Intracellular calcium overloading and oxidative stress in cardiomyocyte necrosis via a mitochondriocentric signal-transducer-effector pathway

Mazen Shaheen MD, Yaser Cheema MD, Atta U Shahbaz MD, Syamal K Bhattacharya PhD, Karl T Weber MD

M Shaheen, Y Cheema, AU Shahbaz, SK Bhattacharya, KT Weber. Intracellular calcium overloading and oxidative stress in cardiomyocyte necrosis via a mitochondriocentric signal-transducer-effector pathway. Exp Clin Cardiol 2011;16(4):109-115.

Congestive heart failure (CHF), a common clinical syndrome, has reached epidemic proportions. Its disabling symptoms account for frequent hospitalizations and readmissions. Pathophysiological mechanisms that lead to CHF and account for its progressive nature are of considerable interest. Important scientific observations obtained from Dr Pawan K Singal's laboratory in Winnipeg, Manitoba, have provided crucial insights to our understanding of the pathophysiological factors that contribute to cardiomyocyte necrosis (the heart is a postmitotic organ incapable of tolerating an ongoing loss of these cells without adverse functional consequences). This increment in knowledge and the mechanistic insights afforded by Dr Singal and his colleagues have highlighted the role of excessive intracellular calcium accumulation and the appearance of oxidative stress in CHF, in which the rate of reactive oxygen species generation overwhelms their rate of detoxification by antioxidant defenses. They have shown that this common pathophysiological scenario applies to diverse entities such as ischemia/reperfusion and hypoxia/reoxygenation forms of injury, myocardial infarction and the cardiomyopathies that accompany diabetes and excess levels of catecholamines and adriamycin. The authors are honoured to be invited to contribute to the present focus issue of *Experimental & Clinical Cardiology* in recognizing Dr Singal's numerous scholarly accomplishments. The present article reviews the authors' recent work on a mitochondriocentric signal-transducer-effector pathway to cardiomyocyte necrosis found in rats with either an acute stressor state that accompanies isoproterenol administration or a chronic stressor state manifested after four weeks of aldosterone/salt treatment.

Key Words: *Antioxidant defenses; Calcium overloading; Cardiomyocyte necrosis; Catecholamines; Mitochondria; Oxidative stress; Parathyroid hormone*

Congestive heart failure (CHF) has reached epidemic proportions due, in part, to the reduced mortality rate observed with acute coronary events. The disabling symptoms that constitute the clinical syndrome of CHF now account for the leading cause of hospitalizations in the United States. Understanding pathogenic origins and pathophysiological expressions of CHF is paramount to developing its optimal medical management.

In this context, the present focus issue of *Experimental & Clinical Cardiology* collectively highlights the important scientific contributions of Dr Pawan K Singal, Professor of Physiology at the University of Manitoba, and Director at the Institute of Cardiovascular Sciences of the St Boniface General Hospital Research Centre in Winnipeg, Manitoba. His laboratory has contributed substantively to our understanding of the cellular-molecular mechanisms leading to cardiomyocyte necrosis, a pathological event accounting for the progressive nature of the failing heart in what is arguably a postmitotic organ with a fixed number of adult cardiomyocytes. Over the past 30 years, his insightful research has expanded our knowledge of the importance of intracellular Ca^{2+} $[Ca^{2+}]_i$ overloading in mediating cell injury. Singal and colleagues reported on the excessive $[Ca^{2+}]_i$ accumulation (EICA) that evolves from diverse pathophysiological origins. These include catecholamine-mediated $[Ca^{2+}]_i$ accumulation that occurs due to a hyperadrenergic state (1); and ischemia/reperfusion injury, in which the rise in $[Ca^{2+}]_i$ occurs during reperfusion when extracellular Ca^{2+} levels remain normal (2). Second, they reported on the pathogenic role of oxidative stress, in which the rate of injurious reactive oxygen species (ROS) generation overwhelms their rate of detoxification through endogenous antioxidant defenses in diverse entities such as myocardial infarction and the cardiomyopathies associated with either catecholamines, diabetes or adriamycin treatment. In these entities, with either acute or chronic oxidative stress, endogenous antioxidant reserves become inadequate while the addition of exogenous antioxidants (eg, probucol and propranolol) provide cardioprotection (3-11).

