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Review Article

Role of Intracellular Ca^{2+}-overload in Cardiac Dysfunction in Heart Disease

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Abstract

Various heart diseases such as genetically-determined heart failure, acute myocardial infarction, ischemia-reperfusion injury and catecholamine-induced cardiomyopathies are associated with cardiac dysfunction, cellular damage, subcellular derangements and metabolic alterations. Since increase in myocardial Ca^{2+} is accompanied by these abnormalities, it is generally held that intracellular Ca^{2+}-overload plays an important role in the pathogenesis of cardiac dysfunction as well as cellular and metabolic defects in different cardiovascular diseases. This view is supported by observations in hearts subjected to Ca^{2+}-paradox, where reperfusion of Ca^{2+}-free perfused hearts with Ca^{2+}-containing medium was found to produce a marked increase in myocardial Ca^{2+}-content, cellular damage and cardiac contracture. The intracellular Ca^{2+}-overload in the heart has also been shown to produce mitochondrial Ca^{2+}-overload, depress ATP production, release different toxic substances and induce cardiomyocyte apoptosis. By virtue of its ability to depress cardiac gene expression and increase proteolysis of sarcolemma (SL) sarcoplasmic reticulum (SR) and myofibrils (MF), the intracellular Ca^{2+}-overload has been reported to reduce SL, SR and MF protein content and activities. Such remodeling of subcellular organelles is associated with dramatic alterations in Ca^{2+} -handling by SL and SR membranes as well as interaction of Ca^{2+} with MF for the impairment of cardiac function. Thus, it is evident that mitochondrial Ca^{2+}-overload, and subcellular remodeling for Ca^{2+}-handling defects are responsible for the occurrence of cardiac dysfunction, metabolic derangements and cellular damage during the development of heart disease.

Keywords: calcium overload; gene expression; sarcoplasmic reticulum; sarcolemma; myofibrils; subcellular organelles.

Short Title: Myocardial Ca^{2+} and Cardiac Function

Introduction

It is now well known that cardiac contraction and relaxation processes are determined by the coordinated functions of different subcellular organelles including sarcolemma (SL), sarcoplasmic reticulum (SR), mitochondria (MT) and myofibrils (MF) [1-6]. The SL proteins such as voltage-sensitive Ca^{2+}-channels, store-operated Ca^{2+}-channels, Na^{+}- Ca^{2+} exchanger and Na^{+}- K^{+} ATPase as well as SR proteins including Ca^{2+}-release channels (ryanodine receptors) and Ca^{2+}-pump ATPase play an essential role in the entry and regulation of Ca^{2+} in cardiomyocytes. On the other hand, MF Ca^{2+}-stimulated ATPase and MT oxidative phosphorylation are involved in the generation of contractile force and ATP production, respectively. It is noteworthy to point out that Ca^{2+} is not only essential for determining the status of cardiac contractile function, but is also intimately involved in the maintenance of membrane permeability, cellular integrity, and cardiac gene expression [3,7-9]. Furthermore, various vasoactive hormones including catecholamines and angiotensin II have been demonstrated to exert marked effects on Ca^{2+}-transport activities in cardiomyocytes [4,10,11]. Thus, defects in any of the components of subcellular organelles can be seen to induce Ca^{2+}-handling abnormalities and contractile dysfunction of the heart [3,9].

Since the identification of Ca^{2+}-overload as a new principle for the pathophysiology of cardiac dysfunction [12-14], several diseases including cardiomyopathies due to high levels of circulating catecholamines [15-20], genetically-determined heart failure [21-25] as well as ischemic heart disease (acute myocardial infarction [26-30] and ischemia-reperfusion injury [31-35]) have been shown to be associated with the development of intracellular Ca^{2+}-overload. It is generally assumed that impaired cardiac performance and functional derangement of subcellular organelles in different diseases are the consequence of intracellular Ca^{2+}-overload. It should also be pointed out that there are other pathophysiologic mechanisms including oxidative stress and myocardial inflammation, which have been proposed to induce cardiac dysfunction and cellular abnormalities during the development of heart disease [36-40]. However, in this article we have attempted to highlight the evidence that intracellular Ca^{2+}-overload plays a critical role in the genesis of metabolic and cellular defects as well as subcellular remodeling for the development of cardiac dysfunction in the heart. Furthermore, the present review is focussed on discussion of events for the occurrence of

intracellular Ca^{2+}-overload in cardiomyocytes and its consequences for inducing myocardial abnormalities.

