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MINERALOCORTICOID RECEPTOR ANTAGONISM CONFERS CARDIOPROTECTION IN HEART FAILURE

Michael R. Seawell, MD, **Fahed Al Darazi, MD**, **Victor Farah, MD**, **Kodangudi B. Ramanathan, MD**, **Kevin P. Newman, MD**, **Syamal K. Bhattacharya, PhD**, and **Karl T. Weber, MD**
Division of Cardiovascular Diseases, University of Tennessee Health Science Center, Memphis, TN

Abstract

The symptoms and signs constituting the congestive heart failure (CHF) syndrome have their pathophysiologic origins rooted in a salt-avid renal state mediated by effector hormones of the renin-angiotensin-aldosterone and adrenergic nervous systems. Controlled clinical trials, conducted over the past decade in patients having minimally to markedly severe symptomatic heart failure, have demonstrated the efficacy of a pharmacologic regimen that interferes with these hormones, including aldosterone receptor binding with either spironolactone or eplerenone. Potential pathophysiologic mechanisms which have not hitherto been considered involved for the salutary responses and cardioprotection provided by these mineralocorticoid receptor antagonists are reviewed herein. In particular, we focus on the less well-recognized impact of catecholamines and aldosterone on mono- and divalent cation dyshomeostasis which leads to hypokalemia, hypomagnesemia, ionized hypocalcemia with secondary hyperparathyroidism and hypozincemia. Attendant adverse cardiac consequences include a delay in myocardial repolarization with increased propensity for supra- and ventricular arrhythmias and compromised antioxidant defenses with increased susceptibility to nonischemic cardiomyocyte necrosis.

Keywords

mineralocorticoid receptor antagonists; congestive heart failure; potassium; magnesium; calcium; zinc; cardioprotection; mitochondria; oxidative stress; antioxidant defenses

Introduction

The congestive heart failure (CHF) syndrome with its disabling symptoms and signs is now the leading admitting diagnosis to U.S. hospitals. All too frequently CHF is recurrent. Its origins are rooted in a salt-avid state induced by an inappropriate and unwanted homeostatic response—neurohormonal activation—evoked by underperfused kidneys. It is this homeostatic response gone awry that causes dyshomeostasis and what has been characterized as a disorder of adaptation [1]. Effector hormones of activated renin-angiotensin-aldosterone (RAAS) and adrenergic nervous (ANS) systems mediate the retention of salt and water. The current medical management of patients with CHF therefore draws on interfering with these effector hormones by either disrupting their formation or receptor binding.

Correspondence: Karl T. Weber, M.D., Division of Cardiovascular Diseases, University of Tennessee Health Science Center, 956 Court Ave., Suite A312, Memphis, TN 38163, Tel: (901) 448-5750, Fax: (901) 448-8084, KTWeber@uthsc.edu.

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Large-scale controlled clinical trials, conducted over the past several decades, have demonstrated the efficacy of interfering with these hormones, especially when pharmacologic agents are administered in optimally tolerated oral doses. This regimen has included mineralocorticoid receptor antagonism (MCRa) with either spironolactone (Spiro) or eplerenone (Epler), given in combination with an angiotensin-converting enzyme inhibitor or AT_1 receptor antagonist, beta adrenergic receptor antagonist, and loop diuretic. Significant benefits and risk reduction for mortal and morbid events were reported in symptomatic patients enrolled in either the RALES or EPHESUS trials with reduced ejection fraction [2, 3]. Pathophysiologic responses which could be favorably intercepted by MCRa in CHF were considered nearly a decade ago and reported in this *Journal* [4].

More recently, another favorable trial with MCRa in patients with comparable systolic dysfunction was reported [5••]. Of note, patients enrolled in the EMPHASIS-HF Study were minimally symptomatic and were receiving standard of care before their double-blind randomization to either Epler or placebo. Primary outcomes were met and included reduced risk of death from cardiovascular causes or hospitalization for heart failure. It is therefore timely to address potential pathophysiologic mechanisms which have not hitherto been considered responsible for the MCRa efficacy in patients with either compensated or decompensated heart failure. Hence, we present a fresh perspective on cardioprotection with MCRa in heart failure. We focus on less well-recognized impact of catecholamines and aldosterone on mono- and divalent cation dyshomeostasis which leads to hypokalemia, hypomagnesemia, ionized hypocalcemia with secondary hyperparathyroidism (SHPT) and hypozincemia.