Parallel to Dr Singal's findings, we present our work on a mitochondriocentric signal-transducer-effector (MSTE) pathway to cardiomyocyte necrosis. Its three major components, representing signal, transducer and effector, respectively, includes EICA, especially Ca^{2+} overloading of the subsarcolemmal population of mitochondria; the generation of ROS by these organelles; and the terminal effector, which involves the opening of the inner membrane-bound mitochondrial permeability transition pore (mPTP). It is our privilege to contribute to the present focus issue of *Experimental and Clinical Cardiology*, which is dedicated to Professor Singal's career and his numerous scholarly contributions to the field.

MYOCARDIAL FIBROSIS: A FOOTPRINT OF CARDIOMYOCYTE NECROSIS

Foci of microscopic scarring are scattered throughout the myocardium of the explanted failing human heart (12). The loss of cardiomyocytes to necrosis and their subsequent replacement with fibrillar stiff collagen each contribute to the pathological remodelling of myocardium and the progressive nature of heart failure. Fibrosis is considered to be the major component of the progressive pathological structural remodelling found in the failing heart (12). Its presence underscores the importance of cardiomyocyte necrosis to the failing heart and implicates it as an ongoing event. Apoptosis, which may also be ongoing and important, is not accompanied by tissue repair and the appearance of scarring. Necrotic cells, on the other hand, spill their contents, including troponins, which serve as 'danger' signals to invoke inflammatory cell and fibroblast responses that lead to wound healing. In patients hospitalized because of CHF, elevations in serum troponin levels are found on admission and recur with subsequent admissions. Accordingly, elevated troponin levels are associated with an increased risk of morbidity and mortality due to cardiovascular events (13-22). Factors other than myocardial infarction, wherein a critical reduction in coronary blood flow leads to the loss of a segment of myocardium, can account for cardiomyocyte necrosis and raises the importance of neurohormonal activation.

Division of Cardiovascular Diseases, University of Tennessee Health Science Center, Memphis, Tennessee, USA
Correspondence and reprints: Dr Karl T Weber, Division of Cardiovascular Diseases, University of Tennessee Health Science Center, 956 Court Avenue, Suite A312, Memphis, Tennessee 38163, USA. Telephone 901-448-5750, fax 901- 448-8084, e-mail ktweber@uthsc.edu
Received for publication June 10, 2011. Accepted June 30, 2011

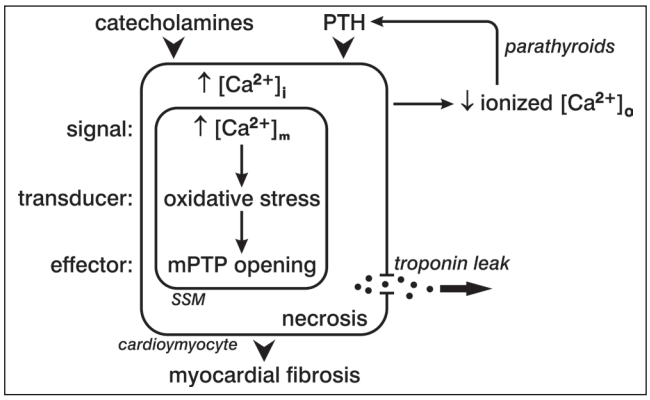

Figure 1) *A subsarcolemmal (SSM) mitochondriocentric signal-transducer-effector pathway to cardiomyocyte necrosis evoked by either catecholamines or parathyroid hormone (PTH). $[Ca^{2+}]_i$ Intracellular calcium; $[Ca^{2+}]_m$ Mitochondrial-free calcium concentration; $[Ca^{2+}]_o$ Extracellular calcium; mPTP Mitochondrial permeability transition pore. Adapted from reference 118*

