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The "chloride theory", a unifying hypothesis for renal handling and body fluid distribution in heart failure pathophysiology

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ABSTRACT

Body fluid volume regulation is a complex process involving the interaction of various afferent (sensory) and neurohumoral efferent (effector) mechanisms. Historically, most studies focused on the body fluid dynamics in heart failure (HF) status through control of the balance of sodium, potassium, and water in the body, and maintaining arterial circulatory integrity is central to a unifying hypothesis of body fluid regulation in HF pathophysiology. The pathophysiologic background of the biochemical determinants of vascular volume in HF status, however, has not been known. I recently demonstrated that changes in vascular and red blood cell volumes are independently associated with the serum chloride concentration, but not the serum sodium concentration, during worsening HF and its recovery. Based on these observations and the established central role of chloride in the renin-angiotensin-aldosterone system, I propose a unifying hypothesis of the "chloride theory" for HF pathophysiology, which states that changes in the serum chloride concentration are the primary determinant of changes in plasma volume and the renin-angiotensin-aldosterone system under worsening HF and therapeutic resolution of worsening HF.

Introduction

Body fluid volume regulation is a complex process involving the interaction of a variety of afferent (sensory) and neurohumoral efferent (effector) mechanisms [1,2]. Maintaining arterial circulatory integrity is central to a unifying hypothesis of body fluid regulation [3]. Until recently, most studies focused on the body fluid dynamics in heart failure (HF) status through control of the sodium (Na), potassium, and water balance in the body [4–7]. A fully developed unifying hypothesis based on the serum biochemical solute (s) has not been developed for HF pathophysiology. Recently, I demonstrated, for the first time, that changes in vascular [8–10] and red blood cell volumes [11] are independently associated with the serum chloride (Cl) concentration, but not the serum Na concentration, during worsening HF and its recovery. Previous reports revealed that Cl is a crucial electrolyte for the reabsorption of filtered Na in the tubules into the extracellular spaces of the body, and for subsequently maintaining arterial pressure [12–15]. For the last several decades, however, Cl has remained largely ignored in the medical literature and in clinical practice for HF as an afterthought to the more popular electrolytes, Na and potassium [16]. Exploration of HF pathophysiology based on the dynamics of Cl is warranted because Cl is an established key electrolyte for tubuloglomerular feedback and subsequent body fluid reabsorption in the kidney [12,17–19].

The hypothesis

General consideration

Plasma volume [2,8,9,20] or hemoconcentration [21–23] should be monitored as part of the clinical assessment of HF patients and, if possible, in association with neurohormonal [24–26] and cytokine [27] profiling. Notably, my recent studies revealed that plasma volume is heterogeneously distributed in 47 HF patients during worsening HF [8] and its recovery [10]: 1) plasma volume contraction (−19% to −0.8%) occurred in 10 patients (21%) and plasma volume expansion (1.2% to 35.8%) occurred in 37 patients (79%) from clinical stability to worsening HF, and 2) the incidence of an increase (2.9% to 21.4%) or decrease (−0.9% to −10.1%) in plasma volume was 6 (13%) and 41 (87%) from worsening HF to its recovery after decongestive therapy, respectively. In both situations, multivariate logistic regression analysis, including serum solutes of electrolytes and albumin, and blood urea nitrogen and creatinine, revealed an independent association between changes in plasma volume and serum the Cl concentration [8,10].

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Based on both my exciting findings of Cl-related vascular volume regulation described above [8–10] and the established central role of Cl in the renin-angiotensin-aldosterone system (RAAS) [12,17–19], I propose a unifying hypothesis for HF pathophysiology called "chloride theory". Central to this hypothesis is that Cl is the key electrolyte for regulating both reabsorption of tubular electrolytes and water in the kidney through the RAAS and distribution of body fluid in each compartment of the body [28], i.e., the intracellular, intravascular, and interstitial compartments. In other words, the proposed hypothesis states that the serum Cl concentration, and presumably its quantity, are the primary determinants of changes in the plasma volume and the RAAS, and, indirectly, the antidiuretic hormone (ADH) system [29,30] under worsening HF (Fig. 1) and therapeutic resolution of worsening HF status (Fig. 2).

Hypothesis of chloride theory underlying worsening HF

My recent study demonstrated that, in patients with worsening HF and increased serum Cl concentrations, the accumulation of serum Cl acts act to maintain or increase intravascular volume [8,9,31]. My hypothesis of the pathophysiology of this type of worsening HF is summarized on the left side in Fig. 1. This type of HF worsening would increase the burden on the failing heart due to vascular volume overloading, although maintaining plasma volume might be beneficial for supplying blood to the vital organs.

