DECOMPENSATION IN HEART FAILURE occurs when the heart is unable to balance venous return with cardiac output, which can lead to fluid congestion in peripheral organs and lungs. Decompensation is a major cause of morbidity and mortality in patients with heart failure. It leads to almost one hospital admission per patient and year and is strongly associated with preexisting kidney disease (7). Decompensated heart failure can cause acute kidney injury (AKI) in the cardiorenal syndrome, which further increases mortality and accelerates disease progression (9, 55).

The Frank-Starling mechanism ensures that increased cardiac preload leads to increased myocardial contractility and thus cardiac output (8, 17, 50). However, an excessive preload will overload the heart and decrease cardiac output by outstretching the contractile mechanism (8). Reduced cardiac output from the failing heart leads to reduced arterial pressure, in turn, activating a number of signaling systems.

This review considers the compensatory neurohormonal mechanisms that drive renal fluid retention and exacerbate decompensation. Concurrently, the renal tubular reabsorption that mediates fluid retention increases renal oxygen consumption and may cause tissue hypoxia and AKI, which in a vicious circle worsens body water and electrolyte balance (Fig. 1).

**Sympathetic Nerves**

Decreased arterial pressure reduces carotid baroreflex signaling leading to increased sympathetic signaling to the kidney (32). Failure to match cardiac output to increased preload leads to high renal sympathetic nerve activity (RSNA) and its modulation in response to altered circulating blood volume is blunted or abolished (52). Normally sympathetic nerve-derived norepinephrine causes afferent arteriolar constriction and reduces renal blood flow (11). The renal vasculature in chronic heart failure shows an increased sensitivity to depolarization but unchanged sensitivity to the α1 agonist phenylephrine and a blunted α2 sensitivity (2). In contrast, systemic arteries show increased α1 sensitivity in most heart failure models, which is mediated by increased calcium transients and enhanced calcium sensitivity (31) and nitric oxide release (62). Norepinephrine increases tubular reabsorption in both the proximal and distal tubules (20). Increased oxygen consumption mediated by increased reabsorption, in combination with decreased blood flow, exacerbates fluid retention in the kidneys and promotes tissue hypoxia leading to AKI.

**Renal Neurohormonal Regulation in Heart Failure Decompensation**

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Submitted 30 April 2014; accepted in final form 10 June 2014

Jönsson S, Becirovic Agic M, Narfström F, Melville JM, Hultström M. Renal neurohormonal regulation in heart failure decompensation. Am J Physiol Regul Integr Comp Physiol 307: R493–R497, 2014. First published June 11, 2014; doi:10.1152/ajpregu.00178.2014.—Decompensation in heart failure occurs when the heart fails to balance venous return with cardiac output, leading to fluid congestion and contributing to mortality. Decompensated heart failure can cause acute kidney injury (AKI), which further increases mortality. Heart failure activates signaling systems that are deleterious to kidneys such as renal sympathetic nerve activity (RSNA), renin-angiotensin-aldosterone system, and vasopressin secretion. All three reduce renal blood flow (RBF) and increase tubular sodium reabsorption, which may increase renal oxygen consumption causing AKI through renal tissue hypoxia. Vasopressin contributes to venous congestion through aquaporin-mediated water retention. Additional water retention may be mediated through vasopressin-induced medullary urea transport and hyaluronan but needs further study. In addition, there are several systems that could protect the kidneys and reduce fluid retention such as natriuretic peptides, prostaglandins, and nitric oxide. However, the effect of natriuretic peptides and nitric oxide are blunted in decompensation, partly due to oxidative stress. This review considers how neurohormonal signaling in heart failure drives fluid retention by the kidneys and thus exacerbates decompensation. It further identifies areas where there is limited data, such as signaling systems 20-HETE, purines, endothelin, the role of renal water retention mechanisms for congestion, and renal hypoxia in AKI during heart failure.