PATHOPHYSIOLOGIC MECHANISMS IN HEART FAILURE

Neurohormonal Activation in Heart Failure: A Brief Overview

CHF is a systemic illness. What begins with a failing muscular pump having reduced EF will eventuate into the clinical CHF syndrome with its characteristic disabling symptoms and debilitating signs. At first and as seen in Figure 1, there is the release of a family of natriuretic peptides (ANP and BNP) from distended atria and ventricles; they maintain urinary Na^+ excretion in proportion to dietary Na^+ intake. Hence, despite reduced EF (<35%) patients are *compensated* and only become symptomatic upon carrying out marked workloads (NYHA Class I and II) or with excessive dietary Na^+. This important dissociation between EF and clinical severity of CHF with RAAS activation was enforced by the SOLVD Study. Herein, asymptomatic patients with EF <35% and normal plasma renin activity were enrolled into the prevention arm of the study prior to receiving enalapril or placebo; symptomatic patients, whose EF was also <35%, had increased plasma renin activity and were enrolled in the treatment arm [6, 7]. Activation of the RAAS overwhelms the natriuretic peptides leading to salt and water retention and the appearance of *decompensated* heart failure. Exaggerated RAAS activity can occur intermittently leading to what is considered salt sensitivity [8].

CHF: A Systemic Illness

Neurohormonal activation involving RAAS hormones and their endocrine properties creates a systemic illness whose collective features have been referred to as a proinflammatory phenotype. Its features include: *i*) oxidative stress, in which the rate of reactive oxygen species generation overwhelm their rate of detoxification largely rendered by Zn^{2+}-based endogenous antioxidant defenses; *ii*) an immunostimulatory state in which activated peripheral blood mononuclear cells (PBMC:lymphocytes and monocytes) release proinflammatory cytokines (e.g., TNF-α and IL-6) and contribute to a vasculopathy of the

intramural coronary, renal and mesenteric vasculatures; and *iii*) a wasting of soft tissues and bone, termed cardiac cachexia.

Neurohormonal Activation and Myocardial Remodeling

In addition to this systemic illness there is a progressive pathologic remodeling of the myocardium. This includes an ongoing loss of cardiomyocytes to necrotic and apoptotic forms of cell death. Elevations in plasma troponins, biomarkers of myocyte necrosis, are found in patients hospitalized because of their CHF [9–15•]. Each episode of decompensated failure is based on neurohormonal activation with recurrent necrosis. Most prominent features of this pathologic remodeling are the appearance of foci of microscopic scars, footprints indicative of cardiomyocyte necrosis, found widely scattered throughout both the failing right and left atria and ventricles, irrespective of the etiologic origins of heart failure [16–18]. Absent are inflammatory cell and fibroblast responses and hence apoptosis is not accompanied by tissue repair and therefore leaves behind no morphologic footprint in the form of scarring [19].

In both the explanted failing human heart and postmortem tissue obtained from the failing myocardium, a progressive fibrosis is recognized as the major component to adverse structural remodeling. The prevalence of fibrosis implicates a crucial pathophysiologic role of ongoing cardiomyocyte necrosis, irrespective of its etiologic origins [16]. The pathophysiologic mechanisms accounting for myocyte necrosis are therefore of fundamental importance.

Neurohormonal Activation and Polycation Dyshomeostasis

The relative importance of angiotensin (Ang) II and aldosterone (Aldo) on proximal and distal Na^+ resorption in the nephron, as well as the colon, and K^+ excretion at these sites of high-density aldosterone receptor binding has been well documented. Herein, we focus on less well-recognized impact of catecholamines and aldosterone on mono- and divalent cation dyshomeostasis which leads to hypokalemia, hypomagnesemia, ionized hypocalcemia and hypozincemia, together with delayed myocardial repolarization and increased propensity for cardiac arrhythmias, compromised antioxidant defenses and susceptibility to cardiomyocyte necrosis.

