



Molecular Mechanisms for Pathophysiology and Therapy of Cardiac Dysfunction in Heart Failure

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Abstract

Extensive work over the past 6 decades in the field of cardiovascular medicine has revealed that haemodynamic, hormonal, metabolic, cellular and molecular mechanisms of heart failure are not only complex but are also dependent upon the type and stage of heart disease. Although various agents such as β -adrenoreceptor blockers, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists and vasodilators are available for the treatment of heart failure, these interventions delay the progression of heart failure without reducing mortality and morbidity. In this article, literature on the pathophysiology of heart failure due to myocardial infarction and haemodynamic overload to identify molecular targets for future drug development is reviewed. Particularly, objective was to focus on the mechanisms of heart failure involving pathways for the generation of oxidative stress, myocardial inflammation and Ca^{2+} -handling abnormalities. It is evident that elevated levels of plasma vasoactive hormones and growth factors as well as increased preload and afterload play critical roles in stimulating various signal transduction pathways for the occurrence of increased ventricular wall stress, cardiac remodelling and subsequent cardiac dysfunction. These alterations are associated with development of oxidative stress, myocardial inflammation, endothelial dysfunction, metabolic defects, intracellular Ca^{2+} -handling abnormalities, apoptosis, fibrosis and changes in the extracellular matrix. In view of such pathogenic abnormalities in failing hearts, it is suggested these parameters may serve as excellent targets for drug development for the therapy of heart failure. In addition, there occurs activation of proteases and phospholipases as well as depression in cardiac gene expression for the induction of subcellular remodelling in failing hearts and thus interventions affecting these parameters may also be considered to exert beneficial effects in heart failure. There is also an urgent need to develop some existing and newer agents such as metabolic inhibitors, antioxidants and sodium-glucose cotransporter-2 inhibitors as well as gene and RNA based therapies for the treatment of heart failure.

Key words: Remodelling, cardiac; Heart failure; Oxidative stress; Inflammation; Calcium; Ca^{2+} -handling abnormalities; Metabolism; Metabolic defects; Remodelling, subcellular.

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Introduction

It is now well known that various cardiovascular diseases such as myocardial infarction, ath-

erosclerosis, hypertension, aortic valve stenosis, mitral valve regurgitation, diabetes, infective

cardiomyopathy, genetic cardiomyopathy and obesity result in heart failure.¹⁻¹⁹ It has been estimated that the world-wide prevalence of heart failure due to cardiovascular diseases is about 70 million, the life-time risk of developing heart failure is one in five and the long-time survival is poor because about 30 % heart failure patients die within one year and about 50 % die within 5 years. The mortality due to heart failure is also gender dependent (60 % in men and 40 % in women). The heart failure patients exhibit clinical signs such as shortening of breath (lung congestion), accumulation of body fluids (oedema), exercise intolerance and fatigue. The heart in this condition is unable to pump sufficient blood to meet the adequate needs of the body and thus other organs including brain, liver, lungs, kidney and skeletal muscles become dysfunctional in heart failure subjects. It may be noted that myocardial infarction, as a consequence of blockade of the coronary artery mainly due to atherosclerosis, is a major cause of heart failure. When this pathological situation is accompanied by arrhythmias, it results in high rate of sudden cardiac death. There is a growing concern that heart failure has become of epidemic proportion due to increasing incidence of diverse infections as well as changes in life-style, nutritional habits and ageing throughout the world.

Several investigations^{11, 12, 20-28} have revealed that heart failure due to most cardiovascular diseases is accompanied by haemodynamic overload as a consequence of increases in either preload and afterload or both. This disorder is invariably associated with cardiac hypertrophy (myocardial growth), which is adaptive in nature at early stages but becomes maladaptive at later stages of pathological stimulus. The adaptive cardiac hypertrophy shows increased or unaltered cardiac function and maintains blood pressure and circulation in the body. On the other hand, maladaptive cardiac hypertrophy is associated with varying degrees of cardiac dysfunction. Since cardiac dysfunction is the hallmark of heart failure and continued deterioration of cardiac performance of the hypertrophied heart is intimately related to the progression of heart failure, it would be prudent to consider maladaptive cardiac hypertrophy as the pre-failure stage. Although the exact mechanisms for the progression of heart failure are still poorly understood, several concepts such as haemodynamic overload, defects in energy production and utilisation, neurohumoral hypothesis, cardiac remodelling, modification

of Ca²⁺-handling and subcellular remodelling, have been developed over the past six decades to explain cardiac dysfunction during the development and progression of heart failure.²⁹⁻³⁷ It should also be mentioned that heart failure is considered to be of two types namely heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HEpEF).³⁸⁻⁵³ About 55 % of patients with systolic dysfunction have been identified to represent the HFrEF category whereas about 45 % of patients with diastolic dysfunction are of HEpEF type. It is also evident that both types of heart failure differ from each other with respect to some biochemical mechanisms as well as responsiveness to several drugs, which are available for the treatment of heart failure. Thus, some caution should be exercised while evaluating the discussion in this article, which is mainly centred around the pathophysiology of HFrEF for identifying molecular targets for drug development for the therapy of heart failure.

