Role of Subcellular Remodeling in Cardiac Dysfunction due to Congestive Heart Failure

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Key Words

Myocardial infarction • Pressure overload • Volume overload • Cardiac hypertrophy • Cardiac gene expression

Abstract

Although alterations in the size and shape of the heart (cardiac remodeling) are considered in explaining cardiac dysfunction during the development of congestive heart failure (CHF), there are several conditions including initial stages of cardiac hypertrophy, where cardiac remodeling has also been found to be associated with either an increased or no change in heart function. Extensive studies have indicated that cardiac dysfunction is related to defects in one or more subcellular organelles such as myofibrils, sarcoplasmic reticulum and sarcolemma, depending upon the stage of CHF. Such subcellular abnormalities in the failing hearts have been shown to occur at both genetic and protein levels. Blockade of the renin-angiotensin system has been reported to partially attenuate changes in subcellular protein, gene expression, functional activities and cardiac performance in CHF. These observations provide support for the role of subcellular remodeling (alterations in molecular and biochemical composition of subcellular organelles) in cardiac dysfunction in the failing heart. On the basis of existing knowledge, it appears that subcellular remodeling during the process of cardiac remodeling plays a major role in the development of cardiac dysfunction in CHF.

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Introduction

Through decades of continuous research, along with the constant rise in the number of patients with failing hearts, congestive heart failure (CHF) is presently considered as a complex progressive disease and not just a single isolated syndrome [1]. The inability of the heart to pump sufficient blood, to maintain a balanced oxygen supply and demand relationship in the human body at both rest and exercise, is the hallmark feature of CHF. Particularly, CHF is associated with an overload of fluid, which drowns peripheral organs such as liver, kidneys, lungs, skeletal muscle as well as the heart, whereby the examination of the etiologies of CHF has become an area of intensive interest [2]. It is noteworthy that CHF is the common concluding pathway for a majority of primary cardiovascular diseases including hypertension, coronary atherosclerosis, cardiomyopathy, diabetes, myocarditis and congenital heart malformations [2, 3]. The lifetime risk of developing CHF is 1 in 5, where the long-term survival is relatively poor; up to one third of those diagnosed with CHF die within the first 12 months, whereas half of the patients survive the 5-year mark [3]. It has also been reported that CHF currently affects more than 5 million Americans and is responsible for more than 700,000 deaths per year, costing the American economy USD 50 billion annually [4]. In fact, CHF has become a concern of epidemic proportion worldwide. Since the progression of CHF emerges as a widespread and coordi-

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nated reaction to cardiac insult, giving a complex cascade of events that underlie changes in the failing myocardium, this review is focused on discussion regarding the mechanisms which have been proposed to explain heart dysfunction in CHF under chronic conditions.

Cardiac Remodeling and CHF

CHF is invariably preceded by cardiac hypertrophy, which occurs due to a wide variety of mechanisms [5–8]. Cardiac myocyte hypertrophy is initiated in response to mechanical alterations such as hemodynamic overload, pressure overload and volume overload, although various cytokines and hormones are considered to be involved in this process. An increase in mechanical load also occurs when the heart experiences an ischemic insult and the contractile elements of the myocardium are lost or rendered dysfunctional [2]. Hypertrophy is most probably intended to promote efficient pumping by intensifying the number of cardiac contractile units, while concomitantly decreasing the amount of wall stress by augmenting the wall thickness of the myocardium [2, 9]. Immediately following an ischemic episode such as myocardial infarction (MI), there is an acute loss of myocardial cells that leads to fibrosis, scar formation as well as uncharacteristic loading conditions, which results in dilatation of the ventricular chamber with a transformation in shape and size [10]. This reconstruction of the heart (cardiac remodeling) is usually associated with deleterious function of the heart as a pump [10]. It is believed that the progression of chamber enlargement following MI is directly related to three factors: the healing of the infarct, the size of the infarct, and the wall stress imposed on the ventricle. Although MI is a major cause of cardiac remodeling and CHF, cardiac remodeling has been observed to be associated with other types of CHF. In fact, 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 [10]. Cardiac remodeling is generally characterized by changes in gene expression, molecular mechanisms and cellular structures which are clinically evident as a result of alterations in cardiac size, shape and function after ischemic injury to the heart, as well as due to pressure overload and volume overload [9, 11–17]. MI invariably leads to infarct expansion, which can be defined as ‘acute dilation and thinning of the area of infarction not explained by additional myocardial necrosis’ [18]. The expansion of the infarct can be observed prior

