Published in final edited form as:
Curr Heart Fail Rep. 2010 June ; 7(2): . doi:10.1007/s11897-010-0009-5.

Venous Congestion and Endothelial Cell Activation in Acute Decompensated Heart Failure

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Abstract

Despite accumulating clinical evidence supporting a key role for venous congestion in the development of acute decompensated heart failure (ADHF), there remain several gaps in our knowledge of the pathophysiology of ADHF. Specifically, the biomechanically driven effects of venous congestion on the vascular endothelium (the largest endocrine/paracrine organ of the body), on neurohormonal activation, and on renal and cardiac dysfunction remain largely unexplored. We propose that venous congestion is a fundamental, hemodynamic stimulus for vascular inflammation, which plays a key role in the development and possibly the resolution of ADHF through vascular, humoral, renal, and cardiac mechanisms. A better understanding of the role of venous congestion and endothelial activation in the pathophysiology of ADHF may provide a strong rationale for near-future testing of treatment strategies that target biomechanically driven inflammation. Targeting vascular and systemic inflammation before symptoms arise may prevent progression to overt clinical decompensation in the ADHF syndrome.

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Disclosure Dr. Paolo C. Colombo has received an investigator-initiated research grant (NCT000698139) from Medtronic, Inc. No other potential conflicts of interest relevant to this article were reported.

Keywords

Endothelium; Heart failure; Inflammation; Congestion

Introduction

Patients with chronic heart failure (CHF) consume considerable health care resources due to frequent hospitalization for acute decompensated heart failure (ADHF), based on clinical evidence of venous congestion [1–3]. Accumulating evidence suggests that venous congestion 1) begins to occur weeks before symptoms worsen, resulting in a need for hospitalization [4, 5•], and 2) is an important hemodynamic predictor of worsening renal function, rehospitalization, and postdischarge mortality in ADHF [6, 7]. Little is known, however, about the role of venous congestion itself in the pathophysiology of ADHF.

The following discussion details the evidence that 1) venous congestion itself may switch the synthetic and endocrine profile of the endothelium from quiescent toward an activated state that is pro-oxidant, proinflammatory, and vasoconstricting, and 2) once "activated," the endothelium can promote additional congestion through humoral, renal, and cardiac mechanisms, resulting in a deleterious positive feedback loop that leads, over time, to overt decompensation in CHF patients.

The Central Role of Venous Congestion in ADHF

It is estimated that hospitalizations for ADHF account for more than three quarters of the approximately $50 billion dollars spent each year on the care of CHF patients [1]. Most hospitalizations for ADHF occur because of symptoms and signs of venous congestion rather than a low cardiac output [2, 3]. Symptoms of congestion that bring patients to the hospital typically worsen a few days before hospital admission [4]. However, recent studies have shown that the natural history of congestion is not rapid, but that there is a distinct period of subclinical venous congestion that occurs well before symptoms of congestion become apparent. Home monitoring of daily weight [5•] and continuous monitoring of intracardiac pressures [8] and pulmonary congestion via intrathoracic impedance [4] all provide evidence that venous congestion begins to occur much earlier than previously thought, ultimately leading to ADHF.

An increase in weight, right-side filling pressures, and intrathoracic fluid marks venous congestion, and these parameters start to increase at least 7–14 days before CHF signs and symptoms worsen, eventually leading the patient to require urgent intravenous therapy [4, 5•]. Despite its importance, physicians often fail in treating congestion. Approximately half of patients do not lose body weight during hospitalization [2], which is a treatment failure that has major consequences. Refractory systemic congestion (neither cardiac index nor systemic blood pressure) is a hemodynamic predictor of worsening renal function, rehospitalization, and postdischarge mortality in patients hospitalized for ADHF [6, 7].

