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DISTURBANCES IN CALCIUM METABOLISM AND CARDIOMYOCYTE NECROSIS: THE ROLE OF CALCITROPIC HORMONES

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Summary

A synchronized dyshomeostasis of extra- and intracellular Ca^{2+} , expressed as plasma ionized hypocalcemia and excessive intracellular Ca^{2+} accumulation, respectively, represents a common pathophysiologic scenario that accompanies a number of diverse disorders. These include low-renin and salt-sensitive hypertension, primary aldosteronism and hyperparathyroidism, congestive heart failure, acute and chronic hyperadrenergic stressor states, high dietary Na^+ , and low dietary Ca^{2+} with hypovitaminosis D. Homeostatic responses are invoked to restore normal extracellular $[\text{Ca}^{2+}]_o$, including increased plasma levels of parathyroid hormone and $1,25(\text{OH})_2\text{D}_3$. However, in cardiomyocytes, these calcitropic hormones concurrently promote cytosolic free $[\text{Ca}^{2+}]_i$ and mitochondrial $[\text{Ca}^{2+}]_m$ overloading. The latter sets into motion organellar-based oxidative stress, in which the rate of reactive oxygen species generation overwhelms their detoxification by endogenous antioxidant defenses, including those related to intrinsically coupled increments in intracellular Zn^{2+} . In turn, the opening potential of the mitochondrial permeability transition pore increases allowing for osmotic swelling and ensuing organellar degeneration. Collectively, these pathophysiologic events represent the major components to a mitochondriocentric signal-transducer-effector pathway to cardiomyocyte necrosis. From necrotic cells there follows a spillage of intracellular contents, including troponins, and a subsequent wound healing response with reparative fibrosis, or scarring. Taken together the loss of terminally differentiated cardiomyocytes from this postmitotic organ and the ensuing replacement fibrosis each contribute to the adverse structural remodeling of myocardium and progressive nature of heart failure. In conclusion, hormone-induced ionized hypocalcemia and intracellular Ca^{2+} overloading comprise a pathophysiologic cascade common to diverse disorders and which initiates a mitochondriocentric pathway to nonischemic cardiomyocyte necrosis.

Keywords

ionized hypocalcemia; hyperparathyroidism; catecholamines; aldosteronism; calcium overloading; zinc; oxidative stress; mitochondrial permeability transition pore

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Introduction

Despite disparate etiologic origins, a number of disorders share a common downstream pathophysiologic cascade revolving around a dyshomeostasis of extra- and intracellular Ca^{2+} . Expressed as ionized hypocalcemia and excessive intracellular Ca^{2+} accumulation (EICA) respectively, this scenario naturally involves calcitropic hormones: the catecholamines; parathyroid hormone (PTH); and $1,25(\text{OH})_2\text{D}_3$, a steroid molecule also known as calcitriol or vitamin D. These disorders include: low-renin and salt-sensitive hypertension; primary aldosteronism and hyperparathyroidism; congestive heart failure; acute and chronic hyperadrenergic states; high dietary Na^+ ; and reduced dietary Ca^{2+} with hypovitaminosis D.

Plasma ionized hypocalcemia represents a relative deficiency of extracellular $[\text{Ca}^{2+}]_o$. It can manifest in response to: i) heightened fecal and/or urinary excretory Ca^{2+} losses in the presence of fixed dietary Ca^{2+} intake; ii) catecholamine-mediated translocation of plasma Ca^{2+} into tissues; and iii) reduced dietary Ca^{2+} , often in association with vitamin D deficiency. Homeostatic responses, invoked by ionized hypocalcemia, seek to restore extracellular $[\text{Ca}^{2+}]_o$. They include the increased secretion of PTH by the parathyroid glands to promote the release of Ca^{2+} stored in bone and PTH-driven renal formation of $1,25(\text{OH})_2\text{D}_3$, which enhances Ca^{2+} absorption from the gastrointestinal tract and Ca^{2+} reabsorption by the kidneys.

