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Inflammatory activation: cardiac, renal, and cardio-renal interactions in patients with the cardiorenal syndrome

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Abstract

Although inflammation is a physiologic response designed to protect us from infection, when unchecked and ongoing it may cause substantial harm. Both chronic heart failure (CHF) and chronic kidney disease (CKD) are known to cause elaboration of several pro-inflammatory mediators that can be detected at high concentrations in the tissues and blood stream. The biologic sources driving this chronic inflammatory state in CHF and CKD are not fully established. Traditional sources of inflammation include the heart and the kidneys which produce a wide range of proinflammatory cytokines in response to neurohormones and sympathetic activation. However, growing evidence suggests that non-traditional biomechanical mechanisms such as venous and tissue congestion due to volume overload are also important as they stimulate endotoxin absorption from the bowel and peripheral synthesis and release of proinflammatory mediators. Both during the chronic phase and, more rapidly, during acute exacerbations of CHF

and CKD, inflammation and congestion appear to amplify each other resulting in a downward spiral of worsening cardiac, vascular, and renal functions that may negatively impact patients' outcome. Anti-inflammatory treatment strategies aimed at attenuating end organ damage and improving clinical prognosis in the cardiorenal syndrome have been disappointing to date. A new therapeutic paradigm may be needed, which involves different anti-inflammatory strategies for individual etiologies and stages of CHF and CKD. It may also include specific (short-term) anti-inflammatory treatments that counteract inflammation during the unsettled phases of clinical decompensation. Finally, it will require greater focus on volume overload as an increasingly significant source of systemic inflammation in the cardiorenal syndrome.

Keywords

Cardiorenal syndrome; Inflammation; Cytokines; Congestive heart failure; Chronic kidney disease

Introduction

Over the past decades, it has become evident that congestive heart failure (CHF) and chronic kidney disease (CKD) are associated with systemic inflammatory activation.

Inflammation represents a physiologic response intended to provide protection and promote healing in the setting of injury. Paradoxically, these same processes which are protective can promote further tissue injury and damage if left unchecked. When attenuation of inflammation does not occur (because normal control mechanisms are overwhelmed) an acute or chronic pathophysiologic response may ensue. Since both CHF and CKD induce inflammation and inflammation in turn worsens CHF and CKD, the resulting downward spiral in cardiovascular and renal functions may progressively aggravate patients' functional status and prognosis.

Of note, cardiac and renal dysfunctions promote fluid retention thereby conspiring to shift human physiology from a healthy biosystem that operates at low pressures to a pathophysiologic milieu where organs are forced to function with significantly elevated venous and interstitial pressures several times above normal. It is conceivable that in this high-pressure environment, biomechanical stress from vascular stretch and tissue congestion may promote additional inflammation that in turn may further impair the function and structure of vital organs such as the heart, the vasculature, and the kidneys.

The following discussion will detail (i) the evidence that systemic inflammatory activation is present in CHF and CKD, and, possibly amplified in the cardiorenal syndrome; (ii) the biological sources of inflammation; (iii) the functional and structural effects of systemic inflammation on the heart, vasculature, and kidneys; (iv) the active role of inflammation in the pathophysiology of the cardiorenal syndrome; and (v) the anti-inflammatory treatment options currently available. Overall, researching the cardiorenal syndrome in clinical and experimental medicine is made problematic by the absence of a clear definition of the syndrome itself. This issue can make pathophysiologic and clinical distinctions among heart failure, renal failure, and cardiorenal syndrome, as well as their relationships to inflammation, quite elusive at the present time.

Inflammatory biomarkers in CHF, CKD, and the cardiorenal syndrome

Circulating biomarkers of inflammation correlate with functional severity and poor clinical outcomes in CHF and CKD, and decline as the clinical situation improves [1–5]. A prime example is the marked downregulation of key plasma biomarkers of inflammation following

resolution of an episode of CHF decompensation [6, 7]. These circulating molecules are not inert, but rather should be viewed as bioactive molecules which exert a direct and often overlapping detrimental effect on exposed tissue (see “Inflammation and end organ damage in the cardiorenal syndrome” for more details). Below, we provide a focused overview of the most prominent, well-characterized inflammatory mediators/markers in CHF and CKD. We have also included B-type natriuretic peptide (BNP) as growing evidence appears to suggest an association between this marker of congestion and markers of inflammation in patients with CHF and CKD. Overall, direct evidence that inflammation is ultimately amplified in the cardiorenal syndrome (combined CHF and CKD) is limited due to lack of a clear definition of the syndrome, and therefore such assumptions remain for the most part speculative.

