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CONGESTIVE HEART FAILURE: WHERE HOMEOSTASIS BEGETS DYSHOMEOSTASIS

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Abstract

Despite today's standard of care, aimed at containing homeostatic neurohormonal activation, 1 in every 5 patients recently hospitalized with congestive heart failure (CHF) will be readmitted within 30 days of discharge because of a recurrence of their symptoms and signs. In light of recent pathophysiologic insights, it is now propitious to revisit CHF with a view toward complementary and evolving management strategies. CHF is a progressive systemic illness. Its features include: oxidative stress in diverse tissues; an immunostimulatory state with circulating proinflammatory cytokines; a wasting of soft tissues; and a resorption of bone. Its origins are rooted in homeostatic mechanisms gone awry to beget dyshomeostasis. For example, marked excretory losses of Ca^{2+} and Mg^{2+} accompany renin-angiotensin-aldosterone system (RAAS) activation, causing ionized hypocalcemia and hypomagnesemia that lead to secondary hyperparathyroidism (SHPT) with consequent bone resorption and a propensity to atraumatic fractures. Parathyroid hormone (PTH) accounts for paradoxical intracellular Ca^{2+} overloading in diverse tissues and consequent systemic induction of oxidative stress. In cardiac myocytes and mitochondria these events orchestrate opening of the mitochondrial membrane permeability transition pore (mPTP) with an ensuing osmotic-based destruction of these organelles and resultant cardiomyocyte necrosis with myocardial scarring. Contemporaneous with Ca^{2+} and Mg^{2+} dyshomeostasis is hypozincemia and hyposelenemia, which compromise metalloenzyme-based antioxidant defenses while hypovitaminosis D threatens Ca^{2+} stores needed to prevent SHPT. An intrinsically coupled dyshomeostasis of intracellular Ca^{2+} and Zn^{2+} , representing prooxidant and antioxidant, respectively, is integral to regulating mitochondrial redox state; it can be uncoupled by a Zn^{2+} supplement in favor of antioxidant defenses. Hence, the complementary use of nutraceuticals to nullify dyshomeostatic responses involving macro- and micronutrients should be considered. Evolving strategies with mitochondria-targeted interventions interfering with their uptake of Ca^{2+} or serving as selective antioxidant or mPTP inhibitor may also prove efficacious in the overall management of CHF.

Keywords

Secondary hyperparathyroidism; intracellular calcium overloading; cardiac myocytes and mitochondria; oxidative stress; antioxidant defenses; fibrosis

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Introduction

Congestive heart failure (CHF), a clinical syndrome comprised of disabling symptoms and disconcerting signs, is the leading cause of hospitalization, especially among the elderly. Currently, over 5 million Americans have heart failure and every year 500,000 new cases are diagnosed. One in every 5 patients recently hospitalized because of their CHF will be readmitted within 30 days of discharge because of its recurrence, despite today's standard of care which relies on pharmaceuticals to contain homeostatic responses embodied in neurohormonal activation. In this context, it is timely to revisit CHF in light of recent mechanistic insights into its pathophysiologic expressions, and with a view toward complementary and evolving novel management strategies.

A failing heart is an essential pathophysiologic component of the CHF syndrome. Irrespective of its etiologic basis, there is an erosion in the structural and functional integrity of this normally efficient muscular pump involving oxidative stress-mediated loss of cardiomyocytes, primarily to the necrotic cell death pathway and terminating in replacement fibrosis or scarring (1–4). From this initial cardiocentric perspective emerges another component, a systemic illness whose origins are rooted in neurohormonal activation and mediated by effector hormones of the renin-angiotensin-aldosterone (RAAS), as well as adrenergic nervous (ANS) systems. It has several major features. First, ongoing oxidative stress where the rate of reactive oxygen (ROS) and nitrogen (RNS) species generation overwhelms that of their detoxification afforded by endogenous antioxidant defenses (2,3,5). This altered redox state affects not only the heart, but systemic tissues as well, including skeletal muscle, peripheral blood mononuclear cells (PBMC; lymphocytes and monocytes), and blood (2,3,5–13). The systemic nature of oxidative stress accounts for elevated serologic biomarkers of lipid peroxidation (11,14). Second, an immunostimulatory state where activated tissue macrophages and PBMC-released chemokines and proinflammatory cytokines synergistically elevate circulating levels of tumor necrosis factor- α and interleukin-6 (15–20). Third, a catabolic loss of soft tissues that eventuates in a wasting syndrome, termed cardiac cachexia (21). Finally, a resorption of bone with a fall in bone density and strength increases vulnerability to atraumatic fractures (22–28).

