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The Road to Wasting is Paved with Lost Minerals

By KARL T. WEBER, MD

Congestive heart failure (CHF), with its characteristic signs and symptoms, is a major health problem of epidemic proportions, particularly amongst the elderly. It is now recognized that this clinical syndrome involves more than a failing heart and salt-avid kidneys. In reaching beyond the traditional cardiorenal perspective, there is the realization that the neurohormonal activation found in CHF is accompanied by a systemic illness that contributes to its progressive nature and downhill clinical course. This issue of *Cardiology Rounds* reviews an emerging body of experimental and clinical evidence that addresses the pathogenic mechanisms involved in the appearance of this illness and its pathophysiologic expressions. These include oxidative stress in diverse tissues, immune cell activation, and a loss of soft tissues and bone that eventuates in a wasting syndrome termed “cardiac cachexia.” In brief, the evidence suggests that “the road to wasting is paved with lost minerals.”

Lost macronutrients – calcium (Ca^{2+}) and magnesium (Mg^{2+}) – contribute to the appearance of secondary hyperparathyroidism (SHPT), with parathyroid hormone (PTH)-mediated intracellular Ca^{2+} overloading that induces oxidative stress in diverse cells. In peripheral blood mononuclear cells (PBMCs; lymphocytes and monocytes), these events account for an immunostimulatory state. Lost micronutrients, zinc (Zn) and selenium (Se), reduce the activities of respective metallo-enzyme-dependent endogenous antioxidant defenses. These trace mineral deficiencies have been associated with cardiomyopathy. In translational studies conducted in African-Americans (AAs) living in Memphis, SHPT, together with hypovitaminosis D, hypozincemia, and hyposelenemia, were found to be co-variants of CHF.

CHF – A salt-avid state

CHF is a clinical syndrome consisting of signs and symptoms that arise from congested organs and hypo-perfused tissues. Its origins are rooted in a salt-avid state, where the urinary sodium/potassium (Na/K) ratio is <1.0 . CHF is largely mediated by effector hormones of the circulating renin-angiotensin-aldosterone system (RAAS) (Figure 1). RAAS activation is based on impaired renal perfusion, in which angiotensin II and aldosterone (ALDO) overwhelm the biologic actions of atrial and brain natriuretic peptides that maintain urinary Na excretion (urinary Na/K >1.0), euolemia, and clinical compensation. Elevations in plasma renin activity, angiotensin II, and ALDO are integral features of the “volume-overloaded” state, expressed as expanded intra- and extravascular volumes, and clinical decompensation found with CHF.^{1,2}

It is important to recognize that, in patients experiencing chronic cardiac failure with systolic dysfunction, reduced ejection fraction (EF) does not predict cardiac output or the amount of systemic blood flow apportioned to the kidneys. Accordingly, EF neither predicts RAAS activation, salt and water retention, nor the clinical severity of heart failure.



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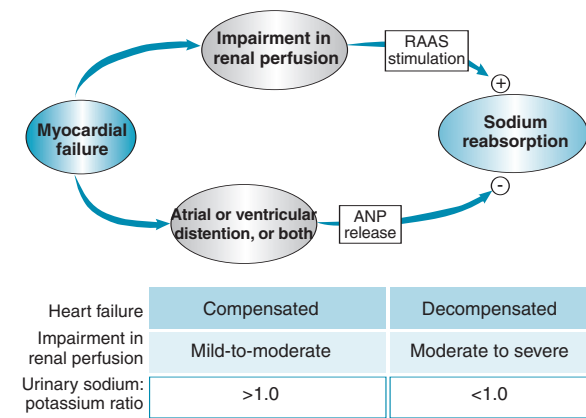
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Figure 1: Compensated and decompensated heart failure (HF) is based on the respective absence or presence of urinary Na⁺ retention, accompanied by signs and symptoms of expanded intra- and extravascular volumes. In compensated HF, with mild to moderate reductions in renal perfusion, natriuretic peptides, eg. atrial natriuretic peptide (ANP), released by distended atria stimulate Na⁺ excretion so that the urinary Na⁺/K⁺ ratio is >1.0. Moderate to severe reductions in renal perfusion activate the renin-angiotensin-aldosterone system (RAAS), overriding the action of natriuretic peptides to stimulate nearly complete urinary Na⁺ resorption with the urinary Na⁺/K⁺ ratio <1.0.



