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FIBROSIS IN HYPERTENSIVE HEART DISEASE: MOLECULAR PATHWAYS AND CARDIOPROTECTIVE STRATEGIES

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Abstract

Fibrosis is a fundamental component of the adverse structural remodeling of myocardium found in hypertensive heart disease (HHD). A replacement fibrosis appears at sites of previous cardiomyocyte necrosis to preserve the structural integrity of the myocardium. However, such scarring has adverse functional consequences. The extensive distribution of fibrosis involving the right and left heart suggests cardiomyocyte necrosis is widespread. Together, the loss of these contractile elements and fibrous tissue deposition in the form of stiff in-series and in-parallel elastic elements contributes to the progressive failure of this normally efficient muscular pump. Pathogenic mechanisms modulating fibrous tissue formation at sites of repair include auto-/paracrine properties of locally generated angiotensin II and endothelin-1. Herein, we focus on the signal-transducer-effector pathway involved in cardiomyocyte necrosis and the crucial pathogenic role of intracellular Ca^{2+} overloading, and subsequent induction of oxidative stress originating within its mitochondria that dictates the opening of the mitochondrial permeability transition pore. The ensuing osmotic destruction of these organelles is followed by necrotic cell death. It is now further recognized that Ca^{2+} overloading of cardiac myocytes and mitochondria functioning as prooxidant is pathophysiologically counterbalanced by an intrinsically coupled Zn^{2+} entry, which serves as antioxidant. The prospect of raising intracellular Zn^{2+} by adjuvant nutraceutical supplementation can, therefore, be preferentially exploited to uncouple this intrinsically coupled Ca^{2+} – Zn^{2+} dyshomeostasis in favor of endogenous antioxidant defenses. Hence, novel cardioprotective strategies may be at hand and deserve to be further explored in the overall management of patients having HHD.

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Introduction

Hypertensive heart disease (HHD) is a major etiologic factor contributing to the appearance of heart failure, a global health problem that has reached epidemic proportions. The hypertrophic growth of cardiomyocytes in HHD is comparable to that found with athletic training [1]. The diastolic and/or systolic function of the hypertrophied myocardium in HHD, on the other hand, is compromised. So too is its morphologic appearance, where fibrous tissue is progressively laid down over time throughout the right and left heart [2]. Cardiac fibrosis is composed predominantly of stiff type I fibrillar collagen that adversely alters myocardial stiffness. It further serves as pathophysiologic substrate for reentrant ventricular arrhythmias.

Pathogenic mechanisms contributing to tissue repair and fibrosis that follow cardiac injury, including auto-/paracrine properties of angiotensin II and endothelin-1 which regulate fibrogenesis, have been addressed elsewhere [3–5]. Herein, we review insights gained with our rat model of chronic aldosteronism associated with low-renin hypertension into molecular pathways leading to cardiomyocyte necrosis. We also review cardioprotective strategies that could prevent this adverse structural remodeling of myocardium. We finally turn to relevant clinical correlates in African-Americans (AA), who often develop low-renin or “wet” hypertension with symptoms and signs of congestive heart failure. The same could be said for patients with the cardiometabolic syndrome or obstructive sleep apnea, which are beyond the scope of this report.

An Animal Model of Low-Renin Hypertension

Eight-week-old male Sprague-Dawley rats are uninephrectomized, followed by subcutaneous implantation of an osmotic minipump to infuse aldosterone (ALDO; 0.75 µg/h). One percent NaCl is added to drinking water provided *ad libitum*, which is further fortified with 0.4% KCl to prevent hypokalemia and associated cardiac lesions [6]. We refer to this as aldosterone/salt treatment (ALDOST). Over the course of several weeks of ALDOST, arterial pressure rises gradually and is accompanied by left ventricular hypertrophy (LVH) [7]. At wk 1 of ALDOST, animals are healthy and the myocardium appears normal by light microscopy. At wk 2 and beyond, this *preclinical stage* gives way to anorexia and a failure to gain weight, compared to unoperated and untreated age-/sex-matched controls. The appearance of cardiac pathology emerges by wk 4 and is considered the *pathologic stage*. It features the appearance of microscopic scarring, a replacement fibrosis, which is scattered throughout both the right and left atria and ventricles [8]. A perivascular/interstitial fibrosis involving the coronary, renal and mesenteric circulations, a reactive fibrosis, is also present. This topic has been reviewed elsewhere [9].

