



REVIEW

Hypochloraemia in Patients with Heart Failure: Causes and Consequences

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ABSTRACT

Hypochloraemia is a common electrolyte abnormality in patients with heart failure (HF). It has a strong association with adverse outcome regardless of HF phenotype and independent of other prognostic markers. How hypochloraemia develops in a patient with HF and how it might influence outcome are not clear, and in this review we explore the possible mechanisms. Patients with HF and hypochloraemia almost invariably take higher doses of loop diuretic than patients with normal chloride levels. However, renal chloride and bicarbonate homeostasis are closely linked, and the latter

may be influenced by neurohormonal activation: it is likely that the etiology of hypochloraemia in patients with HF is multifactorial and due to more than just diuretic-induced urinary losses. There are multiple proposed mechanisms by which low chloride concentrations may lead to an adverse outcome in patients with HF: by increasing renin release; by a stimulatory effect on the with-no-lysine kinases which might increase renal sodium-chloride co-transporter activity; and by an adverse effect on myocardial conduction and contractility. None of these proposed mechanisms are proven in humans with HF. However, if true, it might suggest that hypochloraemia is a therapeutic target that might be amenable to treatment with acetazolamide or chloride supplementation.

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Keywords: Acetazolamide; Chloride; Diuretics; Diuretic resistance; Heart failure; Hypochloraemia; Metabolic alkalosis; Outcome; Prognosis; Sudden death

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Key Summary Points

Low serum chloride levels are associated with adverse prognosis in patients with acute or chronic heart failure (HF) regardless of left ventricular ejection fraction and independently of other prognostic markers such as N-terminal pro-B-type natriuretic peptide levels.

It is not clear how hypochloraemia develops in patients with HF but it may be linked to neurohormonal activation, high-dose loop diuretic usage, and metabolic alkalosis.

It is not known whether hypochloraemia is a marker or mediator of adverse outcome in patients with heart failure, although there are several putative mechanisms that might suggest the latter. For example, hypochloraemia might be linked to increased neurohormonal activation, diuretic resistance, and increased risk of sudden cardiac death.

Acetazolamide may increase natriuresis and diuresis while also increasing chloride reabsorption and bicarbonate excretion and thus might be a useful treatment for patients with HF, hypochloraemia, metabolic alkalosis, and diuretic resistance.

INTRODUCTION

A link between low serum chloride concentrations, loop diuretics, and risk of death in patients following a heart attack was first reported in 1979 [1], and the first reported association between low serum chloride concentrations and increased risk of death amongst patients with heart failure (HF) was in 2007 [2]. The authors of neither paper made even a passing reference to the chloride findings in the discussion [1, 2], perhaps owing to a lack of

understanding regarding the importance of serum chloride: the potential prognostic significance of low chloride has, until recently, not been appreciated.

Hypochloraemia is a common electrolyte disturbance and marker of adverse outcome amongst patients with HF independent of other prognostic markers, including hyponatremia (Table 1) [3–12]. The mechanisms are poorly understood. In this review, we will discuss the aetiology of hypochloraemia in patients with HF, explore the possible mechanisms behind its association with adverse outcome, and consider what, if anything, might be done about it. The present article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

HYPOCHLORAEMIA AND HEART FAILURE

Chloride is the main anion in the plasma and extracellular fluid [13], and is freely filtered in the glomerulus of the kidney into the urinary space (tubular lumen). Renal tubular cells are asymmetric with an apical surface facing the urinary space and a basolateral membrane facing the renal interstitium (peritubular capillaries). The majority of chloride reabsorption occurs in the proximal convoluted tubule (PCT), paracellularly in the intercellular space passively along an electrochemical gradient as the permeability to chloride anions exceeds that of other anions such as bicarbonate [14, 15]. Active, trans-cellular, reabsorption occurs via Cl^- /anion counter transports (antiporters or exchangers) in particular formate amongst others (sulphate, iodide, oxalate, hydroxyl, and bicarbonate) on the apical membrane, and by a sodium-driven $\text{Cl}^-/\text{HCO}_3^-$ antiporter and K^+/Cl^- symporter on the basolateral membrane [16]. In the loop of Henle (LoH), further chloride reabsorption takes place via $\text{Na}^+/\text{K}^+/2\text{Cl}^-$ co-transporters (NKCC2) on the apical membrane (the site of action of loop diuretics) and voltage-gated chloride channels on the basolateral membrane [17]. In the distal convoluted tubule (DCT) and collecting duct (CD)

