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Cardiac remodeling and subcellular defects in heart failure due to myocardial infarction and aging

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Abstract Although several risk factors including hypertension, cardiac hypertrophy, coronary artery disease, and diabetes are known to result in heart failure, elderly subjects are more susceptible to myocardial infarction and more likely to develop heart failure. This article is intended to discuss that cardiac dysfunction in hearts failing due to myocardial infarction and aging is associated with cardiac remodeling and defects in the subcellular organelles such as sarcolemma (SL), sarcoplasmic reticulum (SR), and myofibrils. Despite some differences in the pattern of heart failure due to myocardial infarction and aging with respect to their etiology and sequence of events, evidence has been presented to show that subcellular remodeling plays a critical role in the occurrence of intracellular Ca^{2+}-overload and development of cardiac dysfunction in both types of failing heart. In particular, alterations in gene expression for SL and SR proteins induce Ca^{2+}-handling abnormalities in cardiomyocytes, whereas those for myofibrillar proteins impair the interaction of Ca^{2+} with myofibrils in hearts failing due to myocardial infarction and aging. In addition, different phosphorylation mechanisms, which regulate the activities of Ca^{2+}-cycling proteins in SL and SR membranes as well as Ca^{2+}-binding proteins in myofibrils, become defective in the failing heart. Accordingly, it is suggested that subcellular remodeling involving defects in Ca^{2+}-handling and Ca^{2+}-binding proteins as well as their regulatory mechanisms is intimately associated with cardiac remodeling and heart failure due to myocardial infarction and aging.

Keywords Heart failure · Myocardial infarction · Aging heart · Cardiac remodeling · Subcellular gene expression · Ca^{2+}-handling abnormalities

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Heart failure is regarded as a major challenge for the health care system, as it encompasses high levels of morbidity and mortality [1]. The lifetime risk of developing heart failure is 1 in 5, and the long-term survival is relatively poor; up to one-third of those diagnosed die within the first 12 months, whereas only half of the patients survive the 5-year mark [2, 3]. It has also been reported that this disease currently affects more than 5.5 million Americans and is responsible for more than 700,000 deaths per year, costing the American economy $50 billion annually [4]. In view of the universal aging of the population at the present time, heart failure has become an escalating concern of epidemic proportion [4, 5]. It should be noted that heart failure is a multifactorial problem, and its causes include atherosclerosis, obesity, diabetes, hypertension, valvular defects, genetic cardiomyopathies, aging, and myocardial infarction [6–8]. In fact, several of these risk factors are known to interact with each other for the development of heart failure. For example, obesity has been reported to result in premature cardiac aging and thus contribute to an increased risk of heart failure [9]. Furthermore, hypertension due to hardening of the arteries during the aging process promotes the occurrence of heart failure in the aging population.

Because of the profound metabolic derangements in diabetic patients, diabetes is also seen to enhance the development of pump failure in the aging heart.

Aging itself has been documented to be a risk factor for heart failure [10]; however, it should be pointed out that elderly subjects are more susceptible to myocardial infarction and more likely to die due to the development of heart failure in comparison to younger subjects [11, 12]. The increase in the incidence of myocardial infarction with age is primarily due to the development of atherosclerosis. Age is also considered to increase the risk of mechanical complications of myocardial infarction in elderly patients possibly due to additional changes in myocardial substrate [13]. Despite the role of various risk factors including diabetes, atherosclerosis, and hypertension in predisposing the elderly subjects to heart failure, myocardial infarction is known to be a predominant factor affecting the aging heart. It is also emphasized that different aging animals have been reported to show clinical symptoms of heart failure, like those seen in chronic ischemic heart disease, without any evidence for these risk factors [14, 15].

Although impaired cardiac performance is the hallmark of heart failure [4, 16, 17], the exact mechanisms of cardiac dysfunction in the failing heart are not fully understood. Cardiac dysfunction due to myocardial infarction is considered to be the consequence of the loss of a portion of myocardium, formation as well as expansion of myocardial infarct, hormonal imbalance, myocardial hypertrophy, cardiac fibrosis, and ventricular dilatation [12]. On the other hand, heart failure due to aging is believed to be associated with cardiomyocyte hypertrophy due to increased hemodynamic load and neurohumoral factors, loss of cardiomyocytes due to necrosis and apoptosis, impaired autophagic process, and reduced cardiomyocyte renewal [12]. Nevertheless, it is now generally accepted that heart failure is essentially a result of cardiac remodeling [4, 6, 10, 17], which is intimately associated with remodeling of subcellular organelles such as sarcolemma (SL), sarcoplasmic reticulum (SR), mitochondria, myofibrils, and extracellular matrix [18–21]. Accordingly, it is intended to discuss some salient features of cardiac remodeling and subcellular defects in failing hearts due to myocardial infarction and aging. In view of the central role played by Ca^{2+} in cardiac function [18–22], this article will be focused to review the abnormalities in Ca^{2+}-handling and Ca^{2+}-interaction with some subcellular organelles in the failing heart.

