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Rationale of the "Chloride Theory" as an Explanation for Neurohormonal Activity in Heart Failure Pathophysiology: Literature Review

Hajime Kataoka*

Internal Medicine, Nishida Hospital, Saiki-city, Oita, Japan

***Corresponding author:** Hajime Kataoka, Internal Medicine, Nishida Hospital, Tsuruoka-Nishi-Machi 2-266, Saiki-City, Oita 876-0047, Japan, Tel: +81-972-22-0180; E-mail: hkata@cream.plala.or.jp

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Abstract

We recently proposed a unifying hypothesis of the "chloride theory" for Heart Failure (HF) pathophysiology, which states that changes in the serum chloride concentration are the primary determinant of changes in the plasma volume and neurohormonal activity under worsening HF and its resolution. The proposed hypothesis is based on speculative interactions between changes in the serum chloride concentration and neurohormonal systems, but it has been unclear whether these interactions are physiologically applicable to clinical HF states. Thus, here we review the current literature to provide scientific rationale for the "chloride theory" to explain the activity of neurohormonal systems, mainly the renin-angiotensin-aldosterone system and the antidiuretic hormone axis. Many published clinical studies provide support for the "chloride theory" in real-world HF pathophysiology during both HF worsening ant recovery.

Keywords: Heart failure; Chloride; Neurohormones; Renin-angiotensin-aldosterone system; Antidiuretic hormone

Abbreviations ADH: Antidiuretic Hormone; HF: Heart Failure; RAAS: Renin-Angiotensin-Aldosterone System

Introduction

We recently reported that changes in vascular volume are independently associated with the serum chloride concentration during worsening heart failure (HF) [1] and its recovery [2]. Based on these observations and the established central role of chloride in the Renin-Angiotensin-Aldosterone System (RAAS) [3-7], we proposed 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 neurohormonal activity under worsening HF and its resolution [8,9]. The proposed hypothesis is based on speculative interactions between changes in the serum chloride concentration and neurohormonal systems, but whether their interactions are physiologically applicable in clinical HF pathophysiology has been unclear. Thus, the present article aimed to provide a scientific rationale for the "chloride theory" to explain the activity of neurohormonal systems in HF pathophysiology based on a comprehensive review of the current literature.

Historical Overview of the Development of HF Pathophysiology

Congestive heart failure is a pathologic state in which abnormal cardiac function results in the failure of the heart to pump blood at the requisite rate for metabolism or to pump blood from an increased filling pressure [10]. From approximately 1950 to 1990, physicians viewed and defined congestive HF as a hemodynamic disorder because of the widespread use of principal tools in cardiology for measuring pressure, volume, and flow developed in that era [10-14]. While hemodynamic abnormalities may explain the symptoms of HF, however, they are not sufficient to explain the progression of HF and, ultimately, patient death due to HF [13-16]. Therapeutic interventions may improve the hemodynamic status of HF patients but adversely affect their long-term outcome [13,14].

Subsequent progress in cardiology revealed that HF is not only a result of hemodynamic abnormalities, but it is also associated with numerous metabolic and neurohormonal abnormalities, leading to a new hypothesis to explain the mechanism of HF progression through neurohormonal abnormalities involving the sympathetic nervous system [17], the RAAS [18-22], the Antidiuretic Hormone (ADH) axis [23-26], and vasodilatory/natriuretic pathways [24,27,28]. Many studies have now confirmed the prognostic importance of neurohormonal abnormalities and the favourable effects of their modulation by pharmacologic treatment on the prognosis of HF patients [29-33]. HF is now considered to represent a complex clinical syndrome characterized by abnormal cardiac function and neurohormonal regulation accompanied by effort intolerance, fluid retention, and reduced longevity (European Society of Cardiology guideline) [34]. Thus, central to a unifying hypothesis of body fluid regulation in HF pathophysiology is the maintenance of arterial circulatory integrity, defined by arterial underfilling, through the interaction of various afferent (sensory) and neurohormonal efferent (effector) mechanisms [18-20,35] that regulate the reabsorption of sodium and water in the kidney, and body fluid volume by neurohormonal systems. Despite the fact that plasma volume expansion is a hallmark feature of worsening HF, pathophysiologic background of the biochemical determinants of vascular volume in HF status has not yet been determined [35-37].