to, and during the stage of necrotic tissue resorption, yet before the massive deposition of collagen [19]. Hence, infarct expansion is a model example of coupling amongst global changes in ventricular configuration and the principal cellular adaptations [20].

Although the mechanisms responsible for the transition of cardiac hypertrophy to heart failure have not yet been fully elucidated, cardiac remodeling as a result of marked alterations in the extracellular matrix has been proposed to be closely associated with the advancement of CHF [21–23]. 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, endothelial cells, vascular smooth muscle cells, cardiac fibroblasts and macrophages reside in the cardiac interstitium and are collectively termed as nonmyocyte cells [21]. The growth of nonmyocyte cells is referred to as interstitial structural remodeling, whereby an accumulation of collagen is observed. Due to the fact that nonmyocyte and myocyte growth are independent of each other, hypertrophy of the myocardium occurs as a homogeneous or heterogeneous process that is a result of proportionate or disproportionate nonmyocyte growth, respectively [24]. Fibroblasts, which comprise >90% of the nonmyocyte cells, enhance the production of collagen, in response to injury such as MI, and are one of the key elements in cardiac remodeling that leads to cardiac dysfunction [25, 26]. Review of the literature has revealed that during the transition to CHF, the stiffness of the heart is most probably attributed to extreme collagen deposition, thereby disrupting normal pumping capacity and further contributing to arrhythmogenicity in its progression to sudden cardiac death [25]. During this structural remodeling of the heart, the compilation of fibrous tissue enhances the occurrence of detrimental cardiovascular effects of ventricular dysfunction and arrhythmias [27]. In addition to the alterations observed exterior to the cardiomyocyte, changes in the sarcoplasmic reticulum (SR) and sarcolemma (SL), which modulate the intracellular concentration of free Ca^{2+} and regulate the contractile apparatus in cardiomyocytes [28], have been identified in the failing heart in conjunction with alterations in the sensitivity of the myofibrils (MF) to Ca^{2+} [28–31]. Such observations indicating the role of defects in SL, SR and MF in cardiac dysfunction do not rule out the contribution of changes in the extracellular matrix to cardiac remodeling, but rather incorporate all systems into one network that complement each other in the progression into CHF.

Subcellular Abnormalities in the Failing Heart

Despite the existence of a large amount of information concerning alterations in subcellular organelles in cardiac hypertrophy leading to heart failure, it is apparent that the mechanisms of subcellular remodeling remain poorly understood. In view of the fact that regulation of Ca^{2+} flow in and out of the cardiomyocyte is dependent upon the SL and the SR for efficient contraction and relaxation, there is a large interest concerning the abnormalities in the function of these specific cardiac membrane networks in CHF [31]. During the excitation-contraction process, a small amount of Ca^{2+} entering through SL releases a large amount of Ca^{2+} from the SR stores for the occurrence of cardiac contraction. On the other hand, for cardiac relaxation, approximately 80% of the Ca^{2+} transport throughout the cell occurs via the SR, while the residual 20% is transferred via the $\text{Na}^+/\text{Ca}^{2+}$ exchange and the Ca^{2+} pump located in the SL [28]. Moreover, as a result of this coordinated performance of these cardiac membrane systems in controlling Ca^{2+} transport in parallel with heart function, it has been suggested that cardiac dysfunction is a consequence of remodeling of both the SL and SR membranes [31]. In particular, loss of Ca^{2+} homeostasis has been observed in a diverse spectrum of heart maladies that include cardiac hypertrophy due to pressure overload, primary idiopathic cardiomyopathy and various etiologies that contribute to overall CHF [32, 33].