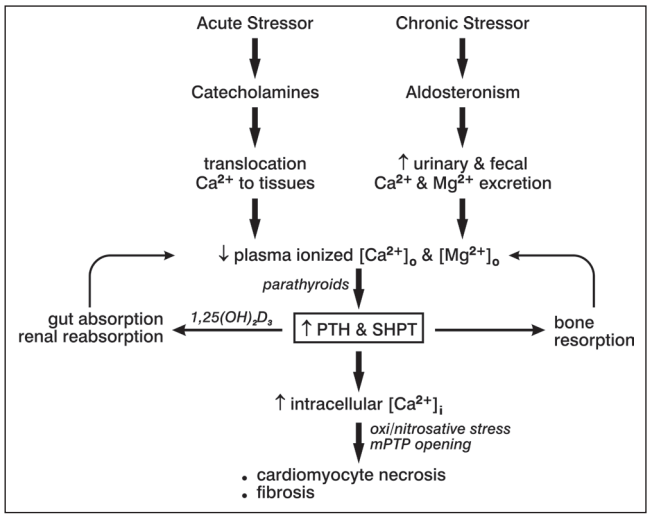

Figure 2) *Acute and chronic stressor states with excess catecholamines or aldosteronism, respectively, can lead to plasma-ionized hypocalcemia with secondary hyperparathyroidism (SHPT), in which elevations in plasma parathyroid hormone (PTH) levels seek to restore extracellular Ca^{2+} $[Ca^{2+}]_o$ homeostasis via bone resorption, and increase Ca^{2+} absorption and reabsorption from the colon and the kidneys, respectively. Paradoxically, PTH raises intracellular Ca^{2+} $[Ca^{2+}]_i$ to induce oxidative stress. $[Mg^{2+}]_o$ Extracellular magnesium; mPTP Mitochondrial permeability transition pore. Adapted from reference 119*

PATHOPHYSIOLOGICAL MECHANISMS IN CARDIOMYOCYTE NECROSIS

Acute stressor states

Acute stressor states are inextricably linked to neurohormonal activation. This includes the hypothalamic-pituitary-adrenal axis, the adrenergic nervous system and the renin-angiotensin-aldosterone system (RAAS) whose effector hormones can be cytotoxic (23-27). The hyperadrenergic state, which accompanies bodily injury (eg, subarachnoid hemorrhage, acute myocardial infarction, burns and trauma), leads to catecholamine-mediated EICA, which importantly includes the accumulation of Ca^{2+} in subsarcolemmal mitochondria. The ensuing dysfunction of these Ca^{2+}-overloaded mitochondria, coupled with diminished synthesis of high-energy phosphate and their structural degeneration, leads to cardiomyocyte necrosis. The adverse consequences of elevated plasma adrenaline levels (eg, 5000 pg/mL) have been well described (27-31). Excess catecholamine levels also accompany marked emotional and/or physical stress and lead to stress-related apical ballooning or Takotsubo cardiomyopathy (32).

Isoproterenol was used to address the cytotoxicity associated with hyperadrenergic states. Myosin labelling of cells was demonstrated within 2 h of isoproterenol treatment (27) using a monoclonal antibody to cardiac myosin, which enters cardiomyocytes through their hyperpermeable membrane when cell death is imminent. Cells residing within the endomyocardium of the left ventricular (LV) apex were particularly vulnerable to necrosis. More recently, a mitochondriocentric pathway was identified, leading to cardiomyocyte necrosis following isoproterenol treatment (33), in which EICA and oxidative stress were self-evident in cardiomyocytes harvested from the LV apex (vis-à-vis the equator or base). These findings were interpreted to be in keeping with the increased density of β1 receptors reported at this site and the known apical to basal activation of the LV where blood is propelled from the apex toward the base and out into the aorta in a peristaltic-like manner (34-36).

$[Ca^{2+}]_i$ overloading involving subsarcolemmal mitochondria is the signal that drives the MSTE pathway to cardiomyocyte necrosis during the acute hyperadrenergic state (Figure 1). The transducer induces oxidative stress, which is invoked in response to EICA, in which the rate of ROS and reactive nitrogen species generation overwhelms their rate of elimination by endogenous antioxidant defenses. Finally, the effector to this pathway is represented by mPTP opening, with consequent solute entry, osmotic swelling and organellar dysfunction with structural degeneration and cell death.