Cardiac remodeling due to myocardial infarction

Heart failure is invariably preceded by cardiac hypertrophy which is an adaptive mechanism due to a wide variety of neurohumoral changes [5, 23–26]. Although cardiomyocyte hypertrophy is initially stimulated in response to mechanical alterations such as pressure or volume overload, various cytokines and hormones may also be involved in this process [27–29]. An increase in the mechanical load occurs when the heart experiences an insult and the contractile elements of the myocardium are lost or rendered dysfunctional [30]. Cardiac hypertrophy leading to dilatation is a common reaction to the hemodynamic overload imposed on the heart [21, 31] and is likely intended to promote efficient pumping by intensifying the number of cardiac contractile units, while decreasing the amount of wall stress concomitantly by augmenting the wall thickness of the myocardium [30]. Immediately following an ischemic episode, there is an acute loss of myocardial cells that leads to uncharacteristic loading conditions that result in the dilatation of the ventricular chamber with a transformation in shape to give a more spherical form [3]. This reconstruction (cardiac remodeling) due to myocardial infarction continues for several months, whereby the ultimate shape of the ventricle eventually becomes deleterious to the general functioning of the heart as a pump [3].

It is believed that the progression of chamber enlargement due to myocardial infarction is directly related to three factors: healing of the infarct, size of the infarct, and wall stress imposed on the ventricle [3, 4]. The phenomenon of cardiac remodeling is now a well-established feature in the progression of cardiovascular disease and is currently prevailing as an important therapeutic target in the failing heart. Cardiac remodeling is generally associated with changes in genome expression, molecular mechanisms, and cellular structures which become evident as a result of alterations in cardiac size, shape, and function after serious injury to the heart [32]. Myocardial infarction invariably leads to infarct expansion which can be defined as acute dilatation and thinning of the area of infarction not explained by additional myocardial necrosis [33]. The expansion of the infarct has been observed prior to and/or during the stage of necrotic tissue resorption before the massive deposition of collagen [34]. Hence, infarct expansion is a model example of coupling among global changes in ventricular configuration and the subsequent principal cellular adaptations [35].

Although the mechanisms responsible for the transition of cardiac hypertrophy to heart failure have not yet been fully elucidated, remodeling of the ventricle as a result of marked alterations in the extracellular matrix has been proposed to be closely associated with its advancement [36–38]. Key indications to support this view can be found in the extracellular space of the myocardium, which is home to a wide variety of cells that are structurally and functionally unique. Unlike the cardiomyocytes that comprise one-third of the cell population in the heart [39],

endothelial cells [40], vascular smooth muscle cells [40], cardiac fibroblasts, and macrophages reside in the cardiac interstitium and are collectively termed as non-myocyte cells [36]. The growth of non-myocyte cells is referred to as interstitial structural remodeling and is usually accompanied by the accumulation of collagen [36]. Since non-myocyte and myocyte growth is independent of each other, hypertrophy of the myocardium can occur as a homogenous or heterogeneous process that is a result of proportionate or disproportionate non-myocyte growth, respectively [41, 42]. Adaptive hypertrophy occurs through the preservation of tissue homogeneity and proportionate non-myocyte growth, whereas maladaptive or pathological hypertrophy arises from the heterogeneity in myocardial structure and disproportionate non-myocyte cell growth [36].

In addition to the alterations observed exterior to the cardiomyocyte, subcellular organelles such as SR, SL, mitochondria, and myofibrils in cardiomyocytes also become altered during the development of heart failure [16, 30, 43]. The ability of the SR and SL to modulate the concentration of Ca^{2+} and to regulate the contractile apparatus in cardiomyocytes [18, 20, 43, 44] has provided a wealth of information to suggest that heart failure is indeed due to a defect in the ability of the SR and SL to regulate intracellular Ca^{2+} in cardiomyocytes. On the other hand, changes in the composition of myofibrils in the failing heart are associated with alterations in the sensitivity of myofibrils to Ca^{2+} [45–47]. Mitochondrial abnormalities with respect to energy production at certain stages of heart failure provide further evidence for the occurrence of subcellular defects/remodeling in the failing heart [16, 19]. However, this view regarding subcellular remodeling in cardiomyocytes does not rule out the contribution of changes in the extracellular matrix to ventricular remodeling, but rather incorporates all systems into one network that compliment each other in the progression of cardiac hypertrophy into heart failure. It is also pointed out that very little information regarding the behavior of subcellular organelles with respect to the regulation of intracellular Ca^{2+} in non-cardiomyocytes during the development of heart failure is available in the literature.

