Subcellular remodelling may induce cardiac dysfunction in congestive heart failure


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1. Introduction

Congestive heart failure (CHF), a devastating clinical problem, is associated with inability of the heart to pump sufficient blood to meet metabolic needs of the body. This cardiovascular disease involves various organs and manifests several symptoms such as fluid retention, breathlessness, and exercise intolerance.1–3 Over the past 50 years, various mechanisms including (a) defects in energy production and utilization, (b) increased preload and afterload, (c) altered neurohormonal profile and signal transduction, as well as (d) occurrence of intracellular Ca^{2+}-overload and Ca^{2+}-handling abnormalities have been indicated to explain cardiac dysfunction in CHF.4–7 Since CHF is invariably associated with changes in the shape and size of the heart (cardiac remodelling), it has been suggested that the progression of heart failure due to loss of cardiac muscle, pressure overload, or volume overload is a consequence of cardiac remodelling.8–12 The enlargement of the heart due to increased muscle mass and/or chamber dilation is considered to occur through alterations in different signal transduction mechanisms involving various protein kinases as well as a shift in myocardial metabolism;13,14 however, the exact reasons for cardiac dysfunction in CHF are poorly understood. Nonetheless, cardiac remodelling seems to develop in response to increased haemodynamic overload, increased workload, increased ventricular wall tension as well as elevated levels of different hormones including angiotensin, catecholamines, and endothelins, which are known to produce vasoconstriction.2,15–17 On the other hand, increased level of aldosterone may affect cardiac remodelling by promoting the retention of body fluid, whereas increased production of nitric oxide by endothelium, as well as elevated levels of different hormones such as atrial natriuretic peptide, may prevent the development of cardiac remodelling by their vasodilatory action.1–3,18,19 Thus alterations in a wide variety of hormones and other factors in CHF may produce a complex set of haemodynamic, metabolic, and signal transduction changes and result in cardiac remodelling.7,12,20,21

Although the heart is known to adapt to increased work load and haemodynamic load by increasing the muscle mass in terms of adding contractile units, it is emphasized...
that cardiac hypertrophy and ventricular dilation are compensatory at initial stages but result in heart failure at late stages of their development. In fact, both physiological and pathological forms of cardiac hypertrophy indicating cardiac remodelling (changes in the size and shape of the heart) have been identified, but the mechanisms which lead to the transition of physiological to pathological hypertrophy are not fully clear. Likewise, a moderate increase in the level of hormones such as catecholamines and angiotensin II may produce beneficial effects during early stages of cardiac hypertrophy but prolonged exposure of the hearts to an excessive amount of such hormones may produce deleterious actions at late stages of cardiac hypertrophy. The initial beneficial actions of these hormones are considered to be due to a transient increase in intracellular Ca\(^{2+}\), whereas their deleterious effects are the consequence of a sustained increase in the level of intracellular Ca\(^{2+}\) (intracellular Ca\(^{2+}\)-overload). Loss of cardiomyocytes due to necrosis and apoptosis as a result of intracellular Ca\(^{2+}\)-overload and elevated levels of different cytotoxic cytokines have also been suggested to explain cardiac dysfunction in hypertrophied hearts. Furthermore, the development of functional hypoxia and subsequent oxidative stress as a result of inadequate development of coronary vasculature as well as inappropriate capillary proliferation may play a critical role in the transition of physiological to pathological cardiac hypertrophy. Varying degrees of alterations in extracellular matrix, sarcolemmal membrane, sarcoplasmic reticulum, myofibrils, mitochondria, and nucleus have also been identified; however, changes in these subcellular organelles during the progression of heart failure were observed to be dependent upon the type and stages of CHF. In fact, changes in different biochemical activities in one or more subcellular organelles have been reported to occur during the development of cardiac hypertrophy as well as cardiac dysfunction under various pathophysiological conditions. Since heart function is determined by precisely coordinated and highly regulated activities of different subcellular organelles, it is likely that remodelling of one or more subcellular organelles may result in cardiac dysfunction during the progression of cardiac hypertrophy and heart failure. The present article is therefore focused on the nature and mechanisms of subcellular remodelling in different types of heart failure.