In cardiomyocytes, these calcitropic hormones, however, simultaneously promote L-type Ca^{2+} channel activity leading to increased cytosolic free $[\text{Ca}^{2+}]_i$, and, in turn, mitochondrial $[\text{Ca}^{2+}]_m$ overloading with organellar-based oxidative stress. The rate of reactive oxygen species generation overwhelms their rate of neutralization by endogenous antioxidant defenses, including closely coupled increments in intracellular Zn^{2+} . EICA in the presence of fallen $[\text{Ca}^{2+}]_o$ levels has prompted Fujita and Palmieri to implicate a scenario of a *Ca²⁺ paradox*.¹ At the subcellular level, and considered a response intended to maintain intracellular Ca^{2+} homeostasis, mitochondrial $[\text{Ca}^{2+}]_m$ rises, targeting the subsarcolemmal population of cardiac mitochondria in particular.^{2–4} This sets into motion a *mitochondriocentric signal-transducer-effector (MSTE) pathway* to cardiomyocyte necrosis with subsequent spillage of cellular contents (e.g., troponins). These contents represent “danger signals” that stimulate the immune system accounting for the invasion of inflammatory cells, as well as phenotypically transformed fibroblast-like cells, or myofibroblasts, to the site of injury. Necrosis is, therefore, referred to as “dirty” cell death evoking a wound healing response that eventuates in a reparative fibrosis.^{5,6} Microscopic scars are indeed morphologic footprints of necrosis. This contrasts to programmed cell death, where apoptotic cardiomyocytes are rapidly scavenged by macrophages, without subsequent tissue repair or fibrosis, to represent “sterile” cell death.

Microscopic scars are scattered throughout the myocardium of the right and left heart in both ischemic and dilated (idiopathic) cardiomyopathies and hypertensive heart disease.^{7–16} Elevations in plasma troponins, a biochemical marker of cardiomyocyte necrosis, are present at the time of hospitalization for decompensated heart failure or poorly controlled hypertension, and are predictive of worsened outcomes and poor prognosis.^{17–26} Elevated troponins are also seen with each admission implicating cardiomyocyte necrosis to be an ongoing event. In what is arguably a postmitotic organ, unable to withstand such losses, given the fixed population of these highly differentiated and specialized cells, necrosis and fibrosis likely contribute to the progressive nature of heart failure.

The purpose of this review is severalfold: i) to highlight the pathophysiologic events pivoting around the dyshomeostasis of Ca^{2+} metabolism, the role of calcitropic hormones

and the MSTE pathway to cardiomyocyte necrosis; ii) to emphasize the metabolism of intrinsically coupled Zn^{2+} , an antioxidant, and its cardioprotective potential. We begin with a relevant historical perspective.

Historical Perspective

Many of the disorders noted earlier have their origins rooted in inappropriate neurohormonal activation which includes the hypothalamic-pituitary-adrenal axis, the adrenergic nervous (ANS) and renin-angiotensin-aldosterone (RAAS) systems and whose effector hormones can prove toxic to cardiomyocytes.^{27–29} Fleckenstein and coworkers, now 50 years ago, hypothesized the hyperadrenergic state which accompanies acute stressors would lead to catecholamine-mediated EICA and dysfunction of mitochondria due to Ca^{2+} overloading. Coupled with the diminished synthesis of high energy phosphates, reduced Ca^{2+} efflux by compromised Ca^{2+} ATPase-dependent pumping, and the degeneration of these organelles accounts for cardiomyocyte necrosis. They validated their working hypothesis using isoproterenol-induced cardiac injury in rodents and by employing cotreatment with a calcium channel blocker, which proved to be cardioprotective.^{30,31} The importance of other calcitropic hormones (PTH and vitamin D) was also emphasized.

Others have confirmed this paradigm and broadened our understanding of cellular-subcellular mechanisms leading to cardiomyocyte necrosis.^{32–35} Singal and Dhalla and coworkers, for example, identified the importance of EICA despite diverse pathophysiologic origins that included not only catecholamine-mediated $[Ca^{2+}]_i$ accumulation,³⁶ but also ischemia/reperfusion injury, in which the rise in $[Ca^{2+}]_i$ occurs during reperfusion. Furthermore, they identified a pathogenic role for oxidative stress, where the rate of injurious reactive species (ROS) generation overwhelm endogenous antioxidant defenses. This included such diverse entities as acute myocardial infarction and the cardiomyopathies associated with catecholamine excess, diabetes or adriamycin. In either of these acute or chronic oxidative stressor states it became evident that endogenous antioxidant reserves could prove inadequate requiring exogenous antioxidants to salvage cardiomyocytes.^{37–45}