Modifications in the Expression of Sarcolemmal Na^+/K^+ ATPase

A prominent member of the SL proteins that was discovered in 1957 by Jens Christian Skou is the Na^+/K^+ adenosine triphosphatase (Na^+/K^+ ATPase), which exists in virtually all animal tissues, as well as the human myocardium [34]. This enzyme is responsible for the active transport of 3 Na^+ ions out of the cell, while simultaneously importing 2 K^+ ions. Hence, the Na^+/K^+ ATPase functions to maintain cell volume, establish ionic gradients and preserve membrane potentials of the cardiomyocyte [35]. Consequently, defects in the function of this enzyme were found to be related to abnormalities in cardiac performance and have been outlined as a salient feature of the subcellular basis of CHF [36, 37].

The Na^+/K^+ ATPase is composed of different subunits such as α_1 , α_2 , α_3 , β_1 , β_2 , and β_3 , and consequently several investigators have examined each subunit individually. Charlemagne et al. [36] reported that in mild and severe stages of hypertrophy, there was a reduction in the

α_2 mRNA and protein levels, while the compensated stage of hypertrophy revealed no alterations in the α_1 and β_1 mRNA and protein levels. Furthermore, the α_3 mRNA and protein levels were increased at 5 days and 30–50 days post-stenosis of the abdominal aorta, respectively. Another study by Semb et al. [38] reported that 6 weeks post-MI showed a reduction in α_2 mRNA and protein levels, with no alterations in the expression of the α_1 and β_1 subunits, but an increase in the α_3 subunit at the transcriptional level. This was supported by Book et al. [39], who reported that at 8 weeks post-stenosis of the left renal artery, there was a decrease in the α_2 mRNA and protein levels with unchanged α_1 expression, and a reduction in the β_1 protein levels. A unique experimental animal models known as the UM-X7.1 cardiomyopathic hamster was studied by Kato et al. [40], who reported a decrease in the α_2 mRNA, protein and α_3 protein levels with enhanced α_1 and β_1 mRNA and protein levels, with contrasting undetected levels of α_3 mRNA.

In terms of the functional alterations in the Na^+/K^+ ATPase, Dixon et al. [37] monitored its activity at 4, 8, and 16 weeks post-MI, and discovered that at 4 weeks, the activity was unchanged, but at 8 and 16 weeks the activity was significantly decreased. This finding suggested that the activity of the Na^+/K^+ ATPase may conceivably play a part in the adaptive mechanism of the heart that occurs during the development of CHF. Auxiliary studies by Shao et al. [41] demonstrated that reduced activity of this SL enzyme was coupled with the reduction in the expression of the α_1 , α_2 , and β_1 mRNA and protein levels, in addition to an elevation in the expression of the α_3 subunit. Shao et al. [41] further concluded that when imidapril (an angiotensin-converting enzyme inhibitor) treatment was administered, the Na^+/K^+ ATPase activity improved and the changes in the gene expression of the SL proteins were attenuated as a consequence of the blockade of the renin-angiotensin system (RAS) in CHF. A more extensive study by Ren et al. [42] revealed that a 37-week treatment with imidapril, 3 weeks post-MI, attenuated the reduction in the activity of the Na^+/K^+ ATPase, with paralleled trends in the expression of both the Na^+/K^+ ATPase and $\text{Na}^+/\text{Ca}^{2+}$ ATPase exchanger.

Modifications in the Expression of Sarcolemmal $\text{Na}^+/\text{Ca}^{2+}$ Exchanger

The $\text{Na}^+/\text{Ca}^{2+}$ exchange protein, which uses the influx of Na^+ to extrude intracellular Ca^{2+} , is a prominent member of the SL proteins and is situated in the T-tubules closest to the sites of Ca^{2+} release from the SR. The fully mature form of the $\text{Na}^+/\text{Ca}^{2+}$ exchanger exists as 120 kDa