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CHF – A systemic illness

The broader perspective of CHF recognizes its systemic nature with these prominent features:

- the presence of oxidative stress with reactive oxygen and nitrogen species that overwhelm endogenous antioxidant defenses in such diverse tissues as skin, skeletal muscle, PBMCs, and blood
- an immuno-stimulatory state with activated PBMCs and elevations in circulating chemokines and cytokines
- a catabolic state with loss of soft tissues and bone that begets cachexia.³

An experimental model

The complex neurohormonal profile found in CHF includes elevated circulating levels of angiotensin II, ALDO, catecholamines, endothelin-1, atrial and brain natriuretic peptides, and arginine vasopressin. Our experimental studies have focused on chronic aldosteronism, where plasma renin activity and angiotensin II are suppressed. In uninephrectomized rats, aldosterone/salt treatment (ALDOST) consists of an implanted minipump that releases ALDO subcutaneously (0.75 µg/h) to raise plasma levels to those found in human CHF and which are inappropriate for dietary Na⁺ intake that consists of 1% sodium chloride (NaCl) in drinking water. A 0.4% potassium chloride (KCl) supplement is provided to prevent hypokalemia.

Using this model, we (and others) have identified the presence of oxidative stress in blood, PBMCs, and immune

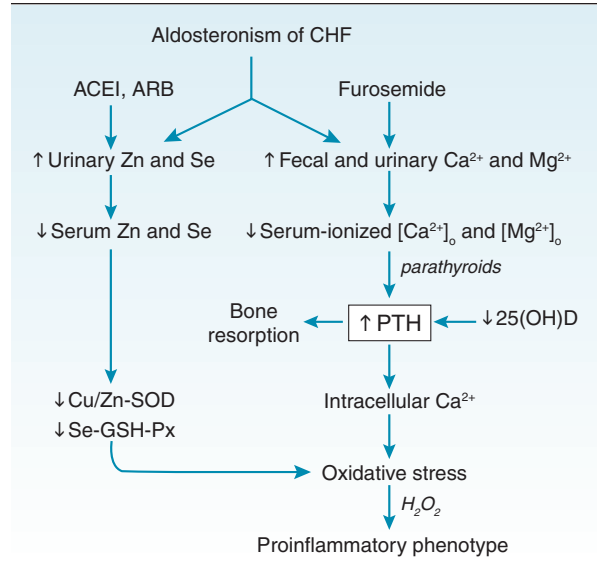
cells that invade the cardiovascular system.^{4,8} This includes multiple lines of evidence: activation of gp91^{phox}, a nicotinamide adenosine dinucleotide phosphate (NADPH) oxidase subunit; the presence of 3 nitrotyrosine, a stable endproduct of short-lived peroxynitrite formation derived from the reaction between superoxide and nitric oxide; activation of a redox-sensitive nuclear transcription factor (NF)κB, and upregulated expression of the proinflammatory genes it controls, including intercellular adhesion molecule (ICAM)1, monocyte chemoattractant protein (MCP)1, and tumor necrosis factor (TNF)α. Co-treatment with various antioxidants has proven vasculoprotective.^{4,7-11}

Mechanisms responsible for the induction of oxidative stress in PBMCs were targeted for investigation. In keeping with the findings of Delva et al¹² in human lymphocytes harvested from patients with aldosteronism, we hypothesized that a fall in intracellular cytosolic-free [Mg²⁺]_i and a putative reduction in Na⁺/K⁺ adenosine triphosphatase (ATPase) activity would lead to increased Ca²⁺ entry with the rise in intracellular Ca²⁺ contributing to the induction of oxidative stress. An early and persistent fall in PBMC cytosolic-free [Mg²⁺]_i was found in ALDOST that was accompanied by a rise in total and cytosolic-free [Ca²⁺]_i and an associated increased production of H₂O₂ by lymphocytes and monocytes, together with upregulated mRNA expression of antioxidant defenses and adhesion molecules.^{5,6} These cellular responses were attenuated when rats with ALDOST were co-treated with spironolactone (spiro), an ALDO receptor antagonist.⁶ Collectively, these findings suggest a direct response of circulating lymphocytes and monocytes to ALDOST and, when *in vitro* studies suggested the involvement of a Na⁺-dependent, the ALDO receptor-mediated Na⁺/Mg²⁺ exchanger.¹² PBMCs have cytosolic mineralocorticoid receptors.¹³