Subcellular defects due to myocardial infarction

In addition to its role in the excitation–contraction coupling, Ca^{2+} is involved in processes as diverse as cell growth, metabolism, hormone secretion, motility, gene expression, protein trafficking, cell regulation, necrosis, and apoptosis [48]. The concentration gradient of Ca^{2+} in and out of the cell is critical to its survival where the intracellular cytoplasmic-free Ca^{2+} concentration is 10^3–10^4 times less than that of the extracellular space [49]. This large Ca^{2+} gradient is sustained through the involvement of Ca^{2+} channels situated in the membrane networks of the cell surface and the inner SR [49]. Upon electrical stimulus in the form of an action potential, the L-type voltage-gated Ca^{2+} channels in the SL membrane open to allow an influx of Ca^{2+} into the cytoplasmic space [50]. This introduction of Ca^{2+} into the intracellular compartment gives rise to a rapid release of Ca^{2+} from the SR Ca^{2+}-stores through its ryanodine-sensitive Ca^{2+}-release channels, located in the area adjacent to the L-type Ca^{2+} channels [51–53]. This entire process is referred to as Ca^{2+}-induced-Ca^{2+}-release [54]. Immediately following the release of Ca^{2+} into the cytosol, inactivation of the L-type Ca^{2+} channel occurs as Ca^{2+} binds to it on the cytosolic side, thereby contributing to a process called Ca^{2+}-dependent inactivation of Ca^{2+} influx [55, 56]. This intricate cycle is maintained in the cell to promote the survival based on a local negative feedback effect. It starts with a large influx of Ca^{2+} that leads to the release of Ca^{2+} from the SR stores and counteracts the Ca^{2+} influx by binding to the L-type channel on the cytosolic side, thereby inactivating the whole process [57].

Ca^{2+} is the ubiquitous second messenger, which once released into the cytosol is the key component for initiating the transition of the resting state to the contractile state via binding to regulatory proteins in the cardiac contractile apparatus [54, 58]. When the concentration of free Ca^{2+} in the cytoplasm $[Ca^{2+}]_i$ is raised above the critical level, Ca^{2+} binds to troponin C [57]. Troponin is a hetero-trimer that is composed of three distinct proteins: the calcium receptor (Tn–C), the inhibitor of the actin–myosin-binding site (Tn–I), and the binding portion of troponin (Tn–T) that effectively relays the Ca^{2+}-binding signal from Tn–C to tropomyosin [58]. The contractile machinery of the cell is turned on as a result of the association of Ca^{2+} with Tn–C, but is quickly turned off for the relaxation process as Ca^{2+} dissociates from Tn–C when the $[Ca^{2+}]_i$ is lowered [57]. Essentially, $[Ca^{2+}]_i$ is lowered mainly by the uptake of Ca^{2+} back into the SR via a Ca^{2+}-pump ATPase (SERCA2a) [59, 60]. In addition, $[Ca^{2+}]_i$ is lowered via: (a) Ca^{2+} exchange for external Na^+ by the SL Na^+–Ca^{2+} exchanger [59, 61], (b) SL Ca^{2+}-pump that expels Ca^{2+} using ATP as an energy source [61], and (c) uptake of Ca^{2+} by the mitochondria [62]. Though the SL Ca^{2+} pump and mitochondria participate in the uptake of Ca^{2+} during the contraction–relaxation cycle, the amount is minimal in comparison to other sites, and the mechanism of mitochondria uptake is not clearly understood [63].

The Na^+–Ca^{2+} exchanger on the other hand is driven by an electrochemical gradient and essentially extrudes Ca^{2+} for the exchange of Na^+ that is brought into the cell [64]. It is interesting to note that the removal of Ca^{2+} from the cell during diastole is species specific. Different studies have

shown that rat ventricular myocardium utilizes SERCA2a to sequester 92% of the Ca^{2+} into the SR, while only 7% of Ca^{2+} is expelled by the Na^{+}–Ca^{2+} exchanger [65]. However, in the human, rabbit, ferret, guinea pig, and cat hearts, it is observed that SERCA2a takes in 70–75% of the Ca^{2+} into the SR, leaving the remainder 25–30% to be removed by the Na^{+}–Ca^{2+} exchanger. The rat heart shows a higher SERCA2a activity in comparison to the rabbit, as it contains a greater concentration of protein pumps, whereas Ca^{2+}-movements in the mouse heart are quantitatively similar to those of the rat [66].