Table 1 Summary of reports of hyponatraemia in patients with heart failure

Study (year)	Population (N)	Findings
Cuthbert et al. (2018) [3]	Outpatients with HeFREF and HeFNEF (N = 4705)	<p>Compared to patients with normal chloride levels, patients with low chloride:</p> <ul style="list-style-type: none"> Had more severe symptoms and higher NTproBNP levels in both HeFREF and HeFNEF phenotypes Were more likely to die or be admitted with HF regardless of HF phenotype and independent of NTproBNP and sodium levels Patients with hyponatraemia and normal sodium levels had higher bicarbonate and lower potassium levels than those with dual hyponatraemia and hyponatraemia There was no association between chloride and NTproBNP levels on MV analysis but both were independently associated with adverse outcome, suggesting they assess different aspects of the HF syndrome Signal towards an association between hyponatraemia and sudden death U-shaped relationship between chloride and outcome: there was a substantial increased risk of death in patients with chloride levels < 100 mmol/l (higher than the arbitrary cut-off that defines hyponatraemia — < 96 mmol/l)
Grodin et al. (2015) [4]	Two different cohorts of inpatients with HeFREF (Cleveland Clinic cohort N = 1318; Pennsylvania cohort: N = 876)	<ul style="list-style-type: none"> Compared to patients with normal chloride levels, patients with low chloride: Had lower LVEF, higher NTproBNP and longer length of hospital stay Greater risk of death independent of sodium levels in two different populations of patients admitted with HF
Ter Maaten et al. (2016) [5]	Inpatients enrolled in the PROTECT trial (N = 2033)	<ul style="list-style-type: none"> Compared to patients with normal chloride levels, patients with low chloride: Had lower diuretic response (weight lost per 40 mg furosemide) despite taking higher doses of diuretic, and were more likely to have “residual congestion” on day 7 Were more likely to require inotropic support and have worsening HF symptoms during admission Were more likely to die 180 days after discharge Patients with low chloride that had resolved by the time of discharge had a similar post-discharge prognosis to those with normal chloride levels throughout admission There was no difference in admission NTproBNP or BNP across quintiles of chloride

Table 1 continued

Study (year)	Population (N)	Findings
Grodin et al. (2016) [6]	Outpatients (N = 1673)	<p>Compared to patients with normal chloride levels, patients with low chloride: Were more likely to take loop diuretics</p> <p>Were more likely to die during 5-year follow-up regardless of sodium levels, after adjustment for BNP and LVEF</p> <p>There was no difference in baseline renal function, LVEF, or BNP levels between patients with low chloride levels and those with normal chloride levels</p>
Tesani et al. (2016) [7]	Outpatients enrolled in the BEST trial (N = 2699)	<p>Compared to patients with normal chloride levels, patients with low chloride: Had worse renal function, lower LVEF and more severe symptoms</p> <p>Were more likely to die during follow-up</p> <p>Modest association between chloride and sodium levels ($r = 0.53$; $P < 0.001$) and only half of patients with hyponatraemia were also hyponatremic</p> <p>Low sodium, was not associated with mortality after multivariable adjustment</p>
Hanberg et al. (2016) [8]	Outpatients with progressive symptoms attending for daily IV furosemide or PO torasemide (N = 162)	<p>Compared to patients with normal chloride levels, patients with low chloride: Were less likely to take either ACEI or βB but more likely to take digoxin or high-dose loop diuretics</p> <p>Had worse renal function</p> <p>Had greater fractional excretion of chloride and potassium but similar fractional excretion of sodium pre-diuretic but lower fractional excretion of all three ions post-diuretic</p> <p>Had lower diuretic efficiency (mmol of Na^+ per doubling of loop diuretic dose)</p> <p>Were at greater risk of all-cause mortality independent of sodium levels or renal function</p> <p>There was no difference in baseline LVEF or NT-proBNP between patients with low chloride levels and those with normal chloride levels</p> <p>Chloride and renin levels were inversely correlated ($r = -0.46$; $P = 0.001$) independent of sodium levels or renal function</p>