Other known aspects of aldosteronism, however, suggested an alternate explanation. Conn noted that hypomagnesemia was a cardinal feature of aldosteronism,¹⁴ while Horton and Biglieri¹⁵ demonstrated that the hypermagnesuria that accompanies it can be attenuated by spiro or adrenal surgery. We, therefore, elected to pursue another line of investigation (Figure 2) that focused on Mg²⁺ and Ca²⁺ excretion by kidneys and colon, given that these tissues are sites of high-density ALDO receptor binding.¹⁶

Metabolic studies, in which 24-hour urinary and fecal Ca²⁺ and Mg²⁺ excretion were monitored, were conducted in rats receiving ALDOST for 1-6 weeks.^{17,18} Compared to age and gender-matched controls on an identical diet, a marked increase in the urinary and fecal excretion of these divalent cations was observed throughout the 1-6 weeks on ALDOST, which was attenuated at each site by spiro co-treatment. In urine, microgram levels of Ca²⁺ and Mg²⁺ were lost while, in feces, milligram quantities were found. In association with these losses, an early and persistent fall in plasma-ionized [Ca²⁺]_o and [Mg²⁺]_o was demonstrated that was accompanied by an elevation in plasma PTH.

Figure 2: A paradigm depicting the appearance of secondary hyperparathyroidism with elevations in circulating parathyroid hormone (PTH). Elevations in circulating PTH may accompany aldosteronism, long-term furosemide treatment, and hypovitaminosis D with reduced stores of 25(OH)D. In addition to promoting bone resorption, PTH causes intracellular Ca^{2+} overloading with induction of oxidative stress and, when H_2O_2 contributes to signal transduction, it eventuates in immune cell activation and a proinflammatory phenotype. Urinary Zn and Se excretion are increased during aldosteronism and in response to ACE inhibitor (ACEI) or AT1 receptor antagonist (ARB) treatment with resultant hypozincemia and hyposelenemia contributing to reduced activities of Cu/Zn superoxide dismutase (SOD) and Se-glutathione peroxidase (GSH-Px).



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In keeping with the presence of SHPT, the resorption of bone manifested as a reduction in bone mineral density of the tibia and femur and a fall in their strength to flexor stress. In concert with the elevations in PTH was an excessive accumulation of intracellular Ca^{2+} in PBMC, heart, and skeletal muscle. The SHPT found in chronic renal failure is known to be accompanied by intracellular Ca^{2+} overloading of diverse cells and can be prevented by administration of a Ca^{2+} channel blocker.¹⁹

Our hypothesis was therefore revised (Figure 2) to suggest that PTH-mediated intracellular Ca^{2+} overloading plays a permissive role in the appearance of oxidative stress in PBMC. Accordingly, parathyroidectomy (PTx) was performed prior to ALDOST.²⁰ PTx abrogated Ca^{2+} overloading in PBMCs, as well as in heart and skeletal muscle, and prevented the appearance of oxidative stress. This was evident by downregulated PBMC H_2O_2 production and a fall in plasma α_1 -antiproteinase activity, an inverse correlate of oxidative stress. In preventing urinary and fecal losses of these cations, spiro co-treatment also mitigated SHPT.¹⁸ The importance of intracellular Ca^{2+} loading as a prerequisite to the induction of oxidative

stress in PBMC was further demonstrated by the protective response to amlodipine co-treatment.²¹

Clinical correlates

These experimental studies draw attention to the importance of Ca^{2+} and Mg^{2+} balance in patients with heart failure. Elevations in serum PTH have been reported in patients with advanced CHF awaiting cardiac transplantation (in whom elevations in serum ALDO are expected), who have been treated long-term with a loop diuretic (which augments urinary Ca^{2+} and Mg^{2+} excretion above that seen with aldosteronism alone).²²⁻²⁴ Moreover, many of these patients were found to have reductions in bone mineral density to levels in keeping with osteopenia and osteoporosis. Among nursing home residents, daily furosemide dosage is an important predictor of SHPT.²⁵

Circulating levels of interleukin (IL)-6 and $\text{TNF}\alpha$ increase in patients with CHF, irrespective of their etiologic origins.^{26,27} These cytokines are also elevated in patients with primary or SHPT and are derived from osteoblasts that are influenced by PTH to promote osteoclastogenesis and bone resorption.²⁸ It is presently unclear if the elevated serum IL-6 and $\text{TNF}\alpha$ levels found in CHF patients are markers of SHPT.