Other pathophysiological responses that accompany catecholamine excess have also proven to be cytotoxic. These include a contemporaneous dyshomeostasis of essential cations manifested as hypokalemia, ionized hypocalcemia and hypomagnesemia (37). The shift in electrolytes from blood to soft tissues accounts for these aberrations and, in turn, invoke secondary hyperparathyroidism (SHPT). The parathyroid glands' elaboration of the calcitropic parathyroid hormone (PTH) seeks to restore Ca^{2+} homeostasis through bone mineral resorption (Figure 2). Acute stressor states are accompanied by plasma-ionized hypocalcemia with elevations in plasma PTH, in which the severity of injury and extent of the catecholamine response directly correlate with the fall in ionized hypocalcemia and corresponding risk of adverse cardiovascular events (38-48). Elevated PTH levels, however, promote $[Ca^{2+}]_i$ overloading, especially 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 increase the opening potential of their inner membrane-bound mPTP (Figure 1). 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 confirming cardiomyonecrosis.

Chronic stressor states

The secondary aldosteronism of CHF, a chronic stressor state, leads to increased fecal and urinary Ca^{2+} excretion and consequent ionized hypocalcemia with elevated plasma PTH levels (Figure 2) (49-53). A dyshomeostasis of divalent cations is found in patients hospitalized with decompensated biventricular failure with a dilated cardiomyopathy of ischemic or nonischemic origin. This cation-hormone profile is also found in patients with primary aldosteronism (54-57), in whom aberrations in serum ionized and total Ca^{2+}, together with elevated PTH levels, are normalized by either a spironolactone – an aldosterone receptor antagonist – or adrenal surgery (56,57). Furthermore, elevated PTH levels serve as an endogenous stimulus to adrenal aldosterone production, and can further account for contemporaneous elevated plasma aldosterone levels. In patients with primary hyperparathyroidism, preoperative PTH levels in excess of 100 ng/mL are independent predictors of abnormal elevations in plasma aldosterone levels (58). However, the relative importance of PTH-mediated $[Ca^{2+}]_i$ overloading and induction of oxidative stress as major pathogenic

events accounting for cardiomyocyte necrosis as contrasted with elevations in circulating aldosterone, per se, remain unclear (59-61).

Abnormal elevations in serum PTH levels (>65 pg/mL) serve as a potent mediator of EICA in cardiomyocytes and mitochondria (59,62,63). They are found in patients hospitalized with decompensated heart failure and those awaiting cardiac transplantation (49,53,64,65), and serve as an independent predictor of CHF and the need for hospitalization (66-68). Moreover, they have been shown to be an independent risk factor for mortality and cardiovascular events in community-dwelling individuals (69-71). SHPT is especially prevalent in the African-American (AA) population with protracted (>4 weeks) decompensated biventricular failure, in which chronic elevations in plasma aldosterone levels contribute to CHF symptoms (53). SHPT is also related to the prevalence of hypovitaminosis D in the AA population; the increased melanin content in dark-skinned individuals serves as a natural sunscreen (53). Accordingly, the presence of hypovitaminosis D, often of marked severity (<20 ng/mL), compromises Ca^{2+} homeostasis, predisposing the AA population to ionized hypocalcemia and consequent SHPT (53,72,73). Vitamin D deficiency is also common in Caucasian and Asian people with heart failure whose effort intolerance promotes an indoor lifestyle (66,74-76).

Other factors that may be associated with compromised Ca^{2+} stores and contribute to the appearance of SHPT, especially in AA individuals with CHF, have been reviewed elsewhere (77). In brief, these include a high-salt diet and consequential hypercalciuria, which predisposes to ionized hypocalcemia and SHPT with bone resorption. Osteopenia and osteoporosis are the adverse outcomes of chronic SHPT; they predispose to atraumatic bone fractures (78,79). 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 (49,64,80-84). The risk of such fractures is further increased in elderly patients with heart failure receiving a loop diuretic, in which hypercalciuria is also contributory, but preventable, when given in combination with spironolactone (85-87).