CHF: A HYPERADRENERGIC STRESSOR STATE WITH CATION DYSHOMEOSTASIS

Mg^{2+}-Dependent Na/K ATPase

Na/K ATPase is a membrane-bound, energy-dependent pump whose activity contributes to the regulation of intracellular K^+; it also has an obligatory dependence on Mg^{2+}. These pumps are abundantly present in skeletal muscle, whose activity is regulated by catecholamines [20••]. Elevations in plasma epinephrine and norepinephrine accompany hyperadrenergic stressor states, such as CHF, where they activate these pumps leading to marked intracellular K^+ uptake by muscle and the appearance of hypokalemia (see Figure 2). Reduction in myocardial K^+ is accompanied by delayed repolarization and prolongation of the QTc interval of the electrocardiogram that predisposes to supra- and ventricular arrhythmias.

Potassium balance preexisting an episode of CHF is a critical determinant of the severity of the ensuing hypokalemia that appears. Diuretic-induced excessive loss of K^+ is also known to predispose to marked hypokalemia in response to the catecholamines [21]. Spironolactone, a K^+-sparing aldosterone receptor antagonist, is protective against hypokalemia and ventricular arrhythmias [22]. Patients with CHF who are receiving long-term loop diuretic treatment may acquire marginal K^+ and Mg^{2+} reserves. These limiting

reserves are further compromised by the hyperadrenergic state that may readily lead to marked hypokalemia and hypomagnesemia with QTc prolongation, thus provoking a propensity for arrhythmias. Spironolactone, by attenuating urinary and fecal K^+ losses, is therefore cardioprotective. Albuterol, a short-acting β_2 adrenergic receptor agonist, predisposes to hypokalemia and hypomagnesemia in normal volunteers, and even more so when they are receiving a diuretic [23, 24]. Chronic excessive use of such a β_2 receptor agonist may lead to marked hypokalemia and a greater propensity for arrhythmias. Antibiotics, antidepressants and antipsychotics can also lead to drug-induced prolongation of myocardial repolarization and QTc interval conducive of arrhythmogenicity.

Elevations in plasma catecholamines are accompanied by hypomagnesemia (see Figure 2). This is related to a cyclic AMP-mediated rise in intracellular Mg^{2+}, together with increased lipolysis with Mg^{2+} binding to free fatty acids and subsequent sequestration in adipocytes causing hypomagnesemia. Predisposing risk factors include hypokalemia, hypocalcemia, thiazide and loop diuretic use, and sepsis. The preexisting hypomagnesemia at the time of admission in these patients may become more severe during their prolonged hospital stay due to ongoing excessive excretory losses and reduced Mg^{2+} intake [25]. Chronic Mg^{2+} deficiency contributes to systolic dysfunction and proinflammatory cardiac phenotype [26••]. By attenuating Mg^{2+} losses, spironolactone would be cardioprotective.

Atrial and ventricular arrhythmias appear when hypomagnesemia is of moderate to marked severity (1.68±0. 7 mg/dL). Mg^{2+}-dependent Na/K ATPase activity is reduced with hypomagnesemia and further prolongs the QTc interval enhancing the propensity for arrhythmias. Pharmacologic reversal of impaired K^+ balance and hypokalemia will prove difficult unless Mg^{2+} is first replaced. Abnormal prolongation of the QTc interval (>440 ms) suggests a deficiency of myocardial K^+ and Mg^{2+}. Daily monitoring of the QTc interval and its normalization via Mg^{2+} and K^+ supplementation can be used to gauge the adequacy of their intracellular replacement in cardiomyocytes. Attainment of normal QTc with these supplements may require several more days than needed for the correction of hypokalemia and hypomagnesemia alone. Less than 1% of Mg^{2+} is extracellular and hence serum Mg^{2+} is not an accurate indicator of intracellular Mg^{2+} stores; therefore the QTc interval can serve as a more reliable surrogate. Digoxin, a Na/K ATPase inhibitor, accentuates the dyshomeostasis of intracellular K^+ and Mg^{2+} predisposing to QTc prolongation and arrhythmias.

Concurrent hypokalemia and hypomagnesemia are common with interactions between K^+ and Mg^{2+} which are diverse and complex, including the importance of Mg^{2+} deficiency, that interferes with K^+ retention while raising urinary K^+ excretion [27, 28]. Mg^{2+} deficiency contemporaneously begets K^+ deficiency. The effective clinical resolution of hypokalemia mandates simultaneous reversal of hypomagnesemia [29].