Translational studies in African-Americans with CHF. macro- and micronutrients

Macronutrients are chemical elements (eg, carbon, hydrogen, nitrogen, oxygen, phosphorus, and sulfur) that are essential to life in large quantities. Other macronutrients include calcium, magnesium, sodium, and potassium.

During 2005, translational studies were conducted in AAs followed at the Regional Medical Center in Memphis, Tennessee. In February, 9 patients (aged 33-60 years; 8 AAs) were hospitalized because of decompensated heart failure, expressed as signs and symptoms of salt and water retention due to systolic dysfunction (ejection fraction <35%) and an ischemic or dilated cardiomyopathy. Five were newly diagnosed and untreated prior to admission and 4 were treated with an ACE inhibitor, furosemide, a loop diuretic, and spiro.²⁹ Serum PTH (mean \pm SEM) was elevated above the normal range (6-65 pg/mL) in all 9; the levels were 204 ± 60 and 134 ± 14 pg/mL in untreated and treated patients, respectively. Calculated creatinine clearance did not differ significantly between untreated and treated patients (74 ± 15 and 83 ± 21 mL/min, respectively). Plasma-ionized $[\text{Ca}^{2+}]_o$ was not measured. Thus, SHPT was present in AAs with untreated CHF, in whom the impact of furosemide on urinary Ca^{2+} and Mg^{2+} excretion could be discounted, as well as in those with treated CHF. Therefore, one must take aldosteronism into consideration, given the expected activation of the RAAS that contributes to active salt and water retention in decompensated failure.

From June to December, 40 additional AA patients (aged 31–79 years) were studied.³⁰ These included 15 hospitalized patients with signs and symptoms of protracted CHF (≥ 4 weeks); 15 hospitalized patients with signs and symptoms of shorter duration CHF (1–2 weeks); and 10 outpatients with compensated failure. All had systolic dysfunction (EF $< 35\%$) of ischemic or idiopathic (dilated) cardiomyopathy origin. The majority were treated with either an ACE inhibitor or an AT₁ receptor antagonist (ARB), furosemide, and spiro. Serum PTH was abnormally elevated in all 15 patients with protracted CHF and in 60% of patients with short-term CHF, but in none of the 10 compensated patients. In patients with decompensated CHF of ≥ 4 weeks duration and in those with CHF of shorter duration (1–2 weeks), serum-ionized [Ca²⁺]_i fell below the expected normal range (1.12–1.30 mmol/L). Serum-ionized [Mg²⁺]_i in decompensated CHF of ≥ 4 weeks duration and 1–2 weeks duration also fell below the normal range (0.53–0.67 mmol/L). None of these patients had sepsis, pancreatitis, blood transfusion, surgery, chronic alcoholism, or metabolic alkalosis that would lead to reduced ionized [Ca²⁺]_i or [Mg²⁺]_i.

Evidence of hypovitaminosis D with reduced serum 25(OH)D (< 30 ng/mL) was found in all 15 patients with CHF of ≥ 4 weeks duration, in 80% of those with CHF of 1–2 weeks duration, and in 80% with compensated failure. Calculated creatinine clearance was statistically indistinguishable amongst the 3 groups. In 9 AA normal volunteers (3 men, 6 women; median age 36 years, 24–58 years), of comparable gender and age to the AA patients with heart failure (but without historical or clinical evidence of cardiovascular disease), serum PTH and 25(OH)D were normal. **Micronutrients** are essential to life, but only in small quantities (< 100 mg/day). Vitamins and trace minerals (eg, zinc, selenium, iron, and copper) are micronutrients obtained predominantly from dietary intake that are not synthesized by the body.