cardiorenal syndrome; acute renal failure; ADHF; glomerular filtration rate; GFR
effects of ANG II on renal blood flow and stimulation of (57), which makes its role difficult to predict. However, strong during low-salt intake and has not been studied in heart failureocal ANG II is not increased by endogenous ANG II production (48) and for the proximal tubular natriuretic effect of ANG In intrarenal ANG II is important for renal function in hyperten-sion (47), although reabsorption may be decreased by ANG II in the proximal nephron (37, 64). ANG II increases afferent arterioles in high renin hypertension models (22, 24) and during ANG II blockade in vivo (61). ANG II increases and during ANG II blockade in vivo (61). ANG II increases tubular reabsorption. Reabsorption in turn increases oxygen consumption further aggravating hypoxia, while the reabsorbed fluid and AKI exacerbates heart failure decompensation in a vicious circle.

flow mediated by increased vascular reactivity and signaling, likely decreases renal oxygen tension. Even though the effects of these systems on renal tissue oxygen tension have been studied in isolation, they are not characterized in heart failure.

Renin-Angiotensin

RSNA and reduced renal perfusion pressure (RPP) stimulate renin release leading to increased systemic angiotensin II (ANG II) (34, 70) and increased renin production in renal granular cells (63). The renal-induced renin-angiotensin-sys-tem (RAS) activation following hypoperfusion also activates afferent RSNA. Both afferent RSNA and ANG II are important positive feedback signals that lead to increased sympathetic nerve activity in heart failure (38). Chronic heart failure does not alter the sensitivity of isolated juxtamedullary nephron afferent arterioles to ANG II (26). Combined inhibition of nitric oxide synthesis and ANG II stimulation uncovers a decreased contractility and almost no nitric oxide production in vessel preparations from animals with heart failure (26). This shows a marked difference from the effect of ANG II on afferent arterioles in high renin hypertension models (22, 24) and during ANG II blockade in vivo (61). ANG II increases tubular sodium reabsorption (47), although reabsorption may be decreased by ANG II in the proximal nephron (37, 64). Intrarenal ANG II is important for renal function in hypertension (48) and for the proximal tubular natriuretic effect of ANG II through stimulation of AT2 receptors (29). However, intrarenal ANG II is not increased by endogenous ANG II production during low-salt intake and has not been studied in heart failure (57), which makes its role difficult to predict. However, strong effects of ANG II on renal blood flow and stimulation of sodium reabsorption makes it a potential mediator of reduced renal oxygen in heart failure.

Aldosterone

Aldosterone release is of pathophysiological importance in heart failure, and it is one of the major pharmacological targets in the treatment of heart failure (5). Interestingly, this is mostly motivated by its cardiac effects (51). However, aldosterone plays a well-known role in stimulating distal tubular sodium reabsorption (39). On the vascular level, it stimulates nitric oxide synthesis to buffer afferent arteriolar contraction (1, 65) and decreases tubuloglomerular feedback (TGF) (19). At the same time it has been reported that aldosterone may induce superoxide production (71). In total, tubular reabsorption is increased, which should increase oxygen consumption, but it is unknown how the vascular effects of aldosterone affects renal oxygen delivery during heart failure.

Purines

Adenosine has received considerable attention for its role in renal function and has been implicated as a target for heart failure treatment (66). Adenosine A1 blockade or knockout abolishes TGF (4) and significantly increases fluid excretion by inhibiting proximal sodium reabsorption. Indeed, adenosine receptor blockade in patients has been shown to reduce fluid retention in heart failure, and early clinical trials show promising results (21, 69). Adenosine potentiates the action of ANG II on the afferent arteriole by reducing tachyphylaxis (36). However, in high renin hypertension, tachyphylaxis does not occur and adenosine has no effect (10). It is difficult to predict how the interaction will work in a high renin-low pressure situation such as heart failure.

The purine ATP is involved in renal regulation and is an important modulator of TGF (53). In addition, ATP directly affects renal signaling by causing rapid afferent arteriolar contraction and increasing responses to norepinephrine (25). On the tubular level, flow in itself induces ATP release and inhibits reabsorption by paracrine activation of P2Y and P2X receptors (43, 67). The tubular effects of ATP may be blunted in heart failure since renal denervation augments them (35). The role or intensity of renal ATP-signaling in heart failure has not been studied directly.