In 1985, Resnick and Laragh began reporting on the dyshomeostasis in Ca^{2+} metabolism they found in patients having low-renin and salt-sensitive hypertension.^{46–48} They explained this scenario with their *ion hypothesis*; it included ionized hypocalcemia with elevations in plasma PTH, together with increased intracellular Ca^{2+} (in platelets), and the efficacy of a calcium channel blocker in controlling blood pressure.⁴⁹ A similar aberrant metabolic profile was reported by these investigators, as well as by E. Rossi and coworkers, for patients with primary aldosteronism which resolved with either adrenal surgery or treatment with spironolactone, an aldosterone receptor antagonist.^{50,51}

Contemporaneously, McCarron and coworkers reported on the efficacy of a Ca^{2+} -supplemented diet in controlling blood pressure and elevated levels of calcitropic hormones in patients with low-renin and salt-sensitive hypertension. They ascribed this as a *calcium paradox*, wherein increased dietary Ca^{2+} intake and gastrointestinal Ca^{2+} absorption corrected ionized hypocalcemia and associated secondary hyperparathyroidism (SHPT) with intracellular Ca^{2+} overloading.^{52–55}

Disturbances in Calcium Metabolism Leading to Plasma Ionized Hypocalcemia

An activation of the ANS and RAAS accompanies acute and chronic stressor states. Effector hormones represented respectively by elevated circulating levels of the catecholamines and

aldosterone each lead to plasma ionized hypocalcemia albeit via different pathophysiologic cascades (see Figure 1).

In the case of an acute hyperadrenergic state, such as accompanies bodily injury (e.g., subarachnoid hemorrhage, acute myocardial infarction, burns or traumatic injury), reductions in plasma ionized $[Ca^{2+}]_o$ appear rapidly due to the prompt translocation of Ca^{2+} from plasma into such diverse tissues as heart, skeletal muscle and peripheral blood mononuclear cells.³ Catecholamine-mediated intracellular Ca^{2+} overloading is an adverse outcome and includes a rise in both cytosolic free $[Ca^{2+}]_i$ and mitochondrial $[Ca^{2+}]_m$, wherein the latter leads to the induction of oxidative stress by these organelles.³ The appearance of ionized hypocalcemia prompts the Ca^{2+} -sensing receptor of the parathyroid glands to augment their secretion of PTH, which promotes PTH-mediated, osteoclast-driven resorption of Ca^{2+} stored in bones to restore $[Ca^{2+}]_o$ homeostasis. This calcitropic hormone, however, also promotes Ca^{2+} entry via L-type Ca^{2+} channels with consequent intracellular Ca^{2+} overloading.⁵⁶ Furthermore, PTH stimulates the kidneys to produce a steroid hormone, $1,25(OH)_2D_3$, also known as vitamin D, or calcitriol; it promotes Ca^{2+} absorption from the small intestine and renal reabsorption of Ca^{2+} . The degree of plasma ionized hypocalcemia and accompanying elevations in plasma PTH correlate with the severity of injury and extent of the catecholamine response, and accordingly the corresponding risk of adverse cardiovascular events.^{57–67}

In chronic stressor states such as congestive heart failure (CHF), in which the RAAS is activated, elevations in plasma aldosterone contribute to marked increments in excretory Ca^{2+} losses in both urine and feces.^{68–71} For a fixed intake of dietary Ca^{2+} , these marked excretory losses eventuate in ionized hypocalcemia with SHPT (see Figure 1). PTH-mediated intracellular Ca^{2+} overloading follows leading to cardiomyocyte necrosis and a replacement fibrosis. The validity of this cascade was tested and confirmed using various interventions which prevented SHPT. They included: cotreatment with a diet supplemented with Ca^{2+} and calcitriol; parathyroidectomy; and a calcimimetic, which raised the threshold of the parathyroid glands' Ca^{2+} -sensing receptor.^{72–74}

A high Na^+ diet is also accompanied by increments in urinary Ca^{2+} excretion, and when hypercalciuria is persistent, ionized hypocalcemia is the outcome with SHPT responsible for bone demineralization. Reduced dietary Ca^{2+} intake, as accompanies lactose intolerance with the avoidance of dairy products rich in Ca^{2+} , can compromise Ca^{2+} reserves and predispose to hypocalcemia. Hypovitaminosis D is associated with reduced Ca^{2+} absorption from the gut. Collectively, these factors hasten the appearance of ionized hypocalcemia with SHPT and PTH-mediated intracellular Ca^{2+} overloading.