In the absence of gastrointestinal losses or diuretic usage, hypomagnesemia and hypokalemia due to impaired renal tubular reabsorption and presenting as urinary K^+ and Mg^{2+} wasting cannot be overlooked in patients with cardiac arrhythmias, including atrial fibrillation. Differential diagnostic evaluation of inheritable renal tubular disorders associated with such excessive urinary Mg^{2+} losses (e.g., Gitelman syndrome) should always be considered via determination of urinary Mg^{2+} excretion. Patients with Mg^{2+} deficiency will retain urinary Mg^{2+} and not waste it. This caveat is also applicable when the resolution of these cations, using standard oral Mg^{2+} and K^+ supplements, proves difficult to achieve. Spironolactone may prove efficacious in many of these Mg^{2+}-wasting disorders.

Mg^{2+} Efflux from Cardiomyocytes

Mg^{2+} is an endogenous antagonist to Ca^{2+} entry in cardiomyocytes and their mitochondria and vice versa [30]. Catecholamines promote the efflux of Mg^{2+} from cardiomyocytes which, in turn, augments Ca^{2+} entry and the potential for intracellular Ca^{2+} overloading [31]. A β_1 adrenergic receptor antagonist prevents catecholamine-induced Mg^{2+} losses. Reduced myocardial Mg^{2+} content slows repolarization and prolongs QTc interval provoking arrhythmogenicity. The efficacy of β_1 and β_2 adrenergic receptor blockade includes their favorable impact on catecholamine-driven dyshomeostasis of K^+ and Mg^{2+} that accompanies hyperadrenergic states.

Intracellular Ca^{2+} Overloading and Oxidative Stress

Reductions in plasma ionized $[Ca^{2+}]_o$, or ionized hypocalcemia, are commonly found in adults presenting to the emergency department or admitted to intensive care units with an acute hyperadrenergic stressor state [32, 33]. The extent to which $[Ca^{2+}]_o$ falls correlates with the severity of the hyperadrenergic response (see Figure 3). Ionized hypocalcemia serves as an in-hospital marker of survival. Hypoalbuminemia can contribute to reduced total Ca^{2+} concentration since a lesser amount of serum proteins are available for Ca^{2+} binding.

The appearance of ionized hypocalcemia in critically ill patients is based on a catecholamine-mediated shift in circulating Ca^{2+} into the intracellular compartment of various tissues that includes the heart, skeletal muscle and PBMC and accounts for intracellular Ca^{2+} overloading. Ionized hypocalcemia is followed by increased release of parathyroid hormone (PTH) and ensuing PTH-mediated excessive Ca^{2+} entry (see Figure 3). Collectively, catecholamine- and PTH-facilitated excessive intracellular Ca^{2+} accumulation in cardiomyocytes leads to Ca^{2+} overloading of their mitochondria accounting for the induction of oxidative stress by these organelles, where the rate of reactive oxygen and nitrogen species overwhelm their rate of detoxification by endogenous antioxidant defenses. The ensuing necrotic death of cardiomyocytes is followed by tissue repair with the resultant fibrous tissue response, or scarring. This replacement fibrosis preserves the structural integrity of the injured myocardium and ventricular function. It constitutes a morphologic footprint of previous necrotic cell death. Fibrosis, however, has adverse consequences. The addition of stiff fibrillar type I collagen in scar tissue compromises ventricular function in diastole and systole and serves as substrate for reentrant arrhythmias.

The catecholamine-induced, Ca^{2+} overload-initiated nonischemic necrosis of cardiomyocytes is accompanied by the release of troponins, an intracellular protein whose release plays a crucial role in discerning myocardial injury. A modest increase in plasma troponins has been reported in diverse stressor states, including decompensated heart failure, sepsis, hemorrhagic shock, subarachnoid hemorrhage, trauma, gastrointestinal bleeding, or pulmonary embolus [34]. The levels to which plasma troponins rise in such patients does not reach the more marked elevations seen with segmental loss of myocardium that accompanies ischemia and infarction or that which follows myocardial contusion.