Mechanisms for the Development of Intracellular Ca^{2+}-overload

Although high levels of circulating catecholamines are known to produce intracellular Ca^{2+}-overload, several mechanisms have been proposed to underlie this phenomenon [9,16,18,20]. These include activation of both α-and β-adrenoceptors, stimulation of SL Ca^{2+}-channels, depression in SL Na^+-Ca^{2+}-exchanger and SL Ca^{2+}-pump ATPase as well as oxidation of catecholamines and formation of oxyradicals. It is pointed out that interventions which reduce the entry of Ca^{2+} as well as prevent the oxidation of catecholamines and development of oxidative stress have been shown to attenuate the catecholamine-induced intracellular Ca^{2+}-overload [9,12,16,18]. Furthermore, the occurrence of intracellular Ca^{2+}-overload in genetically-determined cardiomyopathy has been attributed to the activation of sympathetic nervous system and increase in Ca^{2+}-influx as well as the depression of SL Na^+-K^+ ATPase and increase in intracellular Na^+ [9,21]. Agents such as Ca^{2+}-antagonists which prevent the entry of Ca^{2+} in the heart have been reported to exert beneficial effects in cardiomyopatheic animals by reducing the development of intracellular Ca^{2+}-overload [9,22,25].

Several studies have been conducted to demonstrate mechanisms for the occurrence of intracellular Ca^{2+}-overload due to acute coronary occlusion as well as ischemia-reperfusion injury [9,27,28,30, 33-35]. It has been shown that the lack of oxygen in the ischemic myocardium results in acidification of the cytoplasm which promotes SL Na^+-H^+ exchange and subsequent entry of Ca^{2+} upon stimulation of Na^+-Ca^{2+} exchange system. Lack of oxygen is also known to increase membrane permeability for Ca^{2+} due to incorporation of free fatty acids and other lipid metabolites in the SL membrane. On the other hand, ischemia-reperfusion injury has been associated with the release of norepinephrine from the adrenergic nerve endings for increasing the entry of Ca^{2+} in addition to promoting the development of oxidative stress. These changes are known to cause the occurrence of intracellular Ca^{2+}-overload as a consequence of their dramatic effects on the SL membrane [9,27,33,37,38]. Several other vasoactive interventions and proinflammatory agents have also been shown to produce Ca^{2+}-handling abnormalities in cardiomyocytes [39,40]. It may be noted that reperfusion of the Ca^{2+}-depleted heart with Ca^{2+} containing medium has been shown to exhibit Ca^{2+}-paradox and provide a direct evidence for the occurrence of intracellular Ca^{2+}-overload [9, 41-44]. A massive increase in myocardial Ca^{2+}content due to stimulation of Na^+-Ca^{2+} exchanger in this experimental model was shown to be prevented when perfusion of the heart with Ca^{2+}-free medium was carried out in the presence of low Na^+ [42,43]. High concentrations of Ca^{2+}-antagonists were also found to attenuate the increase in myocardial Ca^{2+} in the Ca^{2+}-paradoxic heart by their action on the SL Na^+-Ca^{2+} exchange activity [44]. Thus, the Ca^{2+}-paradoxic heart is considered to form an excellent model for studying the effects of intracellular Ca^{2+}-overload [42,43].

Cardiac Dysfunction and Cellular Damage

Reperfusion of the Ca^{2+}-depleted hearts with Ca^{2+}-containing medium was found to result in loss of contractility, development of contracture, damage to ultrastructure and leakage of intracellular enzymes from the myocardium [41, 45-48]. The paradoxical effects of Ca^{2+}-deprived hearts were reported to occur in different species [49] and were similar to those seen during the development of oxygen- paradox in normal hearts [50]. The Ca^{2+}-paradox phenomenon was shown to be associated with irreversible changes in the surface electrical activity [41] and a marked increase in the left ventricular end-diastolic pressure (LVEDP) [41,42,51-53]. The occurrence of intracellular Ca^{2+}-overload and the increase in LVEDP (Table 1) as well as the development of cardiac contracture in the Ca^{2+}-paradoxic heart were found to be dependent upon the concentration of Ca^{2+} in the reperfusion medium [42,53,54

$[Ca^{2+}]$ mM	Increase in LVEDP (mmHg)	Myocardial Ca^{2+} Content (µmol/g dry heart wt)
Control	6.8±0.41	3.7±0.39
0	29.3±2.0*	2.6±0.18*
0.03	32.2±1.9*	-
0.05	-	4.5±0.49
0.1	60.7±4.3*	6.9±0.63*
0.25	-	7.2±0.46*
0.3	85.3±6.5*	-
1.00	-	13.2±1.07*
1.25	78.5 ±5.1*	17.6±0.44*

LVEDP in hearts before initiating Ca^{2+}-free perfusion varied between 6 to 8 mmHg. Control hearts were perfused with normal medium containing 1.25 mM Ca^{2+} for 35 min without subjecting to Ca^{2+}-free medium preperfusion. Data taken from our papers: Alto LE and Dhalla NS, Am J Physiol - Heart Circ Physiol. 237:713-719, 1979; Ozcelikay TA, Chapman D, Elimban V and Dhalla NS, Curr Res Cardiol 1:13-16, 2014. *Significantly ($P < 0.05$) different from control.