Table 1 continued

Study (year)	Population (N)	Findings
Hanberg et al. (2016) [8]	Outpatients with stable HF given 21 g lysine chloride per day (115 mmol/l chloride) for 3 days (N = 10)	<p>Serum chloride increased by 2.2 mmol/l from baseline ($P = 0.01$) but there was no difference in urine volume</p> <p>Renin levels were paradoxically higher after chloride supplementation</p> <p>NTproBNP levels decreased by 25% in eight patients ($P = 0.01$)</p>
Grodin et al. (2017) [9]	Inpatients enrolled in the ROSE-AHF trial (N = 360)	<p>Compared to patients with normal chloride levels, patients with low chloride:</p> <ul style="list-style-type: none"> Were more likely to take high-dose loop diuretic on admission and had greater cumulative doses of loop diuretic during admission Had lower diuretic efficiency defined as millilitres of urine passed per 40 mg of furosemide Were more likely to die or be readmitted with HF during 60-day follow-up independent of sodium levels <p>There was no difference in symptom severity, NTproBNP levels, renal function, rate of worsening HF as inpatient, or rate of freedom from congestion after 72 h of treatment between patients with low chloride levels and those with normal levels</p> <p>Average chloride change was -0.9 mmol/l per day during 7 days of treatment, average diuretic dose on admission 80 mg furosemide equivalents</p>
Ferreira et al. (2017) [10]	Patients enrolled in the EPHEBUS and CAPRICORN trials (N = 7195)	<p>Change in chloride levels was not associated with outcome</p> <p>Compared to patients with normal chloride levels, patients with low chloride:</p> <ul style="list-style-type: none"> Were older, more likely to have AF, worse renal function, and LVEF Were more likely to take diuretics and digoxin <p>Low serum chloride was only associated with increased mortality (not hospitalization) in the context of low sodium</p>
Grodin et al. (2018) [11]	Outpatients with HeFNEF enrolled in the TOPCAT trial (N = 942 from North America with available chloride data)	<p>Compared to patients with normal chloride levels, patients with low chloride:</p> <ul style="list-style-type: none"> Had more severe symptoms and more likely to be taking diuretic at a higher average daily dose Had high E/e' ratio indicating greater LV filling pressures Were at greater risk of the composite endpoint of cardiovascular death, hospitalization with HF, or aborted cardiac arrest independent of sodium or NTproBNP levels

Table 1 continued

Study (year)	Population (N)	Findings
Marchenko et al. (2020) [12]	Consecutive inpatients at a single centre (N = 1241)	<p>Compared to patients with normal chloride levels, patients with low chloride:</p> <p>Had higher average daily loop diuretic dose during inpatient stay</p> <p>Had higher average weight loss during inpatient stay — in contrast to other reports in patients admitted with HF detailed above</p> <p>Had a higher LVEF – in contrast to other reports detailed above</p> <p>Had greater 30-day readmission or death rate and 12-month death rate</p>
<p><i>HeFREF</i> heart failure due to a reduced ejection fraction, <i>HeFNEF</i> heart failure with a normal ejection fraction, <i>HF</i> heart failure, <i>BNP</i> B-type natriuretic peptide, <i>NTproBNP</i> N-terminal pro-B-type natriuretic peptide, <i>MV</i> multivariable, <i>LVEF</i> left ventricular ejection fraction, <i>ACEI</i> angiotensin-converting enzyme inhibitor, <i>βB</i> beta-blocker, <i>mls</i> millilitres, <i>AF</i> atrial fibrillation, <i>LV</i> left ventricular</p>		

(responsible for ~ 5% of chloride reabsorption) chloride is reabsorbed by thiazide-sensitive Na⁺/Cl⁻ co-transporter and Cl⁻/HCO₃⁻ antiporter and returns to the bloodstream via voltage-gated chloride channels on the basolateral membrane (Fig. 1) [18].