Despite the existence of a large amount of information concerning alterations in subcellular organelles in cardiac hypertrophy leading to heart failure [18–21], it is apparent that the mechanisms of subcellular remodeling remain poorly understood. In view of the fact that regulation of Ca^{2+} movements in cardiomyocyte is dependent upon the activities of SL and SR membranes for efficient contraction and relaxation, there is a large interest concerning the abnormalities in the function of specific cardiac membrane networks in heart failure [18–20]. Eighty percent of Ca^{2+} movement occurs via the SR, while the remaining 20% of Ca^{2+} is transported across the SL [67, 68]. Any defect in the SR and SL membrane can be seen to cause disturbance in Ca^{2+}-movements in cardiomyocytes. An alteration in the cardiac cellular Ca^{2+} homeostasis can also be attributed to irregular transmembrane movements of other cations including Na^{+} and K^{+} as a consequence of changes in the SL Na^{+}–K^{+} ATPase and SL Na^{+}–Ca^{2+} exchanger in the failing heart [69–73]. Dramatic alterations in the activities of SL Na^{+}–K^{+} ATPase and Na^{+}–Ca^{2+} exchanger have been reported to be associated with corresponding changes in SL gene and protein expressions in heart failure due to myocardial infarction [19, 20, 74]. Likewise, heart failure due to myocardial infarction is associated with marked changes in the SR Ca^{2+}-uptake and Ca^{2+}-release activities as well as alterations in corresponding SR gene and protein expression [19, 20, 75]. Such defects in both SL and SR protein composition have been suggested to result in the development of intracellular Ca^{2+}-overload, abnormalities in mitochondrial function, and impairment of cardiac performance [19, 20].

Cardiac dysfunction in the failing heart due to myocardial dysfunction may also be due to alterations in the interaction of Ca^{2+} with the troponin C in the thin filaments because remodeling of myofibrils as a consequence of changes in myosin isozymes and regulatory proteins have been shown to occur in heart failure [76–79]. Although the circulating levels of catecholamines, which promote the entry of Ca^{2+} into cardiomyocytes, are markedly elevated in the infarcted animals [77], the β-adrenoceptors, adenylyl cyclase, and related signal transduction mechanisms are impaired [80]. Thus, defects

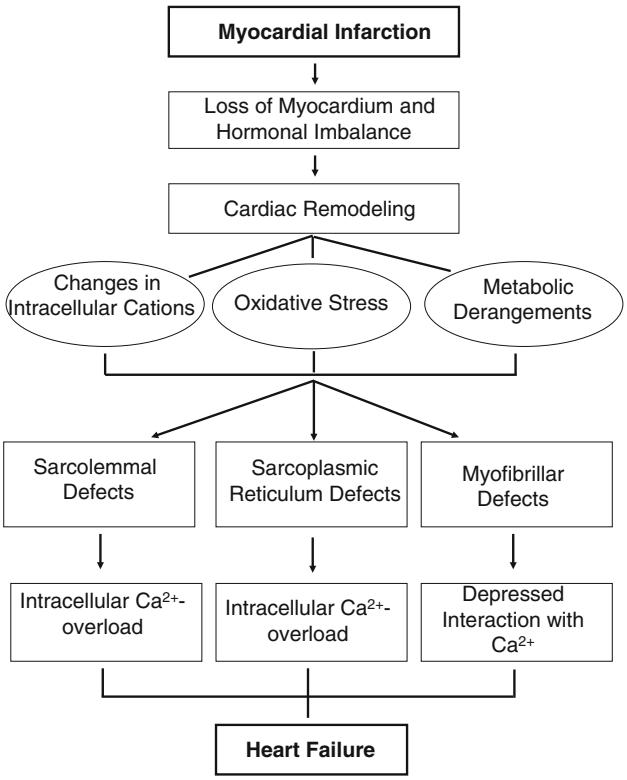

Fig. 1 Involvement of changes in intracellular cations, oxidative stress, and metabolic derangements in inducing subcellular defects during the development of heart failure due to myocardial infarction. It should be pointed out that this *figure* represents only the calcium effects and does not include other effects involved in causing heart failure

in Ca^{2+}-handling by SL and SR membranes as well as changes in the sensitivity of Ca^{2+}-binding sites in myofibrils may be a result of subcellular remodeling in the failing heart. Furthermore, in addition to alterations in gene expression and subsequent remodeling of subcellular organelles, accumulation of reactive oxygen/nitrogen species in cardiomyocytes may play a role in the Ca^{2+}-related abnormalities in heart failure due to myocardial infarction [19, 20, 76, 81]. A schematic diagram showing the role of cardiac remodeling and the involvement of metabolic abnormalities, alterations in the intracellular cation concentrations, and oxidative stress for inducing subcellular defects in the development of heart failure is shown in Fig. 1.

