Exploration of Medicine

Open Exploration

Open Access Review

Role of angiotensin II in the development of subcellular remodeling in heart failure

Sukhwinder K. Bhullar[1], Anureet K. Shah[2], Naranjan S. Dhalla[1,3]*

[1]Institute of Cardiovascular Sciences, St. Boniface Hospital Albrechtsen Research Centre, University of Manitoba, Winnipeg, Manitoba R2H 2A6, Canada

[2]School of Kinesiology, Nutrition and Food Science, California State University, Los Angeles, CA 90032, USA

[3]Department of Physiology and Pathophysiology, Max Rady College of Medicine, University of Manitoba, Winnipeg, Manitoba R3E 3P5, Canada

***Correspondence:** Naranjan S. Dhalla, Institute of Cardiovascular Sciences, St. Boniface Hospital Albrechtsen Research Centre, Winnipeg, Manitoba R2H 2A6, Canada. nsdhalla@sbrc.ca

Academic Editor: Carlos Ferrario, Wake Forest School of Medicine, USA

Received: April 28, 2021 **Accepted:** June 27, 2021 **Published:** August 31, 2021

Cite this article: Bhullar SK, Shah AK, Dhalla NS. Role of angiotensin II in the development of subcellular remodeling in heart failure. Explor Med. 2021;2:352-71. https://doi.org/10.37349/emed.2021.00054

Abstract

The development of heart failure under various pathological conditions such as myocardial infarction (MI), hypertension and diabetes are accompanied by adverse cardiac remodeling and cardiac dysfunction. Since heart function is mainly determined by coordinated activities of different subcellular organelles including sarcolemma, sarcoplasmic reticulum, mitochondria and myofibrils for regulating the intracellular concentration of Ca^{2+}, it has been suggested that the occurrence of heart failure is a consequence of subcellular remodeling, metabolic alterations and Ca^{2+}-handling abnormalities in cardiomyocytes. Because of the elevated plasma levels of angiotensin II (ANG II) due to activation of the renin-angiotensin system (RAS) in heart failure, we have evaluated the effectiveness of treatments with angiotensin converting enzyme (ACE) inhibitors and ANG II type 1 receptor (AT1R) antagonists in different experimental models of heart failure. Attenuation of marked alterations in subcellular activities, protein content and gene expression were associated with improvement in cardiac function in MI-induced heart failure by treatment with enalapril (an ACE inhibitor) or losartan (an AT1R antagonist). Similar beneficial effects of ANG II blockade on subcellular remodeling and cardiac performance were also observed in failing hearts due to pressure overload, volume overload or chronic diabetes. Treatments with enalapril and losartan were seen to reduce the degree of RAS activation as well as the level of oxidative stress in failing hearts. These observations provide evidence which further substantiate to support the view that activation of RAS and high level of plasma ANG II play a critical role in inducing subcellular defects and cardiac dysfunction during the progression of heart failure.

Keywords

Angiotensin II, heart failure, subcellular remodeling, oxidative stress, ACE inhibitors, AT1R antagonists, cardiac function

Introduction

Heart failure affects an estimated 40 million people worldwide and the prevalence of this global pandemic in the United States is expected to increase to about 8 million by 2030 from the current level of 6.4 million [1-3]. It should be noted that heart failure is associated with inability of the heart to pump sufficient blood to meet metabolic requirements of the body. Resulting as a consequence of cardiovascular abnormalities, this progressive and complex clinical disorder includes several organs and reveals various symptoms like fluid retention, breathlessness and exercise intolerance. Several pathological conditions such as hypertension, ischemic heart disease, valvular heart disease, myocarditis and diabetes are known to result in the development of cardiac dysfunction and heart failure. Although heart failure is invariably associated with cardiac hypertrophy (an increase in muscle mass and enlargement of the heart), changes in size, shape, and structure of the myocardium (cardiac remodeling) as well as neurohormonal activation are considered to account for its progression [4-12]. Since heart function is either augmented or unaltered during the development of cardiac hypertrophy, it should be indicated as adaptive cardiac remodeling. On the other hand, heart failure is associated with cardiac dysfunction in hypertrophied myocardium and thus should be indicated as adverse cardiac remodeling. A wide variety of experimental evidence has suggested that degradation of glycocalyx proteins in the extracellular matrix results in the transition of cardiac hypertrophy to heart failure whereas subcellular defects with respect to Ca^{2+}-handling and metabolic abnormalities reflect the progression of heart failure [7-13]. It is pointed out that heart function is mainly determined by the coordinated activities of subcellular organelles such as sarcoplasmic reticulum (SR), sarcolemma (SL), myofibrils (MF) and mitochondria (MT) with respect to Ca^{2+}-handling and metabolic processes in cardiomyocytes. Thus, any defect in the function of these subcellular organelles can be seen to induce heart dysfunction under diverse pathological conditions. Some of the affected sites and associated functional abnormalities in subcellular organelles in failing hearts are shown in Figure 1. Accordingly, it has been suggested that the progression of cardiac dysfunction during the development of heart failure is associated with subcellular remodeling in terms of molecular, biochemical and structural alterations in cardiomyocytes as a consequence of various pathological stimuli [14-24]. Such subcellular remodeling leading to the induction of Ca^{2+}-handling abnormalities, metabolic defects and cardiac dysfunction are promoted by changes in cardiac gene expression as well as activation of different proteases and phospholipases due to prolonged effects of the elevated levels of several neurohormones in the circulation [6, 9, 17, 18, 23-29].

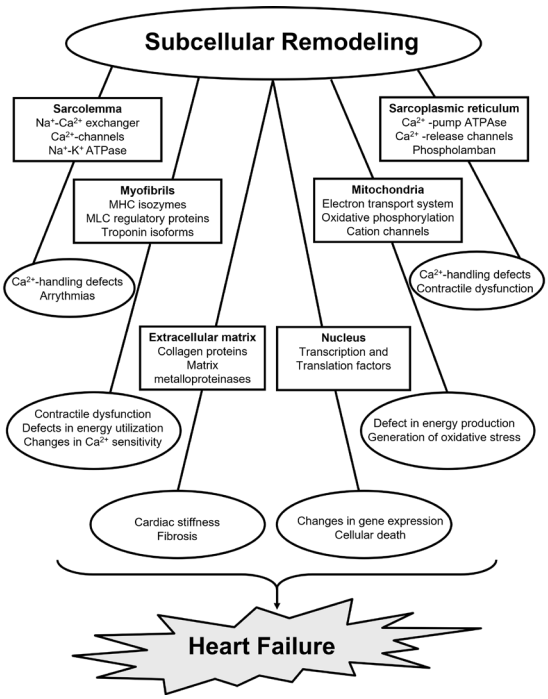

Figure 1. Subcellular targets, sites affected, and functional abnormalities in cardiomyocytes during the development of heart failure. MHC: myosin heavy chain; MLC: myosin light chain

It is now well known that the renin-angiotensin system (RAS) is one of the most important neuro-endocrine systems, which is activated during the development of diabetes, ischemic heart disease and heart failure [6, 7, 19, 20, 30-36]. The RAS is present in both peripheral system and myocardial interstitium, and its activation results in the formation of angiotensin II (ANG II) due to the involvement of different components including angiotensin converting enzyme (ACE). By virtue of its action on ANG II type 1 receptor (AT1R), ANG II activates signal transduction mechanism, increases the intracellular concentration of Ca^{2+} and promotes the occurrence of adaptive cardiac remodeling or cardiac hypertrophy. However, the elevated levels of circulating ANG II for a prolonged period result in the development of heart dysfunction and adverse cardiac remodeling or heart failure [30-36]. In view of the increased clinical severity of heart failure and prognostic value of the elevated levels of ANG II, various ACE inhibitors and AT1R antagonists are considered to represent the most effective pharmacological treatments of heart failure [37-41]. Not only these treatments for ANG II blockade improve heart function and delay the development of end-stage heart failure, this drug therapy also reduces the occurrence of apoptosis, fibrosis and endothelial dysfunction in the failing heart [42-47]. In addition, different ACE inhibitors and AT1R have been reported to attenuate subcellular remodeling and changes in various signal transduction mechanisms in heart failure [44-53].

In view of the complexities of mechanisms for the formation and actions of ANG II [19, 30, 31, 54, 55], a great caution should be exercised while implicating its role in the development of cardiac remodeling and subcellular defects in heart failure. In this regard, it is noteworthy that ANG II is synthetized by circulating (peripheral) RAS involving renin and ACE whereas alternative enzymes such as chymase and cathepsins are involved in its formation in the tissue (intracellular) RAS [55]. The role of chymase in cardiac remodeling is evident from the observation that inhibitors of chymase were found to exert cardioprotection in different types of heart failure [54, 55]. Furthermore, while no chymase-mediated ANG II synthesis was observed in fibroblast, the tissue ANG II synthesis in the cardiac cells was depressed by both renin and ACE inhibitors. It has also been observed that the activity of tissue RAS is increased in some pathological conditions and its regulation is dependent upon the type of tissue and pathological conditions [54]. Nonetheless, the major actions of both circulating and tissue RAS are mediated through the activation of AT1R [19, 30, 31]. Elevated levels of ANG II during early stages of pathological stimulus are considered to induce adaptive changes such as cardiac hypertrophy in the heart for maintaining cardiovascular homeostasis but adverse effects such as heart failure become evident upon prolonged exposure. Various signal transduction mechanisms have been suggested to explain both the adaptive and adverse effects of ANG II and are detailed elsewhere [12, 17, 31, 37, 51-53]. It should be mentioned that a new axis of RAS namely ACE2/ANG 1-7/Mas receptor axis, has been demonstrated to counter-act the adverse effects of ACE/ANG II/AT1R during the development of heart failure [56-59]. It is also pointed out that ACE2, a homologue of ACE, has been shown to convert ANG II into ANG 1-7 involving Mas receptors; its loss has been reported to enhance the susceptibility to heart failure and increase was associated with prevention of the heart failure phenotype [56, 57]. Thus ACE2/ANG 1-7/Mas receptor axis of RAS can be seen as a potential target for the development of improved therapy of heart failure.