Homeostatic neurohormonal responses, coupled to the appearance of SHPT with elevations in plasma PTH and $1,25(OH)_2D_3$, lead to EICA despite the paucity of extracellular Ca^{2+} .¹ The use of a Ca^{2+} supplement will negate plasma ionized hypocalcemia and SHPT.^{53,72}

Lost Intracellular Ca^{2+} Homeostasis

Ca^{2+} is an essential intracellular messenger, especially in contractile cells, such as cardiomyocytes. However, an excessive accumulation of Ca^{2+} , which Rasmussen H, et al. referred to as *Ca²⁺ intoxication*, becomes a cellular toxin.⁷⁵ Normally, EICA is minimized by intracellular autoregulatory responses, wherein the rate of Ca^{2+} influx is limited by specific and specialized L-type Ca^{2+} channels of an otherwise impermeable sarcolemma membrane and which is in equilibrium with the rate of Ca^{2+} efflux. Efflux pathways include energy-dependent Ca^{2+} ATPase and a Na^+/Ca^{2+} exchanger. In addition, several organelles (i.e., sarcoplasmic reticulum (SR) and mitochondria) contribute to intracellular Ca^{2+} homeostasis. The storage capacity of the SR is limited and its Ca^{2+} release and

reaccumulation is driven by stimulus-response coupling. However, mitochondria have a larger capacity to sequester Ca^{2+} when intracellular equilibrium is overwhelmed. Cardiomyocyte necrosis occurs when the imbalance between Ca^{2+} influx and efflux and Ca^{2+} storage capacity of mitochondria is lost.^{30,75} Such scenarios occur when EICA is persistent as is the case when plasma concentrations of calcitropic hormones are elevated.

Mitochondriocentric Signal-Transducer-Effector Pathway to Cardiomyocyte Necrosis

The adverse consequences of elevated plasma epinephrine levels on cardiomyocyte survival that appear with acute bodily injury (e.g., subarachnoid hemorrhage) or adrenal medullary tumor (pheochromocytoma), have been well-described.^{29,32–35} The role of catecholamine excess which accompanies marked emotional stress can putatively account for ballooning (akinesia) of the left ventricular (LV) apex, also termed Takotsubo cardiomyopathy.⁷⁶ Isoproterenol (Isop) has been used to address the cytotoxicity associated with hyperadrenergic states. Using immunohistochemical labeling of cardiac myosin, cell death occurs within 2 hrs of single-dose Isop treatment.²⁹ Cells residing within the endomyocardium of the LV apex are particularly vulnerable. More recently, a mitochondriocentric pathway leading to cardiomyocyte necrosis following Isop was identified³ in which EICA and oxidative stress were self-evident in cardiomyocytes harvested from the LV apex (vis-à-vis the equator or base) in keeping with the greater density of β_1 receptors at this site and the known apical to basal activation of the LV.^{77–79}

Intracellular Ca^{2+} overloading involving subsarcolemmal mitochondria is the *signal* to the mitochondriocentric *signal-transducer-effector pathway* to cardiomyocyte necrosis during acute hyperadrenergic states (see Figure 2). The *transducer* involves the induction of oxidative stress, invoked in response to EICA. Lastly, the *effector* to this pathway is represented by the role of mPTP opening with consequent solute entry, osmotic swelling and organellar dysfunction with structural degeneration that eventuate in cell death. In the presence of acute or chronic stressor states, intracellular cationic shifts, particularly during catecholamine- and PTH-mediated EICA, converge on mitochondria to induce oxidative stress and raise the opening potential of their inner membrane mPTP (see Figure 2).