Summary

Elevations in serum troponin levels – biomarkers of cardiomyocyte necrosis – not due to ischemia-mediated myocardial infarction are found in patients hospitalized with acute or chronic stressor states and are associated with increased in-hospital and overall cardiac mortality (13-22). The role of EICA and oxidative stress induced by neurohormonal activation, which includes the calcitropic hormones, catecholamines and PTH, in promoting necrosis is now evident. An ongoing loss of cardiomyocytes undoubtedly contributes to the progressive nature of heart failure (the heart is a postmitotic organ with a fixed number of these cells).

A progressive downward spiral, in which homeostasis begets dyshomeostasis at the organ, cellular and subcellular levels leading to cardiomyocyte necrosis is depicted in Figure 3. The cycle begins with heart failure and reduced renal blood flow leading to the homeostatic activation of the RAAS. Ionized extracellular hypocalcemia appears to result from 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 SHPT with increased level of circulating PTH. The dyshomeostatic response to SHPT is PTH-mediated $[Ca^{2+}]_i$ overloading, wherein induction of oxidative stress follows with the generation of ROS and reactive nitrogen species. Together, $[Ca^{2+}]_i$ overloading and oxidative stress contribute to the pathological opening of the mPTP and activation of cyclophilin D with ensuing osmotic injury to mitochondria and, ultimately, necrotic cell death.

DEFICIENT ANTIOXIDANT RESERVES

Singal and Kirshenbaum (88), Dhaliwal et al (89), and Kirshenbaum and Singal (90) emphasized the importance of a deficiency in antioxidant reserves as being contributory to the imbalance in the

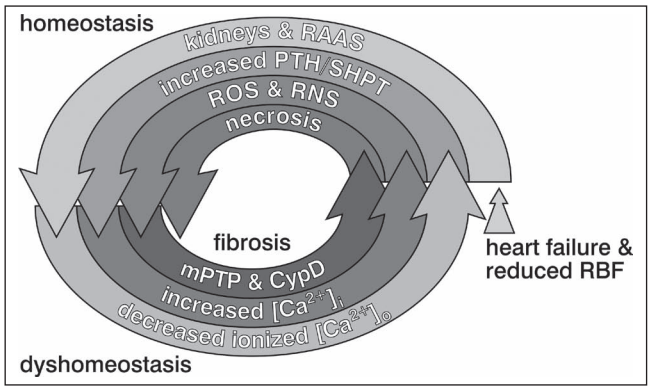

Figure 3) *Homeostasis gone awry begets dyshomeostasis leading to cardiomyocyte necrosis and myocardial fibrosis. $[Ca^{2+}]_i$ Intracellular calcium; $[Ca^{2+}]_o$ Extracellular calcium; CypD Cyclophilin D; mPTP Mitochondrial permeability transition pore; PTH Parathyroid hormone; RAAS Renin-angiotensin-aldosterone system; RBF Renal blood flow; RNS Reactive nitrogen species; ROS Reactive oxygen species; SHPT Secondary hyperparathyroidism. Reproduced with permission from reference 119*

prooxidant to antioxidant ratio leading to cardiomyocyte necrosis, which accompanies neurohormonal activation. In aldosteronism with CHF, together with increased urinary and fecal losses of K^+, Ca^{2+} and Mg^{2+}, there is a simultaneous cellular and subcellular dyshomeostasis of Zn^{2+} with resultant hypozincemia (91,92). Accompanying Zn^{2+} deficiency compromises the activity of Cu/Zn superoxide dismutase – an important metalloenzyme that serves as an antioxidant. Urinary Zn^{2+} excretion is also increased in response to an angiotensin-converting enzyme inhibitor or an angiotensin receptor antagonist, commonly used in the management of CHF; hypozincemia can be associated with abnormalities in taste (or dysgeusia) (93,94). Furthermore, serum Zn^{2+} and Se^{2+} levels are reduced in AA patients (51,52) including those with decompensated failure and compensated failure, as well as those with heart disease without heart failure. Intricate interactions between antioxidants, Zn^{2+} and Se^{2+}, and Zn^{2+} with prooxidant Ca^{2+}, have also been noted (63,95). Underlying causes for the simultaneous deficiencies of these divalent cations in AA patients, including inadequate dietary intake, remain to be investigated.