Initially, hypertension, ischemia, arrhythmias, worsening left and/or right ventricular systolic or diastolic function, dietary indiscretion, and medication noncompliance may all promote fluid retention and venous congestion in patients with CHF [9, 10]. Regardless of the cause of congestion, once fluid accumulates, a deleterious cycle of events is set into motion. Fluid accumulation exerts negative effects on the kidneys [11, 12], on the heart [13], and based on more recent evidence, on the congested vasculature and peripheral tissue, causing release of inflammatory and vasoconstricting mediators into the bloodstream that promote additional fluid retention [14, 15••].

Venous Congestion as a Modulator of the Endothelial Phenotype

The vascular endothelium, aligned between the blood and tissues, is the largest endocrine/paracrine organ of the body. The endothelium generates an impressive number of bioactive and vasoactive molecules such as nitric oxide (NO), prostaglandins (PGs), and cytokines, which play a crucial role both in the physiological adaptations that sustain the compensated state of CHF, and in the patho-physiological dysfunctions that promote the transition to ADHF [16]. Endothelium NO-mediated control of venous tone is important in CHF. Veins represent a low-pressure reservoir that contains greater than 70% of the systemic blood volume [17]. The profound capacity of this reservoir implies that relatively small volume reductions in peripheral veins are followed by substantial increases in central blood volume and cardiac filling pressures.

The vascular endothelium mediates several other physiological and pathological processes besides NO-mediated control of the vasomotor tone. Inflammation, hemostasis, and angiogenesis are all modulated by the endothelium through transitions between quiescent and activated states that occur in response to environmental stressors [18]. The vascular endothelium, akin to a barcode reader, is constantly registering its neighboring environment [19]. Endothelial cells (ECs) sense not only biochemical stimuli, but also biomechanical forces, and translate both types of signals into genetic regulatory events [16]. When exposed to biomechanical stress (circumferential stretch associated with venous congestion), ECs can switch their synthetic profile from a quiescent state toward an activated state, which is pro-oxidant, proinflammatory, and vasoconstricting [20, 21], and the EC phenotype may eventually contribute to the development of ADHF (Fig. 1).

In vitro evidence suggests that biomechanical signals such as stretch modulate endothelial production of reactive oxygen species (ROS) [22, 23] and of inflammatory mediators such as endothelin-1 (ET-1) [24], interleukin-6 (IL-6) [25], and tumor necrosis factor-α (TNF-α) [26]. Excessive oxidative stress exerts pleiotropic damaging effects, including reduction of vascular NO bioavailability. NO is now recognized as a key determinant of vascular health, not only through its vasodilatatory, but also through its anti-oxidant and anti-inflammatory properties [27]. The biosynthesis of endothelial NO is primarily catalyzed by constitutively expressed endothelial NO synthase (eNOS) and by inducible NO synthase (iNOS), the latter expressed in response to proinflammatory stimuli such as cytokines and oxidative stress [28, 29]. The activity of eNOS is modulated by post-translational mechanisms such as phosphorylation at specific serine and threonine residues. Available NO is degraded by superoxide with formation of peroxynitrate, a toxic metabolite that nitrosylates proteins on tyrosine residues [30].

ROS and cytokines may also trigger an inflammatory response through activation of nuclear factor (NF)-κB [31], a transcription factor that promotes expression of iNOS and other proinflammatory genes such as cyclo-oxygenase-2 (COX-2), TNF-α, and adhesion molecules such as intercellular adhesion molecule [32, 33]. iNOS has recently been shown to bind, nitrosylate, and activate COX-2, a key observation that links two major human inflammatory systems in their response to various stimuli [34]. Overall, vascular stretch and oxidative injury may cause ECs to transition from a quiescent to an activated state where, in a vicious cycle, oxidative stress promotes inflammation, which, in turn, increases oxidative stress. In this context, anti-oxidant enzymes are the primary defense mechanism against damage, counteracting a system that has lost internal control. Copper-zinc superoxide dismutase (CuZnSOD), manganese SOD (MnSOD), catalase, and glutathione peroxidase (GPx) inactivate ROS, thereby protecting cells from the pleiotropic detrimental effects of oxidative stress [35, 36••, 37]. In addition, GPx has the unique ability to catalyze the reduction of peroxynitrite [38]. In summary, based on these reports, vascular stretch can

activate endothelial pro-oxidant and proinflammatory programs, an effect that is antagonized by endogenous antioxidant/inflammatory defenses.