Pro-inflammatory cytokines

Tumor necrosis factor- α (TNF- α) is increased in the circulation during CHF decompensation, worsened New York Heart Association (NYHA) functional status, and is a significant independent predictor of cardiac and non-cardiac mortality in CHF patients [8, 9]. Its soluble receptors sTNFR-1 and sTNFR-2, are also associated with heart failure disease and in fact, may be more accurate than TNF- α as a predictor of CHF mortality [10]. A novel biomarker, TNF-related weak inducer of apoptosis (TWEAK), a member of the TNF superfamily, has received some recent attention for its effects in dilated cardiomyopathy. Circulating TWEAK levels are higher in patients with idiopathic dilated cardiomyopathy than in healthy controls [11]. In addition to TNF- α and its related proteins, similar relationships have been found between interleukin-6 (IL-6), members of the interleukin-1 (IL-1) superfamily of cytokines (including IL-1 β and IL-18), and CHF. IL-6 for example increases with worsened NYHA functional status (Fig. 1a) and is regarded as an established predictor of all-cause mortality in CHF patients [12–18].

It has also been repeatedly shown that advanced CKD is associated with elevated levels of the same pro-inflammatory cytokines [19–21]. One of the more well-studied cytokines is IL-6 which, like in CHF, correlates with progression of disease, increasing with worsening CKD stage (Fig. 1b) [22]. It also predicts death better than IL-1 β , TNF- α , C-reactive protein (CRP), and albumin levels in CKD patients on dialysis [23, 24]. Even though dialysis-related factors (type of vascular access, poor dialyzer membrane biocompatibility, or dialysate contamination) may promote a persistent, low-grade inflammatory response [22], IL-6 levels are also elevated in pre-dialysis patients with earlier stages of CKD (Fig. 1b) [22].

Overall, elevation of TNF- α , IL-1 β , and IL-6 in patients with both CKD and CHF may suggest a possible role for these cytokines in modulating inflammation during the cardiorenal syndrome.

Lipopolysaccharide (endotoxin) response

There has been a great deal of interest in lipopolysaccharide (LPS), or endotoxin, since the development of the “cytokine hypothesis”. LPS is a lipoglycan found on the outer membrane of gram-negative bacteria and is one of the strongest inducers of TNF- α and other pro-inflammatory cytokines [25]. Circulating LPS levels are increased in CHF [26]. One hypothesis to explain this elevation is that LPS is derived from gut bacteria which translocate through damaged endothelial cells in the intestinal villi in the setting of bowel edema (see “Venous congestion as a source of inflammation” for more details).

CKD patients also exhibit elevated levels of LPS. In end-stage renal disease (ESRD) patients on dialysis, a number of dialysis-related issues have been proposed as contributors

to a state of chronic inflammation, including type of vascular access, poor dialyzer membrane biocompatibility, and dialysate contamination [22]. However, the documentation of elevated endotoxin levels in patients with earlier stages of CKD who are not on dialysis [27] suggests other important causes of inflammation in this population, such as fluid overload.

Bowel wall edema in the setting of fluid overload is a common complication of patients with cardiorenal disease, and LPS may play a role in modulating inflammation in this setting.

Cell adhesion molecules (markers of endothelial activation)

As markers of inflammation in CHF, cell adhesion molecules comprise selectins (E-selectin, P-selectin, and L-selectin) as well as members of the immunoglobulin superfamily—intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1). These molecules are expressed on the endothelium of blood vessels and on platelets and leukocytes facilitating the migration of immune cells from the circulation into tissue areas of inflammation. They are highly induced by pro-inflammatory cytokines, especially TNF- α . Soluble ICAM-1 (sICAM-1), VCAM-1, E-selectin, and P-selectin increase with the severity of CHF and decrease with treatment and symptom improvement [28–30]. This along with findings of elevated Von Wille-brand factor in the circulation of CHF patients is consistent with a pro-thrombotic state and endothelial activation, both of which may significantly contribute to disease progression and clinical prognosis [28, 29, 31].

Soluble ICAM-1, VCAM-1, and E-selectin are also elevated in CKD patients who are both pre-dialysis and on dialysis, to levels that are not significantly different [32, 33]. Vascular endothelial dysfunction measured by forearm flow-mediated vasodilatation and VCAM-1 levels are more abnormal in pre-dialysis CKD patients compared to patients with stable angina and normal renal function [34]. Elevated ICAM-1 is found in pre-dialysis patients who are malnourished, inflamed, and who have clinical signs of cardiovascular disease, and is an independent predictor of all-cause mortality [35]. The elevated levels of adhesion molecules in CKD likely reflect inadequate clearance as well as enhanced synthesis/release. In patients with pre-dialysis CKD, creatinine clearance is also inversely related to plasma asymmetric dimethylarginine (ADMA) levels, an endogenous inhibitor of nitric oxide, and plasma ADMA is independently related to plasma VCAM-1 and carotid intima-media thickness, a marker of atherosclerosis which has been shown to have prognostic value [36].

Overall, endothelial cell activation occurs in both CHF and CKD. Whether this intracellular event is ultimately amplified in the cardiorenal syndrome remains to be elucidated.