A New Unifying Hypothesis of Body Fluid Regulation in HF Pathophysiology Based on the "Chloride Theory"

My recent studies were the first to demonstrate that serum chloride is a key electrolyte involved in regulating changes in the intravascular volume under transition of chronic HF status [1,2]. Based on both our findings of chloride-related vascular volume regulation [1,2] and the established central role of chloride in the regulation of the RAAS activity in the kidney [3-7], we have proposed a unifying hypothesis for HF pathophysiology named the "chloride theory" [8,9]. This hypothesis is the first to unify the two main platforms of the body fluid-processing organs through one key electrolyte, chloride, in both (1) the kidney, which reabsorbs body fluid mainly under RAAS-control [3-7], and (2) the body, an organ with dynamic storage of body fluid in the intracellular, intravascular, and interstitial compartments [38,39]. The "chloride theory" for HF pathophysiology under worsening HF and its recovery from diuretic therapy [8] is shown in Figures 1 and 2, respectively, in which the RAAS and ADH systems are highlighted in red and blue fonts, respectively.

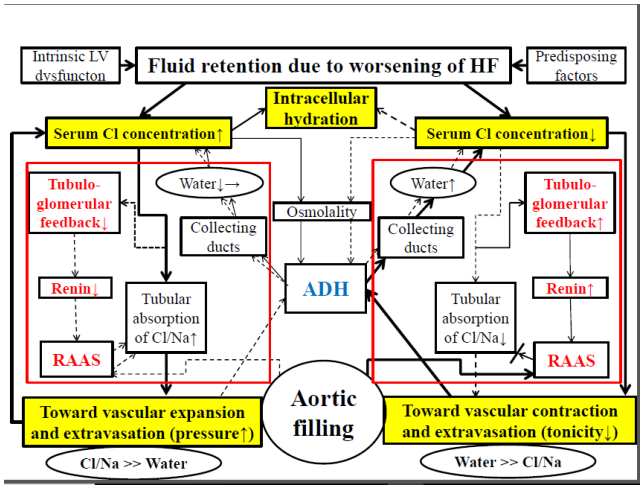

Figure 1: The "chloride theory" for applied to explain fluid dynamics in the course of worsening heart failure. Solid line indicates enhanced supply or excitatory effect, and dotted line, reduced supply or inhibitory effect. Different effect strengths are expressed by the thickness of each line. The 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.

The applicability of this proposed hypothesis, the "chloride theory", to HF pathophysiology is well supported by the fact that "maintenance of arterial circulatory integrity" as the conceptual core of the established "arterial under-filling theory" for HF pathophysiology [18-20] depends deeply on chloride itself because this electrolyte has a central role in maintaining arterial circulatory integrity [3,40-42]. Additionally, interactions between dynamic changes in the serum chloride concentration and hemodynamics are demonstrated through changes in the plasma volume, as shown in Figure 3 (blue arrows). Namely, changes in plasma volume affect venous return to the heart as well as cardiac output, according to the Frank-Starling mechanism [11,43], but the failing heart may have a maladaptive response to the altered plasma volume due to limited preload reserve and afterload mismatch [10,43-45]. Importantly, a recent study by Grodin et al. [46] revealed a significant link between changes in the serum chloride concentration and hemodynamics (Figure 3, red arrows).

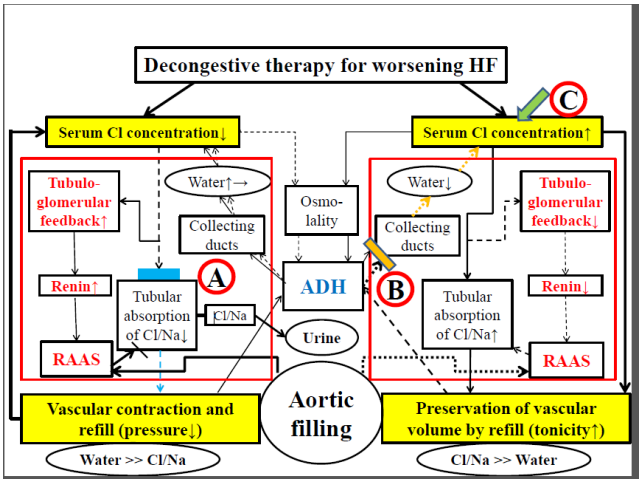

Figure 2: Heart failure treatment and resolution of worsening HF based on the "chloride theory"; conventional diuretic therapy (A), V_2-receptor antagonist (B), and chloride supplementation (C). Blue and yellow blocks represent inhibition of the absorption of chloride/sodium and water in each. Light green arrow indicates chloride supplementation. Therapeutic effect induced by each treatment is indicated by a solid or dotted line using the color corresponding to each treatment. Solid line indicates enhanced supply or excitatory effect, and dotted line indicates 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.