As shown on the right side in Fig. 1, patients with worsening HF and no increase in the serum Cl concentration would result in decreased supply of Cl into the urinary tubules and decreased reabsorption of both filtered Na and Cl from the tubules into the extracellular space [12,17,18], resulting in reduced blood vessel expansion or even blood vessel contraction [12–15]. As a result, this subtype of worsening HF might be accompanied by enhanced ADH activation [29,30] and increased water retention in relation to the serum Cl (and also Na) concentrations to correct arterial underfilling [1–3]. In this subtype of worsening HF, the RAAS might be overactivated due to positive tubuloglomerular feedback because of a decreased supply of filtered Cl to the macula densa, but RAAS activation to increase reabsorption of filtered solutes (Cl, Na, or both) would be ineffective because the supply of these solutes is reduced in the urinary tubules of HF patients with no increase in the serum Cl concentration. Ineffective reabsorption of filtered Cl and Na despite enhanced RAAS activation, probably also including activation of the sympathetic nervous system [32], contributes to deficits in the intravascular accumulation of serum Cl and the resultant loss of plasma volume.

Hypothesis of chloride theory underlying therapeutic resolution of worsening HF

For treatment of patients with worsening HF and increased serum Cl concentrations (pathophysiology shown on left side in Fig. 1), it would be adequate to reduce the excess serum Cl and plasma volume to the individualized optimal aortic filling level in each HF patient (Fig. 2Ⓐ). The consequent hypothetical therapeutic effects on plasma volume, and the RAAS and ADH systems through changes in the serum Cl concentration are summarized on the left side in Fig. 2. According to this hypothesis, RAAS activity would be enhanced under conventional diuretic therapy for worsening HF, which explains the phenomenon of augmented RAAS activation under conventional diuretic therapy [24–26].

For decongestive treatment of patients with worsening HF and decreased serum Cl concentrations (pathophysiology shown on right side in Fig. 1), therapeutic targeting would focus on correcting hypochloremia, such as preserving and enhancing the concentration of serum Cl with aquaresis using a V_2-receptor antagonist (Fig. 2Ⓑ) [31,33–36] or supplementing the Cl by hyperosmotic saline infusion (Fig. 2Ⓒ) [37–39]. The presumed favorable effects on diuresis would be to induce changes in both plasma volume and

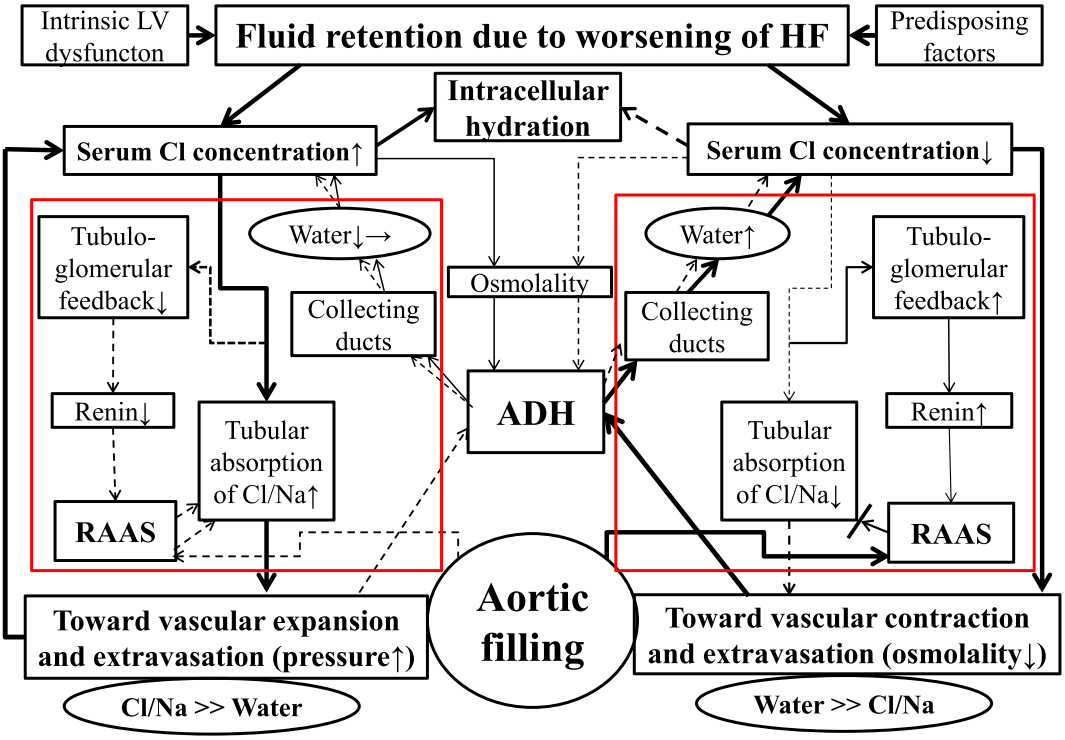

Fig. 1. Hypothesis of chloride theory underlying worsening HF. Solid line indicates enhanced supply or excitatory effect, and dotted line, reduced supply or inhibitory effect. Different effect strengths are expressed by the thickness of each line. The pathway of the RAAS, tubuloglomerular feedback, and ADH in the kidney is outlined in red. ADH, antidiuretic hormone; Cl, chloride; HF, heart failure; Na, sodium; RAAS, renin-angiotensin-aldosterone system.