CHF: A RAAS STRESSOR STATE WITH CATION DYSHOMEOSTASIS

Secondary Aldosteronism of CHF Accompanied by Secondary Hyperparathyroidism

Increased circulating PTH levels, coupled to a resorption of bone, are less well-recognized features of the secondary aldosteronism of CHF. SHPT arises because of the marked urinary and fecal excretory losses of Ca^{2+} and Mg^{2+} and the resultant appearance of ionized hypocalcemia and hypomagnesemia, each transmits stimuli to increased PTH secretion [35–37]. In man with autonomous adrenal aldosterone production, SHPT is corrected by either

adrenal surgery or Spiro treatment [37]. In experimental animals receiving aldosterone/salt treatment, where plasma aldosterone levels are raised to those found in CHF, SHPT can be prevented by: cotreatment with Spiro, which prevents the heightened excretory losses of Ca^{2+} and Mg^{2+} in urine and feces [36]; cotreatment with a Ca^{2+}- and Mg^{2+}-supplemented diet, together with vitamin D, to prevent ionized hypocalcemia and hypomagnesemia [38]; parathyroidectomy [39]; or cotreatment with a calcimimetic, cinacalcet, which resets the threshold of the parathyroid glands' Ca^{2+}-sensing receptor to prevent heightened elaboration of PTH [40]. In preventing SHPT and its attendant pathophysiologic consequences, Spiro is cardioprotective.

A dyshomeostasis of serum K^+ and Ca^{2+} is found in patients hospitalized with decompensated biventricular failure having a dilated cardiomyopathy of ischemic or nonischemic origins. This metabolic profile is also found in patients having low-renin or salt-sensitive hypertension [41–44] and in those with primary aldosteronism [45–47]. Furthermore, elevated PTH, evoked in response to ionized hypocalcemia, serves as a stimulus to adrenal aldosterone production producing contemporaneous elevations in plasma aldosterone [48–51]. In patients with primary hyperparathyroidism, preoperative PTH levels in excess of 00 ng/mL are independent predictors of abnormal elevations in plasma aldosterone [51]. Major pathogenic events accounting for cardiomyocyte necrosis in aldosteronism focus on the relative importance of PTH-mediated intracellular Ca^{2+} overloading and induction of oxidative stress [36, 39, 40]. The role of elevations in circulating aldosterone and which are inappropriate for dietary Na^+ must also be considered [52].

Abnormal elevations in serum PTH (>65 pg/mL) serve as a potent mediator of Ca^{2+} overloading in cardiomyocytes and their mitochondria [36, 53, 54]. This may contribute to the increased cardiovascular morbidity and mortality associated with primary hyperparathyroidism [55, 56]. Elevations in serum PTH are likewise associated with increased mortality in frail elderly persons independent of their 25(OH)D status, bone mass or renal function [57, 58]. In patients having primary hyperparathyroidism, the increased incidence of left ventricular hypertrophy, Ca^{2+} deposits in the myocardium and heart valve leaflets, and intracellular Ca^{2+} overloading may further contribute to increased risk of cardiovascular mortality [55, 59–62].

Elevated PTH levels are found in patients hospitalized with decompensated heart failure and those awaiting cardiac transplantation [63–66], and serve as an independent predictor of CHF, the need for hospitalization and cardiovascular mortality [67–70]. Moreover, PTH levels have been shown to be an independent risk factor for mortality and cardiovascular events in community-dwelling individuals [71–73••]. SHPT is especially prevalent in African-Americans (AA) with protracted (>4 wks) decompensated biventricular failure, where chronic elevations in plasma aldosterone contribute to symptoms and signs of CHF and plasma ionized hypocalcemia [44, 64]. SHPT is also associated with the prevalence of hypovitaminosis D in AA, where the increased melanin content of dark skin serves as a natural sunscreen [64]. Accordingly, the prevalence of hypovitaminosis D, often of marked severity (<20 ng/mL), compromises Ca^{2+} homeostasis predisposing AA to ionized hypocalcemia and consequent SHPT [64, 74, 75]. Vitamin D deficiency is also reported in Caucasians and Asians with heart failure whose effort intolerance predisposes to an indoors lifestyle [67, 68, 76, 77]. Other factors which may be associated with compromised Ca^{2+} stores and contribute to the appearance of SHPT, especially in AA with CHF, have been reviewed elsewhere [78].

Osteopenia and osteoporosis accompany CHF and predispose elderly patients to atraumatic fractures, especially of the hip [79]. In cachectic patients, atrophy of proximal muscle

groups reduce limb strength and predispose to increased falls. Patients with CHF treated with Spiro have a reduced incidence of atraumatic fractures, especially of the hip [80]. Osteopenia and osteoporosis are also accompanying adverse outcomes to chronic SHPT; they predispose to atraumatic bone fractures [81]. Patients with heart failure have reduced bone density, which is related to SHPT and vitamin D deficiency, coupled with effort intolerance due to symptomatic failure and consequent reduced physical activity [63, 65, 82–86]. The risk of such fractures is further increased in elderly patients with heart failure receiving a loop diuretic, where consequent hypercalciuria is also contributory, but preventable when given in combination with spironolactone [79, 80]. In elderly patients with hip fracture, elevated PTH levels are associated with perioperative myocardial injury with elevated serum troponins and all-cause mortality [87].