Venous Endothelial Activation in ADHF: Mechanisms and Human Studies

We used a novel approach that involves sampling of venous ECs coupled with quantification of protein expression by quantitative immunofluorescence analysis [39, 40], and quantification of gene transcripts by real-time polymerase chain reaction [41] to study markers of the oxidant/inflammatory program in the venous endothelium of patients hospitalized for ADHF [42]. Endothelial markers of the oxidant/inflammatory program such as nitrotyrosine, COX-2, and iNOS were significantly increased in venous ECs of patients with ADHF compared with age-matched healthy subjects. Return to a steady compensated state was associated with a weight reduction of ≥5 lbs and resulted in a substantial reduction in endothelial pro-oxidant/proinflammatory markers [42]. eNOS expression was similar in patients and controls. However, preliminary evidence from more recent experiments suggest that the phosphorylated and active form of eNOS, phospho-eNOS, was severely reduced in ADHF patients compared with age-matched compensated CHF patients and age-matched healthy subjects [43]. This finding suggests that not only increased NO degradation (as evidenced by enhanced nitrotyrosine formation), but also decreased NO production, may reduce NO bioavailability in veins and may thereby contribute to inflammation and vasoconstriction in ADHF. Thus, in patients with ADHF who have clinical evidence of congestion, the venous endothelium demonstrates marked abnormalities as evidenced by activation of the oxidant/inflammatory program and by reduced NO bioavailability.

Although these findings were interesting, they did not address whether venous congestion itself was sufficient to trigger the genetic regulatory events related to endothelial activation. As the transition from compensated CHF to ADHF is not easily pinpointed in humans, experimental models are warranted to mechanistically investigate the role of venous congestion in the pathophysiology of endothelial activation in ADHF.

For this purpose, normal dogs were studied at baseline and 1 h after fluid load, resulting in an increase in venous pressure to >20 mmHg [15••]. Systemic fluid load resulted in a twofold increase in mRNA levels of pro-oxidant/proinflammatory genes such as iNOS, COX-2, and TNF-α in venous ECs. An adaptive increase in antioxidant/anti-inflammatory enzymes such as CuZnSOD and GPx-1 was also observed. Concurrently, fluid load caused a profound increase in plasma markers of systemic neurohormonal activation linked to the CHF syndrome, including norepinephrine, IL-6, ET-1, and TNF-α (Table 1). Thus, systemic venous congestion is sufficient to cause endothelial as well as neurohormonal activation in normal dogs.

Once again we “moved back to the bedside” to probe whether these findings were reproducible in humans. For this purpose, we designed a new experimental model of local congestion to characterize endothelial and humoral responses to acute biomechanical stress [44]. Venous arm pressure was increased to 30 mmHg above baseline by inflating a pressure cuff around the nondominant arm. ECs and blood were sampled before and after 60 min of venous congestion. Our preliminary results in healthy individuals suggest that this new experimental model of local congestion can also promote EC activation and peripheral spillover of inflammatory mediators such as ET-1 and Il-6 from the congested tissue into the bloodstream [44].

In summary, endothelial stretch due to systemic or local experimental congestion appears sufficient to activate venous ECs and cause peripheral release of inflammatory neurohormones and cytokines in a manner consistent with that seen in patients with ADHF. These findings are not surprising as high compliance in the venous system implies that

relatively small pressure increments are followed by substantial increases in intravascular volume and circumferential stretch of the vessel wall. This biomechanical stress can, in turn, switch the endothelial synthetic profile from a quiescent towards an activated state, which is pro-oxidant, proinflammatory, and vasoconstricting.