A series of studies have addressed the relevance of hypertension vis-à-vis aldosteronism in contributing to cardiac fibrosis. As reviewed extensively [10], those studies have collectively concluded that hemodynamic factors are not involved. These conclusions were based on the following findings: a) the presence of fibrosis in the nonpressure-overloaded right atria and ventricle; b) the absence of fibrosis when the LV pressure overload is associated with infrarenal aortic banding without renin-angiotensin-aldosterone system (RAAS) activation; c) the prevention of fibrosis with either a small (nondepressor) or large (depressor) dose of spironolactone, an aldosterone receptor antagonist, which either does or does not prevent hypertension; d) an intracerebroventricular infusion of a mineralocorticoid receptor antagonist prevents hypertension but not fibrosis [11]; and e) a cardiac-specific upregulation of aldosterone synthase with increased tissue levels of ALDO is not accompanied by cardiac fibrosis [12]. Thus, the evidence gathered to date indicates the adverse remodeling of myocardium during ALDOST is independent of hypertension and not

related to ALDO per se. Instead, we hypothesized that one or more circulating factors accompany aldosteronism to cause this remodeling.

Molecular Pathways Leading to Cardiomyocyte Necrosis

Several molecular pathways and biochemical processes account for cardiomyocyte necrosis and subsequent reparative fibrosis found at 4 wks ALDOST.

Oxidative stress

Evidence of oxidative stress in the myocardium during chronic mineralocorticoidism has been reported by several laboratories [13–17]. A broad spectrum of experimental variants has been used to substantiate the altered redox state. These include: a) the presence of 3-nitrotyrosine, the result of nitrosylation by peroxynitrite and byproduct of the reaction involving superoxide and nitric oxide; b) an activation of the gp91^{phox} subunit of NADPH oxidase found in inflammatory cells invading the injured myocardium and which contributes to superoxide generation; c) upregulated redox-sensitive nuclear transcription factor (NF)- κ B and a proinflammatory gene cascade it regulates that includes intercellular adhesion molecule (ICAM)-1, monocyte chemoattractant protein (MCP)-1, and tumor necrosis factor (TNF)- α ; and d) increased tissue levels of 8-isoprostane and malondialdehyde, biomarkers of lipid peroxidation. There is also considerable evidence of oxidative stress in blood and urine that are in agreement with the systemic nature of an altered redox state during ALDOST.

Intracellular Ca²⁺ overloading

Our working hypothesis was based upon the original concept of Albrecht Fleckenstein that intracellular Ca²⁺ overloading of cardiac myocytes and their mitochondria is an integral and singular pathophysiologic feature of various stressor states [18], such as catecholamine excess, that has since been further implicated in ischemia/reperfusion injury [19]. Accordingly, we monitored intracellular Ca²⁺ concentrations in the hearts of rats receiving 1 and 4 wks ALDOST. We also did so in peripheral blood mononuclear cells (PBMC), based on our hypothesis that these cells had the potential of serving as a novel biomarker of cardiac events and could be monitored noninvasively and serially. We found that increased Ca²⁺ levels in the myocardium and PBMC at these time points were accompanied by biomarker-mediated evidence of oxidative stress, such as increased levels of malondialdehyde and 8-isoprostane in the heart and increased H₂O₂ production by PBMC [17,20–22]. Nevertheless, the underlying pathophysiologic mechanisms responsible for intracellular Ca²⁺ overloading during ALDOST deserved to be further explored in greater detail.

Calcium and magnesium dyshomeostasis

One percent NaCl intake is inappropriate in this model of aldosteronism. It is accompanied by increased renal tubular Na⁺ and, in turn, increased Ca²⁺ and Mg²⁺ concentrations. ALDO promotes distal tubular epithelial cell channel reabsorption of Na⁺ without influencing Ca²⁺ and Mg²⁺, which then accounts for the marked excretory urinary losses of Ca²⁺ and Mg²⁺ [20]. A similar scenario unfolds in the Na⁺ channels of the colon's epithelial cells that represents another site of high density ALDO receptor binding. The fecal excretion of Ca²⁺ and Mg²⁺ have been found to be manyfold greater than their urinary losses [20].