Cardiac dysfunction and cardiac remodeling due to aging

In spite of the fact that the aging process is confounded by atherosclerosis, diabetes, hypertension, hypertrophy, and myocardial infarction, several investigators have

emphasized that there occurs heart failure due to aging in the absence of these risk factors [9, 10, 12, 15, 22]. It should be mentioned that heart failure in aging population is invariably associated with preserved ejection fraction. The issue of heart failure in aging with respect to preserved ejection fraction and low ejection fraction has been addressed in detail recently [82]. The age-related heart failure has been reported to be accompanied by cardiac remodeling as a consequence of cardiomyocyte hypertrophy, increased fibrosis, and increased number of non-cardio myocytes as well as decreased number of cardiac stem cells, cardiomyocyte proliferation, and cardiomyocyte survival [12]. While cardiac hypertrophy due to aging is attributed to increased hemodynamic overload, changes in neurohumoral factors and other hypertrophic signals, the loss of cardiomyocytes has been explained on the basis of apoptosis, reduced rate of autophagy, and decreased cardiomyocyte mitosis [12]. Cardiac hypertrophy in older animals has also been shown to be associated with varying degrees of changes in the mitochondrial and myofibrillar contents [83]; however, the mitochondrial function has been reported to decline in association with increased production of reactive oxygen species in the aging heart [7]. It should be noted that aging has also been demonstrated to exhibit fewer mitochondria and increased fibrosis in both cardiac and skeletal muscles, which appear to be the consequence of disturbance in protein synthesis and impaired functions of cellular organelles [84].

A wide variety of alterations in the levels of circulating vasoactive hormones, including those due to the activation of sympathetic and renin-angiotensin systems, have been reported to occur in the aging population [85–87]. These studies indicate that cardiac remodeling due to aging is associated with alterations in both extracellular matrix and defects in subcellular organelles as a consequence of hormonal imbalance. The mechanisms of cardiac remodeling due to aging appear to be of complex nature and may involve various stimuli for inducing alterations in the structure and function of the heart. The sequence of events related to cardiac remodeling accompanied by cardiomyocyte growth and non-cardiomyocyte proliferation due to hemodynamic overload, vascular stiffness, and endothelial dysfunction is depicted in Fig. 2. Furthermore, another mechanism of cardiac remodeling due to autophagic failure, apoptosis, and loss of cardiomyocytes as a consequence of changes in the levels of various neurohumoral, cytokines, and growth factors is shown in Fig. 3.

Heart failure in elderly patients is characterized by low cardiac output which may reflect a decrease in the active metabolic tissue [88]. The development of heart failure due to aging is evident from the increase in left ventricular end-diastolic pressure as well as depressions in the rate of rise of pressure, rate of decay of pressure, stroke volume, and ejection fraction [89]. These changes in cardiac pump failure were accompanied by augmented end-diastolic and end-systolic volumes as well as increased ventricular wall

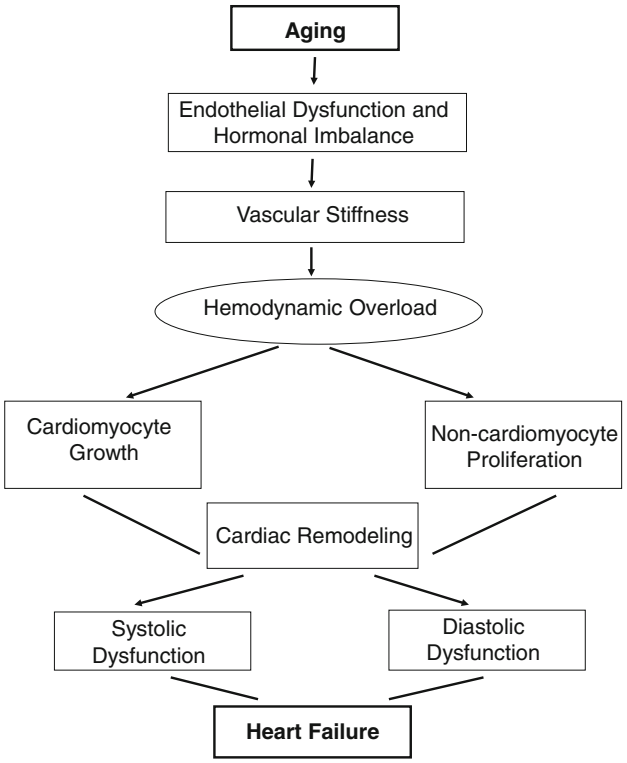

Fig. 2 Involvement of hemodynamic overload in the development of cardiac remodeling and subsequent heart failure due to aging