As summarized in Figure 3, changes in the serum chloride concentration are related to changes in plasma volume (blue arrows), RAAS activation in the kidney (green arrows), and alterations of the hemodynamic status (red arrows) in each case. Thus, the "chloride theory" proposed here incorporates qualitatively different but important main pathways of HF pathophysiology, including biochemical, neurohormonal, and hemodynamic pathways, solely *via* the chloride electrolyte. Although the "chloride theory" is based on speculative interactions between changes in the serum chloride concentration and neurohormonal systems in HF pathophysiology (Figures 1 and 2), whether these interactions are physiologically applicable in real-world clinical setting is unclear. Thus, this comprehensive literature review aims to provide a scientific rationale for the "chloride theory" to explain the activity of neurohormonal systems, mainly the RAAS and the ADH axis, in HF pathophysiology, as follows.

Currently, in the field of HF pathophysiology, only one very recent study investigated the association between changes in the serum chloride concentration and neurohormonal systems [47], presumably because chloride has remained largely ignored in the medical literature and in clinical practice compared with the more popular electrolytes sodium and potassium over the last several decades [48]. Many

previous studies deeply examined the association between the serum sodium concentration and neurohormonal systems.

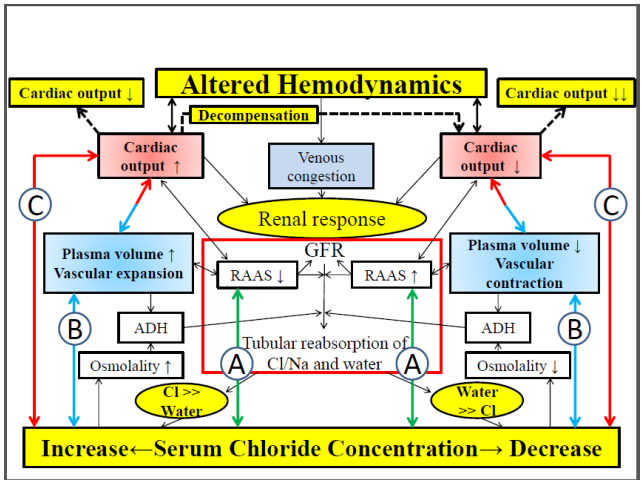

Figure 3: Interactions between changes in RAAS activity (green arrows), plasma volume (blue arrows), and hemodynamics (red arrows) according to changes in the serum chloride concentration in heart failure pathophysiology. ADH: Antidiuretic Hormone; Cl: Chloride; GFR: Glomerular Filtration Rate; Na: Sodium; RAAS: Renin-Angiotensin-Aldosterone System.

Therefore, this literature review mainly includes studies of the relation between sodium and neurohormonal activity in various HF states. Pathophysiologic differences would exist between HF patients stratified by the dynamics of sodium and chloride [9], but it is likely that many of the clinical features, although not all, overlap between each type of worsening of HF.

Neurohormonal Activity under Worsening of HF/Fluid Retention

Hypothesis according to the "chloride theory"

According to the "chloride theory", worsening HF patients comprise those with increased *vs.* non-increased serum chloride concentrations from clinical stability to worsening HF [8,9]. The pathophysiology of the former type of worsening HF patients is summarized on the left side in Figure 1. Hypothetically, the RAAS in this type of worsening HF might be inhibited or not so augmented due to: 1) negative tubuloglomerular feedback resulting from an increased supply of filtered chloride to the macula densa [3-6], and 2) chloride-related preservation of arterial filling [3,40-42]. The latter type of worsening HF (decrease in the serum chloride concentration) is shown on the right side in Figure 1. In this subtype of worsening HF, in addition to the response to lower blood pressure, the RAAS tends to be over activated due to positive tubuloglomerular feedback resulting from a decreased supply of filtered chloride to the macula densa, but the RAAS activation to increase reabsorption of filtered solutes would be ineffective because the supply of these solutes is reduced in the urinary tubules of HF patients with no increase in the serum chloride concentration. It is speculated that a substantial number of the clinical features of this type of worsening of HF overlaps with those of advanced HF patients with hyponatremia [49-53].