Secondary hyperparathyroidism (SHPT)

Our metabolic studies in rats receiving ALDOST demonstrated the marked increase in both the urinary and fecal excretion of Ca²⁺ and Mg²⁺, which led to plasma ionized hypocalcemia and hypomagnesemia. This, in turn, prompted increased plasma parathyroid

hormone (PTH) levels [20]. The accompanying secondary hyperparathyroidism (SHPT) was manifested by a marked and progressive resorption of bone and reduction in bone mineral density and bone strength [23]. We, therefore, hypothesized that the intracellular Ca^{2+} overloading and induction of oxidative stress that accompanies ALDOST is unequivocally PTH-mediated (see Figure 1), and represents a classic pathophysiologic scenario embodying the Ca^{2+} paradox of SHPT reported by Fujita & Palmieri [24]. Massry and coworkers demonstrated PTH-mediated intracellular Ca^{2+} overloading of cardiomyocytes that included: cultured cardiac myocytes incubated with PTH [25]; and cells harvested from normal rats receiving a 2-week infusion of PTH or rats with chronic renal failure having SHPT [26]. In each case, cotreatment with verapamil, a Ca^{2+} channel blocker, prevented the rise in intracellular Ca^{2+} . PTH-mediated intracellular Ca^{2+} overloading is coupled to induction of oxidative stress in diverse tissues that includes cardiomyocytes and their mitochondria. At these sites, reactive oxygen and nitrogen species overwhelm antioxidant defenses. In mitochondria, Ca^{2+} overloading and oxidative stress synergistically induce opening of the mitochondrial permeability transition pore (mPTP), together with the structural and functional degeneration of these organelles that triggers the final common pathway to cardiomyocyte necrosis [27]. The replacement fibrosis appears as an outcome of tissue repair.

The necrosis of cardiomyocytes leads to the release of troponins (see Figure 2) into the interstitial compartment, where lymphatic drainage brings these cardiospecific enzymes to the central venous circulation. As contrasted to an acute myocardial infarction, where the necrotic death of a segment of myocardium and accompanying large troponin release is due to a critical reduction in coronary blood flow, the cardiomyocyte necrosis associated with PTH-mediated Ca^{2+} overloading involves small clusters of cells. Hence the elevation in plasma troponins is modest by comparison. Morphologically, this appears as microscopic foci of scarring (vis-à-vis a macroscopic infarct scar). Nevertheless, repeated episodes of microscopic necrosis over time can ultimately deprive the myocardium of a critical mass of cardiomyocytes leading to ventricular systolic dysfunction. Their replacement by stiff fibrillar collagen inevitably compromises diastolic and systolic function.

A series of experiments were designed in rats receiving ALDOST to validate our hypothesis and to prevent this pathologic sequelae of adverse events. These targeted interventions included: a) cotreatment with spironolactone (Spiro), an ALDO receptor antagonist, which attenuated the enhanced urinary and fecal losses of these cations to prevent hypocalcemia and hypomagnesemia, and thereby abrogating SHPT [20]; b) cotreatment with a Ca^{2+} and Mg^{2+} -supplemented diet, together with vitamin D_3 , to prevent hypocalcemia and SHPT, which is analogous to the paradox described by McCarron [28,29]; c) parathyroidectomy, performed prior to starting ALDOST [30]; d) cotreatment with cinacalcet, a calcimimetic that resets the Ca^{2+} -sensing receptor of the parathyroid glands to prevent SHPT despite ionized hypocalcemia [31]; e) cotreatment with amlodipine (Amlod), a Ca^{2+} channel blocker, which prevents intracellular Ca^{2+} overloading [21]; and finally f) cotreatment with N-acetylcysteine, an antioxidant [16].

Thus, the multitude of evidence gathered to date congruently supports that PTH-mediated intracellular Ca^{2+} overloading is the mechanism involved in the induction of oxidative stress during aldosteronism, where reactive oxygen and nitrogen species overwhelm cellular antioxidant defenses. A hyperadrenergic state also accompanies chronic mineralocorticoidism [32,33]. Catecholamine-induced Ca^{2+} overloading further contributes to the appearance of oxidative stress. This scenario, however, is based solely on the excessive generation of prooxidants. It does not address whether endogenous antioxidant defenses that combat reactive oxygen and nitrogen species have been compromised and

overwhelmed by the overproduction of prooxidants under the pathogenic stimuli leading to intracellular Ca^{2+} overloading.