Various pharmacologic interventions such as inotropic agents (digitalis glycosides), diuretics, β -adrenoreceptor blockers, angiotensin converting enzyme inhibitors and angiotensin II receptor blockers are being used for the treatment of heart failure.^{12, 13, 54-58} Although these agents improve cardiac function and delay the progression of cardiac dysfunction in HFrEF patients, these interventions do not reduce morbidity or mortality. Several sodium-glucose cotransporter 2 inhibitors are now available for the treatment of patients with HEpEF and it is expected that these may prove beneficial in the long run.^{45, 48, 50-52, 59-61} Furthermore, extensive efforts are being made to develop some anti-oxidant and anti-inflammatory agents,⁶²⁻⁶⁶ endothelin antagonists and metabolic modulators⁶⁷⁻⁶⁹ as well as some protein kinase inhibitors^{70, 71} for the therapy of heart failure. It needs to be emphasised that heart failure is a complex disorder which is associated with the occurrence of different cardiac abnormalities depending upon the type of pathological stimulus and stage of the disease. Some of the major cardiac abnormalities occurring during the development and progression of heart failure due to myocardial infarction and haemodynamic overload are depicted in Figure 1. Since there is an urgent need to improve the therapy of heart failure, an updated comprehensive review of the literature on pathophysiology of heart failure is provided in order to identify some molecular targets, which may prove helpful for drug discovery. Particu-

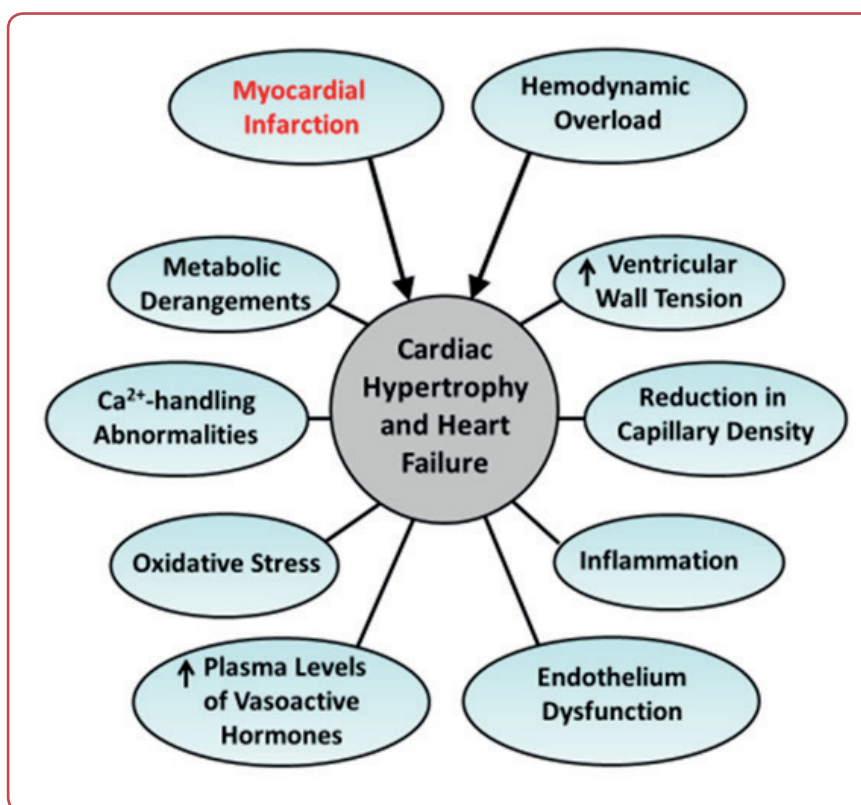


Figure 1: Various abnormalities associated with cardiac hypertrophy and heart failure due to myocardial infarction and haemodynamic overload

↑: increase. Although the pathophysiologic mechanisms for the occurrence of cardiac hypertrophy and heart failure due to myocardial infarction and haemodynamic overload are different from each other, various defects associated with hypertrophied failing hearts are similar.

larly, it is planned to discuss the involvements of various pathogenic factors including myocardial infarction, haemodynamic overload, some vasoactive hormones and endothelial dysfunction in the development of heart failure. In addition, the roles of metabolic defects, oxidative stress, inflammation and intracellular Ca^{2+} -handling abnormalities will be discussed to describe the pathogenesis of cardiac dysfunction during the progression of heart failure. Thus, the objective of this review is to describe several mechanisms underlying heart failure in order to identify some molecular targets for drug development for the treatment of this devastating cardiovascular disease. For this purpose, references on the pathophysiology and therapy of heart failure were searched by using *PubMed* as a database and selected some pertinent articles for the preparation of this review.

Myocardial infarction and haemodynamic overload in heart failure

Blockade of coronary arteries due to atherosclerosis is known to produce myocardial cell damage in the ischaemic portion of the heart and result in the formation of infarcted tissue (myocardial infarction). The loss of myocardium has been shown to activate both the sympathetic nervous system (SNS) and the renin-angiotensin system (RAS) as a consequence of reduction in cardiac output. Thus, catecholamines are released and the formation of angiotensin II (Ang II) is increased in the circulation to maintain cardiac output and blood pressure.⁷²⁻⁷⁷ The plasma levels of several other vasoactive hormones including serotonin (5-HT), vasopressin and endothelin are also elevated following myocardial infarction. The activation of adrenoreceptors by catecholamines and Ang II receptors (AT_1R) by Ang II increases protein synthesis through their respective signal