At first sight, the origin of hypochloraemia seems likely to be similar to the putative aetiology of hyponatremia in patients with HF: low chloride results from either haemodilution or depletion due to loop diuretics [19]. However, patients with hypochloraemia appear to fall into two phenotypes; those with concurrent hyponatremia and those with normal sodium concentrations [3]. The group with normal sodium has higher bicarbonate, and lower potassium concentrations (and a higher rate of clinically significant hypokalaemia (defined as a serum K⁺ < 3.5 mmol/l) [3].

An Association with Metabolic Alkalosis?

In other disease states, such as severe vomiting or mineralocorticoid excess, hypochloraemia is associated with metabolic alkalosis (HCO₃⁻ > 30 mmol/l) [20, 21]. Metabolic alkalosis is the most common acid-base abnormality in patients with HF, affecting up to half of patients admitted to hospital [22]. While activation of the renin–angiotensin–aldosterone system (RAAS) is usually linked to sodium homeostasis [23], data from in vitro and in vivo animal studies suggest that neurohormonal activation might play a significant role in the development and maintenance of a metabolic alkalosis in patients with HF (Fig. 2).

In vitro and in vivo studies suggest that when noradrenaline [24], and angiotensin II [25] levels increase, bicarbonate reabsorption in the first segment of the PCT increases. Additionally, in vivo studies in rats show that aldosterone increases the activity of the H⁺-ATPase pump in the CD which increases H⁺ secretion into the urine [26]. The increased acidification of the urine might result in a net gain of bicarbonate by the body.

Loop diuretics might also contribute to a metabolic alkalosis: a so-called “contraction-alkalosis” due to decreased extracellular fluid

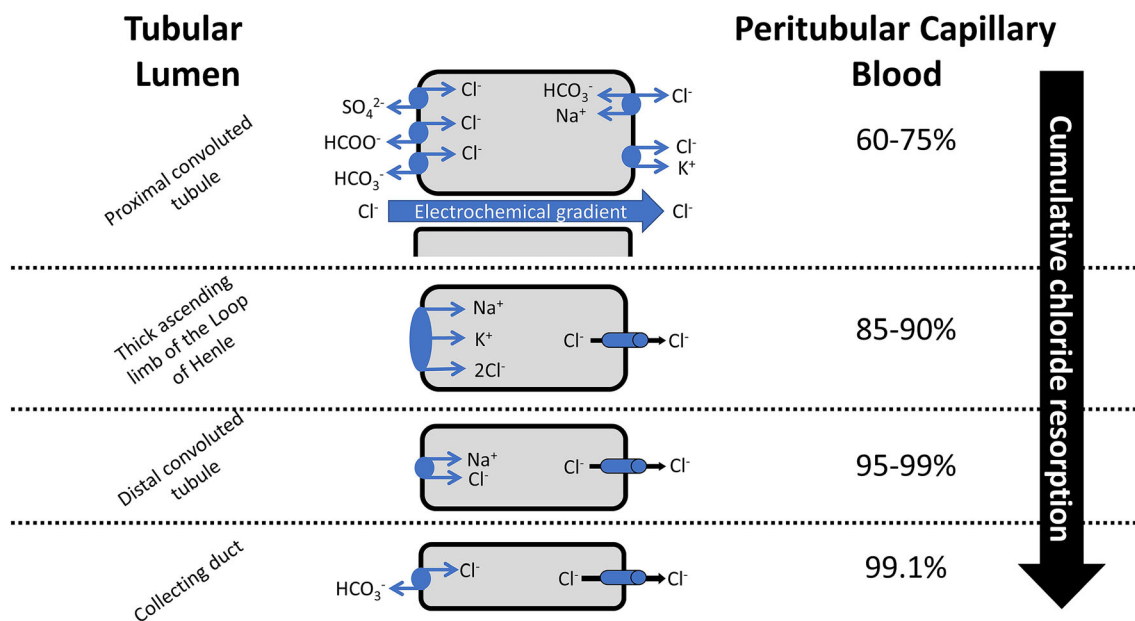


Fig. 1 Chloride reabsorption along the nephron. The majority of renal chloride reabsorption occurs in the proximal convoluted tubule, paracellularly along an

electrochemical gradient although transcellular Cl^- /anion transport also plays a role

volume resulting in increased bicarbonate concentration [27] is well recognized in the literature, but may be an over-simplification. In vivo, increased sodium delivery to the CD (due to apical NKCC2 co-transporter inhibition) increases the activity of the H^+ -ATPase pump, increasing H^+ secretion into the urine [28]. In vitro studies in rats have found that hypokalaemia (a potential complication of loop diuretic use) promotes bicarbonate reabsorption in the PCT [29, 30], and hypokalaemia increases RAAS activation in humans with HF [31, 32], which might further drive bicarbonate reabsorption (Fig. 2).