The origins of this systemic illness are rooted in homeostatic mechanisms that have gone awry to beget dyshomeostasis. These cascading perturbations in equilibrium to the stability of the body's internal environment involve macro- and micronutrients, such as K^+ , Ca^{2+} , Mg^{2+} , Zn^{2+} , Se^{2+} , and vitamin D, each of which plays important cellular and subcellular functional roles involving the heart and other tissues. In recognizing these hitherto under-appreciated aspects of CHF raises the prospect that therapies targeted at controlling dyshomeostatic responses could prove complementary to today's standard of care with pharmaceuticals.

THE CONCEPT OF HOMEOSTASIS

Claude Bernard put forward the concept in 1865 that the body has the innate ability to preserve its *milieu interieur*—a stability to the equilibrium of its internal environment, especially when challenged by a perturbation to its external environment (29). In his book, *The Wisdom of the Body*, published in 1932, Walter Cannon introduced the term *homeostasis* to address Bernard's concept of internal stability owing to the coordinated response to a stimulus that disturbed its equilibrium (30). Homeostasis reflects the body's natural power of adaptation—a continuous cooperation and integration between the internal environment with external surroundings. Based on his experimental findings, Hans Selye reported that a persistent environmental stressor (e.g., extremes of temperature), together with an attendant homeostatic hormonal response, led to tissue injury that he termed diseases of adaptation (31). Dickinson W. Richards subsequently advanced the relevance of disease in invoking and perturbing homeostatic mechanisms, where homeostasis would go awry and contribute to pathology (32). He noted

the “homeostatic effort which in correcting one difficulty produces others much worse” (33). Years later, Albrecht Fleckenstein identified the homeostatic stressor response accompanied by catecholamine excess as causing a dyshomeostasis of the intracellular compartment, i.e., through intracellular and especially mitochondrial Ca^{2+} overloading with ATP depletion. He characterized this as a cytotoxic pathway responsible for mitochondrial injury and subsequent cardiomyocyte necrosis that could be prevented by a Ca^{2+} channel blocker (34).

Drawing on these pioneering concepts, we propose to broaden the perspective of CHF as a chronic neurohormonal stressor state, where homeostasis goes awry to beget dyshomeostasis expressed at systemic, cellular, and molecular levels in diverse tissues, including the failing heart.

CHF: WHERE HOMEOSTASIS BEGETS DYSHOMEOSTASIS

Richards characterized homeostatic responses gone awry as: *inappropriate* for the condition; *excessive*, especially when persistent; and *deficient*, if essential elements to the homeostatic response were inadequate (33).

Inappropriate Homeostasis

The failing heart's impaired systolic or diastolic function is accompanied by a reduction in cardiac output and *pari passu* renal blood flow, causing the kidneys to initiate a homeostatic hormonal response comparable to that found when intravascular volume is contracted due to salt and water deprivation or fluid loss. The reduction in renal perfusion is sensed by baroreceptor-like cells of the juxtaglomerular apparatus which, in turn, elaborate renin. The ensuing rise in plasma renin activity leads to elevations in circulating angiotensin II and aldosterone (35). Together, these effector hormones of the RAAS promote the retention of Na^+ and water, an appropriate homeostatic response to intravascular volume contraction and dietary Na^+ restriction. In the setting of heart failure, however, where intravascular volume and dietary Na^+ intake are normal, the ensuing salt-avid state is inappropriate and unwanted—it proves pathologic. This homeostatic response gone awry leads to dyshomeostasis manifested by the subsequent expansion of intravascular and extravascular volumes with the appearance of symptoms and signs commensurate with the clinical syndrome CHF. Additional dyshomeostatic responses also accompany the inappropriate activation of the RAAS and elevations in circulating angiotensin II that involves the heart and systemic organs, which have been reviewed elsewhere (36,37). Several of these responses that accompany chronic secondary aldosteronism are discussed herein.