Mg^{2+}-Dependent Secretion of Parathyroid Hormone

In response to catecholamine-driven ionized hypocalcemia, the Ca^{2+}-sensing receptor of the parathyroid glands provokes the increased secretion of PTH. In turn, secondary hyperparathyroidism (SHPT) with increased plasma PTH seeks to restore extracellular Ca^{2+} homeostasis by promoting resorption of bone Ca^{2+} and increased Ca^{2+} absorption from the gut and kidneys by $25(OH)_2D_3$ which is synthesized by the kidneys in response to PTH provocation. When hypocalcemia is associated with hypomagnesemia, PTH secretion is impaired and can be corrected by reversing hypomagnesemia [88, 89].

CHF: A DYSHOMEOSTASIS OF ZINC AS ANTIOXIDANT

Excretory Zn^{2+} Losses in Aldosteronism

Deficiency in antioxidant reserves is also an important contributor to the imbalance in prooxidant:antioxidant equilibrium leading to cardiomyocyte necrosis that accompanies neurohormonal activation [90, 91]. Zinc is integral to antioxidant defenses, as well as wound healing [92]. Upregulation of metallothionein, a Zn^{2+}-binding protein, occurs at sites of tissue injury, including the heart, where it promotes local accumulation of Zn^{2+} and its involvement in gene transcription and cell replication [93, 94]. Zn^{2+} deficiency, evident with reduced Zn^{2+} levels in bone and lymphocytes [95, 96], will compromise these antioxidant reserves and healing after cardiomyocyte necrosis.

In the secondary aldosteronism of CHF, increased urinary and fecal losses of Zn^{2+} result in hypozincemia with simultaneous cellular and subcellular dyshomeostasis of Zn^{2+} [94, 95]. Accompanying Zn^{2+} deficiency compromises the activity of Cu/Zn superoxide dismutase, an important endogenous antioxidant. Urinary Zn^{2+} excretion is increased in response to angiotensin-converting enzyme inhibitor or angiotensin receptor antagonist, commonly used in the management of CHF [97, 98]. Serum and myocardial Zn^{2+} levels are reduced in patients with a dilated cardiomyopathy and individuals with arterial hypertension [44, 96, 99–104••]. Underlying causes for Zn^{2+} deficiency, including inadequate dietary intake and excess urinary excretion, remain to be elucidated.

Intricate interactions between Zn^{2+} with Ca^{2+} have long been recognized [54, 92, 105, 106]. The prooxidant effect representing intracellular Ca^{2+} overloading that accompanies elevations in either plasma catecholamines or PTH is intrinsically coupled to increased Zn^{2+} entry in cardiomyocytes acting as an antioxidant [53, 54, 107, 108]. Zn^{2+} entry is known to occur via L-type Ca^{2+} channels, however, it enters predominantly via Zn^{2+} transporters activated by oxidative stress. Increased cytosolic free $[Zn^{2+}]_i$ may also occur via release of inactive Zn^{2+} bound to metallothionein (MT)-1 and can be induced by nitric oxide (NO) derived from endothelial NO synthase [109]. Elevations in $[Zn^{2+}]_i$ can also be achieved by a $ZnSO_4$ supplement [53, 108, 110–115]. Increased cytosolic free $[Zn^{2+}]_i$ activates its sensor, metal-responsive transcription factor (MTF)-1 which, upon its translocation to the nucleus,

upregulates antioxidant defense genes [107]. These observations raise the therapeutic prospect that cation-modulating *nutriceutical supplementation* capable of favorably influencing the extra- and intracellular Ca^{2+} and Zn^{2+} equilibrium enhancing overall antioxidant capacity, could prove pivotal to combating mitochondria-based oxidative injury and cardiomyocyte necrosis, while promoting Zn^{2+}-based endogenous cardioprotective potential.