2. Subcellular remodelling and cardiac dysfunction

Extensive research in hypertrophied and failing hearts have revealed that the biochemical and molecular composition of different subcellular organelles as well as their function and structure are altered during the progression of cardiac disease. In this regard, changes in different subcellular organelles in the hypertrophied and failing hearts are illicit by the activation of various proteases and phospholipases as well as alterations in cardiac gene expression. Although each subcellular organelle is known to carry out more than one function in cardiomyocytes, abnormalities in some of the major functions of subcellular organelles are considered to be directly involved in the genesis of cardiac dysfunction. For example, remodelling of extracellular matrix and nucleus can be seen to induce alterations in cardiomyocyte architecture and gene expression, respectively. Remodelling of sarcolemma would produce changes in ion homeostasis and signal transduction by altering the activities of different receptors, cation channels, and cation transporters, whereas remodelling of mitochondria can be seen to produce changes in energy production and redox status by affecting the electron transport and oxidative phosphorylation systems in cardiomyocytes. Furthermore, remodelling of sarcoplasmic reticulum has been shown to induce alterations in Ca\(^{2+}\)-uptake and release activities due to defects in Ca\(^{2+}\)-cycling proteins while remodelling of myofibrils is known to produce changes in cardiac contraction and relaxation by affecting both contractile and regulatory proteins. These studies indicate that different subcellular organelles are altered to varying extents with respect to their biochemical and molecular composition during cardiac remodelling and such changes can then be seen to result in cardiac dysfunction. It is pointed out that defects in \(\beta\)-adrenoceptor-mediated, phospholipid-mediated, and other receptor-mediated signal transduction mechanisms, which regulate subcellular functions, have also been identified in hypertrophied and failing hearts. Accordingly, it suggested that subcellular remodelling may be intimately involved in the genesis of heart failure during the development of cardiac remodelling. Various subcellular organelles, which undergo remodelling, as well as changes in their corresponding functions during the development of heart function are depicted in Figure 1. Abnormalities in some of the subcellular organelles

![Figure 1](image-url)
in some selected experimental models of cardiac hypertrophy and CHF are described in the following section.

3. Subcellular remodelling in cardiac hypertrophy and heart failure

Since cardiac hypertrophy is generally associated with CHF, it has been a difficult task to sort out whether subcellular remodelling is associated with cardiac hypertrophy or heart failure per se. Nonetheless, pressure overload induced by abdominal aorta in rats has been shown to produce cardiac hypertrophy and cardiac dysfunction without any signs of CHF for a prolonged period.68–70 Furthermore, myofibrillar and myosin ATPase activities as well as mRNA levels for α-form of myosin were decreased but mRNA levels for β-form of myosin were increased in the rat hypertrophied heart.58–60 Alterations in myofibrillar, sarcoplasmic reticulum, mitochondrial, and sarcolemmal characteristics have also been observed in hypertrophied hearts in the absence of heart failure.61–65 Furthermore, Ca\(^{2+}\)-uptake in the sarcoplasmic reticulum was increased at an early stage of cardiac hypertrophy showing hypofunction but was decreased at a late stage of hypertrophy exhibiting hypofunction due to pressure overload.66,67 An increase in both cardiac function and sarcoplasmic reticulum Ca\(^{2+}\)-uptake has also been observed in animals upon exercise68 as well as in hypertrophied right ventricle of animals at early stages of inducing myocardial infarction.59,70 α-adrenoceptor signal transduction mechanisms (β-adrenoceptors, G-proteins, and adenylyl cyclase), located in the sarcosomal membrane, were up-regulated in the non-failing hypertrophied right ventricle at early periods of inducing myocardial infarction.71,72 Since changes in the β-adrenoceptor-induced signal transduction system were found to be dependent upon the type and stage of cardiac hypertrophy,73 it is evident that cardiac hypertrophy and associated subcellular alterations at early stages are adaptive in nature, whereas if cardiac hypertrophy is left unattended for a prolonged period, it becomes associated with remodelling of subcellular organelles and thus results in cardiac dysfunction.