transduction pathways in the heart to produce hypertrophy of the viable myocardium, which is also an adaptive mechanism for promoting cardiac performance. Catecholamines and 5-HT as well as Ang II also get accumulated in the hypertrophied myocardium and produce oxidative stress during the oxidation of catecholamines and 5-HT by mitochondrial monoamine oxidase as well as the activation of mitochondrial NADPH oxidase by Ang II. The elevated levels of these vasoactive hormones are also known to produce vasoconstriction and functional hypoxia for the production of oxidative stress. Thus, oxidative stress generated by different mechanisms is considered to play a critical role in the pathogenesis of cardiac dysfunction and development of heart failure. These events are

depicted in Figure 2. Accordingly, it is evident that different receptors- mediated signal pathways for several vasoactive hormones as well as different mechanisms for the production of oxidative stress may represent appropriate molecular targets for drug developments for the treatment of heart failure due to myocardial infarction. Perhaps, the improvement of cardiac performance in heart failure due to chronic myocardial infarction may require a combination therapy involving several molecular targets such as various sites in signal transduction pathways for different vasoactive hormones as well as oxidative stress generation.

Different cardiovascular diseases such a hypertension, aortic stenosis, valvular regurgitation and

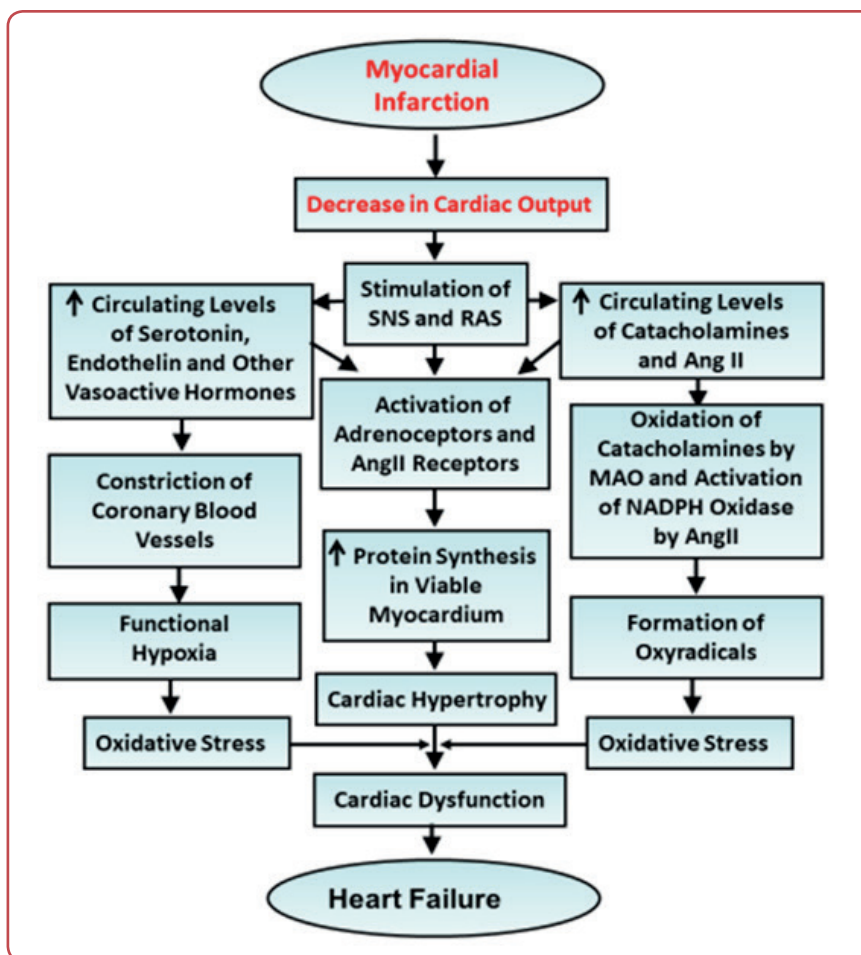


Figure 2: Involvement of some vasoactive hormones and other events during the development of cardiac hypertrophy and heart failure due to myocardial infarction

SNS: sympathetic nervous system; RAS: renin-angiotensin system; Ang II: angiotensin II; MAO: monoamine oxidase; ↑: increase. The development of myocardial infarction results in the activation of SNS and RAS and releases several vasoactive hormones in the circulation. These hormones not only result in the hypertrophy of the viable myocardium but also generate oxidative stress due to the occurrence of functional hypoxia and participation of different enzymes such as NADPH and MAO. Progressive depression of cardiac performance due to the occurrence of oxidative stress results in the development of heart failure. The detailed mechanisms for the induction of myocardial infarction, increase in plasma level of different vasoactive hormones, development of oxidative stress, occurrence of cardiac hypertrophy and development of heart failure due to reduction in coronary blood flow are given elsewhere.^{11, 13}

various forms of cardiomyopathies are known to result in heart failure. However, these abnormalities are considered to be intimately associated with the development of haemodynamic overload as a consequence of either preload and afterload or both.^{2, 4-7, 12, 17, 36} Such pathogenic stimuli activate efferent nerves in the heart and stimulate different centres in the brain to release various vasoactive hormones in the circulation. These hormones initially produce adaptive changes by acting on their respective receptors for the induction of myocardial growth and cellular proliferation in the heart upon stimulating various signal transduction mechanisms. However, over a prolonged period, these hormones promote oxidative stress and inflammation for

the induction of apoptosis and fibrosis in the hypertrophied myocardium and lead to the development of maladaptive cardiac hypertrophy or pre-failure stage. Continued generation of excessive oxidative stress and inflammation produce several metabolic defects and Ca^{2+} -handling abnormalities in the hypertrophied myocardium, which mechanisms are considered to be associated with progressive deterioration of cardiac performance and heart failure. A schematic description of some of these events occurring in the heart due to haemodynamic overload is shown in Figure 3 to help identifying the molecular targets for drug development to treat heart failure due to non-ischaemic diseases.