Molecular Pathways Leading to Antioxidant Defenses and Cardiomyocyte Protection

Zinc dyshomeostasis

Commensurate with the enteral and renal losses of Ca^{2+} and Mg^{2+} seen with aldosteronism, chronic mineralocorticoidism is also accompanied by increased excretory Zn^{2+} losses, the appearance of hypozincemia, and a fall in plasma Cu/Zn-superoxide dismutase (SOD) activity [34]. Like Ca^{2+} and Mg^{2+} losses, the hyperzincuria seen with ALDOST is due to urinary acidification that contributes to a consequent metabolic alkalosis [17]. Also contributory to hypozincemia is a coordinated selective translocation of Zn^{2+} to sites of tissue injury augmented by the upregulation of metallothionein (MT)-1, a Zn^{2+} -binding protein [17,34].

To systematically address Zn^{2+} kinetics in our model of ALDOST, we used ^{65}Zn as a radioactive tracer. We found a simultaneous fall in plasma ^{65}Zn and a selective accumulation of ^{65}Zn at sites of injury, which included its translocations to the damaged skin at wk 1 that was freshly incised to implant the minipump, and to the injured heart and kidneys at wk 4. Intriguingly, this pathophysiology-driven intracellular Zn^{2+} trafficking to injured tissues was accompanied by the temporal upregulation of MT-1 [35]. Contemporaneous with the translocation of Zn^{2+} to sites of injury at wk 4 there was a decline in ^{65}Zn in healed skin and bone, tissues which serve as Zn^{2+} reservoirs. Thus, rapid translocation of circulating Zn^{2+} to injured tissues contributes to hypozincemia found with ALDOST, where increased tissue Zn^{2+} is essential to wound healing at these sites of injury, while the release of Zn^{2+} from reservoirs seeks to restore the fall in extracellular Zn^{2+} [36]. Since a synchronized dyshomeostasis of Zn^{2+} is recognized as another integral feature of aldosteronism-mediated myocardial remodeling, it is crucial to investigate whether the rise in cardiac tissue Zn^{2+} involves its cardiac myocytes and mitochondria and their antioxidant defenses.

Coupled Ca^{2+} and Zn^{2+} dyshomeostasis

The dyshomeostasis of extra- and intracellular Ca^{2+} and Zn^{2+} which accompanies ALDOST contributes to a contemporaneous dysequilibrium between pro- and antioxidants. We hypothesized that an intrinsically coupled dyshomeostasis of intracellular Ca^{2+} and Zn^{2+} in aldosteronism alters the redox state of cardiac myocytes and mitochondria. Toward this investigative goal, hearts were harvested from rats receiving 4 wks ALDOST alone or cotreated with Spiro or Amlod. Compared to untreated, age-/sex-matched controls, we found (see Figure 3) increased cardiomyocyte cytosolic free $[\text{Ca}^{2+}]_i$ and $[\text{Zn}^{2+}]_i$, together with increased mitochondrial $[\text{Ca}^{2+}]_m$ and $[\text{Zn}^{2+}]_m$, each of which could be prevented by Spiro and attenuated by Amlod cotreatment [37].

These iterations in divalent cation composition were accompanied by increased levels of 3-nitrotyrosine and 4-hydroxy-2-nonenal in cardiomyocytes, together with increased H_2O_2 production, malondialdehyde and oxidized glutathione in mitochondria that were also coincident with the increased activities of Cu/Zn-SOD and glutathione peroxidase (GSH-Px) [17,27,37]. Furthermore, these changes in intracellular Zn^{2+} were accompanied by the increased expression of MT-1, Zn^{2+} transporters (Zip1 and ZnT-1) and metal-responsive transcription factor (MTF)-1, an intracellular Zn^{2+} sensor. Thus, in cardiac myocytes and mitochondria from rats with ALDOST, an intrinsically coupled dyshomeostasis of intracellular Ca^{2+} and Zn^{2+} appears that alters the redox state via induction of oxidative