C-Reactive protein

C-reactive protein (CRP) is an acute phase reactant secreted in acute inflammation by hepatocytes in response to pro-inflammatory cytokines, most notably IL-6. In a chronic inflammatory state, it may be minimally elevated and has garnered significant attention because of its correlation with cardiac disease and its prognostic value as a marker for atherosclerosis, coronary artery disease, and CHF [37, 38]. In patients with established CHF, CRP levels increase with worsening functional status and rising left ventricular (LV) end-diastolic pressure as well as with declining left ventricular ejection fraction (LVEF) [37, 39]. It is also a significant independent predictor of the need for hospitalization for CHF decompensation and mortality [37, 39–41].

In CKD, CRP is also elevated [42]. Of note, CRP levels decline concurrently with improved control of blood pressure in ESRD patients on hemodialysis whose volume status is strictly controlled with salt restriction, extended dialysis sessions, and dry weight clinical

assessment and reassessment at every treatment [43]. In hemodialysis patients with persistently elevated CRP, multivariate analysis shows that high CRP levels significantly predict LV dysfunction and cardiac hypertrophy [44]. Finally, higher CRP levels in hemodialysis patients are associated with an increased risk of death indicating a prognostic value for this inflammatory mediator [45].

B-type natriuretic peptide (marker of congestion)

B-type natriuretic peptide (BNP) is a well-known cardiac hormone that is elevated in CHF and CKD. Pro-hormone BNP is secreted by ventricular cardiomyocytes in response to increased wall stress and volume overload. It is subsequently cleaved to form inactive N-terminal pro-BNP (NT-proBNP) and active BNP. Both molecules are well-established markers of volume status in the clinical setting [46]. Interestingly, recent studies in ICU patients show that BNP and NT-proBNP levels correlate with inflammatory markers of CRP and leukocyte count [47, 48]. Similarly, BNP is elevated in septic patients regardless of the presence of a CHF diagnosis [47, 48]. Most recently, Jensen et al. performed a study on 218 patients on a heart failure ward by measuring the association of NT-proBNP and BNP with high CRP states (>30 mg/l) versus low to moderate CRP states (<30 mg/l). They found a relative increase in NT-proBNP/BNP ratio in the high CRP state. The mechanism for why NT-proBNP increased more than BNP is not clear but may be related to separate mechanisms of degradation and clearance [49].

BNP levels are also increased among patients with CKD and could be the consequence of increased LV wall tension related to ventricular dysfunction, hypervolemia or both. NT-proBNP appears to be independently associated with high levels of CRP in pre-dialysis patients with CKD [50].

Overall, these results suggest an association between ventricular filling pressure and inflammation in patients with CHF and CKD, and that NT-proBNP and active BNP might be considered markers for systemic inflammation as well as for congestion.

Sources of inflammation in the cardiorenal syndrome

It is clear that both CHF and CKD are states of chronic inflammation with elevated levels of circulating inflammatory mediators. However, the biologic sources driving this chronic inflammatory state are not fully understood. There is well-established evidence that activation of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS) promotes an inflammatory response in the heart and kidneys of CHF and CKD patients. However, accumulating evidence suggests that volume overload and venous congestion are an additional source of inflammatory mediators.

Neurohormonal sources of inflammation

In CHF and CKD, there is increased activity of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS) [51, 52]. Angiotensin II (Ang II) is the primary bioactive peptide in the RAAS acting through angiotensin type 1 receptor (AT1R) to exert its intracellular effects. Interestingly, chronic blockade of the AT1R in patients with CHF and CKD decreases circulating levels of pro-inflammatory cytokines such as TNF- α [53, 54]. Furthermore, animal and in vitro studies show that Ang II increases TNF- α and IL-6 expression in cardiomyocytes through increased activation of nuclear factor kappa- β (NF κ B) and activator protein 1 (AP-1) [55]. Similarly, in rats, there is increased TNF- α and IL-6 expression in renal cortical and tubular cells exposed in vivo to Ang II as well as heightened production of IL-6 in cultured renal mesangial cells treated with Ang II [53, 56]. The increased local expression of pro-inflammatory molecules is inhibited in all cases by

AT1R blockade. This suggests that the RAAS, and more specifically Ang II may be a source of inflammatory molecules in cardiorenal disease.

The SNS is also activated in CHF and CKD [51]. In CHF specifically, part of the salutary effect of beta-blockers may be related to their anti-inflammatory properties. Animal studies with chronic in vivo beta-adrenergic stimulation with isoproterenol show increased mRNA expression of pro-inflammatory cytokines TNF- α , IL-6, and IL-1 β in myocardial cells and cardiac blood vessels [57]. Beta-blockade with metoprolol selectively decreases TNF- α and IL-1 β expression in the myocardium [57].