Clinical Studies

Renin-angiotensin-aldosterone system

The RAAS is basically involved in the development and progression of HF [18-20,35]. Activation of the RAAS ultimately results in increased afterload and body fluid retention, leading to a vicious cycle of decompensated HF [49-51,54]. Many previous studies concordantly reported an inverse association between the serum sodium concentration and plasma renin activity in populations of HF patients with various disease severities [51,55-58].

Enhanced RAAS activation is frequently observed in advanced HF [58,59] and hypovolemia [54], but not in mild to moderate HF, perhaps due to maintenance of arterial filling under such situations. As shown in Table 1, early studies indicated that plasma renin activity was not increased [60,61], and the plasma aldosterone concentration was not affected [60] or slightly increased [61] in untreated NYHA functional class I-III HF patients. A recent study reported that patients with acute decompensated HF exhibited lower plasma renin activity compared with stable HF patients [62]. Body fluid retention induced by a high sodium diet [63,64] or diuretics withdrawal [65] in mild to moderate HF patients depressed the plasma renin activity. Thus, according to the studies referenced above, a diagram predicting RAAS activation according to the proposed "chloride theory" under worsening HF (Figure 1) seems applicable to the real-world clinical setting because 1) the inverse relationship between their interaction [55-57] and 2) decreased renin secretion under the situation of plasma volume expansion [60-65] and its increase under advanced HF status and hypovolemia [54,58] support the inhibitory (left side in Figure 1) and excitatory effects of serum chloride on RAAS activity (right side in Figure 1) in each type of HF patient under the "chloride theory".

Very recently, an exciting study by Hanberg et al. [47] demonstrated an independent association between the serum chloride concentration and serum renin levels. This study included 162 chronic HF patients taking loop diuretics, of whom 111 had hypochloremia (serum chloride ≤ 96 mmol/L) and 51 had normochloremia (serum chloride>96 mmol/L). They observed that the total renin level was higher in patients with hypochloremia compared to those without hypochloremia. Renin levels were negatively correlated with serum chloride ($r=-0.46$; $p<0.001$) whereas the serum sodium correlation was less pronounced ($r=-0.30$; $p<0.001$). In a multivariable model containing both serum chloride and sodium, chloride remained significantly associated with renin levels ($\beta=-0.08$; $p<0.001$), whereas sodium was no longer associated with the renin level ($\beta=-0.02$; $p=0.49$). These observations by Hanberg et al. [47] strongly support the "chloride theory" for HF pathophysiology.

Antidiuretic hormone system

Antidiuretic Hormone (ADH) is a potentially important neurohormone in HF pathophysiology. This hormone (also called vasopressin) affects free water reabsorption in the kidney, body fluid osmolality, blood volume, vasoconstriction, and myocardial contractile function [66]. The dominant stimulus for ADH secretion is serum osmolality, but nonosmotic factors (e.g., cardiac filling pressure, arterial pressure, and the effects of adrenergic stimuli and angiotensin II in the central nervous system) can modulate the osmotic control of ADH to varying degrees [67]. Lanfear et al. [26] reported that an elevated ADH level in patients hospitalized for worsening chronic

systolic HF was independently associated with the longer term outcomes, including death.

According to the "chloride theory" (Figure 1), it seems that ADH activity could not be correctly estimated because its secretion might be counter-balanced, consistent with changes in opposing directions produced by the serum osmolality or the nonosmotic factor of the baroreceptor response in each type of worsening HF. Under the HF type of increased serum chloride concentration from clinical stability to worsening HF, ADH secretion might be enhanced by increased serum osmolality, but depressed by maintenance of arterial filling, and *vice versa* in the HF type of non-increased serum chloride concentration.

In the clinical setting, ADH activity is ordinarily elevated in HF patients compared with normal subjects [59,68,69]. There is some controversies, however, regarding the correlation of ADH activity with hemodynamic parameters, such as a positive association with the right-sided cardiac pressure [68], a significant correlation of the baseline ADH level with increase in systemic vascular resistance after vasopressin antagonist infusion [70], a weak association with a difference in the left ventricular ejection fraction [59], and an unclear association between them [69]. Vasopressin levels widely vary among individual patients and across studies, and not all HF patients in these studies had elevated levels compared with the normal reference [71].