stress and generation of antioxidant defenses, respectively. These findings underscore the potential clinical relevance of therapeutic strategies that can uncouple these crucial cations and modulate them in favor of increasing $[Zn^{2+}]_i$ and sustained antioxidant defenses. The coupled Ca^{2+} and Zn^{2+} dyshomeostasis seen in aldosteronism is reminiscent of the Ca^{2+} overloading and oxidative stress that exists in the cardiac and skeletal muscles of hamsters with hereditary muscular dystrophy and a cardiomyopathy, which are also accompanied by increased tissue Zn^{2+} [38–40]. This divalent cation dyshomeostasis seen in muscular dystrophy could be prevented by parathyroidectomy [38] or a Ca^{2+} channel blocker [39]. Furthermore, our findings in rats with ALDOST resemble the protective role of increased $[Zn^{2+}]_i$ induced by supplemental $ZnSO_4$ or Zn^{2+} ionophore where intracellular $[Ca^{2+}]_i$ overloading of the heart is present [41,42].

Zinc and antioxidant defenses

In cardiac myocytes and mitochondria harvested from the heart at wk 4 of ALDOST, the pathologic stage when necrotic cell death and scarring occurs, we found increased cytosolic free $[Zn^{2+}]_i$ in cardiac myocytes and total Zn^{2+} concentrations in mitochondria [17]. The rise in cardiomyocyte Zn^{2+} was facilitated by the increased expression of membranous Zn^{2+} transporters which, in turn, was upregulated by oxidative stress. Increased $[Zn^{2+}]_i$ serves to enhance the antioxidant defenses of cardiomyocytes, including their upregulation of MT-1 and activation of MTF-1, which encodes genes related to various antioxidant defenses, such as Cu/Zn-SOD, MT-1, and glutathione synthase. Concurrent with the rise in these defenses were upregulation of biomarkers of oxidative stress, such as 8-isoprostane and malondialdehyde [37].

The efficacy of $ZnSO_4$ supplementation in attenuating these adverse responses, while simultaneously enhancing antioxidant defenses during ALDOST, was addressed in subsequent studies. We found $ZnSO_4$ cotreatment could prevent hypozincemia, but not ionized hypocalcemia and anticipated SHPT by implication. In this context, $ZnSO_4$ attenuated but did not prevent microscopic scarring; neither did it prevent the vasculitis and perivascular fibrosis attendant with PBMC activation [17]. Thus, intracellular Ca^{2+} overloading serves as a prooxidant, while increased intracellular Zn^{2+} exerts an antioxidant stimulus with cardiomyocyte survival based on the intrinsic codependency between these two biologically crucial divalent cations. The cardioprotective properties of a Zn^{2+} supplement have also been demonstrated in mice with streptozocin-induced diabetic cardiomyopathy and in rat models of myocardial ischemia/reperfusion and catecholamine-induced injury following isoproterenol administration [17,41–43].

We subsequently studied and compared the efficacy of $ZnSO_4$ supplement alone to $ZnSO_4$ combined with Amlod, and a Zn^{2+} ionophore alone (pyrrolidine dithiocarbamate, PDTC) [44]. Each of these interventions was associated with a rise in $[Zn^{2+}]_i$ and a concomitant reduction in $[Ca^{2+}]_i$ in cardiomyocytes to indicate the dual efficacy of these agents on the equilibrium between prooxidant:antioxidant. In uncoupling the intrinsically coupled equilibrium between Ca^{2+} and Zn^{2+} , these interventions attenuated oxidative stress in cardiac myocytes and mitochondria and prevented subsequent necrosis with scarring. Thus, the use of these nutraceuticals served to preferentially modify the dysequilibrium between pro- and antioxidant seen during chronic ALDOST which can be cardioprotective in preventing adverse cardiac remodeling.

Translational Studies in African-Americans (AA)

Patients having essential hypertension are categorized into 3 groups based on their plasma renin activity relative to urinary Na^+ excretion [45]. Those with low renin activity, in whom aldosterone excretion fails to be suppressed during dietary Na^+ loading, have low-renin

hypertension with a functional derangement in ALDO secretion [46,47]. These patients, a disproportionate number of whom happen to be AA, have a tendency to retain Na^+ and present with salt-induced hypertension with symptoms and signs of salt and water retention. They therefore are referred to as having “wet” hypertension.