Table 1: Effect of 30 min perfusion with medium containing different concentrations of Ca^{2+} on myocardial Ca^{2+} content and left ventricular end diastolic pressure (LVEDP) in hearts preperfused for 5 min with Ca^{2+}-free medium.

Although some investigators failed to demonstrate Ca^{2+}-paradox associated changes in isolated cardiomyocytes [55], others have shown these alterations upon successive exposure of cardiomyocytes to Ca^{2+}-free medium and Ca^{2+}-containing medium [48, 56-58]. Nonetheless, ischemic preconditioning has been observed to attenuate the Ca^{2+}-paradox associated increase in LVEDP, depression in the left ventricular developed pressure and leakage of myoglobin from the heart [59]. The presence of low Na^+ during perfusion of the heart with Ca^{2+}-free medium

was also found to prevent the development of cardiac dysfunction and the occurrence of intracellular Ca^{2+}-overload upon reperfusion [41-43].

The ultrastructural changes in the Ca^{2+}-deprived and reperfused hearts included swelling of mitochondria and sarcotubular system, occurrence of contractile bands, and partial separation of the intercalated disc as well as basement membrane from sarcolemma [41,43,45,60]. The alterations in ultrastructure of the myocardium were dependent upon the concentration of Ca^{2+} in the reperfusion medium [41,60] and were attenuated by reducing the concentration of Na^{+} during the Ca^{2+}-free perfusion phase [41]. These ultrastructural changes are similar to those seen in the ischemic heart disease [27-28] and may be a consequence of increased activities of cardiac lysosomal hydrolases [61], different intracellular proteases [35] and phospholipases [62]. Although the occurrence of autophagy has been reported in ischemia-reperfused hearts and myocardial infarction [27,28], no information regarding autophagic changes in the Ca^{2+}-paradoxic heart is available at present. It is pointed out that the activation of NFκB and increased production of TNF-α have also been reported to cause cardiac injury due to intracellular Ca^{2+}-overload [63]. Furthermore, the occurrence of cell death (apoptosis) in the Ca^{2+}-paradox heart has been associated with the activation of mitogen-activated protein kinases (p38 and ERK) as well as different apoptotic signal transduction pathways [64]. Thus, the development of cardiac dysfunction and cellular damage due to intracellular Ca^{2+}-overload appears to be occurring as a consequence of complex and diverse mechanisms.

Mitochondrial Ca^{2+}-overload and Energy Depletion

It is now well known that intracellular Ca^{2+}-overload in the heart results in the development of mitochondrial Ca^{2+}-overload and defects in energy production [9,47,65]. Although low concentrations of Ca^{2+} are required for the stimulation of mitochondrial oxidative phosphorylation, high concentrations of Ca^{2+} have been shown to impair the mitochondrial function for ATP production [9,53,65, 66]. Perfusion of hearts with Ca^{2+}-free medium followed by reperfusion with Ca^{2+}-containing medium for the induction of intracellular Ca^{2+}-overload was found to be associated with depressed mitochondrial state 3 respiration, respiratory control index, ADP/O ratio and oxidative phosphorylation without any changes in state 4 respiration [53,67]. These alterations were prevented when the reperfusion was carried out at low concentrations (0.1-0.5 mM) of Ca^{2+} but were not affected by different antioxidants [55]. The impaired mitochondrial function in the Ca^{2+}-paradoxic heart has been associated with elevated levels of citric acid cycle intermediates and is considered to be due to defects in mitochondrial membrane potentials [68,69].

A dramatic decrease in high -energy phosphate stores in the heart has been shown to occur upon the induction intracellular Ca^{2+}-overload [67,70,71]. It may be noted that Ca^{2+}-binding and Ca^{2+}-uptake activities of mitochondria, isolated from the Ca^{2+}-paradoxic hearts, were found to be increased [72]. Such a change in the mitochondrial Ca^{2+}-transport activity was suggested to contribute towards the occurrence of mitochondrial Ca^{2+}-overload as it was attenuated when the perfusion with Ca^{2+}-free medium was carried out in the presence of low Na^{+} [72]. It is also pointed out that mitochondrial Ca^{2+}-overload may release several cytotoxic substances, which may also serve as signals for inducing apoptosis in the Ca^{2+}-paradoxic hearts [64]. Thus, it appears that mitochondrial Ca^{2+}-overload may be involved in cardiac dysfunction and cellular damage in the heart by depressing the high energy phosphate stores as well as inducing apoptosis in the myocardium. A schematic representation of these events is shown in Figure 1.