Over the past two decades, several experimental and clinical observations have uncovered some key molecular and cellular mechanisms in the heart regarding actions of ANG II and its signaling pathways beyond its role in the regulation of blood pressure [51-53, 60-63]. It has now become clear that ANG II released due to the activation of both peripheral and cardiac RAS plays an important role in the development of both adaptive and adverse cardiac remodeling at early and late stages of heart failure. Furthermore, treatments of heart failure subjects with different pharmacological interventions known to not only reduce the increased muscle mass and improve cardiac function but also delay the progression of adverse cardiac remodeling. However, not much attention has been paid with respect to the role of ANG II for the occurrence of subcellular defects, Ca^{2+}-handling abnormalities and metabolic alterations in heart failure. This article is therefore intended to describe the participation of subcellular remodeling in inducing changes in Ca^{2+}-handling and heart dysfunction during the progression of adverse cardiac remodeling. It is also planned to discuss the evidence regarding the beneficial effects of ANG II blockade in attenuating subcellular remodeling for improving cardiac function in some experimental models of heart failure including those due to myocardial infarction (MI), pressure overload, volume overload and chronic diabetes. Although a wide variety of ACE inhibitors and

AT1R antagonists are known to exert beneficial effects in heart failure, we have chosen to show observations regarding the effectiveness of enalapril (an ACE inhibitor) and losartan (an AT1R antagonist) in heart failure. It is also pointed out that renin is an essential component of RAS as well as aldosterone is invariably released during the activation of RAS, and their antagonists have been reported to improve cardiovascular function in heart failure [64-67]; however, discussion on these aspects is considered beyond the scope of this review.

Subcellular remodeling and development of heart failure

Several studies have revealed that heart failure is mainly due to adverse cardiac remodeling [7, 10, 68, 69] and is accompanied by remodeling of subcellular organelles including SL, SR, MT, MF, and extracellular matrix [8, 9, 24, 26, 27, 29, 46]. Depending upon the type and stage of heart failure, varying degrees of defects in the biochemical and molecular composition of these organelles have been identified to account for cardiac dysfunction in the failing heart [17-19, 24, 26, 29, 70-72]. Activation of different proteases and phospholipases, and alterations in gene expression have been demonstrated to explain changes in these organelles [9, 22, 73, 74]. While alterations in cardiomyocyte architecture and gene expression are considered to occur due to remodeling of extracellular matrix and nucleus, respectively [9, 26, 46, 75-77], the transition of cardiac hypertrophy to heart failure has been suggested to be due to the degradation of extracellular matrix proteins [75, 76]. Remodeling of SL can be seen to induce alterations in myocardial cation composition and signal transduction as a consequence of changes in different receptors, cation channels and cation transporters [18, 19, 78, 79]. On the other hand, remodeling of MT would produce defects in the process of energy production as well as redox status in the failing heart due to alterations in electron transport and oxidative phosphorylation systems [50, 80-83]. Impairment of mitochondrial function is generally associated with the generation of oxidative stress [23]. Furthermore, remodeling of SR can be seen to be associated with defects in Ca^{2+}-cycling proteins and changes in Ca^{2+}-uptake and release activities [15-19], whereas changes in MF in the failing heart will induce changes in their sensitivity to Ca^{2+} [84, 85]. Remodeling of MF is also associated with alterations in both contractile and regulatory proteins to produce changes in cardiac contraction and relaxation [24, 26, 86-89]. In addition, marked changes in different receptor-mediated signal transduction mechanisms, which are known to affect subcellular functions, have been reported in the failing hearts [9, 71, 84, 90]. Thus, subcellular remodeling, metabolic defects, Ca^{2+}-handling abnormalities, and oxidative stress play a significant role in cardiac dysfunction during the development of heart failure.

It needs to be emphasized that various subcellular organelles are intimately involved in the generation of cardiac contractile force as a consequence of increase in the cytosolic free Ca^{2+} concentration ($[Ca^{2+}]_i$) due to Ca^{2+}-entry through the SL Ca^{2+}-channels and opening of the SR Ca^{2+}-release channel (ryanodine receptor type 2, RyR2) [91, 92]. This Ca^{2+} then binds with Troponin C (TnC), relieves its inhibitory effect on tropomyosin and promotes the interaction of myosin and actin filaments. It is now well established that the catalytic activity of myosin ATPase enzyme is influenced by the MHC isoforms for the occurrence of the cardiac contraction [93-95]. On the other hand, cardiac relaxation occurs upon the sequestration of $[Ca^{2+}]_i$ and dissociation of myosin filaments from actin filaments. It should be mentioned that Ca^{2+} sequestration is influenced mainly by the sarcoplasmic/endoplasmic reticulum Ca^{2+}-pump ATPase (SERCA2a) and SL Na^+-Ca^{2+} exchanger [19, 94, 96, 97]. It is also pointed out that MT are primarily concerned with the production of adenosine triphosphate (ATP), which is required for cardiac contraction and relaxation; however, these organelles are also known to serve as Ca^{2+}-buffer under conditions when cardiomyocyte is faced with an excessive level of $[Ca^{2+}]_i$ [17, 18, 84]. Thus, it is evident that a defect in any subcellular organelle could produce disturbance in the coordination of the contraction-relaxation cycle and lead to the development of cardiac dysfunction.

In view of the marked activation of RAS, elevated levels of circulating ANG II, cardiac remodeling and cardiac dysfunction in heart failure [98, 99], extensive efforts have been made to understand the mechanisms of cardiovascular actions of ANG II as well as discovering some therapeutic strategies for the management and treatment of heart failure [6, 31, 39, 62, 100-104]. The AT1R-mediated intracellular signal transductions have been shown to contribute to progression of cardiac remodeling, production of reactive oxygen species, elevation of $[Ca^{2+}]_i$ as well as activation of protein kinase C and mitogen-activated protein kinase

(MAPK) [105-109]. Thus, reduction in the formation of ANG II and blockade of its effects have been shown to partially prevent cardiac abnormalities and delay the progression of heart failure. In this regard, various ACE inhibitors such as captopril, benazepril, enalapril, ramipril, perindopril, imidapril and trandolapril [110-115], and different AT1R antagonists including losartan, valsartan, irbesartan, candesartan cilexetil, telmisartan and eprosartan [116-122] have been reported to prevent alterations in the failing heart at subcellular and molecular levels and improve heart function in heart failure. It should also be mentioned that ANG II blockade has been shown to attenuate changes in collagen expression, β-adrenoceptor signal transduction system and ATP-induced increase in $[Ca^{2+}]_i$ in the failing heart [123-126]. These observations support the view that the activation of RAS and elevated plasma levels of ANG II play an important role in the pathogenesis of cardiac dysfunction and subcellular abnormalities in heart failure. Furthermore, these studies have provided justification for the use of ACE inhibitors and AT1R antagonists for the treatment of heart failure.

ANG II and subcellular remodeling in MI-induced heart failure

Ischemic heart disease or MI, which becomes evident as a consequence of blockade of the coronary arteries, is most prevalent among several cardiovascular abnormalities leading to the development of heart failure. Elevated level of plasma ANG II in acute MI activates membrane receptors (AT1R) and produces cardiac hypertrophy by stimulating different signal transduction pathways; the activities of subcellular organelles as well as cardiac function are increased during this early period [5, 12, 127]. On the other hand, prolonged elevation of plasma ANG II in chronic MI has been reported to promote the formation of oxyradicals, induce Ca^{2+}-handling abnormalities, depress cardiac gene expression, activate different proteases and result in the development of cardiac dysfunction in the hypertrophied heart [26, 46, 47, 128]. The role of ANG II in inducing subcellular defects and cardiac dysfunction in MI-induced heart failure was examined in a well-established rat model of heart failure due to coronary occlusion [129, 130] with or without ACE inhibitors and AT1R antagonists treatments [113, 116]. It should be mentioned that myocardial infarct in the experimental animals is fully healed in about 3 weeks, cardiac function begins to decline thereafter and the moderate degree of heart failure was seen at about 7 weeks. Accordingly, drug treatments were started at 3 weeks and the animals were examined at 7 weeks after inducing MI. The data on cardiac function, status of RAS activities and levels of oxidative stress in MI groups with or without enalapril and losartan treatments are given in Table 1. It can be seen that different parameters for cardiac function such as left ventricular (LV) end-diastolic pressure was elevated without any changes in LV systolic pressure whereas both ± dP/dt were depressed in the failing heart. Furthermore, RAS activities as measured by plasma ANG II, plasma ACE and LV ACE were increased in heart failure. High level of oxidative stress in the failing heart was evident from increased content of malondialdehyde, conjugated dienes formation, and oxidized glutathione as well as decreased content of reduced glutathione (Table 1). Treatment of infarcted animals with enalapril and losartan was observed to improve cardiac function and decrease the level of oxidative stress. It should also be noted that enalapril, which inhibits ACE activity, depressed plasma ANG II levels, and plasma as well as LV ACE activities whereas losartan, which inhibits the action of ANG II by blocking AT1R did not reduce any of the parameters for the activation of RAS. These observations provide evidence that ANG II is involved in depressing cardiac function and increasing the level of oxidative stress during the development of MI-induced heart failure.