In vitro and in vivo studies in both rabbits and rats suggest that increased bicarbonate reabsorption is accompanied by increased chloride excretion [33–35]. The same process may occur in humans [36]. One small study ($N = 51$) found that patients with HF and hypochloreaemia had higher serum bicarbonate, and greater fractional chloride excretion than those with normal chloride levels while having similar fractional sodium excretion (Table 1) [8]. “Chloride wasting nephropathy”—persistent

urinary chloride excretion—is seen in patients with hyperaldosteronism [37] and/or severe potassium depletion [38], and similar metabolic states have been reported in patients with HF [39].

An additional factor contributing to the maintenance of an alkalosis is that as serum concentrations of chloride fall (either due to increased excretion in response to increased bicarbonate reabsorption, or diuretic use, or both), there is less and less chloride filtered into in the urinary space. A threshold of low serum chloride may be reached beyond which bicarbonate excretion is inhibited as there is less chloride in the urine to exchange with bicarbonate [36, 37].

Patients can thus be trapped in a cycle of hypochloreaemia and alkalosis, which is only partly due to loop diuretic usage (Fig. 2): for example, among patients admitted with HF, those with serum bicarbonate concentrations above the median (≥ 28 mmol/l) had more severe disease (lower left ventricular ejection fraction, worse renal function, and higher natriuretic peptide levels) but were on lower

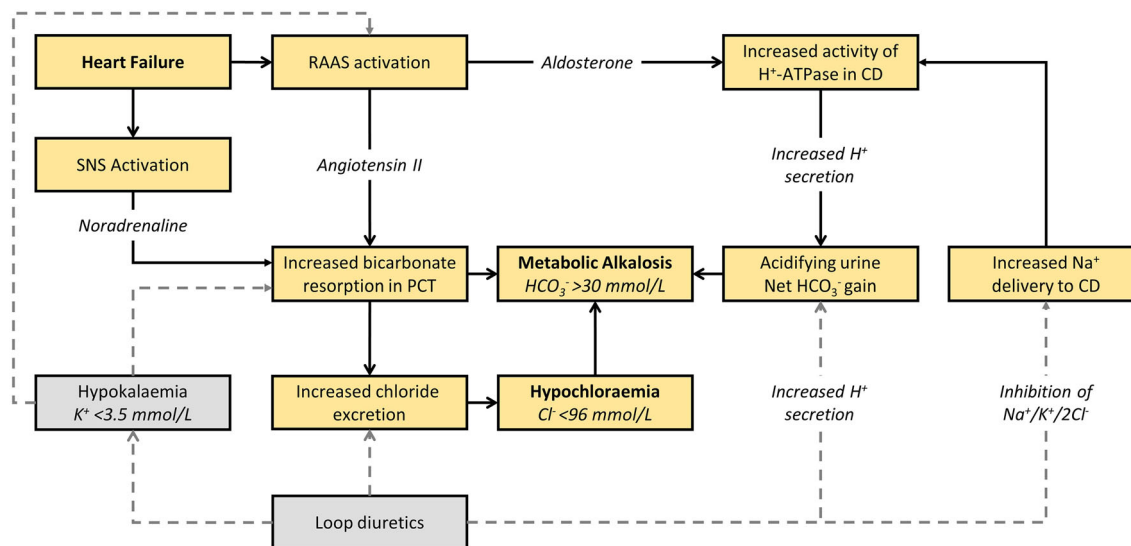


Fig. 2 Possible association between hypochloreaemia, metabolic alkalosis, and neurohormonal activation in patients with heart failure. Our proposed theoretical link between hypochloreaemia, metabolic alkalosis, and neurohormonal activation in patients with heart failure is based on various

in vivo and *in vitro* animal experiments. The dotted greyed lines denote that loop diuretics are only a contributing factor in this proposed model, rather than the driving force

doses of loop diuretic than patients with serum bicarbonate below the median [25].