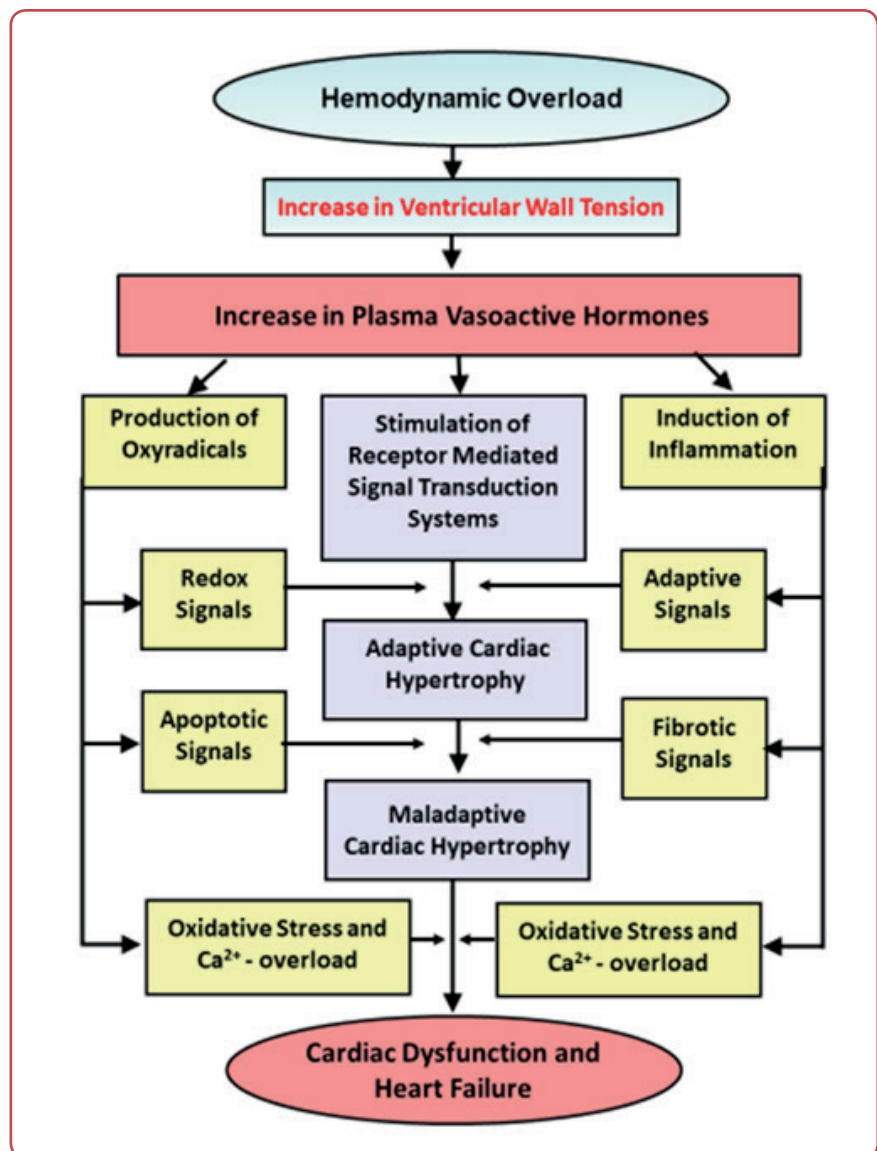


Figure 3: Involvement of some vasoactive hormones and signal transduction events during the development of cardiac hypertrophy and heart failure due to haemodynamic overload

It is pointed out that the pathophysiologic mechanisms for the occurrence of haemodynamic overload in various non-ischaemic cardiovascular diseases are different for each other. However, these parameters of haemodynamic overload increase ventricular wall tension, which provides stimulus for the release of local, central and periph-

eral vasoactive hormones in the circulation. Furthermore, vasoactive hormones at initial stages produce adaptive cardiac hypertrophy involving redox associated signals whereas at later stages, there occurs maladaptive cardiac hypertrophy involving fibrotic signals, which then progresses to heart failure involving oxidative stress.