There is a prevalence of dilated cardiomyopathy in general populations where micronutrient dietary deficiencies are found, such as in the Se-poor soil in Keshan province in China, or in patients administered parenteral nutrition that is deficient in Zn and/or Se.^{31–33} A redistribution of Zn and Se from the vascular compartment into tissues may occur in chronic illness and it has been suggested that this is a predisposing factor to the genesis of a dilated (idiopathic) cardiomyopathy.^{34,35} Incidentally, hypozincemia has been reported in patients with a dilated cardiomyopathy.^{36,37} Of interest, urinary Zn excretion is increased in response to ACE inhibitor or ARB treatment, but not with loop diuretics. Urinary Zn excretion has been held responsible for the appearance of hypozincemia and an associated impairment in taste (dysgeusia)

reported in patients with CHF treated with these agents.^{38–41} A redistribution of trace minerals from tissues has also been reported in response to captopril.⁴²

In addition to reduced serum-ionized [Ca²⁺]_i and [Mg²⁺]_i, elevated PTH, and hypovitaminosis D in AAs with CHF, we found that serum Zn fell below the normal range (75–140 $\mu\text{g/dL}$) in many of the 40 patients noted above (in $> 70\%$ of patients with protracted CHF; in $> 50\%$ with short-term CHF; and in 5 of 10 with compensated failure). Serum Se was also reduced below the normal range (85–125 $\mu\text{g/L}$) in $> 90\%$ of these patients (in all 15 with protracted CHF; in 60% with short-term CHF; and in 9 of 10 with compensated failure).

Zn and Se are integral to the activity of oxidoreductases that serve as antioxidant defenses. Together, Cu/Zn superoxide dismutase (SOD) and Se glutathione peroxidase (GSH-Px) protect against superoxide- and H₂O₂-induced cytotoxicity. We are currently monitoring the activity of these oxidoreductases to determine the functional significance of the hypozincemia and hyposelenemia found in our AA patients.

Thus, in many AA patients with CHF, SHPT is a common covariant of CHF, together with hypovitaminosis D, hypozincemia, and hyposelenemia. However, in our AA patients with either decompensated or compensated failure, the pathophysiologic mechanisms responsible remain to be elucidated. Several possibilities may be considered.

- One possibility is the presence of aldosteronism in patients with decompensated failure having signs and symptoms of salt and water retention and in whom, acidification of urine and feces is accompanied by increased excretion of Ca²⁺ and Zn.^{43–45}
- Secondly, SHPT is associated with hyperzincuria.⁴⁶
- Third, a majority of our patients, both compensated and decompensated, are being treated with either an ACE inhibitor or an AT₁ receptor antagonist, both of which are known to increase urinary Zn excretion and may be accompanied by hypozincemia.

Amongst the ACE inhibitors, it has been suggested that those containing a sulfhydryl group (eg, captopril, zofenopril) are much more likely to bind Zn, leading to hyperzincuria. However, this is not a consistent finding.^{47,48} Reduced Zn levels in PBMCs have been reported with either captopril or enalapril.⁴⁷

Summary and conclusions

An emerging body of evidence suggests that SHPT is an important co-variant of CHF, especially in AAs, in whom hypovitaminosis D with reduced serum 25(OH)D levels are prevalent. This is because melanin mandates prolonged exposure of the skin to sunlight and its UVB component, both of which are necessary for vitamin D synthesis. Moreover, melanin absorbs heat, which can lead patients to

avoid sunlight. Finally, a housebound lifestyle imposed by symptomatic CHF limits outdoor activities and, hence, exposure to sunlight. In addition to the role of hypovitaminosis D in contributing to SHPT, there are increased urinary and fecal losses of macronutrients Ca^{2+} and Mg^{2+} associated with aldosteronism, as well as heightened urinary losses of these macronutrients with furosemide treatment. Thus, the precarious Ca^{2+} balance seen with reduced serum 25(OH)D is further compromised when AAs develop CHF with circulating RAAS activation and are then treated with a loop diuretic. SHPT accounts for a paradoxical Ca^{2+} overloading and induction of oxidative stress in diverse tissues that spills over to the systemic circulation.

In addition to SHPT, hypozincemia and hyposelenemia may be present in AAs with treated compensated and decompensated heart failure. Deficiencies in these micronutrients may originate from dietary insufficiencies, altered rates of absorption or excretion, and/or tissue redistribution. Well over 80% of the 40 AA patients that we have studied to date have an idiopathic (dilated) cardiomyopathy.³⁰ Zn and Se deficiencies may contribute to the severity of heart failure and its progressive nature in this population. Collectively, these findings support the need for nutraceutical treatment, in addition to current pharmaceuticals, in AAs with heart failure, and focus attention on minerals that are lost along the road to wasting and their associated adverse consequences.

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