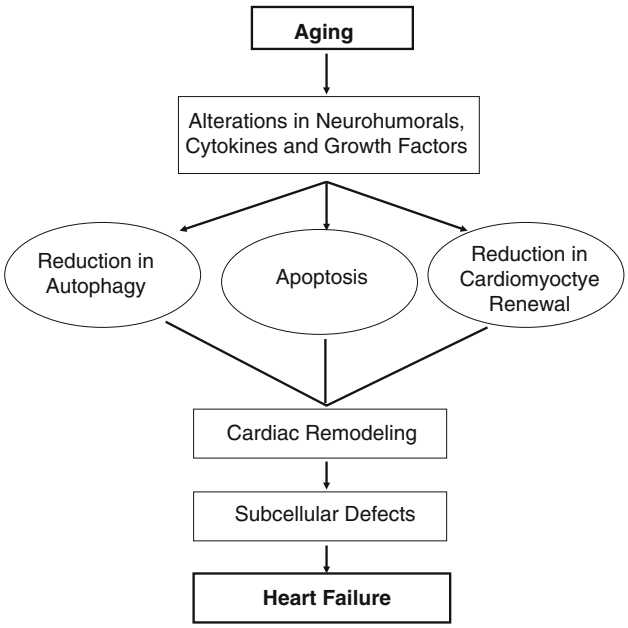

Fig. 3 Role of apoptosis as well as reduction in the processes for autophagy and cardiomyoctye renewal for the development of cardiac remodeling and heart failure due to aging

thickness and wall stress [89]. The decrease in the velocities of contraction and relaxation in the aging myocardium was associated with prolongation of action potential [90] and changes in the distribution or function of SL Ca^{2+}-channels [91]. The global stiffness of the myocardium due to age has been attributed to oxidative stress-induced alterations in myofibrillar proteins [92] and changes in β-myosin heavy chain cross-bridges [93, 94]. Alterations in the mechanical properties of the aging heart have also been explained on the basis of sarcomere disorganization due to increased expression of a new isoform of cardiac myosin-binding protein in cardiomyocytes [95]. Thus, it appears that the depressed cardiac function in heart failure due to aging is accompanied by both cardiac remodeling and subcellular defects.

Subcellular defects in aging heart

Janczewski and Lakatta [22] have recently reviewed literature concerning Ca^{2+}-handling abnormalities in heart failure associated with aging and have identified defects in Ca^{2+}-cycling proteins in cardiomyocytes. The action potential duration, the magnitude of L-type Ca^{2+} current, and Ca^{2+}-transient amplitude were observed to be increased in the aging heart [96, 97]. In addition to a decrease in SL Ca^{2+}-channel density [98], the SL Na^+–Ca^{2+} exchange protein content was depressed in hearts failing due to aging [99, 100]. The cardiac mRNA level for SL Na^+–Ca^{2+} exchanger protein was first decreased and then increased with the progression of age [101]. Although the Na^+–K^+ ATPase activity and number of ouabain-binding sites in the SL membrane were decreased in the aging heart [102], mRNA levels for SL Na^+–K^+ ATPase and SL Ca^{2+}-channels were unaltered [103]. While the depression in SL Ca^{2+}-channel density [98] does not explain the observed increase in the magnitude of L-type Ca^{2+}-current or Ca^{2+}-transient amplitude in the aging cardiomyocyte [96, 97], depressed content for SL Na^+–Ca^{2+} exchanger protein [99, 100] and SL Na^+–K^+ ATPase [102] can be seen to be associated with an increase in the intracellular concentration of Ca^{2+} directly and indirectly, respectively. The increase in the ATP-dependent Ca^{2+}-uptake in SL vesicles [104] would not favor the occurrence of intracellular Ca^{2+}-overload in the aging cardiomyocyte.

The observed changes in SL proteins and activities seem to indicate remodeling of the SL membrane in the aging heart. This view is further supported by the observation that the SL-associated β-adrenoceptors, G-proteins, and adenylyl cyclase system were impaired in heart failure due to aging [15, 22]. The significance of defective β-adrenoceptor-mediated signal transduction system in depressing the cardiac contractile activity is evident from the finding that the activation of adenylyl cyclase 6 expression was found to improve cardiac function of the aging heart [105]. Whether the increased arrhythmogenicity in the aging heart [103] is due to depressed SL Na^+–Ca^{2+} exchanger and SL Na^+–K^+ ATPase activities or defect in some other Ca^{2+}-cycling proteins is not clear at present.