The neurohormonal imbalance of the cardiorenal syndrome with increased RAAS and SNS activity is thus a biologic source of chronic inflammation. However, it is less clear that local production of pro-inflammatory mediators in the heart or the kidney is primarily responsible for the increased levels measured in the peripheral circulation. For example, the above in vivo studies of β -adrenergic stimulation in animals showed no identifiable spillover of the cytokines into the systemic circulation [57]. Previous work also concluded that the mean concentration of inflammatory cytokines in the coronary sinus versus the arterial system is similar. This lack of a concentration gradient suggests that the heart may not be the main contributor to the elevated cytokines in the peripheral circulation [58]. On the same note, Testa et al. demonstrated that consistent elevations in circulating levels of cytokines depend on functional class of CHF rather than level of impairment in LVEF [5]. If the elevation of plasma cytokines was in fact due to an inflammatory response within the heart, one would expect their levels to be elevated in patients who have a substantial amount of myocardial damage, as documented by severely depressed LVEF, even if they exhibit class I or II symptoms. The authors suggest that peripheral rather than cardiac foci of injury may thus be the site for cytokine production [5].

Venous congestion as a source of inflammation

The deleterious role of venous congestion and volume overload in the cardiorenal syndrome is becoming increasingly recognized. Measures of venous congestion including central and jugular venous pressure, peripheral edema, and orthopnea predict the development of worsening renal failure in patients with CHF, more so than measures of renal perfusion including cardiac index and systolic blood pressure [59, 60]. While it is difficult to separate volume overload per se from worsening of heart and renal failure, growing evidence suggests a contributory role of venous congestion to neurohormonal activation and inflammation in CHF and CKD.

As discussed earlier, endotoxemia is a potent inflammatory stimulus in CHF and CKD. Anker et al. in 1997 suggested that volume overload and subsequent mesenteric venous congestion leads to bowel wall edema with translocation of gram-negative bacteria through the endothelial cells of the intestinal villi. LPS is then released into the circulation, interacting with cluster of differentiation 14 (CD14) and activating the inflammatory response [61]. This was further supported by a follow-up cohort study in patients with CHF which showed that LPS was most elevated in patients with peripheral edema and that these levels decreased with acute diuretic treatment [62]. Additional key information arrived in 2003, when Peschel et al. reported higher levels of endotoxin in hepatic veins as compared to the left ventricle during acute heart failure. These findings together with the observation of a subsequent reduction in systemic endotoxin levels at follow-up after resolution of the acute decompensation episode, further support the possibility of a mechanistic link between venous congestion and bacterial or endotoxin translocation in CHF [63].

Similarly, in a recent prospective study, endotoxin levels were higher in CKD patients with signs of fluid overload compared to CKD patients without fluid overload [27]. Circulating

LPS is a potent stimulus for the activation of TNF- α and IL-6, mediated through interaction of LPS with CD14 and the activation of NF- κ B [26]. These cytokines might sustain a vicious cycle of further NF- κ B activation, further proinflammatory cytokine production, cardiorenal depression, worsened bowel edema, and more LPS translocation [26].

Besides the edematous bowel, veins, and peripheral tissue when exposed to high intravascular and interstitial pressures, respectively can be important sources of inflammatory mediators. Data from Tsutamoto et al. support this possibility. Plasma IL-6 concentration was higher in the femoral vein than the femoral artery in patients with advanced CHF. This positive venous-arterial gradient suggests the possibility of a peripheral spillover of IL-6 from the legs which increases with severity of congestion within lower extremity veins and tissue [17].

The vascular endothelium itself may become a primary source of cytokine production in response to biomechanical stress due to intravascular congestion. Several in vitro studies have shown that endothelin-1 (ET-1) [64], IL-6 [65] and TNF- α [66] can be secreted within hours of stretch exposure. Recent animal and human studies indicate that congestion may lead to venous endothelial activation with peripheral synthesis and release of pro-inflammatory mediators. Using a novel endothelial sampling method, we showed that markers of inflammation such as cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) expression were elevated in venous endothelial cells harvested from patients with clinical signs of congestion during decompensation of CHF. After treatment, the expression levels of these proteins decreased to levels seen in healthy subjects [67, 68]. This suggests a pro-inflammatory state of the venous endothelium in times of venous congestion. Additional experiments confirmed that venous congestion itself is sufficient to cause activation of the inflammatory program in venous endothelial cells. Normal dogs exposed to rapid fluid load resulting in a sustained increase in venous pressure to 20 mmHg exhibited a dramatic increase in endothelial markers of inflammatory stress including iNOS, COX-2, and TNF- α . Importantly, venous congestion also caused neurohormonal activation as evidenced by a significant increase in plasma norepinephrine (NE), IL-6, ET-1, and TNF- α [69]. Subsequent preliminary work in healthy human individuals using an arm pressure cuff to artificially induce venous congestion have shown similar results [70].