Table 1. Cardiac performance, status of RAS and oxidative stress in control and MI animals with or without ENP and LOS treatments for 4 weeks starting at 3 weeks after induction of MI

Parameters	Control	MI	MI + ENP	MI + LOS
A. Hemodynamic parameters				
LVEDP (mmHg)	4.0 ± 0.2	15.9 ± 1.3*	7.5 ± 0.6†	6.9 ± 0.5†
LVSP (mmHg)	133 ± 4.9	128 ± 3.2	131 ± 3.8	127 ± 3.9
LV + dP/dt (mmHg/s)	9,208 ± 1075	4,806 ± 745*	7,690 ± 680†	7,544 ± 722†
LV - dP/dt (mmHg/s)	8,788 ± 956	4,326 ± 590*	7,248 ± 702†	7,312 ± 690†

Table 1. Cardiac performance, status of RAS and oxidative stress in control and MI animals with or without ENP and LOS treatments for 4 weeks starting at 3 weeks after induction of MI (*continued*)

Parameters	Control	MI	MI + ENP	MI + LOS
B. RAS activity parameters				
Plasma ANG II (fmol/mL)	8.3 ± 1.4	125 ± 6.9*	34 ± 3.5†	192 ± 9.9†
Plasma ACE activity (nmol/min per mL)	51 ± 3.3	85 ± 7.1*	32 ± 2.4†	145 ± 7.1†
LV ACE activity (nmol/min per mg protein)	0.45 ± 0.03	0.69 ± 0.04*	0.23 ± 0.02†	0.84 ± 0.05†
C. Oxidative stress levels				
LV MDA (nmol/mg tissue lipids)	5.9 ± 0.4	19.1 ± 0.8*	12.7 ± 0.3†	10.1 ± 0.4†
LV conjugated dienes formation (nmol/mg tissue lipids)	33 ± 1.9	56 ± 4.9*	41 ± 3.0†	37 ± 3.3†
LV GSH (μmol/g tissue)	82 ± 1.6	36 ± 4.1*	74 ± 4.1†	68 ± 3.7†
LV GSSG (μmol/g tissue)	12.4 ± 0.8	25.2 ± 2.6*	14.2 ± 1.4†	15.3 ± 1.6†

Values are mean ± standard error (SE) of 4-6 animals in each group. ENP: enalapril (10 mg/kg per day); LOS: losartan (20 mg/kg per day); MI: myocardial infarction; RAS: renin-angiotensin system; ACE: angiotensin-converting enzyme; LVEDP: LV end diastolic pressure; LVSP: LV systolic pressure; + dP/dt: maximum rate of pressure development; - dP/dt: maximum rate of pressure decay; MDA: malondialdehyde; GSH: reduced glutathione; GSSG: oxidized glutathione. Data are based on the analysis of the information in our papers Shao et al. Am J Physiol Heart Circ Physiol. 2005;288:H2637-46 [116]; and Shao et al. Am J Physiol Heart Circ Physiol. 2005;288:H1674-82 [113]. *P < 0.05 compared with control; †P < 0.05 compared with MI group

Since Na^+-K^+-ATPase activity as well as associated gene expression and corresponding protein contents of different isoforms of the enzyme were altered in the failing hearts, it was suggested that there occurs remodeling of SL membrane in MI-induced failure [17, 19]. In this regard, reduction in Na^+-K^+-ATPase activity in MI-induced heart failure and depression in gene expression and protein contents of Na^+-K^+-ATPase isoforms were attenuated by a long acting ACE inhibitor, imidapril [116]. The data in Table 2, show that the depressed activities of both SL Na^+-Ca^{2+} exchange and Na^+-K^+-ATPase activities in the failing hearts were attenuated by treatments with enalapril and losartan. Furthermore, changes in protein content as well as messenger ribonucleic acid (mRNA) levels for different isoforms of Na^+-K^+-ATPase were partially or fully prevented by enalapril and losartan treatments [131]. Likewise, the MI-induced alterations in MF Ca^{2+}-stimulated ATPase activities, myosin gene expression and protein content were attenuated by the blockade of RAS by treatments of infarcted rats with agents such as imidapril [24, 93]. The beneficial effects of enalapril and losartan treatments on changes in MF Ca^{2+}-stimulated ATPase and MHC isoforms and mRNA levels are shown in Table 3 [119].

Table 2. Sarcolemmal activities of Na^+-Ca^{2+} exchange and Na^+-K^+-ATPase as well protein content and mRNA levels of N^+-K^+-ATPase in control and MI animals with or without ENP and LOS treatments for 4 weeks starting at 3 weeks after induction of MI

Parameters	Control	MI	MI + ENP	MI + LOS
A. SL activities				
Na^+-Ca^{2+} exchange activity (nmol Ca^{2+} mg/2s)	8.2 ± 0.51	3.8 ± 0.26*	7.4 ± 0.45†	7.0 ± 0.21†
Na^+-K^+-ATPase activity (μmol Pi/mg per h)	22.1 ± 0.82	12.9 ± 0.64*	18.3 ± 0.59†	18.6 ± 0.84†
B. Na^+-K^+-ATPase isoform protein content (% of control)				
α2	100	79.6 ± 3.4*	89.9 ± 1.6†	92.9 ± 2.5†
α3	100	134.0 ± 5.2*	114.7 ± 4.2†	113.6 ± 5.5†
β2	100	73.6 ± 3.1*	98.6 ± 8.5†	99.2 ± 8.5†
β3	100	66.8 ± 1.6*	81.1 ± 4.5 †	90.3 ± 6.7 †
C. Na^+-K^+-ATPase isoform mRNA level (% of control)				
α1	100	107.5 ± 2.5	110.2 ± 4.8	112.2 ± 4.5
α2	100	72.9 ± 2.1*	86.3 ± 3.6†	85.5 ± 4.5†
α3	100	170.5 ± 9.5*	116.2 ± 4.8†	115.3 ± 14.8†
β1	100	110.7 ± 7.2	120.5 ± 6.5	120.2 ± 7.5

Values are mean ± SE of 6 animals in each group. Data are based on the analysis of the information in our papers Shao et al. Am J Physiol Heart Circ Physiol. 2005;288:H2637-46 [116] and Guo et al. Can J Physiol Pharmacol. 2008;86:139-47 [131]. *P < 0.05 compared with control; †P < 0.05 compared with MI group

Table 3. Myofibrillar ATPase activities, protein content and mRNA levels in control and MI animals with or without ENP and LOS for 5 weeks starting at 3 weeks after induction of MI

Parameters	Control	MI	MI + ENP	MI + LOS
A. MF activities (μmol Pi/mg per h)				
Ca^{2+}-stimulated ATPase activity	10.8 ± 0.4	7.1 ± 0.4*	8.3 ± 0.65	7.9 ± 0.52
Mg^{2+}-ATPase activity	3.6 ± 0.4	3.8 ± 0.45	3.2 ± 0.3	3.2 ± 0.3
B. Myosin heavy chain content (% of total)				
Total MHC	100	96.2 ± 4.9	100.0 ± 4.6	96.0 ± 9.8
α-MHC	93.5 ± 2.4	71.0 ± 1.8*	83.6 ± 1.3†	85.4 ± 1.6†
β-MHC	6.5 ± 0.3	29.0 ± 1.5*	17.6 ± 1.2†	13.8 ± 0.4†
C. Myosin heavy chain mRNA levels (Relative intensity)				
α-MHC	92.25 ± 0.25	71.25 ± 1.25*	81.90 ± 1.9†	82.75 ± 2.5†
β-MHC	7.50 ± 0.25	30.00 ± 1.25*	19.75 ± 1.75†	15.62 ± 0.12†

Values are mean ± SE of 7 animals in each group. Data are based on the analysis of the information in Figures 1, 2 and 3 in our paper Wang et al. Biochim Biophys Acta. 2004;1690:177-84 [119]. *P < 0.05 compared with control; †P < 0.05 compared with MI group

Several studies have reported that SR Ca^{2+} transport and heart function during MI-induced heart failure is attenuated by treatments with agents such as ACE inhibitors, captopril and trandolapril, which are known to reduce the level of ANG II formation or block its action [113, 114, 132]. Both enalapril and cilazapril (ACE inhibitors) as well as AT1R antagonists (telmisartan, losartan), have also been reported to attenuate MI-induced SR remodeling [118, 122, 133]. Imidapril has been demonstrated to prevent the MI-induced changes in cardiac function, protein kinase C (PKC) activities and isoforms, and phospholipase C and D activities as well as SR Ca^{2+} uptake and Ca^{2+} release activities [134-137]. The results shown in Table 4 indicate that marked alterations in SR Ca^{2+} uptake and Ca^{2+} release activities as well as protein content and gene expressions, unlike calsequestrin, in the failing hearts, were partially or fully prevented by treatments with enalapril or losartan [113, 118] (Table 4). These observations provide evidence that ANG II plays an important role in SR remodeling during the development of MI-induced heart failure. It should also be pointed out SR remodeling, like that for SL and MF remodeling, may involve the activations of proteases and phospholipases as well as changes in cardiac gene expressions [17-19]. Furthermore, the actions of ANG II on subcellular remodeling have been suggested to be mediated due to the development of oxidative stress and increased level of $[Ca^{2+}]_i$ in the failing cardiomyocyte [45, 84, 108].

Table 4. Sarcoplasmic reticular Ca^{2+} uptake and Ca^{2+} release activities, protein content and mRNA levels in control and MI animals with or without ENP and LOS treatments for 4 weeks starting at 3 weeks after induction of MI

Parameters	Control	MI	MI+ENP	MI+LOS
A. Ca^{2+} uptake activity (nmol/mg per 2 min)	110 ± 8.15	63.5 ± 4.8*	92 ± 6.3†	82 ± 4.8†
B. Ca^{2+} release activity (nmol/mg per 15 s)	8.25 ± 0.32	4.95 ± 0.43*	7.60 ± 0.37†	7.20 ± 0.24†
C. Protein content (% of control)				
Ryanodine receptor	100	58.5 ± 1.5*	85.9 ± 3.1†	83.8 ± 2.2†
Ca^{2+}-stimulated ATPase	100	50.5 ± 2.5*	78.2 ± 1.8†	67 ± 2.5†
Calsequestrin	100	105.2 ± 4.8	98.3 ± 4.7	96.9 ± 13.1
Phospholamban	100	69.1 ± 5.9*	86.6 ± 4.4†	80.8 ± 8.2†
D. mRNA levels (% of control)				
Ryanodine receptor	100	64.8 ± 5.3*	84.75 ± 2.6†	86.8 ± 4.5†
Ca^{2+}-stimulated ATPase	100	73.9 ± 4.1*	86.7 ± 5.3†	98.6 ± 6.4†
Calsequestrin	100	105.4 ± 1.6	97.9 ± 7.1	97.4 ± 4.6
Phospholamban	100	78.3 ± 3.7*	97.3 ± 5.7†	92.0 ± 6.5†

Values are mean ± SE of 7 animals in each group. Data are based on the analysis of the information in table 5 and figures 3 and 4 in our papers Shao et al. Am J Physiol Circ Physiol. 2005;288:H1674-82 [113] and Guo et al. Mol Cell Biochem. 2003;254:163-72 [118]. *P < 0.05 compared with control; †P < 0.05 compared with MI group