Excessive Homeostasis

Chronic, inappropriate (relative to normal or increased dietary Na^+) elevations in plasma aldosterone (ALDO) are accompanied by increased fecal and urinary excretion of Ca^{2+} and Mg^{2+} that lead to ionized hypocalcemia and hypomagnesemia (see Figure 1) (38–43). The Ca^{2+} -sensing receptor of the parathyroid glands, activated in response to hypocalcemia, promotes increased secretion of parathyroid hormone (PTH) with the ensuing secondary hyperparathyroidism (SHPT) eliciting homeostatic responses aimed at restoring extracellular Ca^{2+} and Mg^{2+} concentrations, including resorption of bone minerals. Sustained elevations in plasma PTH, however, beget further dyshomeostasis. In what has been termed a *Ca^{2+} paradox*, PTH is responsible for a receptor-mediated, G-protein-coupled rise in intracellular Ca^{2+} in diverse cells (44–46). Intracellular Ca^{2+} overloading has unintended pathologic consequences on cardiac myocytes and mitochondria (34).

As Fleckenstein suggested, an acute hyperadrenergic state, such as occurs with bodily injury, head trauma, subarachnoid hemorrhage, burn injury, sepsis, or acute myocardial infarction,

likewise leads to intracellular and mitochondrial Ca^{2+} overloading accompanied by ionized hypocalcemia (47–56). The ensuing SHPT brings about excessive intracellular Ca^{2+} accumulation (EICA). The chronic stressor state of CHF involves an activation of both the ANS and RAAS, thereby predisposing to ionized hypocalcemia, SHPT, and EICA (24,57–59). Other conditions where cardiotoxicity is related to intracellular Ca^{2+} overloading includes ischemia/reperfusion (I/R) injury and hereditary muscular dystrophy (60,61). Abnormal elevations in serum PTH (>65 pg/mL), the mediator of EICA in cardiac myocytes and mitochondria during aldosteronism (45,62,63), are found in patients hospitalized with decompensated heart failure and those awaiting cardiac transplantation (23,24,59,64). In outpatients having heart failure, elevated serum PTH levels are also found and serve as an independent predictor of CHF and the need for hospitalization (65–67). PTH-mediated bone resorption will account for a proportional fall in bone mineral density and strength, where accompanying osteopenia and osteoporosis underlie the increased susceptibility of patients having CHF to atraumatic fractures (22,24,27,28,68–71). In this context, elevated serum levels of alkaline phosphatase, a biomarker of bone resorption and PTH status, are an independent predictor of all-cause and cardiovascular mortality (68,72,73).

Mitochondria are considered the major contributor to ROS generation. Accordingly, they play a crucial role in the development and progression of the heart's failure as a muscular pump. Intracellular Ca^{2+} overloading is responsible for the induction of oxidative stress in the cytosol and mitochondria of cardiomyocytes, where the rate of ROS and RNS generation overwhelms their rate of detoxification by endogenous antioxidant defenses. Ca^{2+} overloading of mitochondria and accompanying oxidative stress culminates in the opening of the mitochondrial permeability transition pore (mPTP) located in the inner membrane of these organelles and potentiated by the activation of cyclophilin D, an mPTP sensitizer (60). Uncoupling proteins of the mitochondrial membrane, which can regulate ROS production, are downregulated in the failing heart (74). Pathologic opening of mPTP is followed by the destruction of these organelles with cardiomyocyte necrosis (60). Figure 2 depicts the progressive downward spiral of homeostatic responses initiated by RAAS activation and leading to SHPT, that begets dyshomeostasis first at the organ level leading to EICA and oxidative stress which ultimately cause mPTP opening. Necrotic cell death is followed by invading inflammatory cells and fibroblasts that account for tissue repair and myocardial scarring that represents a morphologic footprint of prior necrosis. Fibrosis is indeed a homeostatic response which restores structural integrity of the myocardium, but its progressive nature leads to an inevitable adverse structural remodeling of the heart (4).