These results demonstrate that venous congestion and volume overload alone can promote an inflammatory state with elevations of inflammatory mediators in the circulation. Ultimately, the source of chronic inflammation in cardiorenal syndrome is likely a combination of the several biologic mechanisms discussed.

Inflammation and end organ damage in the cardiorenal syndrome

Inflammation has several direct biologic effects on the cardiovascular and renal systems, leading to both functional and structural end-organ damage. Pro-inflammatory cytokines, in particular TNF- α , play a central role in cell damage and dysfunction contributing significantly to the development of CHF and CKD [71]. More recently, there has been growing interest in the direct pathogenic effects of CRP.

Cardiac damage

In several animal models, TNF- α mediates progressive LV dilation and dysfunction as well as increased cardiac mortality [72, 73]. Much work has focused on elucidating the mechanisms causing cardiodepression with TNF- α exposure. High concentration of nitric oxide (NO) production secondary to increased inducible nitric oxide synthase (iNOS) expression has been implicated as one possible pathway. Excessive NO mediates basal myocardial depression through several alterations of intracellular calcium homeostasis.

These include a decreased calcium transient into myocytes, inhibition of ryanodine receptors on sarcoplasmic reticulum, and a decrease in myocyte sensitivity to intracellular calcium [71, 74, 75]. Interestingly, a recent study by Duncan et al. showed that not only TNF- α , but also IL-1 β decreases contraction amplitude, sarcoplasmic reticulum calcium concentration, and calcium transient amplitude in isolated rat ventricular myocytes [76]. TNF- α and its related cytokine TWEAK, as well as IL-1 β also contribute structurally to adverse ventricular remodeling in CHF by increasing cardiac apoptosis [77–80] and extracellular matrix degradation [81–83]. The LV wall thinning seen with chronic TNF- α exposure is associated with significant loss of fibrillar collagen, a typical phenotypic effect of increased matrix metalloproteinase (MMP) activity [73].

While the TNF- α and the IL-1 superfamily of cytokines appear to have a clear pathophysiologic effect on cardiac cells, IL-6 has a less-defined role. Like TNF- α , IL-6 has a negative inotropic effect on myocardium, mediated through the same NO and iNOS-based mechanisms detailed earlier [71]. However, recent evidence suggests that IL-6 might be cardioprotective in CHF through the gp-130-Janus Kinase (JAK)-signal transducers and activators of transcription (STAT) 3 signaling pathway. A recent study by Banerjee et al. showed that IL-6 deficient mice developed cardiac dilatation with increased fibroblast proliferation and cardiomyocyte apoptosis. This effect was mediated through a decrease in STAT3 activation in IL-6 deficient mice [84]. In addition, infusion of IL-6 and its soluble receptor complex prevents myocyte apoptosis and reduces infarct size in an animal model of ischemia/reperfusion [85]. These results raise the intriguing possibility that circulating IL-6 is protective rather than detrimental in CHF [86].

CRP was previously thought to simply be a marker of inflammation in CHF. However, emerging evidence suggests that like the pro-inflammatory cytokines, it exerts a detrimental effect on the heart by amplifying the inflammatory response responsible for adverse ventricular remodeling [87, 88]. Interestingly, high CRP levels also upregulate Ang II receptors in cardiac fibroblasts, myocytes, and vascular cells suggesting a vicious cycle of CRP worsening Ang II mediated cardiovascular disease leading to further increases in CRP production [88].

Finally, fluid overload and high ventricular filling pressures may negatively impact cardiac function, by causing subendocardial ischemia, LV remodeling, impairment of cardiac venous drainage from coronary veins, and a lower threshold for arrhythmias [89]. At a molecular level, mechanical strain stimulates intracellular signaling. Activation of melusin-PI3-Kinase/Akt and muscle LIM protein (MLP)-calcineurin pathways promotes hypertrophy which may be initially protective against hemodynamic overload but becomes detrimental when sustained, eventually leading to contractile dysfunction and CHF [86].

Vascular damage

Endothelial homeostasis is a state of balance between endothelium-derived relaxing and contracting factors. The key endothelium-derived relaxing factor is NO. Pro-inflammatory cytokines such as TNF- α and IL-1 β disrupt this vasomotor balance by enhancing NO degradation through activation of nicotinamide adenine dinucleotide phosphate (NAD(P)H) oxidase and enhanced superoxide production [90, 91]. Thus, increased oxidative stress may be responsible for the depressed NO-mediated vasodilation observed in patients with CKD as well as in those with severely symptomatic CHF. In CHF specifically, reduction of inflammation and endothelial oxidative stress with return to a compensated state [92], may increase NO bioavailability and thereby enhance NO-mediated vasodilation [93]. It is also interesting that systemic infections, a recognized trigger of decompensation in CHF, can cause transient endothelial dysfunction [94, 95]. Vlachopoulos et al. have shown that acute systemic inflammation caused by *Salmonella typhi* vaccination leads to deterioration of