Venous Congestion as a Modulator of Neurohormonal Activation

The idea that the peripheral endothelium may be a primary source of cytokine production in response to biomechanical stress following vascular congestion in CHF is not entirely new. The site of production of circulating proinflammatory neurohormones and cytokines such as TNF-α, IL-1β, IL-6, and ET-1, which acutely increase in patients hospitalized for ADHF and decline as patients clinically improve, has long been debated [45–48]. Several investigators propose that the heart itself may be an important source of cytokines, especially of TNF-α [49, 50]. Alternatively, Testa et al. [45] suggested that peripheral rather than cardiac foci of injury may be the site for cytokine production. This latter hypothesis is supported by their published data showing that circulating levels of cytokines are consistently elevated only in patients with functional class III–IV, whereas left ventricular ejection fraction (LVEF) is similar in patients with symptoms compatible with functional classes I, II, III, and IV. If the elevation of circulating cytokine levels results predominantly from an inflammatory response within the heart, one would expect circulating levels of cytokines to be elevated in those functional class I patients who have already experienced substantial myocardial damage, as documented by severely depressed LVEF; however, this is not the case [45]. The authors thus suggest that peripheral rather than cardiac abnormalities are the predominant source for cytokine production in symptomatic CHF. Recent in vitro and in vivo evidence, the latter from our human and animal experiments [15••, 44], suggests a key role for the endothelium in the paracrine/endocrine production and release of inflammatory and vasoconstricting mediators, which occur in response to biomechanical stress following venous congestion and correlates with severity of CHF symptoms [47].

Hypervolemia and the “Venous”- Renal Syndrome in ADHF

It is well established that in CHF there is a reduction in renal blood flow (RBF), a lesser reduction in glomerular filtration rate (GFR), and retention of sodium (and water) by the kidneys [51, 52]. Contemporary theories regarding worsening renal function in CHF are largely based on the idea that “effective” blood volume is reduced due to diminished cardiac output, and that sodium retention is the result of the kidney responding, as in hemorrhage, to a perception by receptors in the circulation that blood volume is inadequate [11], so-called “forward failure”. However, although decreased cardiac output may contribute to decreased RBF and decreased GFR in late ADHF, elevated renal venous pressure may play an earlier, more progressive, and possibly more important role in the pathophysiology of impaired renal function in CHF [53•]. As early as 1935, it was noted that average values for cardiac output are often similar between patients with compensated and decompensated CHF [54]. It was postulated around this time that diminished cardiac output was not a primary factor of clinical importance, but rather that increased renal venous pressure from “backward failure” was the major phenomenon driving symptomatology in ADHF.

Although the “backward” failure hypothesis did focus on the concept of increased venous pressure as a primary event in ADHF, proponents of this hypothesis believed that increased systemic venous pressure caused increased transudation of fluid into the extravascular space (due to increased hydrostatic pressure in the veins) and led to depletion of intravascular volume, which led to secondary renal sodium and water retention to restore intravascular volume toward normal [55]. However, whether total blood volume is actually increased or decreased in ADHF is difficult to discern from much of the literature published between the

1930s and 1950s, which is limited in terms of methodology used to measure intravascular volume (dye dilution and tagged red cell techniques) as well as the dearth of normal control data [55–58]. Fortunately, more recent studies using radiolabeled albumin, which is a useful and recommended diagnostic tool given reliable normal values [59, 60], demonstrate that intravascular volume is indeed increased in patients with CHF [61]. Volume overload may activate neurohormonal mediators and the oxidative/inflammatory program in ECs of patients with CHF, as we have previously discussed [15••, 42].

