Abrahams Z, Francis GS, et al. Usefulness of isosorbide dinitrate and hydralazine as add-on therapy in patients discharged for advanced decompensated heart failure. Am J Cardiol 2009;103:1113–9.
76. Abraham WT, Adamson PB, Bourge RC, et al. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. Lancet 2011;377:658–66.
77. Cotter G, Metzkor E, Kaluski E, et al. Randomised trial of high-dose isosorbide dinitrate plus low-dose furosemide versus high-dose furosemide plus low-dose isosorbide dinitrate in severe pulmonary oedema. Lancet 1998;351:389–93.
78. Kalaitzidis RG, Karasavvidou D, Siamopoulos KC. Renal sympathetic denervation and renal physiology. Curr Clin Pharmacol 2012 Nov 7 [E-pub ahead of print].
79. Kalambokis GN, Mouzaki A, Rodi M, et al. Rifaximin improves systemic hemodynamics and renal function in patients with alcohol-related cirrhosis and ascites. Clin Gastroenterol Hepatol 2012;10:815–8.

Key Words: congestive heart failure ■ gut ■ microcirculation ■ splanchnic circulation.