Modification of subcellular remodeling by ANG II blockade in pressure overload-induced heart failure

Various reports have indicated that heart failure due to pressure overload is associated with changes in the activities of different subcellular organelles as well as gene expression [138-148]. Accordingly, it has been suggested that cardiac dysfunction due to pressure overload is a consequence of SL, SR, MF and MT remodeling [149]. It is noteworthy that ANG II has been shown to alter gene expression of Ca^{2+}-transport proteins in cardiomyocytes [150]. Furthermore, some ACE inhibitors were demonstrated to increase heart function, lower pressure overload and reduce cardiac hypertrophy [151, 152]. It can be seen from Table 5, that treatment of pressure overloaded animals with both captopril and losartan [153] improved cardiac function and attenuated depressions in SR Ca^{2+}-transport as well as depressed SR Ca^{2+}-stimulated ATPase protein content and mRNA levels. Furthermore, changes in MF Ca^{2+}-stimulated and myosin ATPase activities as well as MHC mRNA were prevented by treatments with these agents. Inhibition of ACE and antagonism of AT1R were also observed to improve cardiac function and SR Ca^{2+}-stimulated ATPase expression in hypertensive cardiomyopathy [154]. It is thus evident that the improvement of cardiac function by RAS blockade may be elicited by prevention of subcellular remodeling in the pressure-overloaded heart. It should be noted that the activity as well as mRNA levels of ACE are increased in the heart due to pressure overload [155] and both ACE inhibitors and AT1R antagonists are used clinically for the therapy of heart disease [156-158].

Table 5. Sarcoplasmic reticular and myofibrillar activities in PO-induced cardiac dysfunction in rats with or without CAP and LOS treatments for 8 weeks

Parameters	Control	PO	PO + CAP	PO + LOS
A. Cardiac function				
LVDP (mmHg)	122 ± 2.8	90 ± 3.1*	114 ± 2.5†	112 ± 2.5†
LVEDP (mmHg)	3.6 ± 1.0	10.8 ± 2.1*	4.5 ± 0.6†	5.7 ± 0.4†
B. SR activity and protein and gene expression				
Ca^{2+}-uptake (nmol Ca^{2+}/mg per min)	80.0 ± 3.6	46.7 ± 1.8*	70.7 ± 1.8†	67.0 ± 3.7†
Ca^{2+}-release (nmol Ca^{2+}/mg per min)	20.5 ± 1.9	13.0 ± 0.9*	18.2 ± 0.9†	17.2 ± 0.9†
Ca^{2+}-stimulated ATPase protein content (% of control)	100	80.0 ± 0.4*	94.0 ± 2.0†	92.06 ± 3.0†
Ca^{2+}-stimulated ATPase mRNA levels (% of control)	100	56.0 ± 2.0*	88.0 ± 3.0†	86.0 ± 3.0†
C. MF and myosin activities				
MF Ca^{2+}-stimulated ATPase (μmol Pi/mg per h)	11.5 ± 0.8	5.9 ± 0.02*	10.1 ± 0.88†	9. 81 ± 0.22†
Myosin Ca^{2+}-ATPase (μmol Pi/mg per h)	18.8 ± 0.5	12.7 ± 0.02*	17.4 ± 0.5†	16.9 ± 0.5†
Myosin mRNA levels (Relative intensity)				
α-MHC	0.28 ± 0.02	0.13 ± 0.03*	0.23 ± 0.02†	0.22 ± 0.01†
β-MHC	0.03 ± 0.01	1.18 ± 0.10*	0.08 ± 0.01†	0.10 ± 0.02†

Values are mean ± SE of 6 animals in each group. CAP: captopril (2 g/L); PO: pressure overload; LVDP: left ventricular developed pressure. Data are based on the analysis of the information in Figures 1, 3, 4, 5 and 6 in our paper Liu et al. Clin Exp Hypertens. 1999;21:145-56 [153]. *P < 0.05 compared with control; †P < 0.05 compared with PO group

Modification of cardiac remodeling and cardiac dysfunction in volume overload-induced heart failure by ANG II blockade

Although ANG II has been reported to play an important role in pathogenesis of different types of cardiac hypertrophy and heart failure [159], Leenen and associates [160-162] have shown both cardiac and peripheral RAS are activated by MI and volume overload. Different functions of cardiac SR were also altered by the induction of volume overload [163]. ANG II elicits its response by acting on AT1R-mediated MAPK signal transduction pathways as well as upon stimulating nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which has further been shown to produce cardiac hypertrophy, oxidative stress, and heart failure [105-108, 164-167]. The effects of both enalapril and losartan on cardiac remodeling and cardiac dysfunction were examined in heart failure due to volume overload. The data in Table 6 show that cardiac remodeling (as reflected by increased heart weight and heart weight to body weight ratio) and cardiac dysfunction (as reflected by depressed LVSP, +dP/dt and -dP/dt as well as increased left ventricular

end diastolic pressure (LVEDP)) are evident in failing hearts due to volume overload [168]. Furthermore, phosphorylated extracellular-signal-regulated kinase (ERK)1 and phosphorylated ERK2 content as well as ERK1/ERK2 activity [as measured by phospho-ERK1/ERK2 activity (phospho-ELK1) content] were also observed to be increased in heart failure due to volume overload. It can also be seen from Table 6 that cardiac remodeling, cardiac dysfunction and changes in phosphorylated MAPK content and activities in hearts failing due to volume overload were attenuated by treatments of animals with enalapril and losartan. It should be mentioned that treatment of heart failure animals with imidrapil has been observed to partially prevent alterations in SL, SR and MF activities due to volume overload (Dhalla-unpublished observations). Thus, activation of RAS is considered to be involved in inducing cardiac remodeling as well as changes in cardiac function and subcellular organelles during the development of heart failure due to volume overload.

Table 6. Cardiac dysfunction, cardiac remodeling and alterations in protein content of phospho- ERK1, ERK2 and ELK1 in rats following the induction of heart failure by VO with or without ENP and LOS treatment for 16 weeks

Parameters	Control	VO	VO + ENP	VO + LOS
A. Cardiac remodeling				
Heart wt (mg)	1364 ± 41	2209 ± 117*	1671 ± 97†	1526 ± 105†
LV wt (mg)	1067 ± 29	1640 ± 142*	1217 ± 61†	1119 ± 66†
RV wt (mg)	300 ± 13	554 ± 42*	462 ± 25†	394 ± 36†
HW/BW ratio (mg/g)	2.23 ± 0.13	3.37 ± 0.14*	2.68 ± 0.14†	2.47 ± 0.17†
B. Phospho-ERK1 and phospho-ERK2 content as well as ERK1/ERK2 activity				
Phospho-ERK1 (% of control)	100	552 ± 81*	309 ± 40†	127 ± 40†
Phospho-ERK2 (% of control)	100	572 ± 52*	312 ± 26†	131 ± 30†
Phospho-ELK1 (% of control)	100	777 ± 28*	144 ± 21†	87 ± 28†
C. Cardiac function				
LVSP (mm Hg)	115 ± 5	85 ± 2*	91 ± 6	93 ± 7
LVEDP (mm Hg)	5.2 ± 1.4	28.0 ± 1.9*	18.6 ± 1.5†	13.8 ± 0.6†
+ dP/dt (mm Hg/sec)	10,000 ± 429	4752 ± 240*	6995 ± 364†	7989 ± 88†
- dP/dt (mm Hg/sec)	10,208 ± 511	4724 ± 259*	7638 ± 380†	8068 ± 409†

Values are mean ± SE of 8 hearts in each group. VO: volume overload; LV wt: left ventricular weight; RV wt: right ventricular wt; BW: body weight; HW: heart weight. Data are based on the analysis of the information in Table 2 and Figures 3, 4 and 5 in our paper Zhang et al. J Cardiovasc Pharmacol Ther. 2010;15:84-92 [168]. *$P < 0.05$ compared with control; †$P < 0.05$ compared with VO group

Subcellular remodeling, cardiac function, and oxidative stress in chronic diabetes

Diabetic cardiomyopathy has been shown to be associated with the activation of RAS and subcellular remodeling [23, 169]. The elevated levels of circulating (level of) ANG II in chronic diabetes have been reported to produce marked alterations in myocardial metabolism and remodeling of SL, SR, MF and MT [170-173]. The data in Table 7 show that the diabetes-induced changes in cardiac function and oxidative stress by treatments with both enalapril and losartan; these changes were not associated with any reduction of hyperglycemia [174, 175]. The decreased SL Na^+-K^+-ATPase and Na^+-dependent Ca^{2+}-uptake activities, reduced SR Ca^{2+}-release and Ca^{2+}-pump activities as well as depressed myosin-ATPase activities in the heart were also attenuated by treatments of diabetic animals with enalapril and losartan (Table 7). These observations support the view that the improvement of cardiac performance by RAS blockade in chronic diabetes may be related to the attenuation of oxidative stress as well as subcellular remodeling.