It is now well established that Ca^{2+}-uptake and Ca^{2+}-release activities of the SR preparations from the aging heart are depressed [106–109], and these changes can be seen to explain the impaired rates of relaxation and contraction in heart failure due to aging, respectively. The defect in the ability of SR to accumulate Ca^{2+} in the aging heart was associated with depressed SERCA2a and phosphoenzyme content [110] as well as mRNA levels for the SERCA2a protein [111, 112]. Overexpression of SERCA2a in the aging heart improved cardiac function [113], and the treatment of old animals with dexamethasone increased cardiac contractile performance and SR Ca^{2+}-transport activity [114]. Since the stimulation of Ca^{2+}-uptake upon phosphorylation by cyclic AMP-dependent protein kinase in the SR vesicles from aging heart was not different from that in the adult heart [115], the reduced response of aged myocardium to β-adrenoceptor activation is considered to be due to the formation of decreased amount of cyclic AMP as a consequence of defective β-adrenoceptor signal transduction [15, 22]. On the other hand, the stimulatory effect of calmodulin on SR Ca^{2+}-uptake was reduced in the aging heart [116, 117] in addition to reduced content of Ca^{2+}/calmodulin-dependent protein kinase (CaM kinase II) as well as CaM kinase-mediated phosphorylation activity in SR membrane [116]. These studies suggest that not only the intrinsic properties of SR Ca^{2+}-transport system are altered but its regulation by CaM kinase II is also impaired in heart failure due to aging. The defective SR Ca^{2+}-transport system in the aging heart has been reported to be due to increased nitrosylation by 3-nitrotyrosine [118] and oxidation of SR proteins by oxidative stress [119, 120] as well as increased levels of histidine-rich Ca^{2+}-binding protein in the myocardium [121, 122]. Such a defect in SR Ca^{2+}-transport system leads to the development of intracellular Ca^{2+}-overload in cardiomyocytes and results in heart failure due to aging.

The depressed cardiac function in the aged heart may also be a consequence of remodeling of myofibrils; this is consistent with the observations that myofibrillar Ca^{2+}-stimulated ATPase and myosin ATPase activities were decreased in heart failure due to aging [22, 123]. Both ATP consumption and Ca^{2+}-sensitivity for force development of the skinned trabeculae from old animals were reduced [124]. Such changes in the aging heart were found to be due to a decrease in α-myosin heavy chain and an increase in β-myosin heavy chain as well as their corresponding mRNA levels [125–128]. It should be mentioned that a

shift in myosin isozymes and corresponding changes in gene and protein expressions have also been reported to occur in the skeletal muscle of old animals [129]. Aging has also been observed to promote proteolysis of cardiac myosins and troponin-T, and these alterations may also account for the decreased Ca^{2+}-sensitivity of myofibrillar Mg^{2+}-ATPase in the aging myocardium [123]. In view of the increased oxidative stress, as a consequence of the generation of reactive oxygen and reactive nitrogen species in the aging heart, proteomic analysis has revealed an increase in the content of nitrated proteins including myosin heavy chain, neurofibromin, tropomyosin, and nebulin-related anchoring protein in cardiac muscle from the old animal [130]. Both troponin I phosphorylation and phospholamban phosphorylation have also been reported to be depressed in the aging heart [22], and these changes are considered to explain the diminished β-adrenergic contractile response. Thus, defects in the structure and function of myofibrils as well as changes in their regulatory mechanisms can be seen to contribute in the development of heart failure due to aging.

Modification of age-induced cardiac dysfunction and subcellular defects

Since aging is invariably associated with hypertension and hypertrophy and the aging hearts are more susceptible to coronary artery disease [10–14], some investigators have attempted to investigate whether the age-induced cardiac dysfunction and subcellular defects are due to the effects of these pathological factors. On the basis of a shift in myosin isozymes, hypertension in young spontaneously hypertensive (SHR) rats was found to accelerate the process of aging but the high blood pressure in adult SHR rats did not contribute to these alterations which were already acquired due to the aging process [131, 132]. Lowering the blood pressure in SHR rats upon treatment with captopril, an angiotensin converting enzyme inhibitor, was found to reduce the age-induced increase in gene expression for β-myosin heavy chain as well as skeletal actin [130]. When the captopril treatment of SHR rats was started before any signs of heart failure, changes in gene expression for α-myosin heavy chain were prevented, whereas these alterations were augmented if the drug treatment was started after the onset of heart failure [133].