and is responsible for maintaining Ca^{2+} homeostasis in the cell [43]. Since its discovery over 30 years ago, the kinetic parameters of this protein suggest that this system can encompass rapid Ca^{2+} transport in and out of the myocardial cell during the cardiac contractile cycle. In a clinical study relating dilated cardiomyopathy and coronary artery disease, Studer et al. [44] evaluated the expression of the Na^+ - Ca^{2+} exchanger together with the SR Ca^{2+} ATPase (SERCA). Amongst the two patient groups employed, the mRNA and protein levels of the Na^+ - Ca^{2+} exchanger were elevated in contrast to the reduction in the mRNA and protein levels of SERCA [44]; this observation gave rise to the idea that the increased expression of the Na^+ - Ca^{2+} exchanger somewhat compensated for the diminished function of the SR to remove Ca^{2+} from the cytosol during relaxation. Furthermore, these findings supplemented by Hasenfuss et al. [45] have affirmed that the decreased levels of SERCA, in concert with unaltered levels of the Na^+ - Ca^{2+} exchanger, accounted for the disorder in diastolic dysfunction. On the other hand, early stages of CHF due to MI have shown a reduction in the activity, mRNA and protein expression of Na^+ - Ca^{2+} exchanger [41, 46]. Schillinger et al. [47] illustrated, in the hours preceding cardiac transplantation, that the increase in the Na^+ - Ca^{2+} exchange, collectively with the reduction in SERCA, provided a substantial association amongst neurohormonal levels of epinephrine and SL activity of the Na^+ - Ca^{2+} exchanger. They further projected that during CHF, the activation of the sympathetic nervous system (SNS) conceivably amplified the expression of the Na^+ - Ca^{2+} exchanger, which may have potentially had a role in the onset of malignant ventricular arrhythmias. The intensifying concern of progressing arrhythmias in CHF was previously examined by Reinecke et al. [48], who observed that the enhanced activity of the Na^+ - Ca^{2+} exchange in end-stage CHF was a result of its increased protein levels. In addition, this increase provided an augmented influx of Na^+ , which was further associated with potential membrane depolarizations to create amplified arrhythmogenesis if the Na^+ - Ca^{2+} sustained movement predominantly in the forward mode.

Alterations in the Expression of SR Ca^{2+} -Pump ATPase

During cardiac relaxation, Ca^{2+} is pumped from the cytosol into the SR through the 105-kDa SR Ca^{2+} -pump ATPase [49]. As this enzyme is responsible for the diastolic phase of the cardiac cycle, any impairments in this process of Ca^{2+} sequestration could possibly contribute to the pathophysiology of cardiac dysfunction in CHF.

Supporting evidence for this postulation regarding cardiac dysfunction in the failing heart include an abnormal force-frequency relationship, whereby increased frequency of stimulation gives a decreased developed tension [50]. Clinical studies performed on the failing human myocardium have shown an overall decrease in SERCA mRNA [51–53] and protein levels [54, 55], in addition to a reduction in the abnormal handling of Ca^{2+} by SERCA itself [56, 57]. To assess the validity of these applications, different investigators have attempted to compare the findings in animal models of CHF with the failing human myocardium. Most of the results have shown to be controversial, yet some unanimity has surfaced. In a report by Movsesian and Schwinger [58], there are findings that show a reduction in the Ca^{2+} sequestration of the failing human myocardium; this is consistent with those of the animal models and can be attributed to decreased levels of SERCA mRNA. Further studies supporting this decrease in SERCA expression and function in the failing heart were carried out in experimental models of the pressure-overloaded rat [49], the tachycardia-induced mongrel dog [59], the volume-overloaded rat [60], infarcted rats [61] and the transgenically engineered hypertensive rat [62]. Though this offers insight into the molecular basis for the pathogenesis of CHF, the data that is accumulated raises more questions than that which have been answered. If in fact the protein level of SERCA remains unchanged in the failing heart, the answer may possibly lie in the complex mechanisms concerning transcription, translation and protein degradation as an entire cumulative process [58].