Table 7. Cardiac performance, status of RAS, oxidative stress and subcellular activities in 8 weeks diabetic rats with or without ENP and LOS treatments

Parameters	Control	Diabetic	Diabetic + ENP	Diabetic + LOS
A. Cardiac function parameters				
LVSP (mm Hg)	140 ± 12.1	85 ± 8.4*	119 ± 7.6†	116 ± 6.9†
+ dP/dt (mm Hg/sec)	8856 ± 815	5380 ± 621*	7176 ± 702†	7044 ± 516†
B. RAS activities				
Plasma ANG II (fmol/ml)	7.2 ± 0.8	7.4 ± 0.5	6.4 ± 0.6	10.9 ± 0.4†
Plasma ACE activity (nmol/min per ml)	48 ± 2.5	52 ± 3.1	49 ± 3.5	57 ± 2.6
LV ACE activity (nmol/min per mg)	0.57 ± 0.03	0.89 ± 0.04*	0.56 ± 0.3†	0.79 ± 0.03
C. Oxidative stress levels				
LV GSH/GSSG Ratio	6.8 ± 0.4	2.5 ± 0.2*	4.3 ± 0.5†	4.8 ± 0.2†
MDA content (nmol/mg tissue lipids)	3.8 ± 0.13	7.1 ± 0.49*	4.9 ± 0.46†	5.4 ± 0.48†
D. Myosin ATPase activities				
Mg^{2+}-ATPase (nmol Pi/mg per 5 min)	1.2 ± 0.03	0.78 ± 0.07*	1.06 ± 0.05†	1.00 ± 0.06†
Ca^{2+}-ATPase (nmol Pi/mg per 5 min)	6.22 ± 0.18	3.14 ± 0.21*	4.91 ± 0.23†	4.86±0.28†
E. SL activities				
Na^+-K^+-ATPase (μmol Pi/mg per h)	23.2 ± 3.5	13.1 ± 1.8*	18.2 ± 1.6†	18.3 ± 1.5†
Na^+-Ca^{2+}-exchanger (nmol Ca^{2+}/mg per 10s)	21.3 ± 1.2	12.1 ± 0.9*	17.3 ± 1.2†	16.1 ± 1.5†
F. SR activities				
Ca^{2+}-stimulated ATPase (nmol Pi/mg per 5 min)	165 ± 7	115 ± 10*	154 ± 5†	153 ± 6†
Ca^{2+}-uptake (nmol Ca^{2+}/mg per 2 min)	62.7 ± 2.3	36.5 ± 3.1*	50.3 ± 2.1†	53.4 ± 2.7†

Values are mean ± SE of 6 to 8 animals in each group. Data are based on the analysis of the information in Tables 1 and 2 in our paper Liu et al. Ann. N.Y. Acad Sci. 2006;1084:141-54 [174] and Figures 1A, 3B, 5A and 6A in our paper Machackova et al. Mol Cell Biochem. 2004;261:271-8 [175]. *Significantly different ($P < 0.05$) from control; †Significantly different ($P < 0.05$) from untreated diabetic

Conclusions

A great deal of progress has been made for the development of therapy for heart failure and various interventions including those for RAS blockade have been observed to improve heart function and delay the occurrence of heart failure but their beneficial effects in reducing mortality and morbidity are not satisfactory. This is primarily due to the fact that heart failure is a complex problem and involves several hormones including ANG II. Thus, any treatment based on the antagonism of a single hormone may not be appropriate and thus a combination therapy may prove to be more beneficial. Furthermore, the current treatments of heart failure are based on the concepts of hemodynamic alterations and cardiac remodeling; however, very little attention has been paid to drug developments targeting at the molecular and subcellular levels. Accordingly, it is suggested that some new targets must be identified for improving the therapy of heart failure. Since it is becoming increasingly evident that remodeling of subcellular organelles such as SR, SL and MF is intimately involved in cardiac dysfunction during the development of heart failure, future therapeutic approaches that may focus on molecular mechanisms for remodeling of subcellular organelles. Particularly, the targeting pathological factors, such as Ca^{2+}-handling abnormalities, metabolic defects, oxidative stress, inflammatory system, protease activation, and cell signaling pathways, which are known to adversely affect subcellular organelles, may improve cardiac performance and prevent the progression of heart failure.

Abbreviations

$[Ca^{2+}]_i$: cytosolic free Ca^{2+} concentration

+ dP/dt: maximum rate of pressure development

ACE: angiotensin converting enzyme

ANG II: angiotensin II

AT1R: angiotensin II type 1 receptor

CAP: captopril

ENP: enalapril

ERK: extracellular-signal-regulated kinase

GSH: reduced glutathione

GSSG: oxidized glutathione

LOS: losartan

LV: left ventricular

LVEDP: left ventricular end diastolic pressure

LVSP: left ventricular systolic pressure

MAPK: mitogen-activated protein kinase

MF: myofibrils

MI: myocardial infarction

MT: mitochondria

PO: pressure overload

RAS: renin-angiotensin system

SL: sarcolemma

SR: sarcoplasmic reticulum

Declarations

Acknowledgments

The infrastructure support for this project was provided by the St. Boniface Hospital Research Foundation, Winnipeg, Canada. Thanks are also due to Ms. Andrea Opsima for typing this manuscript.

Author contributions

SKB searched the literature, analyzed the data and wrote the first draft; AKS analyzed the data and wrote the manuscript; NSD conceived, designed and edited the article. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

Not applicable.

Funding

Not applicable.

References

1. Orso F, Fabbri G, Maggioni AP. Epidemiology of heart failure. Handb Exp Pharmacol. 2017;243:15-33.
2. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2019 update: a report from the American Heart Association. Circulation. 2019;139:e56-528.
3. Lippi G, Sanchis-Gomar F. Global epidemiology and future trends of heart failure. AME Med J. 2020;5:15.
4. Parmley WW. Pathophysiology of congestive heart failure. Clin Cardiol. 1992;15 Suppl 1:15-12.
5. Packer M. Neurohormonal interactions and adaptations in congestive heart failure. Circulation. 1988;77:721-30.
6. Ferrario CM, Strawn WB. Role of the renin-angiotensin-aldosterone system and proinflammatory mediators in cardiovascular disease. Am J Cardiol. 2006;98:121-8.
7. Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling-concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. J Am Coll Cardiol. 2000;35:569-82.
8. Swynghedauw B. Molecular mechanisms of myocardial remodeling. Physiol Rev. 1999;79:215-62.
9. Dhalla NS, Afzal N, Beamish RE, Naimark B, Takeda N, Nagano M. Pathophysiology of cardiac dysfunction in congestive heart failure. Can J Cardiol. 1993;9:873-87.
10. Gajarsa JJ, Kloner RA. Left ventricular remodeling in the post-infarction heart: a review of cellular, molecular mechanisms, and therapeutic modalities. Heart Fail Rev. 2011;16:13-21.
11. Azevedo PS, Polegato BF, Minicucci MF, Paiva SA, Zornoff LA. Cardiac remodeling: concepts, clinical impact, pathophysiological mechanisms and pharmacologic treatment. Arq Bras Cardiol. 2016;106:62-9.
12. Oldfield CJ, Duhamel TA, Dhalla NS. Mechanisms for the transition from physiological to pathological cardiac hypertrophy. Can J Physiol Pharmacol. 2020;98:74-84.
13. Roe AT, Frisk M, Louch WE. Targeting cardiomyocyte Ca^{2+} homeostasis in heart failure. Curr Pharm Des. 2015;21:431-48.
14. Lee SH, Hadipour-Lakmehsari S, Murthy HR, Gibb N, Miyake T, Teng ACT, et al. REEP5 depletion causes sarco-endoplasmic reticulum vacuolization and cardiac functional defects. Nat Commun. 2020;11:965.
15. Dhalla NS, Das PK, Sharma GP. Subcellular basis of cardiac contractile failure. J Mol Cell Cardiol. 1978;10: 363-85.
16. Dhalla NS, Liu X, Panagia V, Takeda N. Subcellular remodeling and heart dysfunction in chronic diabetes. Cardiovasc Res. 1998;40:239-47.
17. Dhalla NS, Saini-Chohan HK, Rodriguez-Leyva D, Elimban V, Dent MR, Tappia PS. Subcellular remodeling may induce cardiac dysfunction in congestive heart failure. Cardiovasc Res. 2009;81:429-38.
18. Dhalla NS, Saini HK, Tappia PS, Sethi R, Mengi SA, Gupta SK. Potential role and mechanisms of subcellular remodeling in cardiac dysfunction due to ischemic heart disease. J Cardiovasc Med (Hagerstown). 2007;8:238-50.
19. Dhalla NS, Dent MR, Tappia PS, Sethi R, Barta J, Goyal RK. Subcellular remodeling as a viable target for the treatment of congestive heart failure. J Cardiovasc Pharmacol Ther. 2006;11:31-45.
20. Duhamel TA, Dhalla NS. New insights into the causes of heart failure. Drug Discov Today Dis Mech. 2007;4:175-84.
21. Babick AP, Dhalla NS. Role of subcellular remodeling in cardiac dysfunction due to congestive heart failure. Med Princ Pract. 2007;16:81-9.

22. Dhalla NS, Rangi S, Babick AP, Zieroth S, Elimban V. Cardiac remodeling and subcellular defects in heart failure due to myocardial infarction and aging. Heart Fail Rev. 2012;17:671-81.
23. Dhalla NS, Shah AK, Tappia PS. Role of oxidative stress in metabolic and subcellular abnormalities in diabetic cardiomyopathy. Int J Mol Sci. 2020;21:2413.
24. Machackova J, Barta J, Dhalla NS. Myofibrillar remodelling in cardiac hypertrophy, heart failure and cardiomyopathies. Can J Cardiol. 2006;22:953-68.
25. Deschamps AM, Spinale FG. Pathways of matrix metalloproteinase induction in heart failure: bioactive molecules and transcriptional regulation. Cardiovasc Res. 2006;69:666-76.
26. Hasenfuss G. Alterations of calcium-regulatory proteins in heart failure. Cardiovasc Res. 1998;37:279-89.
27. Morano I, Hädicke K, Haase H, Böhm M, Erdmann E, Schaub MC. Changes in essential myosin light chain isoform expression provide a molecular basis for isometric force regulation in the failing human heart. J Mol Cell Cardiol. 1997;29:1177-87.
28. Hasenfuss G. Animal models of human cardiovascular disease, heart failure and hypertrophy. Cardiovasc Res. 1998;39:60-76.
29. Prestle J, Quinn FR, Smith GL. Ca^{2+} -handling proteins and heart failure: novel molecular targets? Curr Med Chem. 2003;10:967-81.
30. Nehme A, Zouein FA, Zayeri ZD, Zibara K. An update on the tissue renin angiotensin system and its role in physiology and pathology. J Cardiovasc Dev Dis. 2019;6:14.
31. Bader M. Tissue renin-angiotensin-aldosterone systems: targets for pharmacological therapy. Annu Rev Pharmacol Toxicol. 2010;50:439-65.
32. Nehme A, Zibara K. Efficiency and specificity of RAAS inhibitors in cardiovascular diseases: how to achieve better end-organ protection? Hypertens Res. 2017;40:903-9.
33. Emdin M, Fatini C, Mirizzi G, Poletti R, Borrelli C, Prontera C, et al. Biomarkers of activation of renin-angiotensin-aldosterone system in heart failure: how useful, how feasible? Clin Chim Acta. 2015;443:85-93.
34. Vergaro G, Emdin M, Iervasi A, Zyw L, Gabutti A, Poletti R, et al. Prognostic value of plasma renin activity in heart failure. Am J Cardiol. 2011;108:246-51.
35. Emdin CA, Callender T, Cao J, McMurray JJ, Rahimi K. Meta-analysis of large-scale randomized trials to determine the effectiveness of inhibition of the renin-angiotensin aldosterone system in heart failure. Am J Cardiol. 2015;116:155-61.
36. Dell'italia LJ. Translational success stories: angiotensin receptor 1 antagonists in heart failure. Circ Res. 2011;109:437-52.
37. Mehta PK, Griendling KK. Angiotensin II cell signaling: physiological and pathological effects in the cardiovascular system. Am J Physiol Cell Physiol. 2007;292:C82-97.
38. Flather MD, Yusuf S, Køber L, Pfeffer M, Hall A, Murray G, et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. Lancet. 2000;355:1575-81.
39. McMurray JJ, Pfeffer MA, Swedberg K, Dzau VJ. Which inhibitor of the renin-angiotensin system should be used in chronic heart failure and acute myocardial infarction? Circulation. 2004;110:3281-8.
40. Francis GS, Cohn JN, Johnson G, Rector TS, Goldman S, Simon A. Plasma norepinephrine, plasma renin activity, and congestive heart failure. Relations to survival and the effects of therapy in V-HeFT II. The V-HeFT VA Cooperative Studies Group. Circulation. 1993;87:VI40-8.
41. Singh KD, Karnik SS. Angiotensin type 1 receptor blockers in heart failure. Curr Drug Targets. 2020;21:125-31.
42. Dzau VJ. Implications of local angiotensin production in cardiovascular physiology and pharmacology. Am J Cardiol. 1987;59:A59-65.