large-artery stiffness. These effects are also transient and associated with significant increases in inflammatory markers such as CRP and IL-6 [96]. Given the regulatory role of the endothelium on arterial stiffness, the authors attributed the observed increase in aortic stiffness to the unfavorable effect of inflammation on NO bioavailability. Impaired vasorelaxation carries hemodynamic consequences which are critical in CHF patients as they may hinder preferential distribution of limited cardiac output to essential organs such as the heart and kidney. Kidney under-perfusion results in sodium and water retention with further venous congestion. The vascular endothelium itself may then become a primary source of cytokine production in response to biomechanical stretch (see above in “Venous congestion as a source of inflammation”). Apart from its hemodynamic effects, NO also protects vessels from injury, inflammation, and thrombosis. In ordinary conditions, the endothelium is resistant to leukocyte adhesion. However, pro-inflammatory cytokines, especially TNF- α promote leukocyte adhesion to endothelium via depletion of NO and expression of adhesion molecules (see above). Systemic inflammation may thus set the stage for initiation and progression of atherogenesis within the arterial wall.

Several studies have also investigated the role of CRP in vascular disease and atherosclerosis. From a functional perspective, it has been suggested that CRP might reduce renal blood flow by inhibiting NO synthesis and stimulating Ang II and endothelin-1 production [97]. From a structural perspective, CRP promotes the expression of adhesion molecules including ICAM-1, VCAM-1, and E-selectin and enhances apoptosis in coronary vascular smooth muscle cells thereby promoting instability inside the atherosclerotic plaque [98–101].

Renal damage

There has been long-standing interest in the involvement of inflammatory mediators including TNF- α , IL-6, and CRP in the pathophysiology of progressive renal impairment seen in CKD. In early renal dysfunction, both TNF- α and oxidative stress have been shown to cause intravascular volume expansion by reducing renal sodium excretion [102, 103]. Fluid retention and elevated pressures in renal veins increase intra-renal and systemic concentrations of Ang II [104, 105] and stimulate the SNS [106, 107] with a net reduction in GFR [108] and an increased expression of pro-inflammatory cytokines in response to enhanced neurohormonal activation (see above in “Neurohormonal sources of inflammation”) [109]. As renal function progressively declines, the pathway to irreversible renal damage and fibrosis likely results from a common pathogenic process, independent of initial etiology of CKD, which includes interstitial infiltration of inflammatory cells and the induction of tubular injury. In the tubulo-interstitial compartment, TNF- α and IL-6 promote accumulation of inflammatory cells in the interstitium by increasing monocyte chemoattractant protein-1 (MCP-1), ICAM-1, and VCAM-1 expression [110–112]. Infiltrating cells are thought to activate the renal proximal tubular cells, which in turn continue the vicious cycle by enhancing local secretion of various inflammatory mediators. In addition, tubules in renal biopsies from patients with advanced chronic kidney disease (GFR < 30) also stain strongly for CRP, which correlates significantly with increasing severity of interstitial fibrosis and declining renal function [113]. The end-result is overproduction of matrix components resulting in fibrosis, loss of local tissue integrity, and a progressive decline in renal function [114]. TNF- α also plays a key role in the glomerular damage associated with glomerulonephritis by regulating renal mesangial cell apoptosis. As early as 1990, human recombinant TNF- α induced significant oxidant radical production in adherent human renal mesangial cells with superoxide being the primary radical species formed [115]. Finally, biomechanical stress itself via fluid overload and congestion may cause additional glomerular damage through increased expression of pro-fibrotic and inflammatory genes [116].

In sum, the inflammatory mediators of CHF and CKD are not simply inert markers but rather active participants in the pathophysiology of the disease. Within the cardiovascular and renal system, pro-inflammatory cytokines and CRP exhibit detrimental effects on heart, vasculature, and kidneys leading to progressive organ dysfunction and damage. It is interesting that several of the pro-inflammatory markers induce expression of each other and that many of the signaling pathways activated by these markers overlap. This indicates that the mediators of inflammation work in synchrony while promoting worsening disease and are not independent of each other.

The active role of inflammation in the pathophysiology of the cardiorenal syndrome

The cardiorenal syndrome is a pathophysiological condition in which combined cardiac and renal dysfunction amplifies the progression and failure of each individual organ. Evidence suggests that inflammation is a fundamental stressor in this process and that its burden and duration may chronicle both the acute and chronic courses of cardiorenal disease [117].

Traditional theories have pointed to the direct toxic effects of pro-inflammatory cytokines on the heart and kidney. Contemporary evidence (see above) would favor a broader approach that takes into account the key role of endothelial activation and venous congestion in the hemodynamic and inflammatory events that define the progression of the cardiorenal syndrome.