Progressive accumulation of fibrillar collagen throughout the right and left heart is related to ongoing necrosis of cardiomyocytes. Elevations in plasma troponins, biomarkers of cardiomyocyte necrosis, together with serologic markers of collagen turnover, have been reported in patients hospitalized with decompensated failure, where they serve as predictors of adverse events, including in-hospital and cardiac-related mortality (75–83). Serial monitoring of troponins, together with circulating levels of brain natriuretic peptide, identified a group of ambulatory patients with a persistent elevation of troponins who are at high risk for hospitalization, death, or cardiac transplantation (84,85). Thus, the pathologic remodeling of myocardium is an ongoing process, involving the loss of contractile cells to necrosis. It is accentuated during periods of decompensated failure when circulating catecholamines are elevated and ensuing mitochondrial Ca^{2+} overloading leads to induction of oxidative stress, mPTP opening with organellar degeneration, and cardiomyocyte necrosis (21,86–88). The contemporaneous replacement scarring that follows accounts for ventricular dysfunction and arrhythmias (89,90).

Deficient Homeostasis

The appearance of ionized hypocalcemia during aldosteronism depends on the body's overall Ca^{2+} balance where several factors are likely to compromise Ca^{2+} reserves. Hypovitaminosis D is a prime example, defined as plasma 25(OH)D levels <30 ng/mL, and is particularly prevalent in African-Americans (AA) where the greater melanin content of skin serves as a natural sunscreen mandating longer periods of sunlight exposure for the skin to begin vitamin D steroidogenesis (59). Lactose intolerance, also prevalent in AA, is another cofactor which compromises Ca^{2+} balance because the intake of dairy products, rich in Ca^{2+} , are preferentially curtailed to avoid attendant gastrointestinal symptoms. A preference for high dietary Na^+ is also a contributory factor because the associated increased urinary Na^+ excretion is accompanied by augmented urinary Ca^{2+} excretion, or hypercalciuria. Finally, loop diuretics, commonly prescribed in the management of CHF, promote increased urinary excretion of Ca^{2+} . Thus, in addition to the excretory losses seen with the secondary aldosteronism of CHF, a host of cofactors may compromise Ca^{2+} balance and predispose to ionized hypocalcemia. The subsequent appearance of SHPT and resorption of bone reduces bone mineral density and bone strength predisposing patients with CHF to atraumatic fractures (24,27,28). Spirinolactone, an aldosterone receptor antagonist, attenuates the risk of these fractures (27).

Weglicki et al. (91) have reviewed the adverse consequences that arise with Mg^{2+} deficiency often associated with diuretics, which includes adverse myocardial remodeling with reduced ventricular function and abnormal gastrointestinal permeability to lipopolysaccharide (LPS) predisposing to sepsis, which has been reported in CHF patients with splanchnic congestion (92). In ambulatory patients, with either chronic systolic or diastolic heart failure, hypomagnesemia (serum $\text{Mg}^{2+} <2$ mEq/L) was associated with increased cardiovascular mortality (93). Furthermore, serum $\text{K}^+ <4$ mEq/L was associated with increased mortality in these patients (94). Pathophysiologic mechanisms involved in the appearance of hypokalemia and hypomagnesemia during acute stressor states such as heart failure have recently been reviewed (95). Prolonged deficiency of Zn^{2+} likewise has adverse consequences on the heart and vasculature, where it serves as a risk factor for oxidative damage and vascular disease (96–98).

