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Congestion and the Kidney-Heart Cross Talk in Acute Decompensated Heart Failure

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Abstract

Signs and symptoms of fluid overload are the primary reason for hospital admission of patients with acute decompensated heart failure. It has been shown that congestion is a dynamic state with mutual links to both heart failure and renal dysfunction, which is capable of modifying the impact of these two elements on the outcomes. In this article, we provide an overview of the emerging concepts related to pathophysiological aspects of fluid overload in heart failure. Then, methods for objective evaluation of congestion are discussed with emphasis on newer techniques Future studies are needed to determine whether more precise evaluation of fluid overload combined with close monitoring of decongestion process would have a salutary impact on the outcomes of patients with heart failure.

Keywords: Congestion; Diuretics; Heart failure; Acute kidney injury; Ultrafiltration

Introduction

Congestion is the primary reason for hospitalization of patients with heart failure (HF) and has been shown to be an independent predictor of adverse outcomes in these patients [1]. Different communications between heart and kidney have been defined to elucidate the pathophysiologic relation of the two organs [2,3]. The term "cardiorenal syndrome" (CRS) has been expanded to illustrate a condition in which renal function impairment happens due to heart failure [4], however; the definition has not been clear [5]. Previously, there have been multiple different categories described for CRS, including type I, acute cardiorenal syndrome; type II, chronic cardiorenal syndrome; type III, acute renocardiac syndrome; type IV, chronic renocardiac syndrome; and type V, secondary cardiorenal syndrome [6], nevertheless, these categories are not commonly used. Currently, available treatment regimens often lead to suboptimal decongestion in a significant subset of patients who are hospitalized for acute decompensated heart failure (ADHF) and fluid overload. Several studies have suggested that lingering congestion in patients hospitalized with ADHF is associated with worse prognosis, independent of age and underlying renal function (RF) [7,8]. Given the fact that congestion plays an important role in the mortality of HF patients, and it appears to be often undertreated; the intent of this mini-review is to reassess perceptions concerning the pathophysiology of congestion in HF and to reexamine our understanding of how these processes develop and how we might more effectively determine volume status.

Relief of Congestion Improves Cardiac Function

In the normal heart, the ventricle produces pressure isovolumically which results in the ejection of blood. The volume of ejected blood characterizes the forward effective stroke volume of systolic contraction.

In ADHF, there is a failure of ventricular function and ejection of blood, also due to increased arteriolar vasoconstriction, a progressive shift of blood from the effective circulatory volume to splanchnic capacitance veins might be expected. The splanchnic capacitance function ultimately becomes maladaptive in HF as a result of long-standing venous congestion and increased neurohumoral activation. It is noted that cardiac filling pressures generally start to increase about 5 days preceding an admission for ADHF. This suggests that transient venoconstriction, presumably because of increased sympathetic stimulation with redistribution of blood from venous capacitance beds to the effective circulatory volume, is an alternative cause of increased cardiac filling pressures. 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.

Two main processes have been proposed for the pathogenesis of venous congestion in ADHF which include fluid redistribution and fluid accumulation [9-11]. We herein further discuss the processes resulting in congestion.

Fluid accumulation

Total body fluid excess has traditionally been considered a major component of ADHF syndrome. The maladaptive increase in neurohormonal activity has been suggested as the underlying mechanism for deterioration in cardiac function as well as a cardiorenal syndrome. The increase in body fluid volume preceding an episode of decompensation is supported by the findings from the devices monitoring pulmonary artery (PA) pressure and intra-thoracic impedance as well as increased serum B-type natriuretic peptide (BNP) levels [12].

Although the pathophysiologic pathways leading to volume overload in patients with ADHF are not well known, some mechanisms have been suggested. The principal neurohumoral systems involved in response to HF include the sympathetic nervous system, the renin–angiotensin–aldosterone system, and antidiuretic hormone [13-15]. In addition to the neurohormonal systems, patients with ADHF present with inflammation which may play a role in endothelial dysfunction and resultant volume overload [16,17]. It has been revealed that ADHF is associated with activation of the venous endothelium which may be a consequence of the systemic inflammatory response that accompanies ADHF [17]. Therefore, immunomodulating therapy may be beneficial in this group of patients [18].

Fluid redistribution

It has been suggested that intercompartmental redistribution of fluid, rather than fluid volume excess, could be the main underlying mechanism for congestion in a subset of patients with ADHF. The likely mechanisms underlying fluid redistribution would involve the transformation of a normally compliant splanchnic venous system into a noncompliant structure resulting in redistribution of volume to the cardiopulmonary circulation which can occur rapidly [19]. Previous studies have shown the beneficial effect of vasodilator therapy in the improvement of symptoms in those patients with ADHF possibly supporting the significant pathologic effect of vascular stiffness in this group of patients [20].

Fluid accumulation and redistribution indeed represent two mechanisms for the development of congestion that could be complimentary rather than contradictory. It is possible that they coexist in HF patients undergoing an episode of decompensation with a variable degree of dominance. Future mechanistic studies are needed to shed light on the precise pathophysiologic pathways leading to clinical congestion in ADHF.

Evaluation of Congestion

Congestion often remains unrecognized until conditions develop that require hospitalization.