Alterations in the Expression of Sarcoplasmic Reticular Phospholamban Protein (PLB)

The SR Ca^{2+} uptake is intimately regulated by a SR protein, PLB. Composed of five equal monomers, this 30-kDa protein inhibits the activity of SERCA through direct interaction and depresses the transport of Ca^{2+} into the SR [63]. Compelling evidence to substantiate this phenomenon was seen in mice deficient in the PLB gene in comparison to their control [64]; this study demonstrated that the PLB-deficient mice exhibited high rates of contraction and relaxation in the absence of isoproterenol, but showed no increase in response in the presence of isoproterenol, which correlated well with the fact that the control mice had low rates of contraction and relaxation. Since both the gene expression and protein content of PLB were decreased in the failing heart due to MI [61], it appears that this change is an adaptive mechanism to support SR function in the failing heart.

Alterations in the Expression of SR Ryanodine Receptor

Ca²⁺ release from the SR is achieved through the ryanodine receptor (RyR), which is composed of four monomers of ~560,000 kDa. A decrease in SR Ca²⁺ release channel activity was observed in ischemic cardiomyopathy as well as in hearts failing due to valvular disease [65]. In studies comparing the Ca²⁺ release activity in both pressure-overloaded and volume-overloaded rats, Hisamatsu et al. [60] have shown enhanced Ca²⁺ release in the left ventricular hypertrophy due to pressure overload, with a contrasting decrease in Ca²⁺ release activity and number of RyR in the volume-overloaded model. Cory et al. [66] have observed that both the density of the SR terminal cisternae and the activity of RyR were reduced in the Doberman pinscher dog model of CHF, as well as during rapid ventricular pacing in mongrel dogs. Additionally, Arai et al. [53] documented a reduction in RyR mRNA in patients suffering from end-stage CHF from primary pulmonary hypertension, or ischemic heart disease. The SR Ca²⁺ release activity, RyR protein content and RyR gene expression were depressed in hearts failing due to MI [61].

Remodeling of the MF Proteins

The structural contractile unit of the myocardium controls the transition of the diastolic state to the activated state through various intricate steric, allosteric and cooperative mechanisms of the myofibrillar thick and thin filaments. Various studies have revealed a significant reduction in MF ATPase in the failing heart, including CHF due to mitral valve insufficiency, pressure overload, idiopathic cardiomyopathy, ischemic heart disease and coronary artery disease [67–71]. Of particular importance, there are two genes located in tandem on chromosome 14 that encode the cardiac myosin heavy chain (MHC), and are termed α -MHC and β -MHC. Given that the α -MHC isoform results in a high-power, low-economy ATPase activity, whereas the β -MHC isoform gives rise to a low-power, high-economy ATPase myofilament activity, the events associated with cardiac stress promote a shift in expression toward the β -MHC for a more efficient performance [72, 73]. Eble et al. [74] conducted a molecular study in the failing hearts of rabbits and reported an increase in the MHC synthesis in left ventricular dysfunction due to chronic ventricular tachycardia that could be explained by an increased MHC translational efficiency. This response was further supported by Imamura et al. [75], who reported an elevated synthesis in MHC in dogs subjected to pressure overload. Further-

more, in the rat model of pressure-overload hypertrophy, Toffolo et al. [56] described an augmentation in cell size followed by a change in the expression of myosin, to produce the slow-migrating, economic V₃ isoform, while exhibiting an increased number of MF units during the adaptive process of the myocardium. On the other hand, hearts failing due to MI showed depressed MF ATPase activity, a shift in myosin isozymes and corresponding changes in gene expression [57, 76].