Intrinsically Coupled Ca^{2+} and Zn^{2+} Dyshomeostasis

In CHF, where PTH and catecholamines account for intracellular Ca^{2+} overloading and consequent oxidative stress, endogenous antioxidant defenses are of paramount clinical relevance. These include metalloenzymes, such as Cu/Zn-superoxide dismutase (SOD) and Se-glutathione peroxidase (GSH-Px). A dyshomeostasis of these divalent cations has been reported in patients with CHF (57,58,99–104). Zn^{2+} dyshomeostasis, whereby an increased urinary and fecal excretion of Zn^{2+} contributes to the appearance of hypozincemia, has been documented in chronic aldosteronism (105). Urinary Zn^{2+} excretion is also increased in response to an angiotensin-converting enzyme (ACE) inhibitor or angiotensin (AT_1) receptor blocker, and where the ensuing hypozincemia contributes to abnormal sensation of taste (dysgeusia) (106,107). In experimental animals and in patients hospitalized following trauma, burn injury or sepsis, or following coronary artery bypass surgery, the severity of the hypocalcemia and hypozincemia, together with elevated plasma PTH, are related to the extent of injury and are determinants of survival (47–55,108–112). Ionized hypocalcemia with elevated serum PTH levels are commonly found among patients presenting to the emergency department with diverse disorders, where these are related to the severity of the underlying condition and associated mortality (50). Thus, a coupled dyshomeostasis of Ca^{2+} and Zn^{2+} occurs with either acute or chronic stressor states, and is associated with a critical dysequilibrium between prooxidants and antioxidants. Micronutrient supplementation, including Zn^{2+} , has proven both cardio- and renoprotective in various proinflammatory states, including alcohol-induced or diabetes-related cardiomyopathy, trauma or burn injury, and

ischemia/reperfusion injury (113–122). In a manner similar to a Zn^{2+} supplement, raising intracellular Zn^{2+} concentration via a Zn^{2+} ionophore preserves protein kinase C isoforms which appears to function as a cardioprotective strategy against I/R injury (123).

The coupled intracellular dyshomeostasis of Ca^{2+} and Zn^{2+} that accompanies aldosteronism occurs within days and is persistent, ultimately overwhelming antioxidant defenses (124). Several molecular homeostatic responses are invoked to conserve Zn^{2+} (see Figure 3). These include upregulation of metallothionein (MT)-1, a Zn^{2+} -binding protein, at sites of injury where circulating Zn^{2+} translocates to facilitate tissue repair (62,63,105,125). Increased expression of MT-1 in the liver serves to conserve the body's Zn^{2+} stores while Zn^{2+} reserves in bone are released to restore the fall in extracellular Zn^{2+} (125). Recent findings in cardiac myocytes and mitochondria harvested from rats with chronic aldosteronism indicate that PTH-mediated intracellular Ca^{2+} overloading is accompanied by increased intracellular Zn^{2+} , and this intrinsically coupled dyshomeostasis involves Zn^{2+} entry via L-type Ca^{2+} channels (LTCC) and primarily via a Zn^{2+} importer (Zip1) whose expression is upregulated by ROS/RNS (63). The rise in $[Zn^{2+}]_i$ is detected by its intracellular sensor, metal-responsive transcription factor (MTF)-1, and its translocation to the nucleus where it accounts for the upregulation of a number of genes involved in endogenous antioxidant defenses, including MT-1, Cu/Zn-SOD and glutathione synthase. Thus, several molecular homeostatic mechanisms are at play by Zn^{2+} dyshomeostasis and are primarily aimed at cytoprotection through antioxidant defenses.