CHLORIDE AND OUTCOME

Whether a low chloride concentration is a marker or a mediator of adverse outcome is unknown although there are possible pathophysiological mechanisms, which might suggest the latter (Fig. 3).

Diuretic Resistance

The with-no-lysine (WNK) kinases (WNK1, WNK3, and WNK4) are the first step in an enzymatic cascade which increases activity of the Na⁺/K⁺/2Cl⁻ and Na⁺/Cl⁻ co-transporters [40–43]. Chloride binds to the catalytic site of the kinases, thus inactivating them [44, 45]. *In vitro* and *in vivo* studies suggest that the activity of WNK1 and WNK4 is reduced at high chloride concentrations [44, 46], but increased at lower concentrations [47, 48]. Thus, hypochloreaemia may increase the activity of both Na⁺/K⁺/2Cl⁻ and Na⁺/Cl⁻ co-transporters, meaning greater doses of loop diuretic are required to induce a

diuresis. In addition, chronic use of loop diuretic leads to an increase in sodium delivery to the distal tubule with consequent hypertrophy of cells in the distal nephron. The hypertrophied cells reabsorb sodium more avidly, an effect that can be mitigated by increasing the dose of loop diuretic and/or the additional use of a thiazide diuretic [49].

Consistent with this idea, patients with hypochloreaemia take higher doses of loop diuretics than those with normal chloride levels [3–12], but whether a high-dose diuretic is the cause of hypochloreaemia or becomes necessary because of hypochloreaemia-induced diuretic resistance is uncertain.

Effect on the RAAS

Renin secretion is controlled by the macula densa. These specialized cells are sensitive to sodium chloride, low concentrations of which in the urinary space leads to renin secretion from the juxtaglomerular cells of the afferent and efferent arterioles. Increased chloride (but not increased sodium) delivery to the macula densa suppresses renin release from the granular

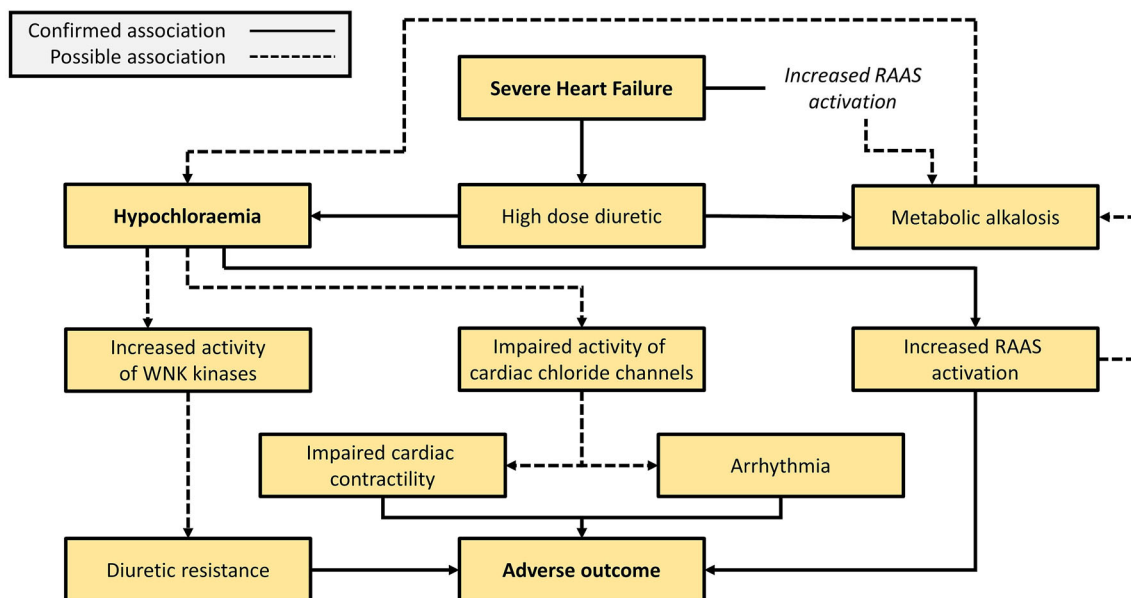


Fig. 3 Confirmed and possible associations between hypochloreaemia and adverse outcome in patients with heart failure. The *dotted lines* denote possible links