Cardiac remodelling due to pressure overload and volume overload is associated with concentric and eccentric types of cardiac hypertrophy, respectively.74–76 In addition, cardiac remodelling of right ventricle in infarcted animals is characterized by the development of concentric hypertrophy and that in viable left ventricle is characterized by both concentric and eccentric hypertrophy.77 Such a differential cardiac remodelling in right and left ventricles was associated with corresponding differential changes in Ca\(^{2+}\)-transport system of the sarcoplasmic reticulum and β-adrenoceptor signal transduction system located in sarcolemma in right and left ventricles of animals with myocardial infarction.70–72 Remodelling of extracellular matrix and contractile proteins, as well as phospholipid-mediated and β-adrenoceptor-mediated signal transduction systems in sarcosomal membrane was also observed during the development of both cardiac hypertrophy and heart failure due to volume overload.78–83 An increase in PLC-β1 isozyme and a decrease in PLC-δ1 isozyme with respect to their activity, gene expression, and protein content in sarcolemma were seen during both cardiac hypertrophy and CHF due to volume overload.83 On the other hand, an increase and a decrease in the activity, mRNA level, and protein content for sarcolemmal PLC-γ1 were observed in cardiac hypertrophy and CHF in rats upon induction of volume overload, respectively.83 An upregulation of β-adrenoceptor signal transduction system, as measured by changes in the density of β1-adrenoceptors and protein content for GRK isoforms and β-arrestin-1, activities and protein content for adenylyl cyclase as well as activities and mRNA levels for Gsα- and Giα-proteins, indicate sarcolemmal remodelling in a moderate degree of CHF due to volume overload.81,82 It should be noted that downregulation of β-adrenoceptor mechanisms, indicating the loss of adrenergic support to the failing myocardium, was seen at advanced stages of CHF due to volume overload.73

Several investigators have been employing different models of cardiomyopathic hamsters for studying defects in subcellular organelles during the development of CHF.41,84–86 Alterations in gene expression and protein content indicating changes in extracellular matrix in cardiomyopathic hamsters have been identified.42 Biochemical and molecular abnormalities in different contractile and regulatory proteins in failing hearts from cardiomyopathic hamsters have been reported.84,85 Varying degrees of changes in α- and β-adrenoceptors, G-proteins, and adenylyl cyclase activities indicating sarcolemmal remodelling have also been observed.43,86–89 In addition to alterations in sarcosomal Na\(^{+}\)-K\(^{+}\) ATPase, Ca\(^{2+}\)-pump ATPase, Na\(^{+}\)-Ca\(^{2+}\)-exchanger, and Ca\(^{2+}\)-channel activities, mitochondrial oxidative phosphorylation and Ca\(^{2+}\)-transport activities90–95 were found to occur in cardiomyopathic hamster hearts. Furthermore, the behaviour of sarcoplasmic reticulum with respect to Ca\(^{2+}\)-release and Ca\(^{2+}\)-uptake activities was found to alter during the development of CHF in cardiomyopathic hamster hearts.96–98 CHF due to myocardial infarction was also observed to be associated with dramatic alterations in sarcosomal Ca\(^{2+}\)-channels, Na\(^{+}\)-K\(^{+}\) ATPase, and Na\(^{+}\)-Ca\(^{2+}\)-exchange activities as well as α- and β-adrenoceptors.71,99–102 In addition, varying degrees of alterations in myofibrillar and myosin ATPase activities103 extracellular matrix,104 and sarcoplasmic reticulum Ca\(^{2+}\)-pump mechanisms70,105,106 have been identified in failing hearts due to myocardial infarction. These observations support the view that cardiac remodelling in CHF is associated with remodelling of subcellular organelles and thus its role in the pathophysiology of cardiac dysfunction should not be overlooked.