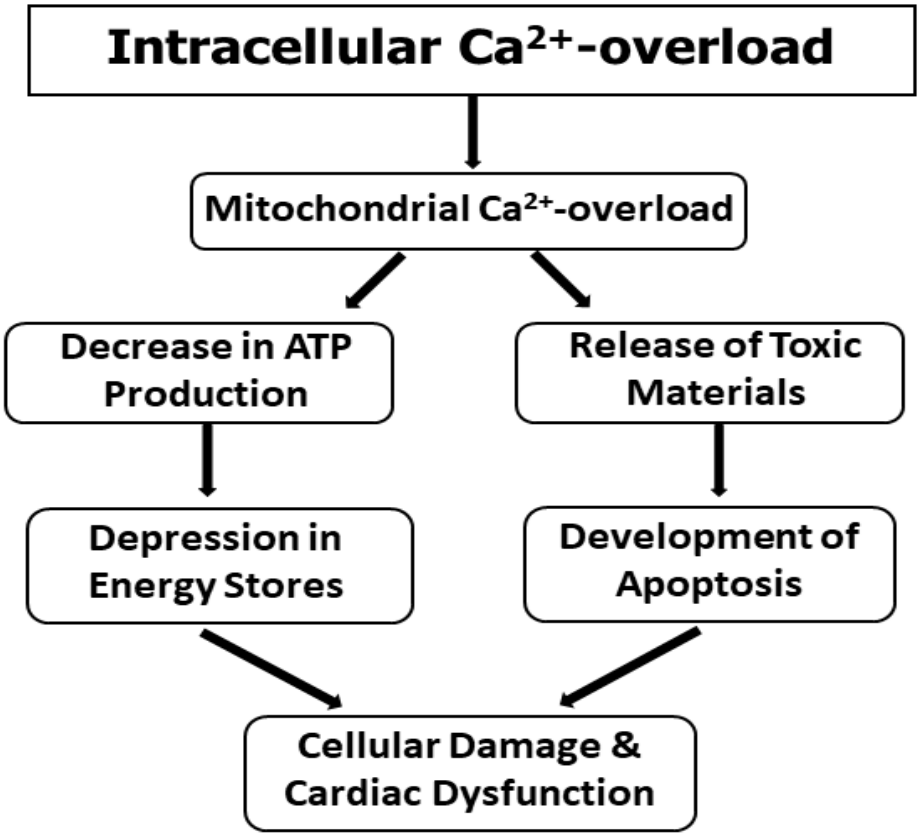

Figure 1: Schematic representation depicting events for the occurrence of cardiac dysfunction and cellular damage due to mitochondrial Ca^{2+}-overload in hearts subjected to intracellular Ca^{2+}-overload.

Subcellular Defects and Ca^{2+}-handling Abnormalities

While the SL membrane is concerned with influx and efflux of Ca^{2+} for maintaining Ca^{2+}-homeostasis in cardiomyocytes, the SR tubular system is involved in raising and lowering the concentration of Ca^{2+}, whereas the interaction of Ca^{2+} with MF proteins determines the contractile status of the myocardium [3,4]. Reperfusion of Ca^{2+}-deprived hearts with Ca^{2+}-containing medium has been shown to exert profound effects on the activities of different subcellular organelles (Table 2) [73-75].

Parameters	Control Hearts	Ca^{2+}- overload Hearts
SL Na^+-K^+ ATPase (μmol Pi/mg protein/hr)	26.4 ± 1.8	8.2 ± 0.6*
SL Na^+-Ca^{2+}- exchange (nmol Ca^{2+}/mg protein/ 2sec)	6.2 ± 0.21	2.6 ± 0.34*
SL Ca^{2+}-pump activity (nmol Ca^{2+}/mg protein/min)	12.4 ± 0.92	5.8 ± 0.44*
SR Ca^{2+}-uptake activity (nmol Ca^{2+}/mg protein/5 min)	269 ± 12.0	81 ± 6.0*
SR Ca^{2+}-stimulated ATPase (μmol Pi/mg protein/5min)	0.86 ± 0.10	0.21 ± 0.01*
MF Ca^{2+}-stimulated ATPase (μmol Pi/mg protein/hr)	12.08 ± 0.57	8.40 ± 0.22*
MF Mg^{2+}-stimulated ATPase (μmol Pi/mg protein/hr)	3.20 ± 0.25	7.21 ± 0.36*

Data are taken from papers: Makino N, Panagia V, Gupta MP, Dhalla NS, Circ Res 63:313-321, 1988; Alto LA, Dhalla NS, Circ Res 48:17-24, 1981; Kovacs A, Kalasz J, Pasztor ET et al. Mol Cell Biochem 430: 57-68, 2017. *_ $P < 0.05$ vs control.