demonstrated in animal studies and the *thick lines* denote confirmed links in patients with heart failure

cells in the afferent arteriole and a subsequent fall in angiotensin II levels [50, 51]. Chloride and renin are inversely related in patients with HF [8]. This is the rate-limiting event in the RAAS.

Sudden Death

Chloride channels play a role in ventricular repolarization [52, 53], and in regulating the positive chronotropic effect of cardiac pacemaker activity [54]. Myocyte volume and pH are regulated, in part, by chloride-dependent co-transporters [55, 56]. Abnormalities of the chloride channels and co-transporters may be arrhythmogenic [57, 58] and can impair contractility [59]. Consistent with these observations, a large study of outpatients with HF found that patients with hypochloreaemia had an increased risk of sudden death (Table 1) [3].

A THERAPEUTIC TARGET?

Hypertonic saline (HS) increases diuresis and may improve outcome when given alongside

intravenous furosemide in patients admitted with HF [60, 61]. However, data on changes in chloride levels are absent from almost all reports of HS and whether any observed benefit is due a change in chloride levels is pure speculation. A proof-of-concept study of oral chloride supplementation in patients with HF (N = 10) found that lysine chloride increased chloride levels but required enormous doses to affect only small changes in serum chloride (Table 1) [8]. Further work is ongoing (NCT03446651) [62].

Acetazolamide

Acetazolamide (ACZ) is a carbonic anhydrase (CA) inhibitor. CA catalyses the interconversion between carbon dioxide and water on the one hand, and hydrogen (H⁺) and bicarbonate ions on the other (Fig. 4). CA on the apical membrane of the PCT cell converts free H⁺ and bicarbonate to water and carbon dioxide in the urinary space; the water then diffuses back into the cell via aquaporin 1 channels, carbon dioxide freely diffuses across the apical membrane [63, 64]. There, the water and carbon