43. Hartupee J, Mann DL. Neurohormonal activation in heart failure with reduced ejection fraction. Nat Rev Cardiol. 2017;14:30-8.
44. Tham YK, Bernardo BC, Ooi JY, Weeks KL, McMullen JR. Pathophysiology of cardiac hypertrophy and heart failure: signaling pathways and novel therapeutic targets. Arch Toxicol. 2015;89:1401-38.
45. Dhalla NS, Shao Q, Panagia V. Remodeling of cardiac membranes during the development of congestive heart failure. Heart Fail Rev. 1998;2:261-72.
46. Guo X, Saini HK, Wang J, Gupta SK, Goyal RK, Dhalla NS. Prevention of remodeling in congestive heart failure due to myocardial infarction by blockade of the renin-angiotensin system. Expert Rev Cardiovasc Ther. 2005;3:717-32.
47. Shao Q, Takeda N, Temsah R, Dhalla KS, Dhalla NS. Prevention of hemodynamic changes due to myocardial infarction by early treatment of rats with imidapril. Cardiovasc Pathobiol. 1996;1:180-6.
48. Hsieh CC, Li CY, Hsu CH, Chen HL, Chen YH, Liu YP, et al. Mitochondrial protection by simvastatin against angiotensin II-mediated heart failure. Br J Pharmacol. 2019; 176:3791-804.
49. Wang X, Yuan B, Dong W, Yang B, Yang Y, Lin X, et al. Humid heat exposure induced oxidative stress and apoptosis in cardiomyocytes through the angiotensin II signaling pathway. Heart Vessels. 2015;30:396-405.
50. Zhou B, Tian R. Mitochondrial dysfunction in pathophysiology of heart failure. J Clin Invest. 2018;128:3716-26.
51. Higuchi S, Ohtsu H, Suzuki H, Shirai H, Frank GD, Eguchi S. Angiotensin II signal transduction through the AT1 receptor: novel insights into mechanisms and pathophysiology. Clin Sci (Lond). 2007;112:417-28.
52. Touyz RM, Schiffrin EL. Signal transduction mechanisms mediating the physiological and pathophysiological actions of angiotensin II in vascular smooth muscle cells. Pharmacol Rev. 2000;52:639-72.
53. Crowley SD, Coffman TM. Recent advances involving the renin-angiotensin system. Exp Cell Res. 2012;318:1049-56.
54. Kumar R, Boim MA. Diversity of pathways for intracellular angiotensin II synthesis. Curr Opin Nephrol Hypertens. 2009;18:33-9.
55. Doggrell SA, Wanstall JC. Cardiac chymase: pathophysiology role and therapeutic potential of chymase inhibitors. Can J Physiol Pharmacol. 2005;83:123-30.
56. Patel VB, Zhong JC, Grant MB, Oudit GY. Role of the ACE2/angiotensin 1-7 axis of the renin-angiotensin system in heart failure. Circ Res. 2016;118:1313-26.
57. Dorsainval W. ACE2/Ang1-7 Mas axis: the counter-regulator of the classical renin angiotensin system. Mako: NSU Undergrad Stud J. 2020;2020:Article 2.
58. Dang Z, Su S, Jin G, Nan X, Ma L, Li Z, et al. Tsantan sumtang attenuated chronic hypoxia-induced right ventricular structure remodeling and fibrosis by equilibrating local ACE-Ang II- AT1R/ACE2-Ang1-7-Mas axis in rat. J Ethnopharmacol. 2020;250:112470.
59. Sukumaran V, Veeraveedu PT, Gurusamy N, Yamaguchi K, Lakshmanan AP, Ma M, et al. Cardioprotective effects of telmisartan against heart failure in rats induced by experimental autoimmune myocarditis through the modulation of angiotensin-covering enzyme-2/angiotensin 1-7/mas receptor axis. Int J Biol Sci. 2011;7:1077-92.
60. Te Riet L, van Esch JH, Roks AJ, van den Meiracker AH, Danser AH. Hypertension: renin-angiotensin-aldosterone system alterations. Circ Res. 2015;116:960-75.
61. Vukelic S, Griendling KK. Angiotensin II, from vasoconstrictor to growth factor: a paradigm shift. Circ Res. 2014;114:754-7.
62. Forrester SJ, Booz GW, Sigmund CD, Coffman TM, Kawai T, Rizzo V, et al. Angiotensin II signal transduction: an update on mechanisms of physiology and pathophysiology. Physiol Rev. 2018;98:1627-738.

63. Ferrario CM, Ahmad S, Nagata S, Simington SW, Varagic J, Kon N, et al. An evolving story of angiotensin-II-forming pathways in rodents and humans. Clin Sci (Lond). 2014;126:461-9.
64. Sepehrdad R, Frishman WH, Stier CT Jr, Sica DA. Direct inhibition of renin as a cardiovascular pharmacotherapy: focus on aliskiren. Cardiol Rev. 2007;15:242-56.
65. Seed A, Gardner R, McMurray J, Hillier C, Murdoch D, MacFadyen R, et al. Neurohumoral effects of the new orally active renin inhibitor, aliskiren, in chronic heart failure. Eur J Heart Fail. 2007;9:1120-7.
66. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med. 1999;341:709-17.
67. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med. 2003;348:1309-21.
68. Chaudhry SI, Mattera JA, Curtis JP, Spertus JA, Herrin J, Lin Z, et al. Telemonitoring in patients with heart failure. N Engl J Med. 2010;363:2301-9.
69. Lakatta EG. Cardiovascular regulatory mechanisms in advanced age. Physiol Rev. 1993;73:413-67.
70. Pelouch V, Dixon IM, Golfman L, Beamish RE, Dhalla NS. Role of extracellular matrix proteins in heart function. Mol Cell Biochem. 1993;129:101-20.
71. Dhalla NS, Wang X, Sethi R, Das PK, Beamish RE. β-adrenergic linked signal transduction mechanisms in failing hearts. Heart Fail Rev. 1997;2:55-65.
72. Panagia V, Pierce GN, Dhalla KS, Ganguly PK, Beamish RE, Dhalla NS. Adaptive changes in subcellular calcium transport during catecholamine-induced cardiomyopathy. J Mol Cell Cardiol. 1985;17:411-20.
73. Tappia P, Singal T, Dent M, Asemu G, Rabban M, Dhalla NS. Phospholipid-mediated signaling in diseased myocardium. Future Lipidol. 2006;1:701-17.
74. Singh RB, Dandekar SP, Elimban V, Gupta SK, Dhalla NS. Role of proteases in the pathophysiology of cardiac disease. Mol Cell Biochem. 2004;263:241-56.
75. Spinale FG. Myocardial matrix remodeling and the matrix metalloproteinases: influence on cardiac form and function. Physiol Rev. 2007;87:1285-342.
76. Rysä J, Leskinen H, Ilves M, Ruskoaho H. Distinct upregulation of extracellular matrix genes in transition from hypertrophy to hypertensive heart failure. Hypertension. 2005;45:927-33.
77. Li YY, McTiernan CF, Feldman AM. Proinflammatory cytokines regulate tissue inhibitors of metalloproteinases and disintegrin metalloproteinase in cardiac cells. Cardiovasc Res. 1999;42:162-72.
78. Weisser-Thomas J, Kubo H, Hefner CA, Gaughan JP, McGowan BS, Ross R, et al. The Na^+/Ca^{2+} exchanger/SR Ca^{2+} ATPase transport capacity regulates the contractility of normal and hypertrophied feline ventricular myocytes. J Card Fail. 2005;11:380-7.
79. Camors E, Charue D, Trouvé P, Monceau V, Loyer X, Russo-Marie F, et al. Association of annexin A5 with Na^+/Ca^{2+} exchanger and caveolin-3 in non-failing and failing human heart. J Mol Cell Cardiol. 2006;40:47-55.
80. Tsutsui H, Ide T, Kinugawa S. Mitochondrial oxidative stress, DNA damage, and heart failure. Antioxid Redox Signal. 2006;8:1737-44.
81. Ishikawa K, Kimura S, Kobayashi A, Sato T, Matsumoto H, Ujiie Y, et al. Increased reactive oxygen species and anti-oxidative response in mitochondrial cardiomyopathy. Circ J. 2005;69:617-20.
82. Javadov S, Karmazyn M. Mitochondrial permeability transition pore opening as an endpoint to initiate cell death and as a putative target for cardioprotection. Cell Physiol Biochem. 2007;20:1-22.
83. Matsushima S, Ide T, Yamato M, Matsusaka H, Hattori F, Ikeuchi M, et al. Overexpression of mitochondrial peroxiredoxin-3 prevents left ventricular remodeling and failure after myocardial infarction in mice. Circulation. 2006;113:1779-86.