Selenium is another essential trace mineral and cofactor of antioxidant selenoenzymes, such as GSH-Px and thioredoxin reductase, that promote optimal antioxidant/oxidant balance (126). A Se-deficient diet is associated with a diminished activation potential of nuclear transcription factor (NF) κ B and downregulation of Se-GSH-Px activity which detoxifies peroxides and hydroperoxides in such diverse tissues as kidney, cardiovascular, and PBMC (127–132), and is readily reversible when dietary Se is adequately fortified (129,133). A dilated cardiomyopathy has been widely recognized to occur in patient populations where dietary Se deficiencies are found, such as in the Se-poor soil of the Keysan Province of China and in patients on prolonged parenteral nutrition where their regimen is deficient in Se (133–137). A redistribution of serum Zn^{2+} and Se^{2+} into tissues may take place in patients with chronic illness predisposing them to a dilated (idiopathic) cardiomyopathy (138,139).

Vitamin D is another micronutrient that is essential to preserving homeostasis through its regulation of systemic Ca^{2+} balance. Environmental factors, such as hypovitaminosis D, reduced dietary Ca^{2+} intake with lactose intolerance and the hypercalciuria associated with high dietary Na^+ and/or loop diuretic, would also compromise the body's Ca^{2+} stores to incite the appearance of SHPT with bone resorption and paradoxical EICA. Vitamin D receptors are ubiquitous, including in the heart. A deficiency of vitamin D, as expressed in vitamin D receptor knockout mice, is associated with cardiac fibrosis (140). Furthermore, hypovitaminosis D is also prevalent, especially in AA (59). Zittermann and colleagues (66,141) have addressed the importance of hypovitaminosis D in patients with CHF. Therefore, the prospect that correcting vitamin D deficiency may reverse adverse cardiac remodeling and dilated cardiomyopathy in adults is intriguing, but remains to be systematically addressed and the appropriate dose of vitamin D supplement determined. However, a favorable response to and reversibility of dilated cardiomyopathy has been recently reported in children whose hypovitaminosis D was corrected (142).

CHF: MANAGEMENT STRATEGIES

Pharmaceuticals

As currently envisaged, the management of CHF is focused on the pharmacologic regulation of the inappropriately invoked homeostatic imbalances expressed by effector hormones of the

RAAS and ANS, using ACE inhibitors, AT1 receptor blockers, aldosterone receptor antagonists, and β -adrenergic receptor blockers. Given the propensity for aberrant outcomes of the homeostatic mechanisms gone awry with excretory losses of Ca^{2+} and Mg^{2+} , potent loop diuretics should be used with due diligence. Once euvolemia has been established, other diuretics such as spironolactone with its favorable impact on maintaining electrolyte profile and reducing all-cause and cardiac-related mortality and sudden cardiac death should be considered (143). Salt sensitivity, an inability to excrete the dietary Na^+ load which is common in patients with heart failure (144,145), can be managed by less potent diuretics, such as spironolactone, provided associated renal dysfunction is not severe (serum creatinine <2.0 mg/dL) and K^+ supplements are discontinued.

Nutriceuticals

The prospect that multiple nutritional dyshomeostasis associated with CHF, especially those involving macro- and micronutrients, can be reversed by nutriceuticals is mechanistically attractive and needs to be thoroughly explored. It is our contention that a polynutrient supplement will be necessary, given the complexity and multiplicity of deficiencies that exist and which include vitamin D, Ca^{2+} , Mg^{2+} , Zn^{2+} , and Se^{2+} , at the least. Two randomized studies examining this option in patients with left ventricular (LV) dysfunction have been reported to date (146,147). These studies, albeit small in sample size, suggest that patients having CHF would benefit from a polynutrient supplement.

Emerging Strategies and Cardioprotection

PTH- and catecholamine-mediated Ca^{2+} entry via LTCC each leads to intracellular Ca^{2+} overloading of cardiomyocytes and their mitochondria. Especially, EICA in mitochondria compromises their structural and functional integrity, including oxidative phosphorylation and induction of global oxidative damage. In the failing heart, these pathogenic events represent a signal-transducer-effector pathway leading to cardiomyocyte necrosis and consequent remodeling of myocardium by fibrous tissue. Persisting EICA accounts for ongoing cell loss and contributes to the progressive accumulation of fibrous tissue.