A chronic stressor state, such as primary aldosteronism or the secondary aldosteronism of CHF, leads to increased fecal and urinary Ca^{2+} excretion and consequent ionized hypocalcemia with elevated plasma PTH levels that promote EICA in diverse tissues (see Figure 1).^{69–71,80–82} The ensuing loss of intracellular cationic homeostasis and cardiomyocyte necrosis is followed by the spillage of cell contents, including the leakage of troponins, which ultimately appear in the circulation as a biomarker confirmatory of cardiomyonecrosis. Elevations in serum troponins, but not due to ischemia-mediated myocardial infarction, are found in patients hospitalized with acute or chronic stressor states and patients with hypertension, where they are associated with increased risk of hospitalization, as well as in-hospital and overall cardiac mortality.^{17–26,83,84}

The role of EICA and oxidative stress, induced by calcitropic hormones in promoting necrosis is now evident. An ongoing loss of cardiomyocytes undoubtedly contributes to the progressive nature of heart failure, in what is arguably a postmitotic organ with a fixed number of these cells.

Clinical Correlates of Calcium Dyshomeostasis with Cardiomyocyte Necrosis

A dyshomeostasis of divalent cations is found in patients hospitalized with decompensated biventricular failure having a dilated cardiomyopathy of ischemic or nonischemic origins, and in low-renin and salt-sensitive hypertension.^{46–48,70} This aberrant cation-hormone profile is also present in patients with primary aldosteronism.^{50,51,85,86} Elevated PTH serves as a stimulus to adrenal aldosterone production and contemporaneous elevations in plasma aldosterone. In patients with primary hyperparathyroidism, preoperative PTH levels in excess of 100 ng/mL are independent predictors of abnormal elevations in plasma aldosterone.⁸⁷ 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.^{69,73,74} The role of elevations in circulating aldosterone and which are inappropriate for dietary Na^+ must also be considered.⁸⁸

Abnormal elevations in serum PTH (>65 pg/mL) serve as a potent mediator of EICA in cardiomyocytes and mitochondria.^{69,89,90} Primary hyperparathyroidism is associated with increased cardiovascular mortality.^{91,92} 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.^{93,94} In patients with primary hyperparathyroidism, the increased incidence of left ventricular hypertrophy, Ca^{2+} deposits in the myocardium and heart valve leaflets, and EICA may contribute to increased risk of cardiovascular mortality.^{91,95–99} Elevated PTH levels are found in patients hospitalized with decompensated heart failure and those awaiting cardiac transplantation,^{71,80,100,101} and serve as an independent predictor of CHF, the need for hospitalization and cardiovascular mortality.^{102–105} Moreover, PTH levels have been shown to be an independent risk factor for mortality and cardiovascular events in community-dwelling individuals.^{106–108} 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.^{70,71} SHPT is also related to the prevalence of hypovitaminosis D in AA, where the increased melanin content of dark skin serves as a natural sunscreen.⁷¹ 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.^{71,109,110} Vitamin D deficiency is also reported in Caucasians and Asians with heart failure whose effort intolerance predisposes an indoors lifestyle.^{102,103,111–113} 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.¹¹⁴

Osteopenia and osteoporosis are also accompanying adverse outcomes to chronic SHPT; they predispose to atraumatic bone fractures.^{115,116} 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.^{80,100,117–121} 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.^{122–124} In elderly patients with hip fracture, elevated PTH levels are associated with perioperative myocardial injury with elevated serum troponins and all-cause mortality.¹²⁵

A Dyshomeostasis of Zinc as Antioxidant

The importance of a deficiency in antioxidant reserves is also contributory to the imbalance in prooxidant:antioxidant equilibrium leading to cardiomyocyte necrosis that accompanies

neurohormonal activation.^{126–128} Zinc is integral to antioxidant defenses, as well as wound healing.¹²⁹ An increased expression 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.^{130–132} Zn^{2+} deficiency will compromise these reserves and healing after cardiomyocyte necrosis.

In aldosteronism, increased urinary and fecal losses of Zn^{2+} result in hypozincemia with simultaneous cellular and subcellular dyshomeostasis of Zn^{2+} .^{132–134} Accompanying Zn^{2+} deficiency compromises the activity of Cu/Zn superoxide dismutase, an important 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.^{135,136} Serum Zn^{2+} levels are reduced in patients with a dilated cardiomyopathy and individuals with arterial hypertension.^{70,82,137–140} Underlying causes for Zn^{2+} deficiency, including inadequate dietary intake and excess urinary excretion, remain unclear and need to be investigated.