While cardiac remodelling is considered to be implicated in the pathophysiology of CHF,12,107,108 very little information concerning the involvement of subcellular remodelling in the development of heart failure is available in the literature. Since subcellular remodelling in different experimental models of CHF is dependent upon the species of animals employed as well as stage and type of CHF,5,30,31 it is difficult to implicate remodelling of any particular organelle in the genesis of cardiac dysfunction. Since studies from our laboratory have indicated progressive alterations in extracellular matrix, sarcosomal membrane, sarcoplasmic reticulum, and myofibrils at early, moderate, and late stages of CHF in both cardiomyopathic hamsters and myocardial infarction in rats,70,71,90–99,101,103,104 it is likely that remodelling of these subcellular organelles is involved in the progression of CHF. Some investigators
have suggested the role for remodelling of extracellular matrix, cytoskeletal system, and myofilaments in heart failure and dilated cardiomyopathy, whereas others have shown remodelling of sarcoplasmic reticulum at early stage and that of myofibrils at late stage of heart failure. Likewise, Ca^{2+}-handling abnormalities due to remodelling of sarcoplasmic reticulum and sarcosomal membrane as well as changes in extracellular matrix and responses of myofibrils to Ca^{2+} have been observed in both systolic and diastolic forms of human heart failure. In fact, in view of the lack of sufficient information, it is difficult to suggest the involvement of remodelling of any particular subcellular organelle for systolic or diastolic dysfunction. Although extensive work by employing different experimental models needs to be carried out for making any meaningful conclusion, it can be argued that remodelling of one or more subcellular organelles may explain the transition of compensatory cardiac hypertrophy to heart failure. Ding et al. have reported that the transition from cardiac hypertrophy to heart failure due to volume overload is associated with altered intracellular Ca^{2+} homeostasis as a consequence of sarcoplasmic reticulum remodelling.

4. Mechanisms of subcellular remodelling in heart failure

In view of changes in the functional activities of extracellular matrix, sarcolemna, sarcoplasmic reticulum, myofibrils, and mitochondria in various types of cardiac hypertrophy and CHF, it is evident that subcellular remodelling is associated with the development of cardiac dysfunction. Because renin-angiotensin system is activated in cardiac remodelling and CHF, we examined the role of renin-angiotensin system in remodelling of some subcellular organelles by employing a rat model of CHF upon treatment with an angiotensin II converting enzyme (ACE) inhibitor, imidapril (1 mg/kg/day for 4 weeks), 3 weeks after the induction of myocardial infarction. It can be seen from Figure 2 that elevated levels of plasma and tissue ACE activities as well as β-myosin heavy chain (MHC) mRNA and protein content, and depressed myofibrillar Ca^{2+}-stimulated ATPase activity as well as α-MHC mRNA and protein content without any changes in Mg^{2+}-ATPase activity in the failing hearts were partially prevented by imidapril treatment. The data in Figure 3 indicate that sarcoplasmic reticulum

![Figure 2](image-url)
Ca\textsuperscript{2+}-uptake, Ca\textsuperscript{2+}-release, Ca\textsuperscript{2+}-pump ATPase, and ryanodine binding activities were decreased in heart failure; these changes in the failing hearts were also partially prevented by imidapril treatment. Furthermore, depressions in sarcoplasmic reticulum protein content and gene expression for ryanodine receptors, Ca\textsuperscript{2+}-pump ATPase and phospholamban were partially attenuated upon treating the infarcted animals with imidapril (Figure 4). The results in Figures 5 and 6 show that a decrease in sarcolemmal Na\textsuperscript{+}\textendash K\textsuperscript{+} ATPase in failing hearts was associated with depressions in protein content and mRNA levels for \( \alpha_{-1} \), \( \alpha_{-2} \), and \( \beta_{1} \)-isoforms as well as increases in protein and gene expression for \( \alpha_{-3} \) isoyme of Na\textsuperscript{+}\textendash K\textsuperscript{+} ATPase. In addition, sarcolemmal Na\textsuperscript{+}\textendash Ca\textsuperscript{2+}-exchange activity, mRNA level, and protein content were depressed; these alterations in sarcolemmal biochemical and molecular characteristics in the failing hearts were prevented by imidapril (Figures 5 and 6). Since the beneficial effects of another ACE inhibitor, enalapril, and an angiotensin II receptor antagonist, losartan, on subcellular remodelling were similar to these seen with imidapril,\textsuperscript{119–121} it appears that the activation of renin–angiotensin system plays a role in remodelling of sarcolemma, sarcoplasmic reticulum, and myofibrils. Remodelling of extracellular matrix and sarcolemma as well as changes in signal transduction mechanisms were also partially prevented by angiotensin blockade with various agents in different types of heart failure.\textsuperscript{122–127}