Mitochondria-targeted strategies—There is ample evidence that mitochondrial pathophysiology is integral to the genesis of the heart's failure as a muscular pump and its progressive nature. Targeting these organelles with reagents that selectively accumulate therein, enhancing mitochondrial structural-functional correlates preventing oxidative damage and cell death, could mechanistically offer cardioprotective strategies. The newer generation β blockers (e.g., carvedilol and nebivolol) and various nutriceuticals (e.g., flavonoids and Zn^{2+}) may offer promise as antioxidants and anti-inflammatory agents (148–151).

Metabolic remodeling of mitochondria—As an obligate aerobic organ, the heart is dependent on ATP for its energy demand which is primarily generated by its mitochondria. In the failing heart, ATP synthesis from endogenous fatty acids falters to threaten available and recruitable energy reserves. This pathophysiologic scenario has led to experimental interventions aimed at a metabolic remodeling of mitochondria and transcriptional control of pathways regulating their synthesis of ATP (reviewed in 152).

Uncoupling Ca^{2+} - Zn^{2+} dyshomeostasis—This approach is based on the dysequilibrium that exists between prooxidant (Ca^{2+}) and antioxidant (Zn^{2+}), and draws on strategies that preferentially raises $[\text{Zn}^{2+}]_i$ thus enhancing antioxidant defenses in cardiac myocytes and mitochondria (see Figure 3) (63,153). Furthermore, increased $[\text{Zn}^{2+}]_i$ attenuates intracellular Ca^{2+} overloading by serving as an inherent competitive inhibitor to Ca^{2+} entry via LTCC. Therefore, by increasing intracellular Zn^{2+} and reducing intracellular $[\text{Ca}^{2+}]_i$, a ZnSO_4

supplement renders dual salutary properties. Favorable antioxidant responses to supplemental Zn^{2+} have been reported in various disorders (98,121,122,154).

SUMMARY AND CONCLUSIONS

Homeostasis refers to the power of adaptation in preserving the equilibrium of vital life-sustaining functions involving the continuous cooperation and integration between the internal environment with external surroundings. However, in seeking to correct and restore normality in the presence of chronic disease, inappropriate and excessive homeostatic responses beget dyshomeostasis and even worse outcomes—diseases of adaptation. CHF has its origins rooted in inappropriate neurohormonal activation, a homeostatic mechanism invoked when the failing heart does not sustain renal perfusion. When excessive and persistent, this homeostatic response gone awry begets dyshomeostasis at organ, cellular, and subcellular levels. Aldosterone-related excretory losses of Ca^{2+} and Mg^{2+} lead to ionized hypocalcemia and hypomagnesemia, and the induction of SHPT with PTH-mediated intracellular Ca^{2+} overloading of diverse tissues and the induction of oxidative stress. Unless reversed by endogenous antioxidant defenses, chronic oxidative stress has serious pathologic consequences. A concomitant dyshomeostasis of essential micronutrients, Zn^{2+} and Se^{2+} , impairs corresponding metalloenzymes involved in antioxidant defenses. In the case of cardiomyocytes and their mitochondria, this adverse redox signaling eventuates in the structural and functional degeneration of mitochondria and necrotic cell death with subsequent myocardial fibrosis.

This broader perspective of CHF offers the potential to optimize its clinical management. Current pharmaceuticals interrupt many maladapted homeostatic responses involving neurohormonal activation and the accompanying adverse impact of effector hormones. However, the complementary use of nutraceuticals to nullify hitherto unabated dyshomeostatic responses involving macro- and micronutrients has not yet been thoroughly explored. Novel strategies involving mitochondria-targeted interventions will offer mechanistic insights into what may prove to be optimal management of CHF.