Intricate interactions between Zn^{2+} with Ca^{2+} have been noted.^{90,129,131,141,142} 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.^{2,89,90,143} Zn^{2+} entry is known to occur via L-type Ca^{2+} channels, however, more substantive amounts enter 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 which is induced by nitric oxide (NO) derived from endothelial NO synthase.¹⁴⁴ Elevations in $[Zn^{2+}]_i$ can also be achieved by a $ZnSO_4$ supplement.^{37,89,143,145–149} Increased cytosolic free $[Zn^{2+}]_i$ activates its sensor, metal-responsive transcription factor (MTF)-1 which, upon its translocation to the nucleus, upregulates the expression of antioxidant defense genes.² These observations raise the therapeutic prospect that cation-modulating *nutriceuticals* capable of favorably influencing the extra- and intracellular Ca^{2+} and Zn^{2+} equilibrium to enhance overall antioxidant capacity, could prove pivotal to combating mitochondria-based oxidative injury and cardiomyocyte necrosis while promoting Zn^{2+} -based cardioprotective potential.

Overall Summary and Conclusions

Acute and chronic stressor states are accompanied by neurohormonal activation that includes the ANS and RAAS. An ensuing hyperadrenergic state, coupled with SHPT via ionized hypocalcemia, provokes cardiomyocyte Ca^{2+} overloading, including $[Ca^{2+}]_m$ of the subsarcolemmal population of mitochondria with induction of oxidative stress and opening of their inner membrane mPTP. These events represent the major components of a MSTE pathway to organellar degeneration and ultimately cardiomyocyte necrosis. The MSTE pathway to necrosis also accompanies increased excretory losses of Ca^{2+} or reduced dietary Ca^{2+} , each of which eventuate in ionized hypocalcemia with consequent SHPT. The release of cell contents from nonischemic but necrotic cardiomyocytes accounts for elevated serum troponins and causes a wound healing response leading to foci of microscopic scarring. The ongoing nature of necrosis is reflected in scarring found scattered throughout the right and left heart, especially the endomyocardium of the LV apex. The loss of terminally differentiated cardiomyocytes from this postmitotic organ and their replacement by fibrous tissue each contribute to the progressive nature of heart failure. Fibrosis is a major component to the adverse structural remodeling of the failing myocardium.

Other pathophysiologic responses orchestrated by neurohormonal activation are hyperzincuria and the coordinated translocation of Zn^{2+} to injured tissues in which Zn^{2+} contributes to tissue repair. This facilitates the simultaneous induction of ionized

hypocalcemia and hypozincemia. Intracellular cationic shifts adaptively regulate redox equilibrium, a critical determinant of myocardial cell survival. The intrinsically coupled dyshomeostasis of Ca^{2+} and Zn^{2+} representing prooxidant and antioxidant, respectively, can be uncoupled in favor of increased intracellular free Zn^{2+} , thus enhancing antioxidant defenses aimed at mitochondria to prevent oxidative damage.¹⁵⁰ In like fashion, the use of nutraceuticals to rescue cardiomyocytes susceptible to necrotic cell death ought to be considered as complementary strategies to the current standard of care which draws upon pharmaceuticals alone.^{151,152}

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List of Abbreviations

AA	African-Americans
ANS	adrenergic nervous system
CHF	congestive heart failure
EICA	excessive intracellular Ca^{2+} accumulation
Isop	isoproterenol
LV	left ventricular
MSTE	mitochondriocentric signal-transducer-effector
PTH	parathyroid hormone
RAAS	renin-angiotensin-aldosterone system
SHPT	secondary hyperparathyroidism

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Figure 1.

Diverse disorders of Ca²⁺ metabolism follow a common pathophysiologic cascade through plasma ionized hypocalcemia with consequent elevations in parathyroid hormone (PTH). Secondary hyperparathyroidism (SHPT) with bone resorption and vitamin D-mediated (1,25(OH)₂D₃) increments in gut absorption and renal reabsorption of Ca²⁺ follow, together with PTH-mediated intracellular Ca²⁺ overload of cardiomyocytes leading to the necrosis of these cells. mPTP, mitochondrial permeability transition pore. See text.

Figure 2.

A mitochondriocentric signal-transducer-effector pathway to cardiomyocyte necrosis. SSM, subsarcolemmal mitochondria. See text.