In summary, adenosine tends to increase renal oxygen tension by reducing tubular reabsorption, which may be of benefit in cardiorenal syndrome. The role of renal ATP in heart failure is unknown, but one may hypothesize that vascular effects are deleterious while tubular effects may be beneficial but down regulated.

Eicosanoids

In heart failure prostaglandins are important for maintaining renal perfusion (54). In heart-failure patients with RAS inhi-bition, prostaglandins are even more important as evidenced by the highly nephrotoxic effects of nonsteroidal anti-inflamma-tory drugs in this patient group (6, 49). Recently the arachi-donic acid metabolite 20-hydroxyeicosatetraenoic acid (20-HETE) has been shown to be an important molecule in renal vascular function (72), and specifically in ANG II-induced vascular signaling (12). However, it is unknown how 20-HETE influences renal function during heart failure.
Natriuretic Peptides

As reduced perfusion pressure leads to activation of deleterious signaling, high central venous pressure leads to stretching of the myocardium and cardiac release of atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP). Increased preload in heart failure induces acute phase ANP release, but as the disease stabilizes production may decrease (45). In the kidney ANP modulates renal blood flow autoregulation by affecting TGF regulation of extracellular volume; interestingly, it is severely blunted in heart failure (42). Furthermore, the tubular effect of ANP, particularly on the inner medullary collecting duct, is blunted in heart failure but the mechanism is not completely understood (40, 46). The situation is similar for BNP with significant blunting of the natriuretic effect in heart failure (28). In summary, natriuretic peptides act to protect the kidney in heart failure, but reduced target organ sensitivity both at the renal tubular and vascular level blunts their effect.

Endothelin

Endothelin is an endothelium-signaling molecule important for fluid and sodium excretion (30). Endothelin ETA and ETB receptors show differential regulation in heart failure with and without decompensation with a loss of medullary expression of the dilatory ETB (16), which affects sodium excretion (15). However, ETA signaling has been linked to afferent renal nerve activity in heart failure (33). Interestingly, endothelin blockade causes development of congestive heart failure in patients with hypertension because of fluid retention, while reducing proteinuria, used as a surrogate measure for kidney damage (41). The effect of endothelin on renal oxygenation in heart failure or the risk of AKI with tubular ischemic damage is unknown.

Vasopressin

During heart failure vasopressin levels are increased as a consequence of nonosmotic release (56). The vasopressin V1 receptor causes contraction of afferent arterioles and reduces renal blood flow (27, 68). Vasopressin regulates water reabsorption through the V2 receptor by affecting aquaporin 2 translocation, an important mechanism for fluid retention in heart failure (3, 60). Vasopressin further stimulates sodium reabsorption by stimulating epithelial Na+ channel in the distal nephron (44), potentially through oxytocin receptors (58). Urea transport through the urea transporter A is important for the concentrating ability by regulating the medullary concentration gradient (14) and is regulated by vasopressin (13), but little is known about the regulation of urea transport in heart failure. Finally, renal medullary hyaluronan counteracts reabsorption by acting as a diffusion barrier in the interstitium and is affected by vasopressin (59). However, its role in heart failure-associated fluid retention is unknown. In summary, vasopressin is a major factor in the renal contribution to decompensation by its direct effects on water reabsorption and subsequent exacerbation of renal hypoxia.

Perspectives and Significance

 Decompensated heart failure is characterized by increased neurohormonal signaling to the kidney. Signaling systems that tend to increase fluid retention and reduce renal blood flow such as sympathetic signaling, RAS, and vasopressin retain or even increase their responses. Concurrently, systems that tend to promote fluid excretion and increase renal blood flow such as eicosanoids and natriuretic factors show blunted signaling, although their levels are increased. This not only worsens fluid retention and decompensation but increases kidney reabsorption and thereby renal oxygen consumption while reducing renal blood flow and oxygen delivery. This potentially leads to tissue hypoxia and kidney injury (18), which may be a common pathway for AKI in circulatory failure (23). However, kidney tissue hypoxia and the effects of changes in renal oxygen delivery and consumption during heart failure decompensation is an area with many open questions.

GRANTS

This work was supported by grants from the Swedish Heart and Lung Foundation, Åke Wiberg Foundation and the Swedish Society for Medical Research (SSMF).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


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