Several investigators including Cotter et al. [119] have found that afterload–preload mismatch plays a significant role in the pathophysiology of CHF. Such mismatches stemming from i) enhanced arterial stiffness and afterload impeding the forward flow out of the LV, and ii) venous activation reducing venous capacitance and increasing venous pressure, can directly decrease cardiac output and increase cardiac filling pressures. More recent evidence suggests that key endothelial regulatory events—possibly linked to inflammation—may be responsible for this hemodynamic derangement [118]. Increased pressure in the central venous system is especially important as it directly increases renal venous pressure, thereby promoting kidney dysfunction and progressive damage [119, 120]. How is inflammation central to this process? First, inflammation can beget vascular dysfunction via endothelial activation and enhanced arterial stiffness. Second, inflammation may reduce myocardial contractility either through functional suppression of the contractile apparatus or through increased myocardial cell death. Third, inflammation may cause progressive renal dysfunction and fibrosis. Finally, inflammation may increase the permeability of the endothelium allowing extravasation of fluids into the alveolar space of the lungs and absorption of pro-inflammatory endotoxin from the bowel. Furthermore, we have shown that venous congestion can promote venous activation and peripheral release of pro-inflammatory cytokines. Overall, a vicious cycle appears to link inflammation and congestion through progressive vascular, cardiac, and renal failure (Fig. 2). Water and sodium retention are central to this process as inflammation—either inherent to the cardiorenal syndrome or triggered by an external modifier such as infection—may increase preload and afterload leading to congestion begetting more congestion and ultimately more inflammation. This process can also progressively alter fundamental aspects of normal human physiology by shifting the body from a healthy biosystem that operates at low pressures to a pathophysiologic milieu where organs and tissues are forced to function (or malfunction) within a high-pressure environment. The time-course of these hemodynamic and pro-inflammatory events will chronicle the course of the cardiorenal syndrome: chronic when smoldering, acute when more abrupt. The resulting deterioration in clinical status, whether acute or chronic, will carry dramatic consequences in patients' prognoses with more frequent hospitalizations and increased risk of death.

Anti-inflammatory treatments options

Accumulating evidence supports a central role of inflammation in the pathophysiology of CHF and CKD. However, recent attempts to translate this evidence to large clinical trials testing anti-inflammatory treatment strategies have been for the most part disappointing.

In CHF, several randomized placebo-controlled trials of anti-TNF- α therapies (i.e., Randomized Etanercept North American Strategy to Study Antagonism of CytokineEs (*RENAISSANCE*), Etanercept Cytokine Antagonism in Ventricular dysfunction (*RECOVER*) and Anti-TNF Therapy Against Congestive Heart failure (*ATTACH*)) [121–123] showed no benefit in clinical outcome. This may reflect the redundancy of the cytokine cascade and the fact that anti-TNF- α therapies do not stimulate increased activity of the anti-inflammatory arm of the immune system. Such considerations provided the rationale for subsequent studies that investigated broad-spectrum immunomodulation using ex vivo exposure of autologous blood to controlled oxidative stress and subsequent intramuscular administration [124]. The advanced chronic heart failure clinical assessment of immune modulation therapy (*ACCLAIM*) did not find any significant reduction in mortality or cardiovascular hospitalization with the exception of two prespecified subgroups of patients, those without a history of previous myocardial infarction (MI) and those with NYHA class II CHF, who had a significant reduction in their primary endpoint [125]. Initial experiences with intravenous immunoglobulin, interferon treatment, and immunoadsorption have also led to conflicting results [125–128]. The value of these treatment strategies remains overall uncertain at this stage. Surprisingly, no other form of anti-inflammatory therapy has been examined in large scale studies though suggestions have been made that some of the beneficial effects of angiotensin-converting enzyme inhibitors (ACEi's), angiotensin receptor blockers (ARBs), and statins are due to their pleiotropic anti-inflammatory actions [52, 129–132]. However, recent results from the Controlled Rosuvastatin Multinational Trial in Heart Failure (*CORONA*) that randomized 5,011 CHF patients to placebo or rosuvastatin challenge this interpretation. Rosuvastatin failed to show benefit despite a significant reduction in CRP levels during follow-up [133]. Based on the data that we presented above, optimization of fluid status per se may also be considered an anti-inflammatory intervention in view of its downstream vascular, cardiac, and renal effects [134]. The Pulmonary Artery Catheterization Effectiveness (*ESCAPE*) trial tested Swan-Ganz directed fluid optimization versus clinical assessment in patients with decompensated CHF. Results were somewhat mixed. On one side hemodynamic monitoring did not improve clinical outcome; on the other, renal function remained stable when treatment was directed using the invasive strategy, while it declined when treatment was guided by clinical assessment alone [135].