Experimental evidence from classic experiments demonstrate that blood flow through the kidney is reduced more by an increase in venous pressure than by an equivalent decrease in arterial pressure, and that there is a steeply graded relationship between change in renal venous pressure and reduction in urine flow [62]. Distention of the venules surrounding the distal end of the renal tubule may obliterate the lumen of the tubule until the pressure of the fluid within it exceeds that in the veins, and then urine flow is restored [62]. These changes occur independently of reduction in cardiac output and mean arterial pressure, which occur much later in the progression of CHF [12]. As shown in an experimental canine model [12], a rise in venous pressure (well within the range of pressures found in CHF) from unilateral renal vein constriction is associated with abrupt sodium and water retention, without an initial decrease in RBF and GFR. When the rise in renal venous pressure is persistent and prolonged, RBF and GFR eventually fall. These effects are local, limited to the kidney in which renal venous pressure is raised, and do not depend on arterial pressure [12].

Although these classic experiments highlighted the important fact that independent of cardiac output, elevations in renal venous pressure can directly lead to sodium and water retention, and are followed by decline in RBF and GFR, the precise mechanisms involved in worsening renal function associated with CHF were not elucidated. More recent neurophysiological studies indicate that increases in renal venous pressure and distention of intrarenal veins can stimulate mechanoreceptors and enhance local sympathetic renal nerve activity, resulting in intrarenal arterial vasoconstriction and a fall in GFR [63–65]. When the kidney is acutely surgically denervated, the vasoconstrictor response to renal venous pressure elevation is largely abolished [66]. In addition, renal vasoconstriction in the congested kidney may also result from hormone-mediated mechanisms. Angiotensin II has been widely implicated in the physiology of intrarenal vasoconstriction [67]. ET-1 is a potent and long-acting vasopressor peptide that is released by the activated endothelium in response to biomechanical stress [68, 69]. On the other side of the equation, upon exposure to higher venous pressure, the endothelium itself may secrete vasodilating PGs that counteract renal vasoconstriction [70]. After unilateral renal vein constriction in the rabbit, there is a marked increase in PGE_2 biosynthesis, which is dependent on new protein synthesis within the endothelium [71]. These results are in accordance with our recent evidence that venous endothelial COX-2 expression and PGE_2 production are increased in patients with ADHF and later subside after return to a steady compensated state [42]. The importance of COX synthesis and PG-induced vasodilation, as a compensatory mechanism to counteract renal vasoconstriction, is emphasized by an experiment in healthy human subjects showing a heightened fall in RBF by 33% when ET-1 is infused 30 min after intravenous infusion of the COX inhibitor diclofenac [72].

Overall, these studies suggest that an elevation in renal venous pressure through hemodynamic, neurohormonal, and endothelial mechanisms can decrease RBF and GFR, thus providing mechanistic insights into the aforementioned classic physiologic experiments reported between the 1930s and the 1950s.

Venous Congestion as a Modulator of Cardiac Function

The cardiac endocardium is structurally identical to and in continuity with the vascular endothelium, and is thus likely exposed to the same process of biomechanically driven activation that has been detailed above. Importantly, high ventricular filling pressures and local release of proinflammatory mediators [13] may further compromise cardiac function by causing subendocardial ischemia, myocyte loss, and ventricular and atrial arrhythmias. The resulting deterioration in cardiac performance may exacerbate “backward failure,” leading to worsening venous congestion and additional fluid retention.

The Active Role of Venous Congestion and Endothelial Activation in the Pathophysiology of ADHF

Figure 2 summarizes the impact of venous congestion on the pathophysiology of ADHF. Although venous congestion and fluid accumulation represent the effect rather than the cause of CHF exacerbation, once initiated, venous congestion may cause additional fluid retention through endothelial, neurohormonal, renal, and cardiac mechanisms. Vascular stretch associated with venous congestion may switch the synthetic and endocrine profile of the venous endothelium from a quiescent toward an activated state, which, in turn, promotes peripheral release of proinflammatory and vasoconstricting neurohormones. In the kidneys, vascular congestion and activation of the stretched endothelium, now itself a source of oxidative stress and proinflammatory cytokines, may cause additional sodium and water retention. In the heart, high filling pressures further impair systolic and diastolic function, thus worsening venous congestion. When the initial insult (s) subsides, it may be too late to prevent tissue damage, as vicious cycles that link venous congestion to progressive fluid retention are already in place. Symptoms will eventually worsen after weeks of progressive fluid accumulation, eventually leading to hospitalization for overt decompensation.