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Abbreviations used

ANS	adrenergic nervous system
CHF	congestive heart failure
EICA	excessive intracellular Ca^{2+} accumulation
GSH-Px	glutathione peroxidase
I/R	ischemia/reperfusion
mPTP	mitochondrial permeability transition pore
MT-1	metallothionein-1
MTF-1	metal-responsive transcription factor-1

NFκB	nuclear transcription factor-κB
PBMC	peripheral blood mononuclear cells
PTH	parathyroid hormone
RAAS	renin-angiotensin-aldosterone system
RNS	reactive nitrogen species
ROS	reactive oxygen species
SHPT	secondary hyperparathyroidism
SOD	superoxide dismutase
ALDO	aldosterone
AA	African-Americans
LPS	lipopolysaccharide
ACE	angiotensin-converting enzyme
AT	angiotensin
LTCC	L-type calcium channel
LV	left ventricle

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Figure 1.

Inappropriate (relative to dietary Na^+) elevations in plasma aldosterone comparable to those found in human CHF accompany aldosterone/salt treatment (ALDOST) in rats. This chronic aldosteronism is responsible for increased urinary and fecal excretion of Ca^{2+} and Mg^{2+} . This leads to plasma ionized hypocalcemia and hypomagnesemia. Secondary hyperparathyroidism (SHPT) is invoked to restore extracellular Ca^{2+} and Mg^{2+} balance via parathyroid hormone (PTH)-mediated bone resorption and increased absorption and reabsorption of these cations from the gut and kidneys, respectively, mediated by the steroid hormone $1,25(\text{OH})_2\text{D}_3$ synthesized by the kidneys. Paradoxically, PTH is responsible for intracellular Ca^{2+} overloading, which leads to oxi-/nitrosative stress and a proinflammatory phenotype with cardiomyocyte necrosis.

Figure 2.

A progressive downward spiral, where homeostasis begets dyshomeostasis at organ, cellular and molecular levels leading to cardiomyocyte necrosis. The cycle begins with heart failure and reduced renal blood flow (RBF) leading to the homeostatic activation of the renin-angiotensin-aldosterone system (RAAS). Ionized hypocalcemia $[Ca^{2+}]_o$ appears due to an accompanying increased excretory loss of Ca^{2+} . In turn, this dyshomeostatic reaction accounts for the subsequent homeostatic response which is initiated by the appearance of secondary hyperparathyroidism (SHPT) with increased circulating parathyroid hormone (PTH). The dyshomeostatic response to SHPT is PTH-mediated intracellular $[Ca^{2+}]_i$ overloading wherein induction of oxidative stress follows with the generation of reactive oxygen and nitrogen species (ROS/RNS). Together, intracellular Ca^{2+} overloading and oxidative stress contribute to the pathologic opening of the mPTP pore and activation of cyclophilin D with the ensuing osmotic injury to mitochondria and ultimately necrotic cell death.

Figure 3.

As shown on the right, aldosteronism is accompanied by ionized hypocalcemia $[Ca^{2+}]_o$ and elevated plasma PTH that accounts for intracellular Ca^{2+} entry via L-type Ca^{2+} channels (LTCC), and Ca^{2+} overloading of the cardiac myocyte $[Ca^{2+}]_i$ and mitochondria $[Ca^{2+}]_m$ with the induction of oxidative stress and mPTP opening, leading to necrosis and replacement fibrosis. Mitochondria-targeted interventions could prove cardioprotective by inhibiting the Ca^{2+} uniporter involved with Ca^{2+} entry, antioxidant, or mPTP opening inhibitor.

As seen on the left and center, the altered redox state upregulates the expression of Zn^{2+} transporters (Zip1 and ZnT-1) and releases Zn^{2+} bound to metallothionein (MT-1) in the cytosol. Cytosolic $[Zn^{2+}]_i$ and mitochondrial $[Zn^{2+}]_m$ are increased to the extent possible promoted by Zn^{2+} entry through LTCC where the majority of $[Zn^{2+}]_i$ and $[Zn^{2+}]_m$ is derived through its entry via the membrane-bound importer Zip1. Intracellular Zn^{2+} contributes to antioxidant defenses and can be increased by a $ZnSO_4$ supplement.