Zn^{2+} dyshomeostasis

The prooxidant effect representing $[Ca^{2+}]_i$ overloading that accompanies elevations in either plasma catecholamines or PTH levels is intrinsically coupled to Zn^{2+} entry, which acts as an antioxidant (62,63,96,97). Although less robust, Zn^{2+} entry is known to occur via L-type Ca^{2+} channels, whereas more substantive amounts enter via Zn^{2+} transporters activated by oxidative stress. Increased cytosolic-free intracellular zinc $[Zn^{2+}]_i$ also occur via release of inactive Zn^{2+} bound to metallothionein-1 induced by nitric oxide derived from nitric oxide synthase. Elevations in $[Zn^{2+}]_i$ can also be achieved via a $ZnSO_4$ supplement (3,62,97-102). Increased cytosolic-free $[Zn^{2+}]_i$ activates its sensor, metal-responsive transcription factor 1 which, on its translocation to the nucleus, upregulates the expression of antioxidant defense genes. These observations raise the therapeutic prospect that cation-modulating nutriceuticals capable of favourably influencing the $[Ca^{2+}]_o$, $[Ca^{2+}]_i$ and Zn^{2+} equilibrium, enhancing overall antioxidant capacity, could prove pivotal to combating oxidative injury and cardiomyocyte necrosis while promoting Zn^{2+}-based cardioprotective potential.

Se^{2+} dyshomeostasis

Se^{2+} is a cofactor of metalloenzyme-based antioxidants, such as glutathione-peroxidase and thioredoxin reductase, each of which promote optimal antioxidant/oxidant balance at the cellular and subcellular levels (103). Monitoring serum Se^{2+} and Se^{2+}-dependent enzyme activities could be useful in addressing optimal Se^{2+} status and

the need for Se^{2+} supplementation (104,105). Appearance of a dilated cardiomyopathy has been reported in populations in whom dietary Se^{2+} deficiencies are found, such as in the Se^{2+}-poor soil of the Keshan Province of China, or when parenteral nutrition is deficient in Se^{2+} (106-108). The Se^{2+}-deficiency-induced cardiomyopathy is often reversible with Se^{2+} supplementation (109).

MITOCHONDRIA-TARGETED ANTIOXIDANTS

Quercetin and cyclosporine A

Our previous studies indicated that the MSTE pathway leading to necrotic cell death during either isoproterenol administration or chronic aldosterone/salt treatment (ALDOST) includes intramitochondrial Ca^{2+} overloading, together with induction of oxidative stress and opening of the mPTP. To further validate this concept, we hypothesized that the mitochondria-targeted interventions would be cardioprotective. Accordingly, eight-week-old male Sprague-Dawley rats receiving four weeks of ALDOST were cotreated with either quercetin, a flavonoid with mitochondrial antioxidant properties, or cyclosporine A, an mPTP inhibitor, and compared with ALDOST alone or untreated age/sex-matched controls. Compared with controls, the following results were obtained in the rats treated with ALDOST: a marked increase in mitochondrial H_2O_2 production and 8-isoprostane levels, an increased propensity for mPTP opening, and greater concentrations of mitochondrial-free calcium $[Ca^{2+}]_m$ and total tissue Ca^{2+}, coupled with a five-fold rise in collagen volume fraction without any terminal deoxynucleotidyl-transferase-mediated dUTP nick-end labelling (TUNEL)-based evidence of cardiomyocyte apoptosis. Each of these pathophysiological responses to ALDOST were prevented by quercetin or cyclosporine A cotreatment (110). Thus, mitochondria play a central role in initiating the cellular-subcellular pathway that leads to necrotic cell death and myocardial scarring. This destructive cycle can be interrupted, and myocardium salvaged with its structure and function preserved by mitochondria-targeted cardioprotective strategies.