Table 2: Effect of intracellular Ca^{2+}-overload on sarcolemmal (SL) and sarcoplasmic reticular (SR) membranes, as well as myofibrillar (MF) ATPase activities in perfused hearts

Depressions in the SL Na^+-K^+ ATPase, SL Na^+-Ca^{2+} exchanger and SL Ca^{2+}-pump ATPase activities in the Ca^{2+}-paradoxic heart can be seen to contribute towards the occurrence of intracellular Ca^{2+}-overload in cardiomyocytes [73,76,77]. These SL defects were attenuated when the perfusion with Ca^{2+}-free medium was carried out in the presence of low Na^+ (35mM) or at low temperature (21^0C) [42,78]. On the other hand, the density of SL Ca^{2+}-channels was increased upon subjecting the heart to Ca^{2+}-paradox and this change was also attenuated by carrying out the perfusion with Ca^{2+}-free medium in the presence of low Na^+ or at low temperature [79]. Furthermore, alterations in the SL membrane were also apparent because the activities of β-AR – G-protein – adenylyl cyclase complex were observed to be increased [80] and the activity of SL Ca^{2+}/Mg^{2+}-ecto ATPAse was decreased [81] in the Ca^{2+}-paradoxic heart. Although the status of SL store-operated Ca^{2+}-channels [6] in the Ca^{2+}-paradoxic heart has not be determined, their participation in inducing intracellular Ca^{2+}-overload cannot be ruled out at present.

The induction of Ca^{2+}-paradox in the heart upon perfusion with Ca^{2+}-free medium followed by Ca^{2+}-containing medium was seen to be associated with marked depression in the SR Ca^{2+}-uptake and release activities [72,74]. These changes in Ca^{2+}-handling by SR were dependent upon the concentration of Ca^{2+} in the reperfusion medium and were attenuated when the perfusion with Ca^{2+}-free medium was carried out in the presence of low Na^+ or at low temperature. Although MF Ca^{2+}-stimulated ATPase activity was not altered during the initial (5 min) reperfusion phases of Ca^{2+}-paradox development [67], reperfusion of Ca^{2+}-deprived hearts with Ca^{2+}-containing medium for 10 min was found to depress the MF Ca^{2+}-stimulated ATPase activity and increase the MF Mg^{2+}-ATPase activity [75]. These alterations were associated with degradation of MF α -myosin heavy chain and troponin T proteins in the Ca^{2+}-paradoxic hearts. The activation of proteases such as calpain by elevated levels of intracellular Ca^{2+} in cardiomyocytes is considered to be involved in alterations of the SL, SR and MF activities upon reducing their protein content [35]. These events for inducing subcellular defects due to the occurrence of intracellular Ca^{2+}-overload in the Ca^{2+}-paradoxic hearts are shown in Figure 2.

It should be recognized that Ca^{2+}-handling abnormalities in SL and SR due to intracellular Ca^{2+}-overload may also be induced by changes in the phospholipid composition of these membranes [62]. It is also noteworthy that similar Ca^{2+}-handling defects have also been observed in heart failure and ischemic heart disease [27, 28, 82-85].

Alterations in cardiac Gene Expression

In view of the role of cardiac gene expression in maintaining the function of different subcellular organelles in the heart [27,28, 85], it has been suggested that subcellular remodeling in the Ca^{2+}-paradoxic heart may be due to changes in gene expression for different subcellular proteins [9,73,74]. Accordingly, subcellular remodeling due to intracellular Ca^{2+}-overload may be occurring as a consequence of both the activation of calpain and the depression in mRNA levels for different cardiac genes (Figure 2).

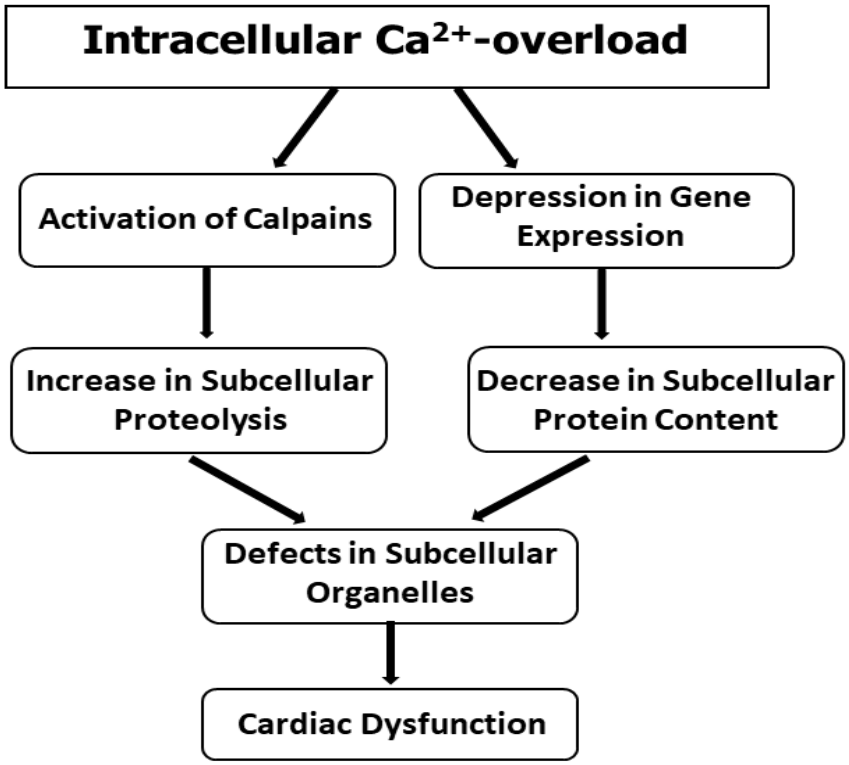

Figure 2: Development of cardiac dysfunction due to defects in subcellular organelles as a consequence of increased proteolysis and depressed gene expression in hearts subjected to intracellular Ca^{2+}-overload.