SUMMARY AND CONCLUSIONS

A dyshomeostasis of extra- and intracellular K^+, Mg^{2+}, ionized Ca^{2+} and Zn^{2+} accompanies CHF—a coupled hyperadrenergic stressor state with RAAS activation. This includes catecholamine- and aldosterone-driven translocation of these cations: *i*) from the intravascular compartment to intracellular sites of storage in such organs as muscle, adipose tissue and liver, *ii*) to sites of injury, where they participate in tissue repair, and *iii*) increased urinary and fecal excretory losses. Hypokalemia, hypomagnesemia, ionized hypocalcemia and hypozincemia are consequences of this neurohormonally-driven dyshomeostasis of cations. The myocardium is particularly vulnerable to these pathophysiologic events. This includes a delay in repolarization, as reflected in QTc interval prolongation on the ECG, with increased propensity for supra- and ventricular arrhythmias. Intracellular Ca^{2+} overloading of its cardiomyocytes and mitochondria, mediated by catecholamines and/or PTH, leads to the induction of oxidative stress by these organelles and opening of their inner membrane permeability transition pore. There ensues mitochondrial degeneration followed by cell necrosis and consequent tissue repair with reparative fibrosis, or scarring. The cardioprotective potential of a MCRa therefore includes the rescue of these mono- and divalent cations and their attendant adverse consequences with protection from arrhythmias and pathologic remodeling of myocardium.

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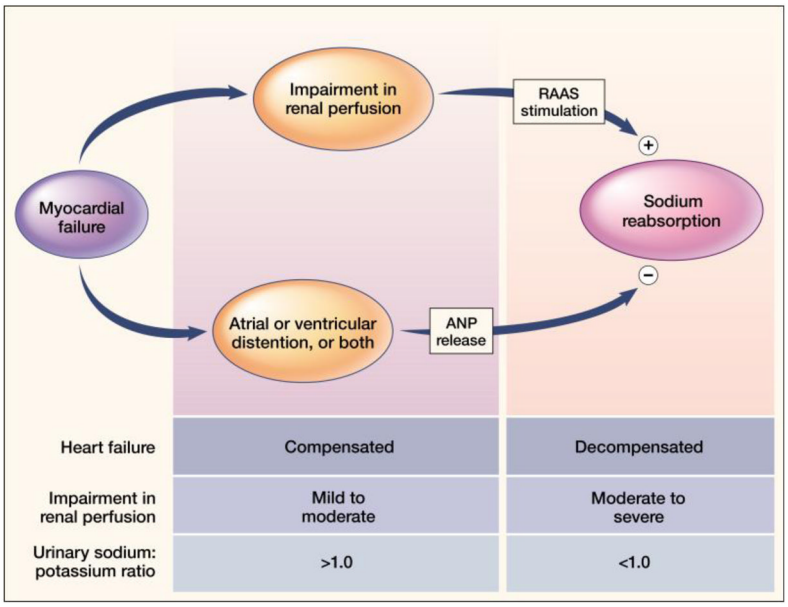

Figure 1.

An overview of compensated and decompensated phases of heart failure relative to renal perfusion and urinary Na^+/K^+ ratio. Myocardial failure elicits an interplay between atrial (ANP) and brain (BNP, not shown) natriuretic peptides, elicited by atrial and/or ventricular distention, and effector hormones of the renin-angiotensin-aldosterone system (RAAS) on urinary sodium reabsorption. When the impairment in renal perfusion is mild to moderate, ANP and BNP dominate with urinary Na^+/K^+ ratio >1.0. There is no retention of Na^+ and water with the patient compensated (minimally or asymptomatic). When renal perfusion is more markedly impaired, the RAAS dominates with urinary Na^+ retention and a Na^+/K^+ ratio <1.0 leading to decompensated (symptomatic) failure. Patients can transition back and forth between compensated and decompensated phases of failure. From *N Engl J Med*, Weber KT, "Aldosterone in Congestive Heart Failure," Volume 345, Pages 1689–97. Copyright ©2001 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