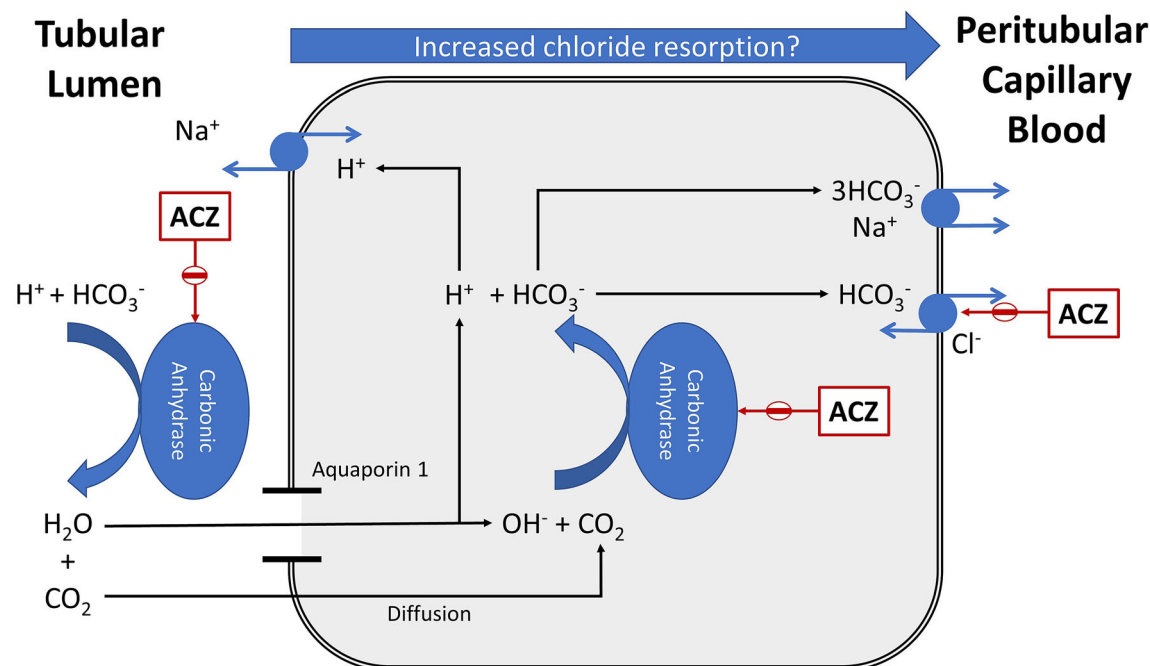


Fig. 4 Renal carbonic anhydrase and acetazolamide. Inhibition of renal carbonic anhydrase with acetazolamide might increase luminal bicarbonate concentrations, reduce intracellular hydrogen ion concentrations thus reducing

sodium reabsorption via the Na^+/H^+ antiporter, and reduce movement of chloride out of the peritubular capillaries. *ACZ* acetazolamide

dioxide are converted back to H^+ and bicarbonate ions by intracellular CA.

The newly formed H^+ ions in the cell are excreted in exchange for urinary sodium via Na^+/H^+ co-transporters on the apical membrane [65, 66], and bicarbonate returns to the circulation via $\text{Na}^+/\text{HCO}_3^-$ and $\text{Cl}^-/\text{HCO}_3^-$ antiporters on the basolateral membrane (Fig. 4) [67]. Inhibition of intracellular CA reduces production of intracellular H^+ , thus reducing sodium reabsorption via the Na^+/H^+ antiporters on the apical membrane, and inhibition of luminal CA reduces production of water and carbon dioxide, thus increasing urinary bicarbonate levels (Fig. 4).

ACZ increases bicarbonate excretion and chloride reabsorption in vivo [32, 68], and increases serum chloride levels in humans [69, 70]. The reasons behind this are not clear but may result from two potential mechanisms: firstly, increased HCO_3^- in the urinary space increases the negative charge thus increasing the electrochemical gradient along which

chloride is reabsorbed in the PCT. Secondly, in vivo studies suggest that ACZ, separately from CA inhibition, also inhibits the basolateral $\text{Cl}^-/\text{HCO}_3^-$ antiporter in the PCT thus reducing movement of chloride out of the blood and into the cell (Fig. 4).

There are thus three ways in which ACZ might be beneficial for patients with HF: (1) increasing sodium excretion and increasing diuresis [71, 72]; (2) increasing bicarbonate excretion, which may reduce metabolic alkalosis [73, 74]; and (3) increasing renal chloride reabsorption, which may reverse hypochloaemia [69, 70].

The ADVOR study of ACZ in patients admitted with HF is aiming to recruit ~ 500 patients, the largest study of ACZ in patients with HF to date. The primary endpoint is treatment success (i.e., clinical decongestion defined as the absence of pleural effusion, ascites, and significant peripheral oedema) after 3 days of treatment. Secondary endpoints include mortality and morbidity alongside

changes in natriuresis, body weight, and natriuretic peptide levels [75]. There is no planned analysis of either chloride or bicarbonate changes but the data will give an insight into the usefulness of ACZ as a treatment for patients with HF.

FUTURE PERSPECTIVE: IS PREVENTION BETTER THAN CURE?

Amongst patients admitted with HF, those with hypochloraemia that resolves by the time of discharge have a similar post-discharge prognosis to those with normal chloride concentrations throughout admission [5]. Conversely, incident hypochloraemia during admission is associated with an increased risk of adverse outcome post-discharge [5]. If hypochloraemia results from the inevitable combination of severe HF and high-dose loop diuretics, it may be that prevention of hypochloraemia, rather than the correction of an existing abnormality, may have the greater effect on outcome. Whether acetazolamide might be best employed as a preventative measure is unknown, but should be the focus of future research.

CONCLUSIONS

Hypochloraemia is a common electrolyte abnormality in patients with HF and is an important marker of poor prognosis. There are many unknowns as to how hypochloraemia develops and whether it has a pathophysiological effect in patients with HF. If the latter is true, it may be a therapeutic target. As ever, more work is needed.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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