Treatment of primary glomerular disease relies on anti-inflammatory agents, such as corticosteroids and other immunomodulatory agents, as they reduce inflammation and slow disease progression [97]; however, the mainstay of therapy in CKD remains RAAS inhibition. Blockade of the RAAS and lipid-lowering agents have shown promise in their ability to reduce inflammation and slow CKD progression. Angiotensin receptor blockers and ACE inhibitors appear equally effective at reducing proteinuria [136, 137]. Data from small studies in glomerular disease suggest that statins decrease proteinuria [138]. Until recently, the only major randomized trial of statins ever conducted in dialysis patients with diabetes, the German Diabetes and Dialysis Study (*4D*), did not find atorvastatin to have any benefit compared with placebo in reducing a composite end point of death from cardiac causes, stroke, and nonfatal MI over a median of 4 years of follow-up, despite a decrease in LDL-C of over 40% in the treatment group [139]. However, the largest-ever statin trial in patients with CKD is the recent Study of Heart and Renal Protection (*SHARP*), in which 9438 CKD patients (both pre-dialysis and on dialysis) were randomized to either 20 mg simvastatin plus 10 mg ezetimibe, or placebo. The trial showed a significant reduction of

16.5% in cardiovascular events over 4.9 years of follow-up. This favorable treatment effect was more evident in pre-dialysis than in dialysis patients [140].

Physical training offers a non-pharmacologic alternative for attenuation of inflammation in CHF and CKD. Aerobic exercise is associated with significant reduction in circulating pro-inflammatory mediators such as TNF- α , TNF receptors, sICAM, sVCAM [141–144] as well as increased expression of anti-oxidative enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx) in skeletal muscles [145]. Endurance training improves peak exercise capacity [146], reverses endothelial dysfunction [147, 148] and may also improve survival in patients with CHF [149–151]. Physical training improves peak exercise capacity in CKD as well. This improvement may be associated with reduced mortality in this patient population [152–154].

Overall, despite early promising results, most clinical trials of anti-inflammatory therapies have to date failed to show clear benefit, particularly in CHF patients. The consensus document by the Heart Failure Association of the European Society of Cardiology provides important recommendations regarding future testing of anti-inflammatory therapies [155]. Firstly, more careful and precise patient selection appears warranted. For example, inflammatory activation may be different in the early stages after acute MI compared with CHF, and it would be worthwhile undertaking different clinical trials in these two patient groups. Similarly, the diversity of different forms of CHF such as diabetic, ischemic, hypertensive, viral, and idiopathic as well as gender differences in CHF should be taken into account when considering specific inflammatory pathways to target [155]. Finally, it is possible that some of the above mentioned failures relate to the fact that anti-inflammatory therapy was implemented in stable patients with chronic CHF, while the vicious cycle of inflammation, vascular activation, and cardiorenal impairment might be most sensitive to treatment during the unsettled phases of smoldering disease progression and/or acute decompensation. It is conceivable that a new anti-inflammatory treatment approach targeting these dynamic phases of the cardiorenal syndrome may be more successful. Interestingly, in a small study Zhang et al. [156] have shown that adjuvant steroid therapy in patients with acute decompensated CHF resistant to 1 week of intravenous diuretics induces some additional diuresis and improves symptoms suggesting that anti-inflammatory therapy may be beneficial in such patients. However, these results should be confirmed in larger prospective randomized studies.

Conclusion

Chronic inflammation within the heart, kidneys, and vasculature is implicated in the pathophysiology of the cardiorenal syndrome. While inflammation represents the effect of CHF and CKD rather than the original cause, once initiated and sustained, it leads to several pathophysiological effects that may contribute to progressive end-organ dysfunction and damage. Taken together, it appears that multiple inflammatory stressors from CHF and CKD may amass over time causing progressive fluid accumulation, which is a pro-inflammatory stressor itself, stimulating a dramatic downward spiral in patients' functional status and prognosis. Treatment strategies that have tried to reverse this inflammatory process have been disappointing thus far. A paradigm shift in our treatment focus thus appears warranted. This new approach may involve specific anti-inflammatory strategies for different etiologies and stages of the disease. It may also include, as one may infer from our data (short-term) anti-inflammatory treatments that may aggressively counteract inflammation and congestion during the unsettled phases of the syndrome until biologic and clinical compensation is regained and sustained.

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Fig. 1.

Plasma concentrations of interleukin-6 (IL-6) increase with worsening functional status of congestive heart failure (CHF) (a) as well as with worsening stage of chronic kidney disease (CKD) (b). CKD Stage 5D refers to Stage 5 CKD on hemodialysis. Images reproduced from Aukrust et al. [12] (a) and from Barreto et al. [22] (b)

Fig. 2.

The active role of inflammation in the pathophysiology of the cardiorenal syndrome. While venous congestion represents the effect rather than the cause, once initiated and sustained, it may cause additional fluid retention through cardiac, vascular, and renal dysfunction and damage that in a vicious cycle promotes additional inflammation