Unlike the young SHR rats, older animals show decreased SR Ca^{2+}-release, decreased contribution of SR Ca^{2+}-uptake, and increased contribution of SL Na^{+}–Ca^{2+} exchanger, although both young and old animals exhibited cardiac hypertrophy [134]. Differences for changes in contractile parameters, action potential and Ca^{2+}-handling by cardiomyocytes due to cardiac hypertrophy and aging were also observed by using SHR rats of various age groups [135]. Cardiac hypertrophy induced by aortic coarctation was observed to increase both SL Na^{+}–K^{+} ATPase and SL Ca^{2+}-ATPase activities in young rats but only SL Ca^{2+}-ATPase activity was increased in old rats [136]. Since some of the investigators have shown that changes in mechanical properties as well as gene expression for α- and β-myosin heavy chains and SERCA2a in cardiomyocytes due to aging and cardiac hypertrophy induced by pressure overload were similar [137], it is difficult to rule out whether or not the observed changes due to aging are the effect of cardiac hypertrophy. Thus, some caution should be exercised while interpreting these data, and further studies are required to demonstrate that the age-induced cardiac remodeling and subcellular defects in heart failure are not elicited by hypertension or cardiac hypertrophy.

The aging heart is not only more susceptible to myocardial infarction [12] but it also shows higher vulnerability to low-flow ischemia in comparison to the adult heart [138]. In particular, low-flow ischemia in the isolated aged heart was observed to induce a greater fall in the left ventricular developed pressure and a greater increase in coronary resistance as well as a greater increase in mRNAs encoding for SL Na^{+}–Ca^{2+} exchanger and SERCA2a proteins than those seen in the adult heart [138]. Perfusion of the isolated aged heart with isoproterenol was found to produce smaller increases in the positive inotropic and lusitropic effects as well as cyclic AMP level compared with the adult hearts [139]. These diminished responses of aged hearts to β-adrenoceptor stimulation were associated with lower degree of phosphorylation of SR phospholamban and myofibrillar tropinin I [139]. The impaired functional responses of the aging heart to isoproterenol were also shown to be related to decreased rate of removal of cytosolic Ca^{2+} because of the lower SERCA2a to phospholamban ratio and SL Na^{+}–Ca^{2+} exchanger content in comparison to the adult heart [99].

The significance of alterations in cardiac subcellular organelles in old animals is evident from experiments in which exercise training was found to improve cardiac function and enhance SR Ca^{2+}-transport [140]. The improvement in cardiac function in the aging animals by exercise training was also associated with increases in the activities as well as gene and protein expressions for SERCA2a and mitochondrial cytochrome oxidase [141]. The beneficial effects of exercise training in aging heart with respect to heart function as well as gene and protein expressions of SERCA2a and α-myosin heavy chain were shown to be mediated through the improvement of thyroid hormone receptor signaling [142]. Since refeeding was found to reverse the malnutrition-induced cardiac myosin shifts in aged rats through growth hormone [143], it is likely that the beneficial effects of exercise training on

heart function in aging animals may be due to participation of several hormones including thyroid and growth hormones. These studies seem to suggest that subcellular defects and cardiac dysfunction in the aging heart are due to transcriptional changes in subcellular proteins as well as their regulatory mechanisms, and these sites may represent potential targets for the development of improved therapy of heart failure due to aging.

Conclusions

From the foregoing discussion, it is evident that aging population is more susceptible to myocardial infarction, and therefore, this article has discussed the development of heart failure in both infarcted and aging hearts. In spite of several differences in the pathogenesis and hemodynamic characteristics, both myocardial infarction and aging result in heart failure as a consequence of cardiac remodeling. In particular, cardiac dysfunction in failing hearts due to myocardial infarction and aging seems to be intimately associated with defects in the functions of SL, SR, mitochondria, and myofibrils. Such subcellular abnormalities in cardiomyocytes seem to be due to changes in hormonal imbalance, alterations in intracellular cations, oxidative stress, and metabolic derangements due to myocardial infarction and aging. In view of the focus of this article with respect to Ca^{2+}-handling abnormalities in the failing heart, we have omitted discussion regarding the role of changes in intracellular matrix in heart failure due to myocardial infarction and aging.

It should be mentioned that most of the work on heart failure and cardiac remodeling due to both myocardial infarction and aging has been carried out in male subjects. Thus, extensive studies need to be undertaken in women to examine the pattern of gender difference with respect to susceptibility of the heart to myocardial infarction and aging. Likewise, comparative examination of cardiac changes due to myocardial infarction and aging in different animal species would yield important information for identifying major targets for drug development. Furthermore, most of the work on subcellular defects in hearts failing due to myocardial infarction and aging has been done by employing animal models. Thus, it would be prudent to investigate the occurrence of subcellular defects in hearts from patients with myocardial infarction and aging population. Accordingly, it is suggested that a great deal of caution should be exercised in the interpretation of the viewpoints outlined in this review.

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Conflict of interest The authors declare no conflicts of interest.

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