Future Directions: Targeting Congestion-mediated Inflammation in ADHF

If venous congestion proves to be an early and fundamental hemodynamic and inflammatory stimulus leading to ADHF, a paradigm shift in the treatment focus of ADHF would be warranted, away from current rescue measures, including late intravenous interventions, and toward new preventive measures, which may include oral interventions that target congestion-mediated inflammation prior to the onset of symptoms. From this perspective, closer monitoring of patient volume status using new diagnostic tools for continuous monitoring of intracardiac pressures [8] and intrathoracic impedance [4] may then be used to time early medical interventions, which may prevent progression to overt decompensation. This early treatment strategy may include not only diuretics, but also (as one may infer from our data) adjuvant therapies such as short-term antioxidant and/or anti-inflammatory drugs.

Conclusions

We have reviewed the role of venous congestion and endothelial activation in the pathophysiology of ADHF. Congestion within peripheral vascular tissues, in addition to renal and cardiac tissues, triggers local followed by systemic inflammatory responses, which promote additional fluid retention when endogenous antioxidative, anti-inflammatory, and vasodilating defenses are overwhelmed. Our “venocentric” approach is aimed at complementing rather than replacing other more traditional “cardiocentric”, “nephrocentric”, and “arteriocentric” views, as all systems (i.e. the heart, kidneys, arteries, and veins) appear involved in the sequence of events that trigger and sustain ADHF [11–15••].

Considerable additional work is still needed 1) to further support the validity of venous congestion and EC activation as key mediators of the ADHF syndrome and 2) to test,

possibly in the near future, the clinical application of these advances such that patients experience reduced levels of CHF morbidity and mortality.

Acknowledgments

Dr. Paolo C. Colombo's work is supported by an NIH R01 HL-3001996. Dr. Ryan T. Demmer's work is supported by an NIH K99 DE-018739.

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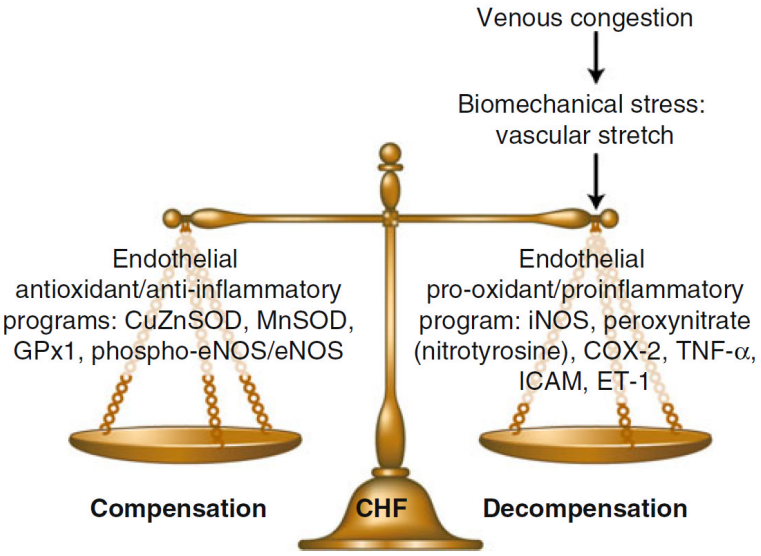

Fig. 1.