Involvement of vasoactive hormones in heart failure

A detailed analysis of extensive investigations in the field of heart failure has revealed a complex

role of various vasoactive hormones including Ang II, catecholamines, serotonin, endothelins

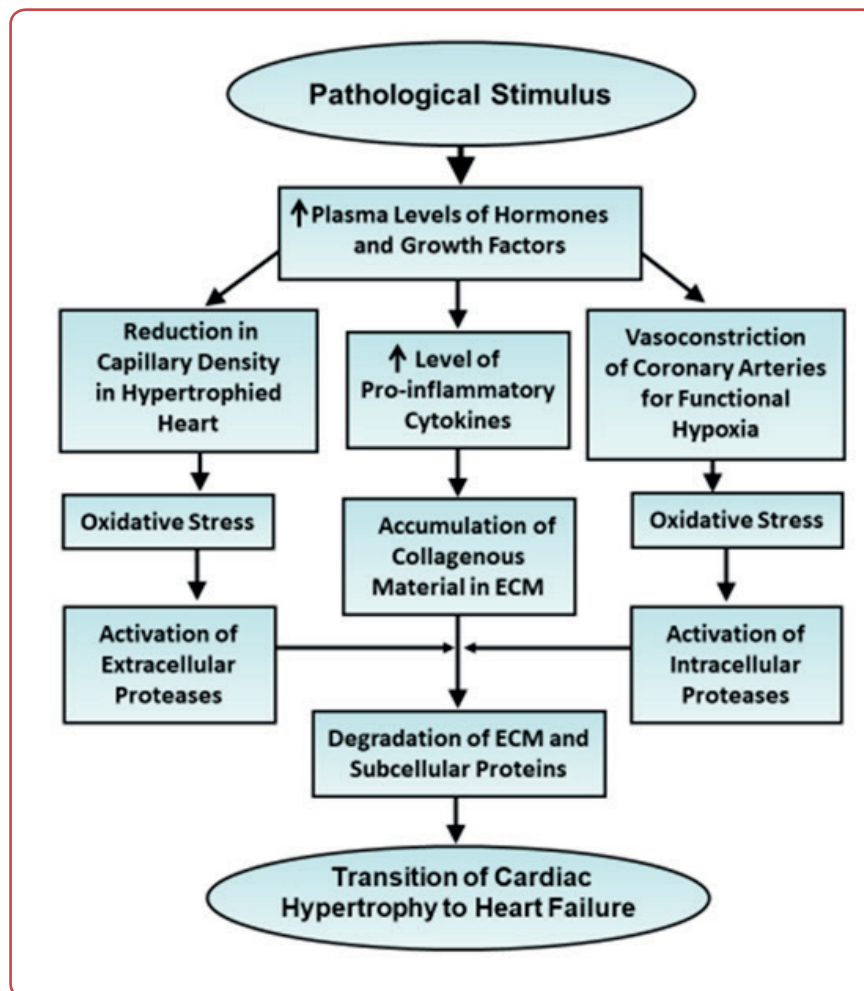


Figure 4: Role of some hormones and growth factors during the transition of cardiac hypertrophy to heart failure

ECM: extracellular matrix; ↑: increase. Chronic exposure of the hypertrophied heart to circulating vasoactive hormones results in the accumulation of collagenous material in the extracellular matrix due to increased formation of pro-inflammatory cytokines. In addition, vasoactive hormones produce oxidative stress due to reduction in capillary density in comparison to cardiomyocyte growth as well as due to functional hypoxia upon vasoconstriction of coronary arteries. Oxidative stress so developed then activates different proteases to degrade myocardial proteins and resulting in the transition of hypertrophied myocardium to heart failure.