84. Dhalla NS, Wang X, Beamish RE. Intracellular calcium handling in normal and failing hearts. Exp Clin Cardiol. 1996;1:7-20.
85. Davies CH, Harding SE, Poole-Wilson PA. Cellular mechanisms of contractile dysfunction in human heart failure. Eur Heart J. 1996;17:189-98.
86. O'Brien PJ, Ianuzzo CD, Moe GW, Stopps TP, Armstrong PW. Rapid ventricular pacing of dogs to heart failure: biochemical and physiological studies. Can J Physiol Pharmacol. 1990;68:34-9.
87. Pagani ED, Alousi AA, Grant AM, Older TM, Dziuban SW Jr, Allen PD. Changes in myofibrillar content and Mg-ATPase activity in ventricular tissues from patients with heart failure caused by coronary artery disease, cardiomyopathy, or mitral valve insufficiency. Circ Res. 1988;63:380-5.
88. Neagoe C, Kulke M, del Monte F, Gwathmey JK, de Tombe PP, Hajjar RJ, et al. Titin isoform switch in ischemic human heart disease. Circulation. 2002;106:1333-41.
89. Huang X, Li J, Foster D, Lemanski SL, Dube DK, Zhang C, et al. Protein kinase C-mediated desmin phosphorylation is related to myofibril disarray in cardiomyopathic hamster heart. Exp Biol Med. 2002;227:1039-46.
90. Mudd JO, Kass DA. Tackling heart failure in the twenty-first century. Nature. 2008;451:919-28.
91. Catterall WA. Structure and regulation of voltage-gated Ca^{2+} channels. Annu Rev Cell Dev Biol. 2000;16:521-55.
92. Meissner G. Ryanodine receptor/ Ca^{2+} release channels and their regulation by endogenous effectors. Annu Rev Physiol. 1994;56:485-508.
93. Wang J, Liu X, Ren B, Rupp H, Takeda N, Dhalla NS. Modification of myosin gene expression by imidapril in failing heart due to myocardial infarction. J Mol Cell Cardiol. 2002;34:847-57.
94. Bers DM. Cardiac excitation-contraction coupling. Nature. 2002;415:198-205.
95. de Tombe PP. Cardiac myofilaments: mechanics and regulation. J Biomech. 2003;36:721-30.
96. Dhalla NS, Ziegelhoffer A, Harrow JA. Regulatory role of membrane systems in heart function. Can J Physiol Pharmacol. 1977;55:1211-34.
97. Egger M, Niggli E. Regulatory function of Na-Ca exchange in the heart: milestones and outlook. J Membrane Biol. 1999;168:107-30.
98. McMurray JJ. Clinical practice. Systolic heart failure. N Engl J Med. 2010;362:228-38.
99. Ames MK, Atkins CE, Pitt B. The renin-angiotensin-aldosterone system and its suppression. J Vet Intern Med. 2019;33:363-82.
100. Szczepanska-Sadowska E, Czarzasta K, Cudnoch-Jedrzejewska A. Dysregulation of the renin-angiotensin system and the vasopressinergic system interactions in cardiovascular disorders. Curr Hypertens Rep. 2018;20:1-24.
101. Bakogiannis C, Theofilogiannakos E, Papadopoulos C, Lazaridis C, Bikakis I, Tzikas S, et al. A translational approach to the renin-angiotensin-aldosterone system in heart failure. Ann Res Hosp. 2019;3:11.
102. Dasgupta C, Zhang L. Angiotensin II receptors and drug discovery in cardiovascular disease. Drug Discov Today. 2011;16:22-34.
103. Jin M, Wilhelm MJ, Lang RE, Unger T, Lindpaintner K, Ganten D. Endogenous tissue renin-angiotensin systems: from molecular biology to therapy. Am J Med. 1988;84:28-36.
104. Sadoshima J, Xu Y, Slayter HS, Izumo S. Autocrine release of angiotensin II mediates stretch-induced hypertrophy of cardiac myocytes in vitro. Cell. 1993;75:977-84.
105. Griendling KK, Sorescu D, Ushio-Fukai M. NAD(P)H oxidase: role in cardiovascular biology and disease. Circ Res. 2000;86:494-501.
106. Hunyady L, Catt KJ. Pleiotropic AT1 receptor signaling pathways mediating physiological and pathogenic actions of angiotensin II. Mol Endocrinol. 2006;20:953-70.

107. Suzuki H, Motley ED, Frank GD, Utsunomiya H, Eguchi S. Recent progress in signal transduction research of the angiotensin II type-1 receptor: protein kinases, vascular dysfunction and structural requirement. Curr Med Chem Cardiovasc Hematol Agents. 2005;3:305-22.
108. Dhalla NS, Temsah RM, Netticadan T. Role of oxidative stress in cardiovascular diseases. J Hypertens. 2000;18:655-73.
109. Sethi R, Shao Q, Ren B, Saini HK, Takeda N, Dhalla NS. Changes in β-adrenoceptors in heart failure due to myocardial infarction are attenuated by blockade of renin-angiotensin system. Moll Cell Biochem. 2004;263;11-20.
110. SOLVD Investigators, Yusuf S, Pitt B, Davis CE, Hood WB Jr, Cohn JN. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med. 1992;327:685-91.
111. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. Lancet. 1993;342:821-8.
112. Pfeffer JM, Pfeffer MA, Braunwald E. Hemodynamic benefits and prolonged survival with long-term captopril therapy in rats with myocardial infarction and heart failure. Circulation. 1987;75:I149-55.
113. Shao Q, Ren B, Saini HK, Netticadan T, Takeda N, Dhalla NS. Sarcoplasmic reticulum Ca^{2+} -transport and gene expression in congestive heart failure are modified by imidapril treatment. Am J Physiol Heart Circ Physiol. 2005;288:H1674-82.
114. Shao Q, Ren B, Zarain-Herzberg A, Ganguly PK, Dhalla NS. Captopril treatment improves the sarcoplasmic reticular Ca^{2+} transport in heart failure due to myocardial infarction. J Mol Cell Cardiol. 1999;31:1663-72.
115. Sanbe A, Tanonaka K, Kobayashi R, Takeo S. Effects of long-term therapy with ACE inhibitors, captopril, enalapril and trandolapril, on myocardial energy metabolism in rats with heart failure following myocardial infarction. J Mol Cell Cardiol. 1995;27:2209-22.
116. Shao Q, Ren B, Elimban V, Tappia PS, Takeda N, Dhalla NS. Modification of sarcolemmal Na^+-K^+-ATPase and Na^+/Ca^{2+} exchanger expression in heart failure by blockade of renin-angiotensin system. Am J Physiol Hear Circ Physiol. 2005;288:H2637-46.
117. Semb SO, Lunde PK, Holt E, Tønnessen T, Christensen G, Sejersted OM. Reduced myocardial Na^+, K^+-pump capacity in congestive heart failure following myocardial infarction in rats. J Mol Cell Cardiol. 1998;30:1311-28.
118. Guo X, Chapman D, Dhalla NS. Partial prevention of changes in SR gene expression in congestive heart failure due to myocardial infarction by enalapril or losartan. Mol Cell Biochem. 2003;254:163-72.
119. Wang J, Guo X, Dhalla NS. Modification of myosin protein and gene expression in failing hearts due to myocardial infarction by enalapril or losartan. Biochim Biophys Acta. 2004;1690:177-84.
120. Dickstein K, Kjekshus J. Optimaal steering committee of the optimaal study group. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Lancet. 2002;360:P752-60.
121. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet. 2003;362:777-81.
122. Awwad ZM, El-Ganainy SO, ElMallah AI, Khattab MM, El-Khatib AS. Telmisartan and captopril ameliorate pregabalin-induced heart failure in rats. Toxicology. 2019;428:152310.
123. Dixon IM, Ju H, Jassal DS, Peterson DJ. Effect of ramipril and losartan on collagen expression in right and left heart after myocardial infarction. Mol Cell Biochem. 1996;165:31-45.
124. Shao Q, Saward L, Zahradka P, Dhalla NS. Ca^{2+} mobilization in adult rat cardiomyocytes by angiotensin type 1 and 2 receptors. Biochem Pharmacol. 1998;55:1413-8.