Because of the increased activation of the sympathetic activity and excessive formation of endothelins during the development of CHF,\textsuperscript{34,36,128} it is possible that subcellular remodelling in the failing hearts may be related to high levels of circulating catecholamines and endothelins. In fact, various \( \beta \)-adrenoceptor blocking agents were found to produce beneficial effects on sarcoplasmic reticulum,
sarcolemmal, and myofibrillar remodelling. Likewise, remodelling of sarcoplasmic reticulum, mitochondria, and myofibrils was also prevented by endothelin antagonists. Since different antioxidants were found to produce beneficial effects on myofibrilar, mitochondrial, sarcolemmal, and sarcoplasmic reticulum remodelling in failing hearts, the possibility of involvement of oxidative stress in subcellular remodelling seems attractive. Metabolic interventions, which improve oxidation of glucose over fatty acids, were not only found to improve cardiac function and prevent cardiac remodelling but were also observed to attenuate sarcolemmal, myofibrillar, sarcoplasmic reticulum and mitochondria remodelling in the failing myocardium. In addition, unloading the heart and decreasing the increased ventricular wall stress by the use of some ventricular assist devices were found to reverse remodelling of sarcoplasmic reticulum, myofibrils, mitochondria, extracellular matrix, and sarcolemma in failing hearts. Thus, it seems that various mechanisms such as increased wall stress, excessive amounts of circulating hormones including angiotensin II, catecholamines, and endothelins as well as oxidative stress are involved in the development of subcellular remodelling and subsequent cardiac dysfunction in CHF.

5. Concluding remarks

From the foregoing discussion, it is evident that cardiac remodelling during the development of cardiac hypertrophy

Figure 4 Sarcoplasmic reticulum (SR) remodelling in rats failing due to 7 weeks myocardial infarction (MI) with or without imidapril (IMP; 1 mg/kg/day for 4 weeks) treatment. Various parameters including SR protein content and gene expression for ryanodine receptors (Ca$^{2+}$-release channels), Ca$^{2+}$-pump ATPase, and phospholamban were measured and the data from our paper are redrawn. * -vs. sham; # -vs. MI.

Figure 5 Sarcolemmal remodelling in rats failing due to 7 weeks myocardial infarction (MI) with or without imidapril (IMP; 1 mg/kg/day for 4 weeks) treatment. Various parameters including Na$^{+}$-K$^{+}$ ATPase and Na$^{+}$-dependent Ca$^{2+}$-uptake activities as well as protein content for α, α2, α3, and β1-isoforms of Na$^{+}$-K$^{+}$ ATPase were measured and the data from our paper are redrawn. * -vs. sham; # -vs. MI.
and heart failure is associated with remodelling of different subcellular organelles such as extracellular matrix, sarcolemma, sarcoplasmic reticulum, mitochondria, myofibrils, and nucleus. Such a subcellular remodelling seems to occur as a consequence of the activation of proteases and phospholipases as well as changes in cardiac gene expression in the hypertrophied and failing hearts. Several mechanisms including (a) activation of both renin–angiotensin and sympathetic nervous systems, (b) excessive formation of different hormones which produce vasoconstriction, (c) increased oxidative stress and cytokine content, and (d) increased ventricular wall tension, may account for the occurrence of subcellular remodelling in CHF. Remodelling of extracellular matrix may induce changes in cardiomyocyte structure and cellular permeability, whereas sarcolemmal remodelling may be associated with defects in receptor-mediated signal transduction as well as activities of cation channels and transporters. Furthermore, sarcoplasmic reticulum remodelling is associated with changes in the activities of Ca$^{2+}$-cycling proteins, whereas myofibrillar remodelling is associated with abnormalities in both contractile and regulatory proteins. Alterations in energy production and redox status of cardiomyocytes may reflect mitochondrial remodelling, whereas changes in cardiac gene expression may be due to remodelling of the nucleus. Since heart function is determined by precisely coordinated activities of subcellular organelles and since different subcellular organelles undergo varying degrees of remodelling in the hypertrophied and failing hearts, it is suggested that differential subcellular remodelling results in cardiac dysfunction during the development of CHF.

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Subcellular remodelling in heart failure