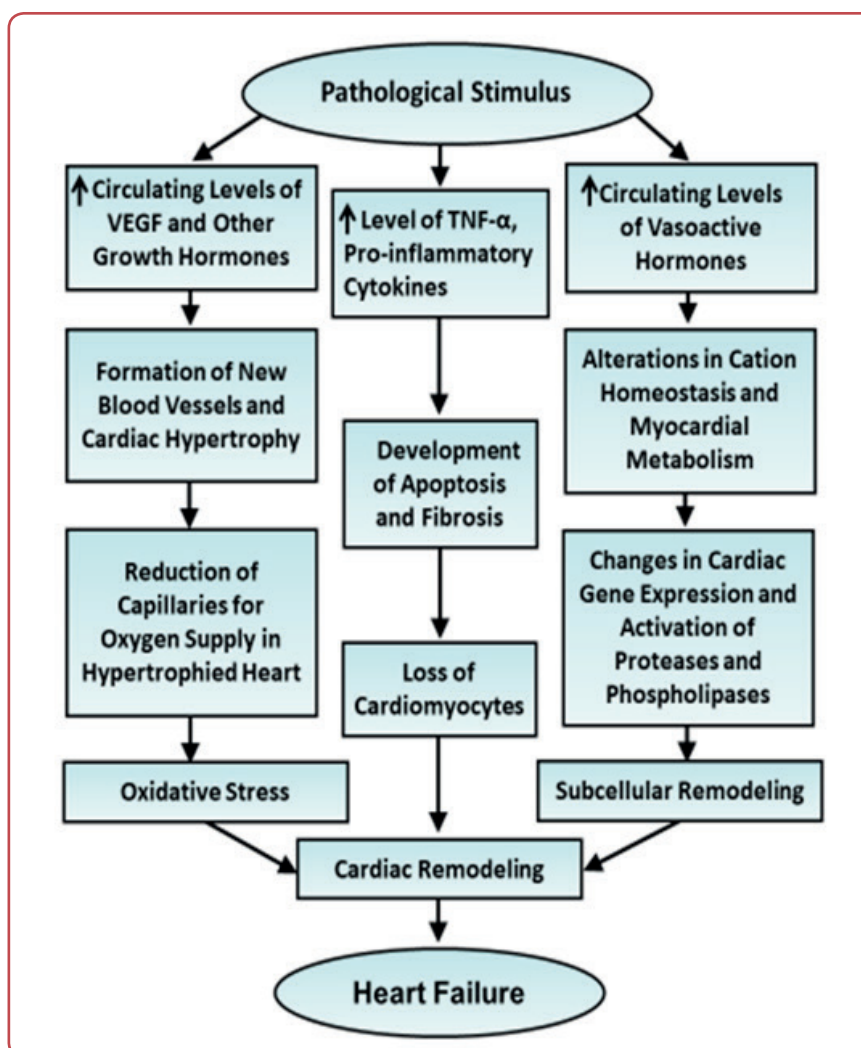


Figure 5: Role of vasoactive hormones, growth factors and pro-inflammatory cytokines in the development of oxidative stress and subcellular remodelling during the development of heart failure

VEGF: Vascular endothelium growth factor; TNF- α : tumour necrosis factor- α ; $\uparrow$, increase. Under various pathological conditions, elevations of circulating levels of vasoactive hormones, growth factors and proinflammatory cytokines produce oxidative stress due to functional hypoxia, subcellular remodelling due to changes in myocardial metabolism, cation content and gene expression, as well as loss of cardiomyocytes due to activation of apoptotic and fibrotic pathways. These events lead to the development of cardiac-remodelling and heart failure.

and vasopressin, as well as some growth factors like vascular endothelial growth factor (VEGF) at various stages of this disease.^{10, 13, 16, 56, 57, 67} As indicated earlier, these hormones induce hypertrophic signals upon acting on their respective receptors. Furthermore, increased levels of these hormones and growth factors promote the formation of pro-inflammatory cytokines like tumour necrosis factor - α (TNF- α) for the accumulation of collagenous material in the extracellular matrix in the hypertrophied heart. In addition, vasoconstriction of coronary blood vessels and reduction of capillary density relative to cardiac growth induce functional hypoxia

and oxidative stress in the hypertrophied heart by these hormones and VEGF. Such pathogenic events are associated with the activation of different proteases. Thus, there occurs degradation of extracellular matrix and subcellular proteins, development of fibrosis and transition of cardiac hypertrophy to heart failure. A schematic representation of these events is shown in Figure 4. The elevated levels of circulating vasoactive hormones and growth factors as well as increased levels of pro-inflammatory cytokines also result in the loss of cardiomyocytes and subcellular alterations for the occurrence of cardiac remodeling and subsequent heart failure (Figure 5).

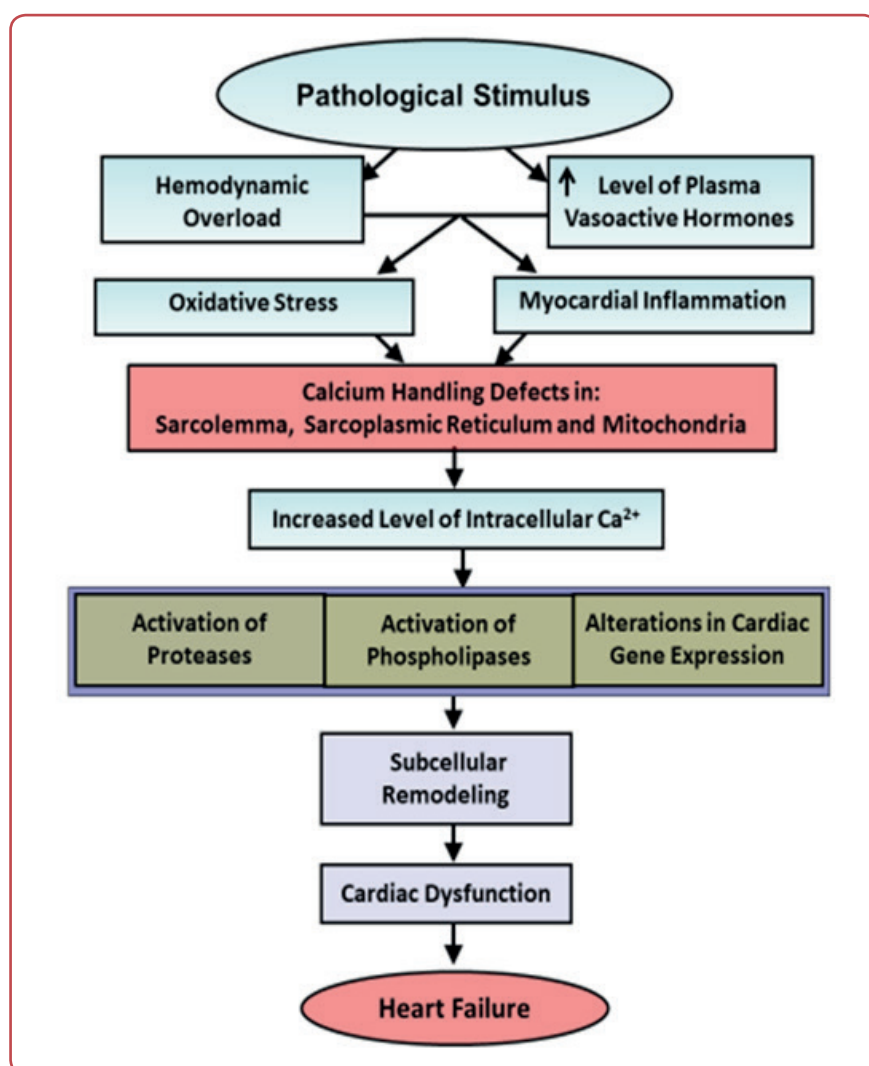


Figure 6: Role of oxidative stress and myocardial inflammation in Ca^{2+} -handling defects and subcellular abnormalities during the development of cardiac dysfunction and heart failure

↑: increase. Both oxidative stress and myocardial inflammation under different pathological conditions result in Ca^{2+} -handling abnormalities and activation of proteases and phospholipases as well as alterations in cardiac gene expression. These events result in subcellular remodelling and subsequent cardiac dysfunction and heart failure.