In studies reported by Resnick and coworkers, the metabolic-hormonal profile of patients with low-renin hypertension was elucidated. The profile included the following: a) reduced plasma renin activity coupled with inappropriate elevations in plasma ALDO which could not be adequately suppressed upon salt loading; b) ionized hypocalcemia accompanied by elevations in serum PTH; and c) increased intracellular Ca^{2+} (e.g., platelets) [48]. These investigators proposed an association between Ca^{2+} and Na^+ metabolism that contributes to the pathophysiology of salt-induced hypertension and the blood pressure lowering effects of: a) oral Ca^{2+} supplementation, which corrects the ionized hypocalcemia and prevents SHPT; and b) Ca^{2+} channel blockade, which attenuates PTH-mediated intracellular Ca^{2+} overloading. SHPT is a recognized, albeit underappreciated, clinical feature of aldosteronism. Elevations in serum PTH found in patients with primary aldosteronism are reduced by either spironolactone treatment or by adrenal surgery [49].

Furthermore, we found SHPT to be prevalent in AA with the secondary aldosteronism associated with congestive heart failure. The susceptibility of AA to SHPT is based on several factors. First, the increased melanin content of skin in AA serves as a natural sunscreen, which mandates longer duration of sunlight exposure to produce vitamin D. This results in the prevalence of hypovitaminosis D, often of marked severity ($<10 \text{ mg/mL}$), that compromises Ca^{2+} homeostasis predisposing these patients to hypocalcemia and subsequent SHPT [50–52]. Hypomagnesemia is also a recognized feature of aldosteronism and, it too, is corrected by spironolactone or adrenal surgery [53,54]. In addition to vitamin D deficiency seen in AA is the ionized hypocalcemia and hypomagnesemia that accompany aldosteronism, where urinary and fecal losses of these divalent cations are markedly increased. Subsequent studies have identified a concomitant dyshomeostasis of Zn^{2+} with hypozincemia [55,56]. Other factors that play critical roles in the genesis of compromised Ca^{2+} stores and appearance of SHPT in AA include: a) reduced dietary Ca^{2+} intake because of increased prevalence of lactose intolerance and an active avoidance of dairy products rich in Ca^{2+} ; and b) a preference for a high Na^+ diet that increases urinary Ca^{2+} excretion. A high salt diet normally suppresses plasma renin activity in healthy subjects, but fails to do so in patients with low-renin hypertension; it is accompanied by increased excretory losses of Ca^{2+} with resultant hypercalciuria and ionized hypocalcemia and, in turn, SHPT with a resorption of bone invoked to restore extracellular Ca^{2+} homeostasis. Over time, osteopenia and osteoporosis accompany the hypercalciuria of long-term dietary Na^+ excess predisposing patients to atraumatic bone fractures [57]. Hence, the pathophysiologic link between Na^+ -induced aberration in Ca^{2+} metabolism, where increased urinary Na^+ promotes augmented urinary Ca^{2+} excretion is again noted, and it also encompasses the clinical scenario defined with salt-induced hypertension and low-renin hypertension.

Summary and Conclusions

In both man and rats, inappropriate elevations in plasma ALDO (relative to dietary Na^+), not suppressed by dietary Na^+ loading, are accompanied by heightened excretory losses of Ca^{2+} , Mg^{2+} , and Zn^{2+} . The resultant hypocalcemia, hypomagnesemia, and hypozincemia that accompany low-renin hypertension individually and collectively contribute to the appearance of SHPT, where the elevation in plasma PTH seeks to restore extracellular homeostasis of these divalent cations through bone resorption. At the same time, PTH-mediated intracellular Ca^{2+} overloading occurs in diverse cell types, including cardiac myocytes and their mitochondria. The Ca^{2+} overloading of mitochondria gives way to the

induction of oxidative stress, mPTP opening, organellar destruction, and cardiomyocyte necrosis. The subsequent reparative fibrosis, or scarring, contributes to the adverse structural remodeling of the heart, with its attendant pathologic influence on myocardial stiffness while serving as substrate for re-entrant arrhythmias.