With regard to a correlation of ADH activity with serum sodium concentrations, one study did not demonstrate a significant association between them [69] whereas other studies confirmed ADH elevation in HF patients with hyponatremia [70,72,73]. A positive association between ADH level and plasma renin activity was reported by Goldsmith et al. [69], but not by Creager et al. [70]. Further investigation is needed to clarify the interaction between changes in the serum chloride concentration and ADH activity, and its relation to the "chloride theory" under HF pathophysiology.

Sympathetic nervous system

The "chloride theory" does not incorporate the central nervous system because a direct interaction cannot be speculated between chloride itself and the central nervous system. The sympathetic nervous system, however, would strongly communicate with the RAAS and ADH axis under HF pathophysiology [49,74] in parallel with the hemodynamic severity (see under subheading "Importance of hemodynamic effects on neurohormonal activity in HF syndrome"). Besides an interaction between the RAAS and ADH axis, increased activity of the sympathetic nervous system would reduce venous compliance, leading to the mobilization of fluid from the venous capacitance vessels to the effective circulatory volume, culminating in HF pathophysiology [74,75].

In brief, activation of the sympathetic nervous system under worsening HF status induces peripheral and renal vasoconstriction and renin release *via* stimulation of renal sympathetic nerves, subsequently activating the RAAS from the macula densa and releasing ADH from the supraoptic and paraventricular nuclei in the hypothalamus [19,20,23,49,74]. Notably, the action of angiotensin II in the central nervous system may be deeply involved in HF pathophysiology, including promotion of thirst behaviour and salt appetite, regulation of ADH, regulation of sympathetic outflow, and modulation of the sensitivity of the arterial baroreflex, as well as many other important cardiovascular reflexes [74,76].

As shown in Table 1, in the clinical setting, various types of sympathetic activity occur in response to the mode of body fluid retention in HF patients: noradrenaline is elevated before decongestion treatment [60,61], but high sodium intake [64] or diuretic withdrawal [65] do not induce sympathetic activation.

Neurohormonal Activity under Resolution of HF/Fluid Retention

Hypothesis according to the "chloride theory"

The working hypothesis of the "chloride theory" during worsening HF (Figure 1) could provide rational pharmacologic strategies for interrupting the vicious cycle of worsening HF. Considering the hypothesis of the "chloride theory" for worsening HF, manipulation of the serum chloride concentration would become an attractive therapeutic target for HF treatment. Based on the "chloride theory" for worsening HF, hypothetical therapeutic effects on plasma volume and the RAAS and ADH systems through changes in the serum chloride concentration are shown in Figure 2. According to this hypothesis, RAAS activity would be enhanced under conventional diuretic therapy for natriuresis in worsening HF (Figure 2A). For diuretic treatment of patients with worsening HF and decreased serum chloride concentrations, therapeutic targeting would focus on correcting the hypochloremia, such as preserving and enhancing the concentration of serum chloride with aquaresis using a V_2-receptor antagonist (Figure 2B) [77-82] or supplementing the chloride by dietary salt intake and/or infusing hyperosmotic saline (Figure 2C) [83-85]. Though concomitant restoration of cardiac functional reserve may be required [10,43-45], presumed favourable effects on diuresis would induce changes in both plasma volume and blood pressure by: 1) promoting capillary vascular system refilling, thus inhibiting plasma volume contraction by chloride-induced enhancement of tonicity [86,87], and 2) restoring or preserving arterial pressure by chloride-related vascular expansion [3,40-42]. Importantly, chloride is a key electrolyte for the regulation of renin release in the macula densa, and therefore preserving the supply of filtered chloride to the macula densa by chloride-regaining therapy described above is expected to reduce RAAS activation *via* tubuloglomerular feedback [3-6].

Clinical Studies

Renin-angiotensin-aldosterone system

As presented in Table 2, during decongestive treatment for HF patients with conventional natriuretic diuretics, almost all studies indicate enhanced plasma renin activity [58,60,88,89], and an increased [60] or decreased [89] plasma aldosterone concentration.

The main mechanism for the RAAS activity under usage of conventional diuretics is reported to be diuretic-induced plasma volume contraction [90], but other potential mechanisms of enhanced RAAS activity due to a decreased supply of chloride into macula densa cells and consequent positive tubuloglomerular feedback are as follows: 1) blockade of the entrance of chloride into the macula densa cells by loop diuretics [7], and/or 2) decreased chloride supply to macula densa cells due to hypochloremia, as predicted by the "chloride theory" [8].