Noninvasive methods for measurement of the volume include history and physical examination, biomarkers such as BNP, NT-proBNP, hemoconcentration (HC), echocardiography, and Impedance Cardiography (ICG). Acute changes in hemoglobin (Hb) during hemodialysis have long been used by nephrologists as a surrogate for HC to guide volume removal during renal replacement therapy. By analogy, rising Hb over a longer time interval in hospitalized HF patients may be a marker of decongestion and diuretic response. In general, these studies were able to show that patients with HC had better outcomes. Several questions remain to be answered including which markers of HC should be used and how it can be defined. Moreover, there are several other factors that can potentially affect Hct and Hb during hospitalization (e.g. subclinical bleeding, serial phlebotomy, and nutritional status). Therefore, future studies are needed to help determine the clinical utility of HC as a guide to decongestion therapy in this setting.

Echocardiography has been used to provide information about ventricular size and function as well as estimation of volume. Assessment of PCWP is done *via* the ratio (E/Ea or E/E') of tissue Doppler of early mitral inflow velocity (E) to the early diastolic velocity of the mitral annulus (Ea or e'). Patients with significant mitral valve disease (either mitral stenosis or mitral regurgitation). In patients with mitral valve disease, a preliminary report indicates that the ratio of isovolumetric relaxation time to the time interval between the onset of E and Ea (TE-Ea) correlates with PCWP [21].

A non-invasive and objective method for estimation of fluid volume is a measurement of intra-thoracic impedance. Devices that measure changes in impedance across the thorax are available commercially which allow measurement of the impedance *via* the blood flow through the aorta. Stroke volume and cardiac index (CI) can then be determined. ICG is performed by Thoracic Bioimpedance Monitoring device that consists of four dual sensors with eight leads placed on the chest and neck. ICG measures baseline impedance (resistance) to the current that is transmitted through the chest and with each heartbeat, blood volume, and velocity in the aorta change. ICG measures the corresponding change in impedance and then uses the baseline and changes in impedance to measure and calculate hemodynamic parameters. The BioImpedance CardioGraphy in Advanced Heart Failure (BIG) sub study was conducted within the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial to determine the utility of ICG monitoring as an adjunct tool for HF intense care in hospitalized patients with advanced HF. A total of 170 patients with advanced HF (NYHA class IV) with severely reduced EF, underwent blinded ICG measurements and of those, 82 underwent a right heart catheterization (RHC). They found an only modest correlation between ICG and invasively measured CO (r=0.4 to 0.6 on serial measurement). There was a poor agreement between ICG and invasively measured hemodynamic profiles. Therefore, the precise role of ICG remains to be clarified in this setting.

Given the limitations of the conventional and newer noninvasive methods for assessment of hemodynamics and volume status, the role of routine invasive measurement (i.e.

right heart catheterization) has also been investigated. However, a multicenter randomized controlled trial (i.e. ESCAPE) demonstrated that invasive measurement of hemodynamics is not superior to clinical assessment for monitoring of decongestion. Later, a meta-analysis, which included the ESCAPE trial, confirmed that the effect of RHC on mortality outcomes was neutral. Therefore, routine RHC in patients with ADHF for monitoring of decongestive therapy does not seem to be justified based on the currently available data.

One of the major recent technological advances has been the development of implantable devices to assess volume status on an ongoing basis. The CardioMEMS heart sensor/transmitter is a small-sized sensor which is implanted in PA during RHC. Once it is in place, the patient will be able to record PA pressure readings at home that could be sent to the treating physician. Based on the pressure readings, the physician can evaluate the volume status and adjust the dose of diuretics and other medications accordingly. The device was tested in the multicenter Wireless pulmonary artery hemodynamic monitoring in chronic heart failure randomized controlled trial (CHAMPION trial), that enrolled 550 patients with NYHA class IIIHF, irrespective of LVEF, and a previous hospital admission for HF. Patients were randomly assigned to management with a wireless implantable hemodynamic monitoring (treatment group) or to a control group for at least six months. In the treatment group, clinicians used the daily measurement of PA pressures in addition to standard of care versus standard of care alone in the control group. The primary efficacy endpoint was defined as the rate of HF-related hospitalizations at six months. In this study, patients randomized to PA monitoring showed a significant 30% reduction in the rate of hospitalization in the six months following randomization. This trial is the first large trial to demonstrate improved outcomes with an implantable monitoring device and demonstrates that care directed towards a reduction in LV filling pressures, as measured through PA pressure, may lead to improved outcomes.

To summarize, hemoconcentration needs more characterization as there are several questions that need to be answered including the definition and the timing of HC. ICG does not provide information on ventricular filling pressures in patients admitted with advanced ADHF. Although invasively measured hemodynamics *via* a right heart catheter allows a direct measure of the PCWP and CO, it does not seem to be helpful if done routinely for all patients. Currently, a PA catheter would be indicated for patients with ADHF who are not responding as expected when decision making is based on noninvasive methods and also in those patients in whom therapies with significant risks are being considered. Technologies are emerging that allow serial monitoring of hemodynamics, including hand-held echocardiography and implantable hemodynamic monitors.

Conclusion

Congestion has an important effect on HF outcomes and unfortunately is often undertreated. Multiple methods have been suggested to assess congestion including non-invasive and invasive procedures. However further trials are needed to determine the effective and safe methods to evaluate congestion. The management of AKI in ADHF remains an important but unresolved clinical challenge as the pathophysiology of WRF is still incompletely understood. Future trials are needed to investigate the precise underlying mechanisms of WRF and therapeutic options as well as the individualization of therapeutic strategies for RF impairment in ADHF.

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