In addition to producing elevated levels of vasoactive hormones in the circulation, a wide variety of pathologic stimuli are also known to produce haemodynamic overload by virtue of their ability to induce vasoconstriction of the peripheral vascular system. Such alterations have been associated with the generation of oxidative stress and development of inflammation in the hypertrophied heart for the induction of Ca^{2+} -handling abnormalities in subcellular organelles.^{7, 8, 11, 13, 30, 36, 62, 63, 65, 66, 78} Although the exact mechanisms for the subcellular defect by oxidative stress and myocardial inflammation are not fully understood, alterations in Ca^{2+} -handling activities have been demonstrated to raise the intracellular con-

centration of Ca^{2+} . In fact, there occurs an excessive accumulation of Ca^{2+} in mitochondria and depression in the ability of sarcoplasmic reticulum to retain Ca^{2+} during the development of heart failure. Furthermore, there occurs the activation of proteases and phospholipases as well as alterations in cardiac gene expression. These changes are considered to produce subcellular remodeling and subsequent cardiac dysfunction as well as progression of heart failure. These molecular events are considered to be excellent targets for drug development and are depicted in Figure 6.

The increased levels of circulating vasoactive hormones as well as the release of endogenous

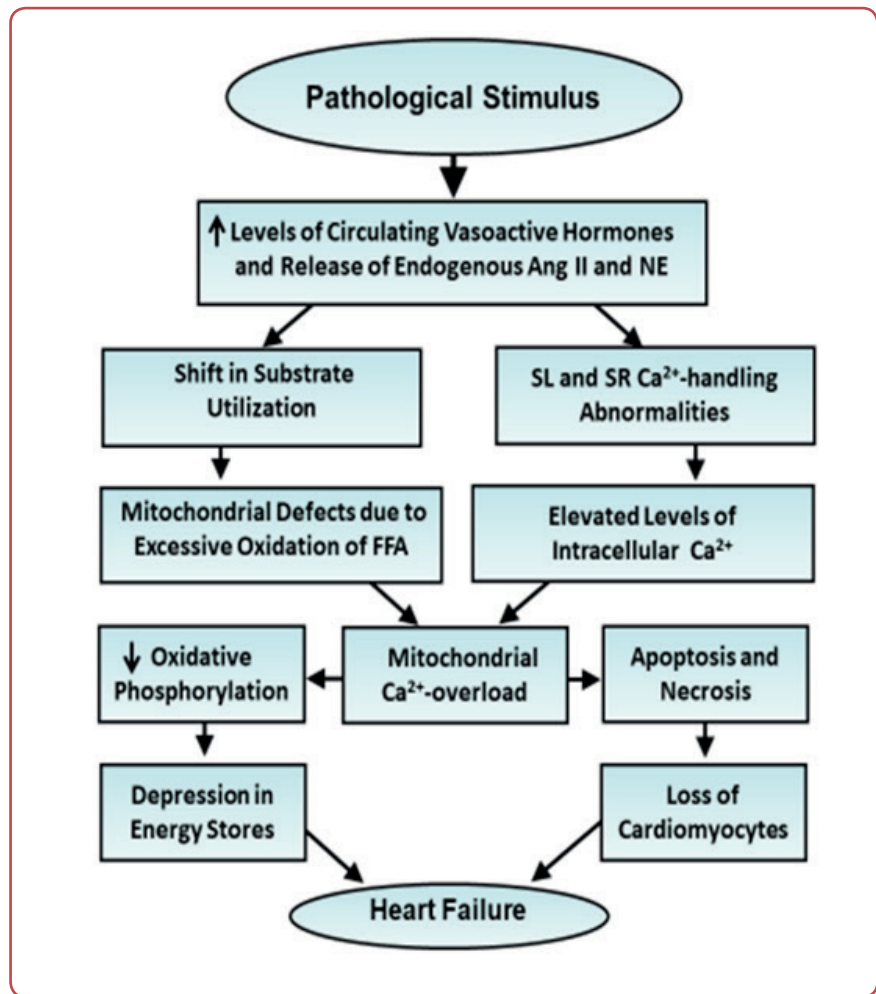


Figure 7: Role of circulating and cardiac vasoactive hormones in the occurrence of mitochondrial Ca²⁺-overload during the development of heart failure

Ang II: angiotensin II; NE: norepinephrine; SL: sarcolemma; SR: sarcoplasmic reticulum; FFA: free fatty acids; ↑: increase; ↓: decrease. There occurs a shift in substrate utilisation and Ca²⁺ - handling abnormalities in the heart due to elevated levels of circulating vasoactive hormones under various pathological conditions. These alterations produce mitochondrial Ca²⁺ - overload, defect in energy production as well as apoptosis and necrosis. Subsequently, there occurs depression in energy stores and loss of cardiomyocytes for the development of heart failure.