Situation	First author (Ref. #)	Subjects	Study design (duration)	Neurohormonal findings in HF patients			Comments
				RAAS	ADH	Others	
Untreated HF patients	Bayliss et al. [60]	Twelve NYHA functional class II-III HF patients	Frusemide + amiloride daily (1 month)	Before treatment: Renin, normal; aldosterone, normal	NA	Before treatment:: noradrenaline↑	Vascular expansion might depress renin level at the upper end of the normal range in patients with "moderate HF".
	Remes et al. [61]	51 controls; 60 HF patients, G-1 26 unlike HF, G-2 15 possible HF, and G-3 19 definite HF (48 NYHA class I-III and 12 NYHA class IV patients)	Untreated HF status	Renin activity, not different from controls ; aldosterone, wide range variation and G-3>controls	NA	ANP G-3>G-2>G-1>controls; adrenaline, G-3, G-2>controls	Plasma renin activity was not increased in HF patients except 4 patients. Activation of RAAS is uncommon in untreated HF.
Different stages of HF worsening	Nijst et al. [62]	G-I: 72 ADHF with REF G-II: 72 CHF with REF G-III: 53 CHF with NEF	Cross-sectional findings during different stages of HF	Renin activity; G-II > G-III> G-I	NA	NT-proBNP; G-I > > G-II > G-III	The RAAS system is highly activated in stable HF with REF and HF with NEF patients, and downregulated in ADHF.
High sodium diet	Volpe et al.[63]	Ten NYHA functional class-I stable HF patients and 10 normal volunteers	Drug off. One weak of low sodium (100 mmol/d), followed by 8-day of a high sodium (250 mmol/d) diet (15 days)	Renin ↓ ; aldosterone↓	NA	ANP↑; BNP↑	Plasma renin and aldosterone concentrations significantly fall to a similar extent in both groups in response to increased salt intake.
	Damgaard et al. [64]	Twelve compensated HF patients (NYHA class II and III) and 12 age-matched controls	One weak of a low-sodium (70 mmol/d) and 1 weak of a high-sodium diet (250 mmol/d). (14 days)	Angiotensin II↓	NA	Norepinephrine ↓ ; Epinephrine→; Pro-BNP→	High sodium intake improves hemodynamics and suppresses vasoconstrictor hormones in compensated HF patients.
Diuretics withdrawal	Galve et al. [65]	26 stable CHF (NYHA class II) patients	Withdrawal of diuretics. (3 months)	Renin ↓ ; aldosterone→	Vasopressin →	ANP↑; Endothelin-I →; Norepinephrine →	Diuretic withdrawal is associated with an improvement in some neurohumoral parameters.

Table 1: Clinical studies on the relation between heart failure worsening/fluid retention and neurohormonal systems. ADH: Antidiuretic Hormone; ADHF: Acute Decompensated Heart Filure; ANP: Atrial Natriuretic Peptide; BNP: B-type Natriuretic Peptide; CHF: Chronic Heart Failure; d: day; G: Group; HF: Heart Failure; NYHA: New York Heart Association; NEF: Normal Ejection Fraction; REF: Reduced Ejection Fraction.

As shown in Table 2, in concordance with the prediction by the "chloride theory", aquaresis using a V_2-receptor antagonist for decongestive therapy in HF does not induce the activity of renin [79-81] and aldosterone [80,81] in the RAAS. Jujo et al. [81] elegantly demonstrated different clinical effects on RAAS activity between furosemide and a V_2-receptor antagonist, the former having a stimulating-effect and the latter having a non-stimulating effect on RAAS activity, as demonstrated in experimental studies [91,92].

According to the "chloride theory", RAAS activity is expected to be reduced or not activated by chloride supplementation therapy. One study reported that salt supplementation for refractory HF did not significantly activate serum renin and aldosterone levels, even under concomitant usage of furosemide [84].

In another recent study, lysine chloride supplementation [47] induced favourable decongestive effects in 10 HF patients, but the serum renin activity was enhanced after this therapy. In this study, however, furosemide was used concomitantly, which favours RAAS activation and may be a confounding factor for the analysis.

In summary, a literature review supports the status of the RAAS activity predicted by the "chloride theory" during resolution of worsening HF based on the successful effects of several specific decongestion therapies in a real clinical setting.