Another pathway leading to cardiomyocyte necrosis during aldosteronism relates to impaired antioxidant defenses which accompany Zn^{2+} dyshomeostasis with hypozincemia. The dyshomeostasis of intracellular Ca^{2+} and Zn^{2+} in cardiac myocytes and mitochondria are intrinsically coupled, where Ca^{2+} serves as prooxidant and Zn^{2+} as antioxidant. This raises the prospect for uncoupling of Ca^{2+} and Zn^{2+} dyshomeostasis in favor of antioxidant defenses. Adjuvant nutraceuticals may have the potential of offering such therapeutic promise. In addressing the importance of a dyshomeostasis of macro- and micronutrients in AA with low-renin hypertension, it may be possible to prevent the adverse structural remodeling of myocardium which contributes to their increased risk of adverse cardiovascular events.

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Abbreviations

AA	African-Americans
ALDO	aldosterone
ALDOST	aldosterone/salt treatment
Amlod	amlodipine
GSH-Px	glutathione peroxidase
HHD	hypertensive heart disease
LVH	left ventricular hypertrophy
mPTP	mitochondrial permeability transition pore
MT	metallothionein
MTF	metal-responsive transcription factor
NF	nuclear transcription factor
PBMC	peripheral blood mononuclear cells
PTH	parathyroid hormone
RAAS	renin-angiotensin-aldosterone system
SHPT	secondary hyperparathyroidism
SOD	superoxide dismutase
Spiro	spironolactone
TNF	tumor necrosis factor

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Figure 1.

In low-renin hypertension associated with chronic aldosteronism, heightened urinary and fecal losses of Ca^{2+} lead to ionized hypocalcemia that, in turn, stimulates increased secretion of parathyroid hormone (PTH) by the parathyroid glands. The appearance of secondary hyperparathyroidism (SHPT) provokes increased resorption of bone minerals and augmented absorption and reabsorption of these cations from the gut and kidney, respectively. Characterized as a Ca^{2+} paradox, PTH-mediated intracellular Ca^{2+} overloading leads to the induction of oxidative and nitrosative stress that eventuates in cardiomyocyte necrosis and subsequent replacement fibrosis, or scarring.

Figure 2.

As depicted in Figure 1, the ionized hypocalcemia presented with aldosterone/salt treatment (ALDOST) is associated with SHPT and PTH-mediated intracellular Ca^{2+} overloading with oxidative stress. In the case of cardiomyocytes, this pathophysiologic scenario leads to an opening of the mitochondrial permeability transition pore (mPTP) and the entry of solutes that contributes to osmotic degeneration of mitochondria. The ensuing necrosis of cardiomyocytes is associated with the efflux of cardiac troponins into the interstitial space and its subsequent appearance in the circulation. A replacement fibrosis, or scarring, appears at sites of lost cardiomyocytes to preserve the structural integrity of the myocardium, but not without adverse functional consequences on myocardial stiffness and arrhythmogenicity.

Figure 3.

Ionized hypocalcemia ($\downarrow[\text{Ca}^{2+}]_o$) seen with ALDOST leads to PTH-mediated intracellular Ca^{2+} overloading of cardiomyocytes ($[\text{Ca}^{2+}]_i$) via L-type Ca^{2+} channels (LTCC) and their mitochondria ($[\text{Ca}^{2+}]_m$). This pathophysiologic Ca^{2+} entry is intrinsically coupled to Zn^{2+} entry, which initially occurs via LTCC to facilitate instantaneous raise in cytosolic $[\text{Zn}^{2+}]_i$ and mitochondrial $[\text{Zn}^{2+}]_m$. The Ca^{2+} overloading-mediated promotion of oxidative stress is accompanied by the upregulation of Zn^{2+} transporters that facilitate excessive Zn^{2+} entry and the release of inactive Zn^{2+} bound to its binding protein, metallothionein (MT)-1. The rise in $[\text{Zn}^{2+}]_i$ activates its sensor, metal-responsive transcription factor (MTF)-1, which then translocates to the nucleus, where it activates genes related to antioxidant defenses. These defenses seek to detoxify and impede the rate of oxidative stress generation preventing cardiomyocyte necrosis. Adapted from Kamalov G, et al. *Am J Physiol Heart Circ Physiol* 2010;**298**:H385-H394.