Mechanisms of Subcellular Remodeling in CHF

From the foregoing discussion, it is evident that SL, SR, MF and extracellular matrix become altered in terms of chemical composition and molecular structure in CHF. However, the mechanisms of such subcellular remodeling are understood poorly. Since both SNS and RAS are activated in CHF [2, 7, 10, 77], it is likely that elevated levels of circulating levels of norepinephrine and angiotensin II (Ang II) may produce subcellular remodeling in the failing hearts. Notwithstanding the fact that the SNS offers a means of supporting cardiac contractile function, it has been documented that the failing human heart becomes less sensitive to stimulation of the SNS [78–82]. Overstimulation of the SNS is accompanied by different biochemical alterations including an increase in the expression of the α -subunit of inhibitory G proteins in the failing heart [83]. Furthermore, Lai et al. [84] have documented that norepinephrine infusion in dog hearts produced a decrease in the mRNA and protein levels of SERCA, which paralleled those hearts of pacing-induced CHF, with no change in the RyR, calsequestrin and PLB mRNA levels. It should be mentioned that RAS is also a critical entity in the regulation of cardiovascular function, as it plays a major role in the impairment of endothelial cell function, improvement of growth, progression of apoptosis, and the development of oxidative stress [77]. It has been shown by Ju et al. [85] that Ang II increased levels of mRNA for the sarcolemmal Na⁺-Ca²⁺ exchange, the SR ryanodine Ca²⁺ receptor, and the SR SERCA protein in cardiomyocytes. Rouet-Benzineb et al. [86] observed that the transcription factor NF- κ B was translocated into the nucleus from the cytoplasm via the protein kinase C pathway in neonatal rat cardiomyocytes, which were subjected to Ang II stimulation and this process was blocked with the administration of calphostin C, a specific protein kinase C inhibitor.

Throughout years of research, extensive efforts have been made to improve heart function in the infarcted an-

imals upon treatments with various pharmacological interventions. Certain therapies include angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers [77]. In a long-term study focusing on the effects of the ACEI captopril on left ventricular remodeling of the myocardial infarcted canine model, Jugdutt et al. [87] revealed attenuation of early infarct expansion, the absence of late wall thinning, a reduction in diastolic bulging, and eradication of aneurysms, as well as a general restitution in overall cardiac systolic function. In another study involving ACEI treatment, McDonald et al. [88] discovered that during progressive ventricular remodeling in the myocardial infarcted rat, late captopril therapy attenuated further increase in cell length, which is associated with myocyte hypertrophy and growth of the cardiac interstitium due to MI. Furthermore, Dixon et al. [89] have observed that the administration of both the ACEI and Ang II type-1 receptor antagonist in infarcted rats showed an overall reduction in cardiac fibrosis and suggested that Ang II may be involved in the regulation of cardiac collagen synthesis after MI at the post-transcriptional site. Thus, these investigations have provided evidence that in addition to SNS, RAS is intimately involved in the pathogenesis of cardiac dysfunction in CHF.

Findings from basic research studies, compiled with discoveries from important clinical trials, have proven significant transformations in both the extent of treatments available and in the continuing development of the knowledge of mechanisms underlying CHF [90–92]. It is due to the efforts of different investigators that changes amongst the many organelle systems have been identified and thus far, have been formulated into new concepts of subcellular remodeling for the development of CHF [93]. Several investigators by employing cDNA microarrays, proteomics, and other molecular approaches have identified defects in signal transduction mechanisms during the progression of CHF [94–100]. Essentially, CHF is preventable predominantly through the control of hormonal disturbances and other various factors, and the past 15 years of multiple trials have reported a significant decline in mortality in patients suffering from CHF [90–93]. It is also critical to note that profound alterations in cardiac structure and function are heavily dependent on aging. It has been well established that aging is one of the prominent risk factors involved in the development of CHF [101]. As significant changes such as increased ventricular wall thickening, myocardial fibrosis and valvular fibro-calcification contribute to decreased ventricular compliance [102], it is evident that the path to CHF is in-

evitably a major medical concern of the elderly. To support this notion, studies of advanced aging-associated CHF in the rat model by Pacher et al. [102] have characterized a decrease in systolic performance in association with prolonged relaxation that is accompanied by a rise in cardiac diastolic stiffness. While the significance of cardiac remodeling in CHF still remains to be elucidated, it is apparent that the cardiac subcellular organelles need to be selectively treated and appropriate therapy needs to be designed. It is therefore of greatest importance to acquire the underlying mechanisms involved as we are challenged to study the prevention of structural modification in the myocardium as well as changes in subcellular organelles using diverse approaches and experimental methodologies for inducing CHF [103–105]. In addition, it will be essential to carry out experiments showing the reversal of subcellular remodeling using a wide variety of pharmacological and surgical interventions.

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