Carvedilol and nebivolol

Using cardiomyocytes and subsarcolemmal mitochondria (SSM) harvested from rats receiving four weeks of ALDOST, major components of the MSTE pathway to necrosis were identified. Mitochondria-targeted pharmaceutical interventions were used as cardioprotective strategies using four weeks cotreatment with either carvedilol (Carv) or nebivolol (Nebiv). Compared with controls, the following results were obtained in the rats treated with ALDOST: elevated levels of cardiomyocyte-free $[Ca^{2+}]_i$ and SSM-free $[Ca^{2+}]_m$; increased H_2O_2 production and 8-isoprostanes in SSM, increased cardiac tissue and plasma levels; and enhanced opening of mPTP and myocardial scarring. Overall, antioxidant capacity was augmented by increased levels of cytosolic-free $[Zn^{2+}]_i$. Cotreatment with either Carv or Nebiv attenuated $[Ca^{2+}]_i$ and $[Ca^{2+}]_m$ overloading, prevented oxidative stress and reduced mPTP opening, while further enhancing $[Zn^{2+}]_i$ and conferring cardioprotection. Thus, major components of the MSTE pathway to cardiomyocyte necrosis seen with ALDOST include $[Ca^{2+}]_i$ overloading coupled with oxidative stress and mPTP opening. This subcellular pathway can be favourably regulated by Carv or Nebiv cotreatment to salvage cardiomyocytes and prevent fibrosis (111).

Summary

The prooxidant pathophysiological scenario anticipates assertions to whether the ensuing adverse consequences are the result of excessive generation of prooxidants, compromised endogenous antioxidant defenses, or both. Clearly, deficiencies of Zn^{2+} and Se^{2+} can be counterproductive to metal-dependent antioxidant enzymes. Zn^{2+} supplementation, as an antioxidant, has shown promise in enhancing antioxidant defenses and serving as a cardioprotective strategy in rodents receiving ALDOST or having streptozocin-induced diabetes (62,97,98,112). A polynutrient supplement, which includes Ca^{2+}, Mg^{2+}, Zn^{2+} and Se^{2+}, together with a vitamin D supplement, however, will likely be necessary to address the contemporaneous dyshomeostasis of these cations. Promising results with a polynutrient supplement have been reported in critically ill patients including those with heart failure (113-117).

SUMMARY AND CONCLUSIONS

Acute and chronic stressor states are each accompanied by neurohormonal activation that include the adrenergic nervous system and RAAS. The ensuing hyperadrenergic state and SHPT provoke cardiomyocyte Ca^{2+} overloading, including $[Ca^{2+}]_i$ and $[Ca^{2+}]_m$ of SSM, with mitochondria-based induction of oxidative stress and opening of their inner membrane-bound mPTP representing the major components of the MSTE pathway to organellar degeneration and cardiomyocyte necrosis. The release of troponins from nonischemic necrotic cardiomyocytes causes elevated serum troponin levels and a wound healing response leading to foci of microscopic scarring. The ongoing nature of the necrosis accounts for scarring to be scattered throughout the endomyocardium of the LV, especially its apex. The loss of cardiomyocytes and their replacement by fibrous tissue contributes to the progressive nature of failure. Fibrosis is a major component of the adverse structural remodelling of the failing myocardium.

Further adverse events, orchestrated by neurohormonal activation, are the coordinated translocation of cations to injured tissues. This facilitates the concordant appearance of hypokalemia, ionized hypocalcemia and hypomagnesemia, hypozincemia and hyposelenemia. Intracellular cationic shifts adaptively regulate the equilibrium between prooxidants and antioxidants – a critical determinant of myocardial cell survival. The intrinsically coupled dyshomeostasis of Ca^{2+} and Zn^{2+}, representing prooxidant and antioxidant, respectively, can be pharmacologically uncoupled in favour of increased $[Zn^{2+}]_i$ and enhanced antioxidant defenses. In doing so, cardiomyocytes susceptible to necrotic cell death can be rescued. The use of nutriceuticals to achieve these goals should be considered as complementary strategies to the current standard of care based on pharmaceuticals.

NOTE: This work was supported, in part, by National Institutes of Health grants R01-HL73043 and R01 HL90867 (KTW). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health. The authors have no conflicts of interest to declare.

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