Proposed relationship between venous congestion, endothelial activation, and decompensation in CHF: venous congestion ↔ inflammation. ECs sense both biochemical stimuli and biomechanical forces, and translate both types of signals into genetic regulatory events. When exposed to biomechanical stress (circumferential stretch associated with venous congestion), ECs release pro-oxidant, proinflammatory, and vasoconstricting mediators, which contribute to the development of ADHF. Antioxidant enzymes are the primary defense mechanism against oxidative and inflammatory damage. ADHF—acute decompensated heart failure; CHF—chronic heart failure; COX—cyclo-oxygenase; CuZnSOD—copper-zinc superoxide dismutase; EC—endothelial cell; eNOS—endothelial nitric oxide synthase; ET—endothelin; GPx1—glutathione peroxidase; ICAM—intercellular adhesion molecule; iNOS—inducible nitric oxide synthase; MnSOD—manganese superoxide dismutase; TNF—tumor necrosis factor

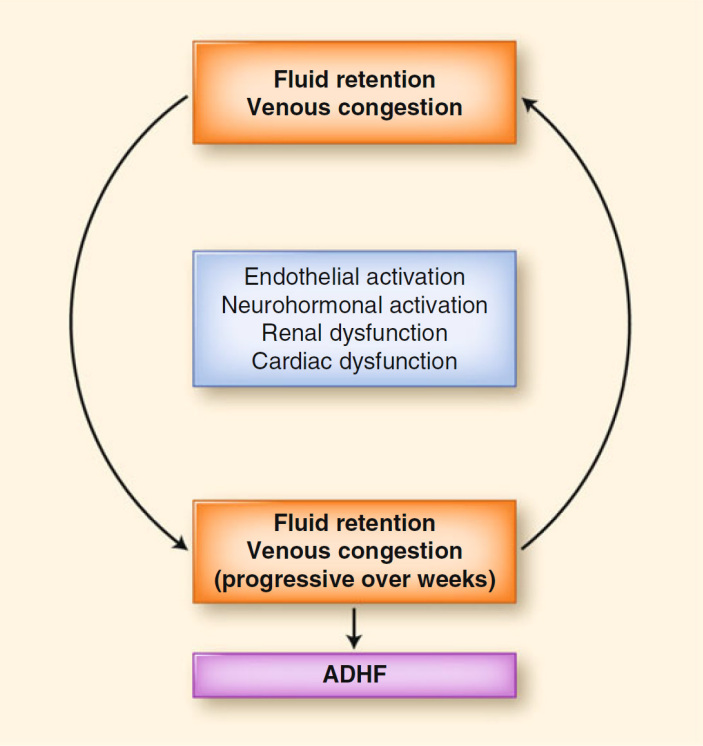

Fig. 2.

The active role of venous congestion in the pathophysiology of ADHF. Although venous congestion represents the effect rather than the cause, once initiated and sustained, it may cause additional fluid retention through endothelial, neurohormonal, renal, and cardiac mechanisms. ADHF—acute decompensated heart failure

Table 1

Markers of endothehal activation and plasma levels of neurohormones before and after systemic experimental congestion in normal dogs

	NL ***CVP* = 8 ± 2 mmHg**	**NL + V** ***CVP* = 22 ± 4 mmHg**
Markers of endothelial activation		
iNOS, du	0.26±0.09	0.48±0.13*
COX-2, du	0.44±0.14	0.67±0.06*
TNF-α, du	0.29±0.02	0.47±0.11*
CuZnSOD, du	1.05±0.08	1.23±0.04*
GPx-1, du	1.33±0.12	2.10±0.01*
Plasma levels of neurohormones		
NE, pg/mL	130±11	491±128*
IL-6, pg/mL	3.3±1.2	15.8±4.3*
ET-1, pg/mL	0.2±0.1	1.8±0.2*
TNF-α, pg/mL	1.1±0.7	2.7±0.3*

COX cyclo-oxygenase, *CuZnSOD* copper-zinc superoxide dismutase, *CVP* central venous pressure, *du* densitometric units (normalized to GADPH [glyceraldehyde 3-phosphate dehydrogenase]), *ET* endothelin, *GPx* glutathione peroxidase, *IL* interleukin, *iNOS* inducible nitric oxide synthase, *NE* norepinephrine, *NL* normal, *TNF* tumor necrosis factor, *V* volume

(Modified from Colombo et al. [15••])

*=$P<0.05$ vs. NL