HF therapy	First author (Ref. #)	Subjects	Study design (duration)	Neurohormonal findings in HF patients			Comments
				RAAS	ADH	Others	
Loop diuretics	Bayliss et al. [60]	Twelve NYHA functional class II-III HF patients	Furosemide + amiloride daily (1 month)	Renin ↑ ; Aldosterone↑	NA	Noradrenaline↓	Diuretics induce clinical improvement, but stimulate the RAAS.
	Francis et al. [88]	56 control subjects		Reference value	Reference value	Reference value	Neurohormonal activation occurs in patients with LV dysfunction and no overt HF, which is further increased as overt HF ensues and diuretics are added to therapy.
		151 LV dysfunction without overt HF	13% diuretic use	Renin↑	Vasopressin↑	Norepinephrine↑	
		81 overt HF	59% diuretic use	Renin → without diuretics; Renin ↑ with diuretics	Vasopressin↑	Norepinephrine↑	
	Johnson et al. [89]	34 advanced CHF	Hemodynamically guided therapy of furosemide + vasodilators (mean 3.4 days)	Renin ↑ ; Aldosterone↓	NA	Norepinephrine↓; Endothelin↓	Neurohormonal activation (except renin) rapidly decreases after therapy.
	Mentz et al. [58]	427 ADHF	Continuous (High vs. low dose) vs. bolus furosemide i.v. (72-96 hours)	Renin ↑ with continuous > Renin ↑ with bolus; Aldosterone→	NA	NA	High-dose loop diuretic therapy did not result in RAAS activation greater than that with low-dose diuretic therapy.
Vasopressin antagonists	Udelson et al. [79]	240 CHF	Tolvaptan (n=120) or placebo (n=120) (1 year)	Renin →	Vasopressin↑	Norepinephrine →; BNP→	Vasopressin levels increase as expected during tolvaptan usage.
	Kadota et al. [80]	26 CHF	Tolvaptan (15 mg p.o./d; n=26) (7 days)	Renin → ; Aldosterone→	NA	BNP↓	Tolvaptan treatment prevents RAAS activation in CHF patients.
Loop diuretics vs. vasopressin antagonists	Jujo et al. [81]	60 ADHF	Furosemide (40 mg i.v./d; n=30) (5 days)	Renin ↑ ; Aldosterone→	NA	Catecholamine↓; BNP↓	As compared with furosemide, tolvaptan induces less activation of RAAS.
			Tolvaptan (7.5 mg p.o./d; n=30) (5 days)	Renin → ; Aldosterone→		Catecholamine↓; BNP↓	
Chloride supplementation							
Saline infusion	Okuhara et al. [84]	44 ADHF	1.7% salt infusion (500 mL)+furosemide (40 mg) (n=22) (24 hours)	Renin → ; Aldosterone→	Vasopressin →	Norepinephrine↓; BNP↓	Contrary to expectation, plasma renin activity was not different between groups. The failure of renin activity suppression might be due to a repulsive activation secondary to favorable diuresis and furosemide use.

			5%glucose infusion (500 mL) + furosemide (40 mg) (n=22) (24 hours)	Renin → ; Aldosterone→	Vasopressin↓	Norepinephrine↓; BNP →	
Lysine chloride	Hanberg et al. [47]	10 CHF	Before and after 3 days of 115 mmol/d chloride supplement and 29 ± 15 mg torsemide on each of the study day (6 days)	Renin ↑	NA	NT pro-BNP↓	The majority of patients showed hemoconcentration, weight loss, BNP decrease, but unexpected increase in serum renin activity. Effect of torsemide on renin is not discussed.

Table 2: Clinical studies on the relation between therapeutic resolution of heart failure and neurohormonal systems. ADH: Antidiuretic Hormone; ADHF: Acute Decompensated Heart Failure; BNP: B-type Natriuretic Peptide; CHF: Chronic Heart Failure; d: day; HF: Heart Failure; i.v.: intra-venous; p.o.: per oral; NA: Not Available; RAAS: Renin-Angiotensin-Aldosterone System.

Antidiuretic hormone system

As mentioned previously, ADH activity may not be correctly estimated because its secretion might be counter balanced with chloride (Figure 2). In the clinical setting, as presented in Table 2, serum ADH levels are elevated both under loop diuretic therapy [88] and V_2-receptor antagonist therapy [79] administered for decongestion in HF patients, but hypersaline infusion therapy does not activate the ADH axis [84].