125. Sethi R, Shao Q, Takeda N, Dhalla NS. Attenuation of changes in Gi-proteins and adenylyl cyclase in heart failure by an ACE inhibitor, imidapril. J Cell Mol Med. 2003;7:277-86.
126. Saini HK, Shao Q, Musat S, Takeda N, Tappia PS, Dhalla NS. Imidapril treatment improves the attenuated inotropic and intracellular calcium responses to ATP in heart failure due to myocardial infarction. Br J Pharmacol. 2005;144:202-11.
127. Cahill TJ, Kharbanda RK. Heart failure after myocardial infarction in the era of primary percutaneous coronary intervention: mechanisms, incidence and identification of patients at risk. World J Cardiol. 2017;9:407-15.
128. Sag CM, Wagner S, Maier LS. Role of oxidants on calcium and sodium movement in healthy and diseased cardiac myocytes. Free Radic Biol Med. 2013;63:338-49.
129. Dixon IM, Lee SL, Dhalla NS. Nitrendipine binding in congestive heart failure due to myocardial infarction. Circ Res. 1990;66:782-8.
130. Dixon IM, Hata T, Dhalla NS. Sarcolemmal calcium transport in congestive heart failure due to myocardial infarction in rats. Am J Physiol. 1992;262:H1387-94.
131. Guo X, Wang J, Elimban V, Dhalla NS. Both enalapril and losartan attenuate sarcolemmal Na^+-K^+-ATPase remodeling in failing rat heart due to myocardial infarction. Can J Physiol Pharmacol. 2008;86:139-47.
132. Yamaguchi F, Sanbe A, Takeo S. Effects of long-term treatment with trandolapril on sarcoplasmic reticulum function of cardiac muscle in rats with chronic heart failure following myocardial infarction. Br J Pharmacol. 1998;123:326-34.
133. Yoshiyama M, Takeuchi K, Hanatani A, Shimada T, Takemoto Y, Shimizu N, et al. Effect of cilazapril on ventricular remodeling assessed by Doppler-echocardiographic assessment and cardiac gene expression. Cardiovasc Drugs Ther. 1998;12:57-70.
134. Hosoya K, Ishimitsu T. Protection of the cardiovascular system by imidapril, a versatile angiotensin-converting enzyme inhibitor. Cardiovasc Drug Rev. 2002;20:93-110.
135. Tappia PS, Liu SY, Shatadal S, Takeda N, Dhalla NS, Panagia V. Changes in sarcolemmal PLC isoenzymes in postinfarct congestive heart failure: partial correction by imidapril. Am J Physiol. 1999;277:H40-9.
136. Wang J, Liu X, Sentex E, Takeda N, Dhalla NS. Increased expression of protein kinase C isoforms in heart failure due to myocardial infarction. Am J Physiol Heart Circ Physiol. 2003;284:H2277-87.
137. Yu CH, Panagia V, Tappia PS, Liu SY, Takeda N, Dhalla NS. Alterations of sarcolemmal phospholipase D and phosphatidate phosphohydrolase in congestive heart failure. Biochim Biophys Acta. 2002;1584:65-72.
138. Heyliger CE, Ganguly PK, Dhalla NS. Sarcoplasmic reticular and mitochondrial calcium transport in cardiac hypertrophy. Can J Cardiol. 1985;1:401-8.
139. Heyliger CE, Takeo S, Dhalla NS. Alterations in sarcolemmal Na^+-[19, 94, 96, 97]Ca^{2+} exchange and ATP-dependent Ca^{2+} -binding in hypertrophied heart. Can J Cardiol. 1985;1:328-39.
140. Heyliger CE, Dhalla NS. Sarcolemmal Ca^{2+} binding and Ca^{2+}-ATPase activities in hypertrophied heart. J Appl Cardiol. 1986;1:447-67.
141. Ito Y, Suko J, Chidsey CA. Intracellular calcium and myocardial contractility V. Calcium uptake of sarcoplasmic reticulum fractions in hypertrophied and failing rabbit hearts. J Mol Cell Cardiol. 1974;6:237-47.
142. Lamers JM, Stinis JT. Defective calcium pump in the sarcoplasmic reticulum of the hypertrophied rabbit heart. Life Sci. 1979;24:2313-9.
143. Limas CJ, Spier SS, Kahlon J. Enhanced calcium transport by sarcoplasmic reticulum in mild cardiac hypertrophy. J Mol Cell Cardiol. 1980;12:1103-16.
144. Sordahl LA, McCollum WB, Wood WG, Schwartz A. Mitochondria and sarcoplasmic reticulum function in cardiac hypertrophy and failure. Am J Physiol. 1973;224:497-502.

145. Mercadier JJ, Lompré AM, Wisnewsky C, Samuel JL, Bercovici J, Swynghedauw B, et al. Myosin isoenzyme changes in several models of rat cardiac hypertrophy. Circ Res. 1981;49:525-32.
146. Alpert NR, Mulieri LA. Heat, mechanics, and myosin ATPase in normal and hypertrophied heart muscle. Feb Proc. 1982;41:192-8.
147. Rupp H, Elimban V, Dhalla NS. Modification of subcellular organelles in pressure-overloaded heart by etomoxir, a carnitine palmitoyltransferase I inhibitor. FASEB J. 1992;6:2349-53.
148. Zarain-Herzberg A, Rupp H, Elimban V, Dhalla NS. Modification of sarcoplasmic reticulum gene expression in pressure overload cardiac hypertrophy by etomoxir. FASEB J. 1996;10:1303-9.
149. Dhalla NS, Heyliger CE, Shah KR, Sethi R, Takeda N, Nagano M. Remodeling of membrane systems during the development of cardiac hyertrophy due to pressure overload. Basic Res Cardiol. 1994:76:27-49.
150. Ju H, Scammell-La Fleur T, Dixon IM. Altered mRNA abundance of calcium transport genes in cardiac myocytes induced by angiotensin II. J Mol Cell Cardiol. 1996;28:1119-28.
151. Dunn FG, Oigman W, Ventura HO, Messerli FH, Kobrin I, Frohlich ED. Enalapril improves systemic and renal hemodynamics and allows regression of left ventricular mass in essential hypertension. Am J Cardiol. 1984;53:105-8.
152. Linz W, Schölkens BA, Ganten D. Converting enzyme inhibition specifically prevents the development and induces regression of cardiac hypertrophy in rats. Clin Exp Hypertens A. 1989;11:1325-50.
153. Liu X, Sentex E, Golfman L, Takeda S, Osada M, Dhalla NS. Modification of cardiac subcellular remodeling due to pressure overload by captopril and losartan. Clin Exp Hypertens. 1999;21:145-56.
154. Flesch M, Schiffer F, Zolk O, Pinto Y, Stasch JP, Knorr A, et al. Angiotensin receptor antagonism and angiotensin converting enzyme inhibition improve diastolic dysfunction and Ca^{2+} -ATPase expression in the sarcoplasmic reticulum in hypertensive cardiomyopathy. J Hypertens. 1997;15:1001-9.
155. Schunkert H, Dzau VJ, Tang SS, Hirsch AT, Apstein CS, Lorell BH. Increased rat cardiac angiotensin converting enzyme activity and mRNA expression in pressure overload left ventricular hypertrophy. Effects on coronary resistance, contractility, and relaxation. J Clin Invest. 1990;86:1913-20.
156. Ferrario CM, Mullick AE. Renin angiotensin aldosterone inhibition in the treatment of cardiovascular disease. Pharmacol Res. 2017;125:57-71.
157. Weir MR, Dzau VJ. The renin-angiotensin-aldosterone system: a specific target for hypertension management. Am J Hypertens. 1999;12:205S-13S.
158. Oparil S, Yarows SA, Patel S, Fang H, Zhang J, Satlin A. Efficacy and safety of combined use of aliskiren and valsartan in patients with hypertension: a randomised, double-blind trial. Lancet. 2007;370:221-9.
159. Wollert KC, Drexler H. The renin-angiotensin system and experimental heart failure. Cardiovasc Res. 1999;43:838-49.
160. Leenen FHH, Skarda V, Yuan B, White R. Changes in cardiac Ang II postmyocardial infarction in rats: effects of nephrectomy and ACE inhibitors. Am J Physiol Circ Physiol. 1999;276:H317-25.
161. Ruzicka M, Skarda V, Leenen FHH. Effects of ACE inhibitors on circulating versus cardiac angiotensin II in volume overload induced cardiac hypertrophy in rats. Circulation. 1995;92:3568-73.
162. Ruzicka M, Leenen FH. Relevance of blockade of cardiac and circulatory angiotensin-converting enzyme for the prevention of volume overload-induced cardiac hypertrophy. Circulation. 1995;91:16-9.
163. Hisamatsu Y, Ohkusa T, Kihara Y, Inoko M, Ueyama T, Yano M, et al. Early changes in the functions of cardiac sarcoplasmic reticulum in volume-overloaded cardiac hypertrophy in rats. J Mol Cell Cardiol. 1997;29:1097-109.
164. Yoshida K, Yoshiyama M, Omura T, Nakamura Y, Kim S, Takeuchi K, et al. Activation of mitogen-activated protein kinases in the non-ischemic myocardium of an acute myocardial infarction in rats. Jpn Circ J. 2001;65:808-14.

165. Bogoyevitch MA, Andersson MB, Gillespie-Brown J, Clerk A, Glennon PE, Fuller SJ, et al. Adrenergic receptor stimulation of the mitogen-activated protein kinase cascade and cardiac hypertrophy. Biochem J. 1996;314:115-21.
166. Shimizu N, Yoshiyama M, Omura T, Hanatani A, Kim S, Takeuchi K, et al. Activation of mitogen-activated protein kinases and activator protein-1 in myocardial infarction in rats. Cardiovasc Res. 1998;38:116-24.
167. Kim S, Iwao H. Activation of mitogen-activated protein kinases in cardiovascular hypertrophy and remodeling. Jpn J Pharmacol. 1999;80:97-102.
168. Zhang W, Elimban V, Xu YJ, Zhang M, Nijjar MS, Dhalla NS. Alterations of cardiac ERK1/2 expression and activity due to volume overload were attenuated by the blockade of RAS. J Cardiovasc Pharmacol Ther. 2010;15:84-92.
169. Dhalla NS, Takeda N, Rodriguez-Leyva D, Elimban V. Mechanisms of subcellular remodeling in heart failure due to diabetes. Heart Fail Rev. 2014;19:87-99.
170. Fein FS, Sonnenblick EH. Diabetic cardiomyopathy. Prog Cardiovasc Dis. 1985;27:255-70.
171. Stanley WC, Lopaschuk GD, McCormack JG. Regulation of energy substrate metabolism in the diabetic heart. Cardiovasc Res. 1997;34:25-33.
172. Pierce GN, Russell JC. Regulation of intracellular Ca^{2+} in the heart during diabetes. Cardiovasc Res. 1997;34:41-7.
173. Feuvray D. The regulation of intracellular pH in the diabetic myocardium. Cardiovasc Res. 1997;34:48-54.
174. Liu X, Suzuki H, Sethi R, Tappia PS, Takeda N, Dhalla NS. Blockade of the renin-angiotensin system attenuates sarcolemma and sarcoplasmic reticulum remodeling in chronic diabetes. Ann N Y Acad Sci. 2006;1084:141-54.
175. Machackova J, Liu X, Lukas A, Dhalla NS. Renin-angiotensin blockade attenuates cardiac myofibrillar remodelling in chronic diabetes. Mol Cell Biochem. 2004;261:271-8.