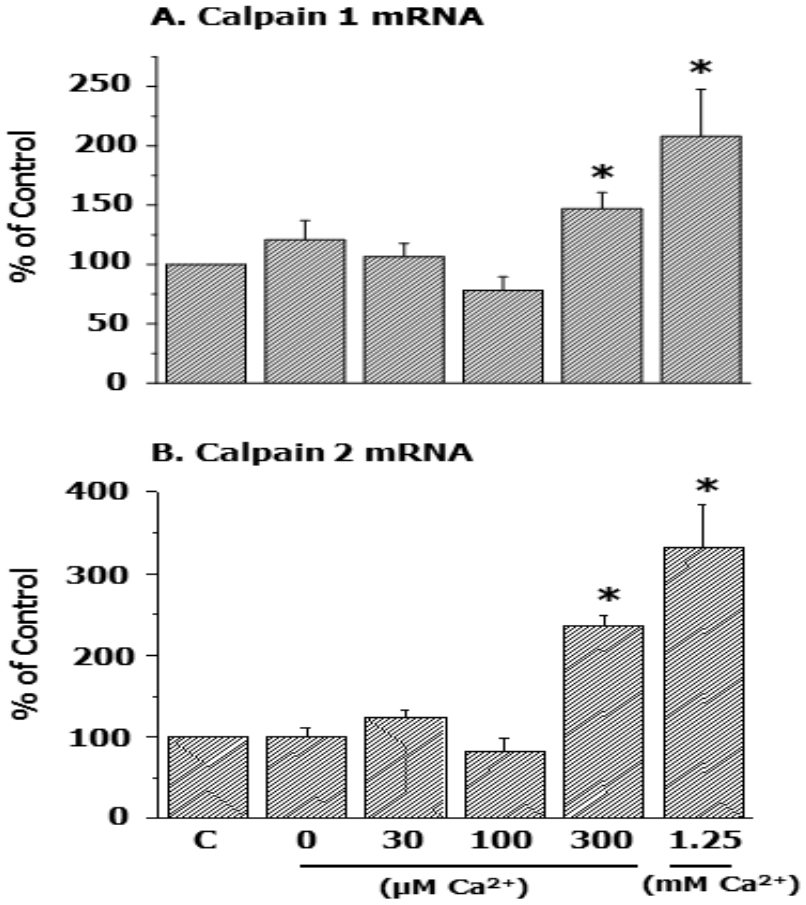

Figure 3: Dependence of changes in mRNA levels for calpain-1 and 2 upon Ca^{2+}concentrations in the reperfusion medium. These hearts were preperfused with Ca^{2+}-free medium for 5 min before reperfusion for 30 min. The data are taken from our paper Ozcelikay AT, Chapman D, Elimban V, Dhalla NS, Curr. Res. Cardiol.1:13-16, 2014. *_ P<0.05 vs control (C).

Furthermore, it was demonstrated that depressions in gene expression for SL Na^+-Ca^{2+} exchanger as well as different isoforms of SL Na^+- K^+ ATPase protein due to Ca^{2+}-paradox were dependent upon the concentration of Ca^{2+} in the reperfusion medium (Figure 4) [54].