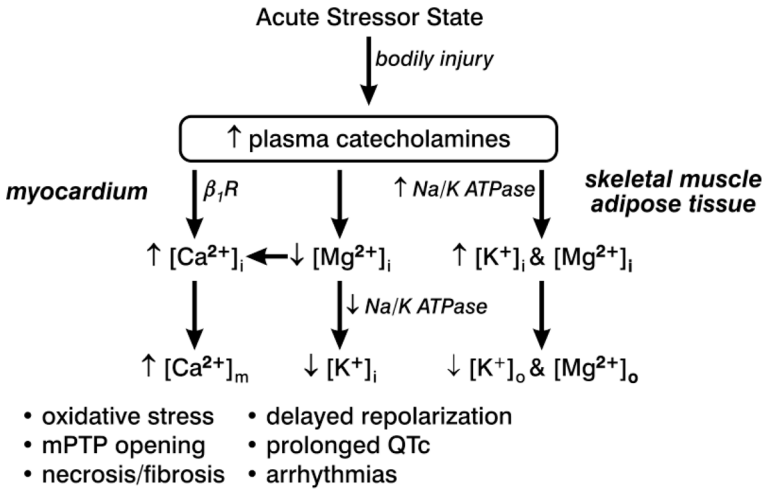

Figure 2.

An acute stressor state, such as CHF or bodily injury, is associated with increased circulating concentrations of epinephrine and norepinephrine. These catecholamines have an impact on mono- and divalent cations involving skeletal muscle, adipose tissue and heart. See text for further discussion. Reprinted from Khan MU, et al., "Cation Interdependency in Acute Stressor States," *Am J Med Sci* 2012 (In press), with permission.

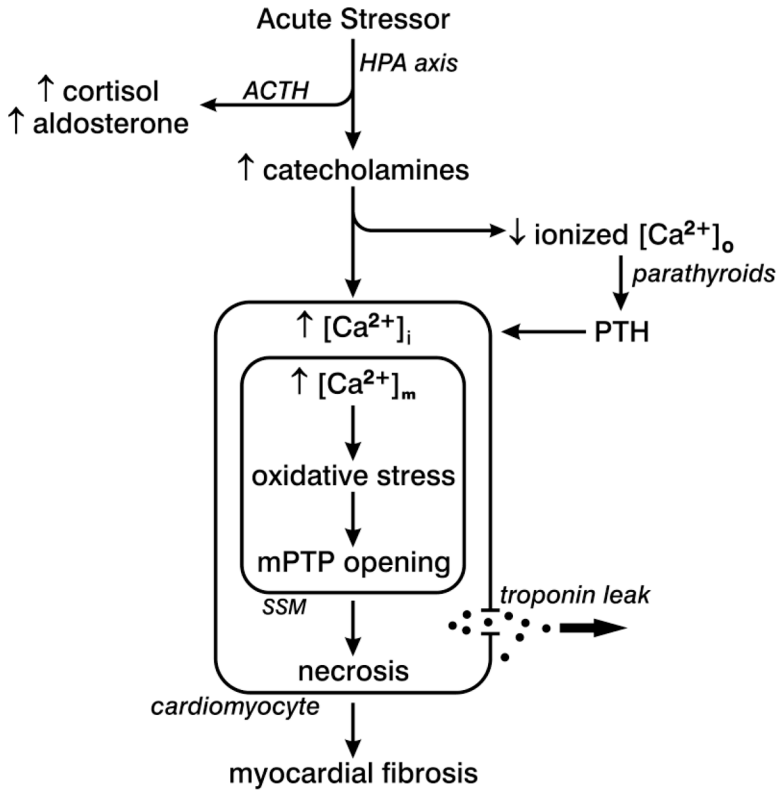

Figure 3.

An acute stressor state with elevated circulating catecholamines is responsible for intracellular Ca^{2+} overloading with a subsequent fall in plasma ionized $[Ca^{2+}]_o$ which, in turn, provokes the parathyroid glands to release parathyroid hormone (PTH), a calcitropic hormone. PTH likewise contributes to intracellular Ca^{2+} overloading. In cardiomyocytes Ca^{2+} overloading is accompanied by the induction of oxidative stress by subsarcolemmal mitochondria (SSM), which leads to the opening of their permeability transition pore (mPTP) with ensuing osmotic swelling and injury. The necrosis of cardiomyocytes follows accompanied by the leak of intracellular troponins into the interstitial space accounting for the ultimate rise in plasma troponins. Cardiac myocytes lost to necrosis are replaced by fibrous tissue, or scarring, which preserves the structural integrity of this hollow muscular organ. Reprinted from Khan MU, et al., "Cation Interdependency in Acute Stressor States," *Am J Med Sci* 2012 (In press), with permission.