Sympathetic nervous system

As presented in Table 2, changes in the serum norepinephrine level under decongestive therapy by loop diuretics are contradictory, that is, either decreased [60,89] or enhanced [88]. Effective decongestion treatment by a V_2-receptor antagonist [79,81] or saline infusion [84] does not induce increase in the serum norepinephrine level.

Importance of Hemodynamic Effects on Neurohormonal Activity in HF Syndrome

Activation of the RAAS by which reabsorption of filtered body fluid is regulated in the kidney depends on the following two main stimuli, other than intracellular chloride levels inside the macula densa cells, i.e., 1) decreased arterial blood pressure, sensed by baroreceptor cells in the arteriolar vessel walls and 2) sympathetic activation [7,74]. Thus, the effects of altered hemodynamics defined by arterial filling/pressure [93,94] on the renal response as determined by RAAS activation [95,96] (not shown in Figures 1-3) should be always kept in mind for correct interpretation of the neurohormonal responses under the "chloride theory" of HF pathophysiology.

As mentioned above, though chloride contributes to maintain arterial circulatory integrity, derangement of the hemodynamics should be the primary outstanding determinant of the efficiency of arterial filling under HF pathophysiology. Thus, neurohormonal activation might vary widely in an individual HF patient according to the HF severity, HF state (such as acute or chronic decompensated condition), and treatments used [49-51,58,59,97] from near normal (A), moderate (B), and severe (C), as shown in Figure 4. For example, the effect of fluid removal on RAAS activation by different therapeutic modalities, such as high- *vs.* low-dose loop diuretic therapy, or ultrafiltration, might depend on the plasma refill rate, which regulates intravascular volume change, and maintenance of intravascular volume can inhibit neurohormonal activation [58]. It is not yet clear, however, how the hemodynamics and serum chloride condition contribute to the arterial filling status, but the intensity of the baseline neurohormonal status under the "chloride theory" should optimally be interpreted individually, taking into consideration the corresponding hemodynamic status, particularly the status of arterial-filling in each HF patient (Figure 4).

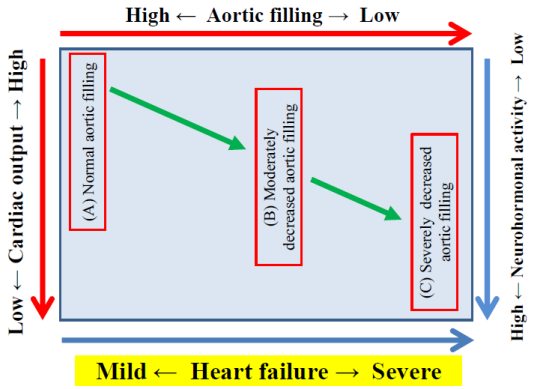

Figure 4: Association of changes in aortic filling (heart failure status) with neurohormonal activity; normal (A), moderate (B), and severe (C) levels.

Enhanced RAAS activation is frequently observed in advanced HF [58,59] and hypovolemia [54], but not in mild to moderate HF. Therefore, it must be emphasized that the clinical significance and prognostic importance of similar levels of hypochloremia clearly differ between HF patients with mild *vs.* severe cardio-renal dysfunction because the severity of the cardio-renal function is top of other clinical importance. Hence, the presence of hypochloremia as a leading prognostic marker might be quite reasonable when compared with other blood biomarkers [98-101], but it loses its clinically relevant prognostic status in comparison with other well-established prognostic

variables, such as age, sex, comorbid illnesses, and hemodynamic and renal variables [102].

Nonetheless, irrespective of the severity of cardio-renal function, it is important to monitor the changes in serum electrolytes and, if present, is correct the electrolyte(s) disturbance by tailoring therapeutic strategies [103-106].

Future Perspectives

The "chloride theory" of HF pathophysiology predicts a working association between changes in the serum chloride concentration and activation of neurohormonal systems.

As described in this article, this literature review of clinical HF pathophysiology substantially supports the activity of neurohormonal systems in accordance with this theory, but the real-world linkage of dynamic changes between chloride and neurohormonal systems remains unclear. Further studies are required to evaluate the applicability of this hypothesis to a wider spectrum of clinical HF pathophysiology.

Conclusions

Previous studies indicating that neurohormonal systems function correctly under clinical HF pathophysiology during both worsening and recovery substantially support the rationale of the "chloride theory". A timely investigation of the clinical significance, features, and pathophysiologic roles of this electrolyte in HF is warranted.

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