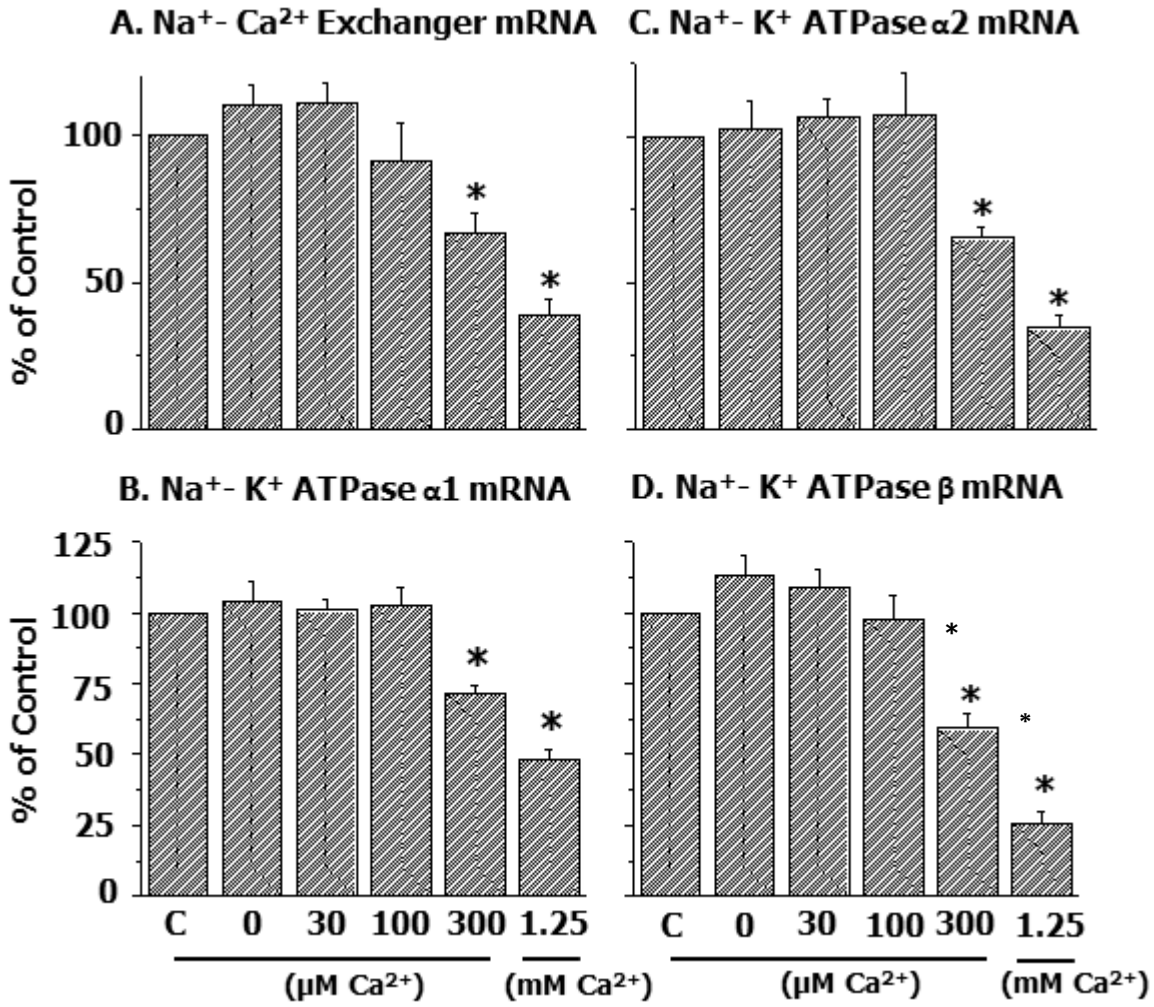

Figure 4: Dependence of changes in mRNA levels for sarcolemmal Na^+-Ca^{2+} exchanger and different isoforms of Na^+ K^+ ATPase upon Ca^{2+} concentrations in the reperfusion medium. These hearts were perfused for 5 min with Ca^{2+}-free medium before reperfusion for 30 min. The data are taken from our paper Ozcelikay AT, Chapman D, Elimban V, Dhalla

Likewise, alterations in mRNA levels for SR Ca^{2+}-pump protein and Ca^{2+}-release channels as well as MF α- and β- myosin proteins in the Ca^{2+}-paradoxic heart were observed to be dependent upon the concentration of Ca^{2+} in the reperfusion medium (Figure 5) [54].

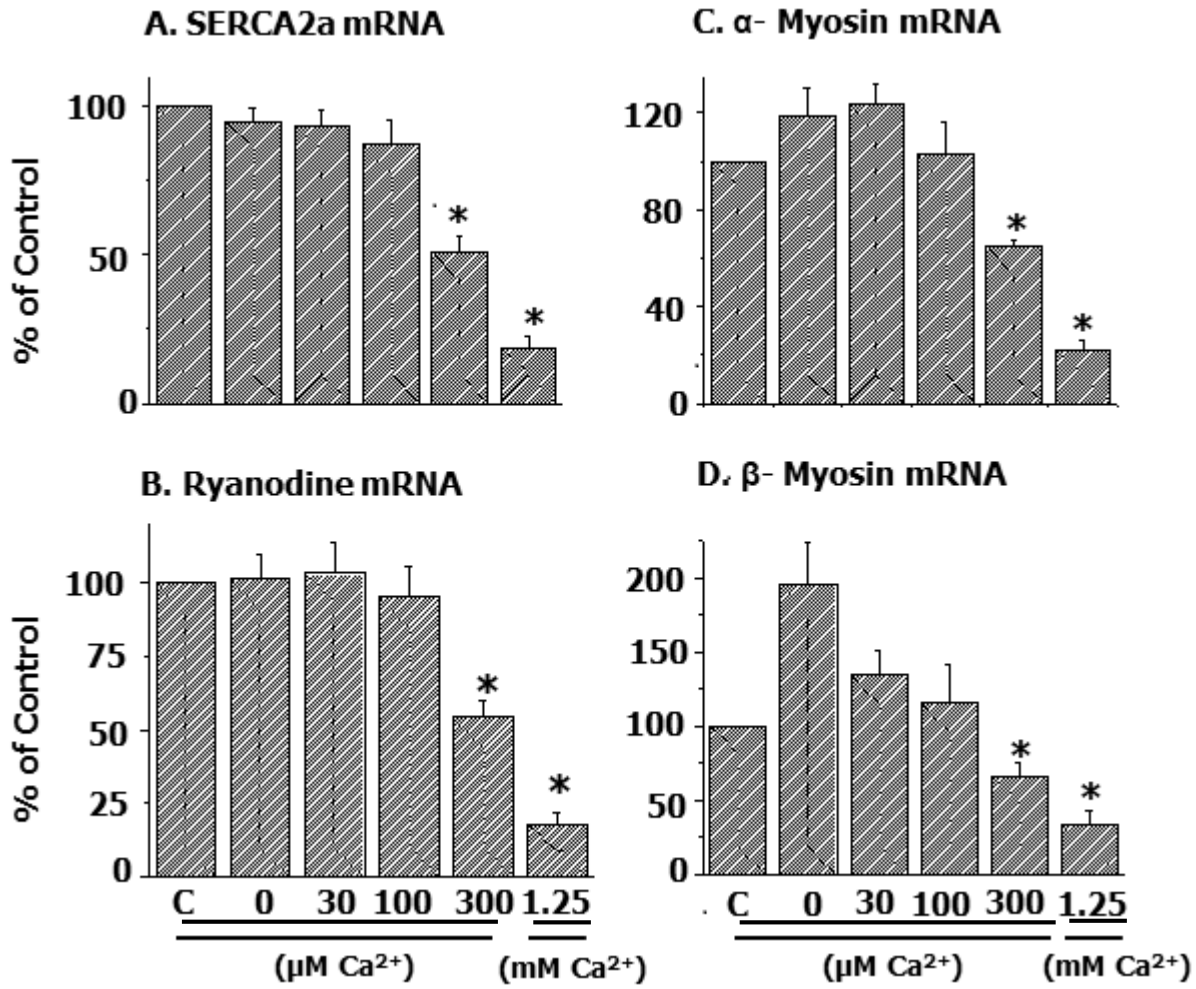

Figure 5: Dependence of changes in mRNA levels for sarcoplasmic reticular SERCA2a and ryanodine receptor (Ca^{2+}-release channel) as well as α- and β-myosin heavy chain upon Ca^{2+} concentrations in the reperfusion medium. These hearts were perfused with Ca^{2+}-free medium before reperfusion for 30min. The data are taken from our paper Ozcelikay AT, Chapman D, Elimban V, Dhalla NS, Curr. Res. Cardiol.1:13-16, 2014. *_ P<0.05 vs control (C).

These observations provide evidence for a defect in the formation of subcellular proteins resulting in subcellular remodeling due to intracellular Ca^{2+}-overload. Thus, cardiac genes can be seen as excellent molecular targets for the development of novel interventions for the improved therapy of heart disease.

Conclusion

From the forgoing discussion, it is evident that two major mechanisms, namely energy depletion due to mitochondrial Ca^{2+}-overload and subcellular remodeling due to increased proteolysis and reduced gene expression, are likely to explain the development of cellular damage, metabolic alterations and cardiac dysfunction due to intracellular Ca^{2+}-overload. It is emphasized that the occurrence of intracellular Ca^{2+}-overload in heart disease may become apparent due to increase in Ca^{2+} entry as a consequence of depressions in SL Na^{+}-K^{+} ATPase and Na^{+}-Ca^{+} exchange activities as well as increase in Ca^{2+}-channel density in the SL membrane. Depressions in SL Ca^{2+}-pump ATPase as well as SR Ca^{2+}-uptake and SR Ca^{2+}-release activities in heart disease can also be seen to participate in the development of intracellular Ca^{2+}-overload. Since the observed changes in subcellular Ca^{2+}- handling due to intracellular Ca^{2+}-overload are similar to those seen in failing hearts and thus may be responsible for the development of cardiac dysfunction in different types of heart types of heart disease. It may be noted that the SL and SR defects during the development of heart disease are also induced by prolonged exposure of the heart to elevated levels of vasoactive hormones such as catecholamine's and angiotensin II in the circulation. The accumulation of Ca^{2+} by mitochondria under conditions of intracellular Ca^{2+}-overload may be beneficial at initial stages but the resultant mitochondrial Ca^{2+}-overload can be seen to impair ATP production and promote the development of cellular damage. Thus, different interventions which can attenuate the Ca^{2+} entry into cardiomyocytes, reduce the occurrence of mitochondrial Ca^{2+}-overload, inhibit the activation of proteases and promote cardiac gene expression can be seen to exert beneficial effects in preventing the development as well as progression of heart disease.

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Conflict of Interest

The authors declare that there was no conflict of interest.

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