Ang II and norepinephrine not only produce sub-cellular Ca²⁺-handling activities but also induce marked alterations in myocardial metabolism during the development of heart failure.^{13, 30, 68, 69, 79} A shift in substrate utilisation in the failing heart is associated with reduced utilisation of glucose and excessive oxidation of free fatty acids. These metabolic alterations along with subcellular abnormalities in Ca²⁺-handling result in the occurrence of mitochondrial defect as well as mitochondrial Ca²⁺-overload for the impairment of energy production and depression in the energy stores. It should be emphasised that progressive depletion of energy stores in the myocardium is

considered to play a critical role in the occurrence of cardiac dysfunction during the progression rather than the development of heart failure. Furthermore, mitochondrial defects lead to the generation of different apoptotic signals as well as release of cytotoxic substances for the occurrence of cardiac cell damage, necrosis and loss of cardiomyocytes during the progression of heart failure. Thus, exposure of myocardium to various vasoactive hormones for a prolonged period has been shown to induce metabolic defects and mitochondrial dysfunction, which are intimately involved in the progression of heart failure. These events are shown in Figure 7.

Role of oxidative stress, increased ventricle wall tension and endothelial dysfunction in heart failure

It is becoming evident that the levels of various hormones in the circulation are elevated and there occurs haemodynamic overload during the development of heart failure in a wide variety of cardiovascular diseases. Furthermore, both Ang II and catecholamines produce oxyradicals by the stimulation of their receptor-mediated signal transduction pathways for the development of oxidative stress; Ang II has also been shown

to produce oxyradicals upon activating the sarcolemmal NADPH oxidase and mitochondrial NADPH oxidase whereas catecholamines have been shown to produce oxyradicals upon oxidation by the mitochondrial monoamine oxidase. On the other hand, haemodynamic overload has been shown to produce an increase in the ventricular wall tension for the occurrence of cardiac remodelling as well as circulatory turbulence for the induction of endothelial defects. It should also be mentioned that both Ang II and catecholamines are known to increase the ventricular wall tension as well as circulatory turbulence during the development of heart failure. Accordingly, it appears that oxidative stress, increased ventricular wall tension and endothelial dysfunction seems to serve as major mechanisms for the develop-

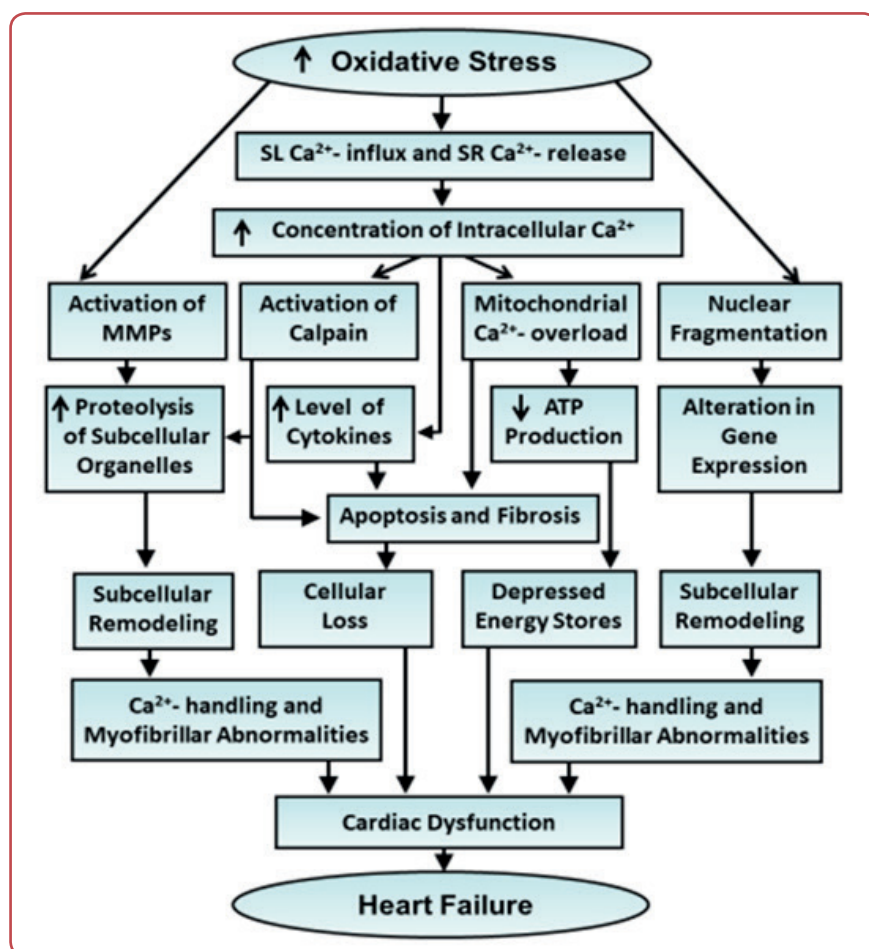


Figure 8: Role of oxidative stress in myocardial alterations and Ca^{2+} -handling abnormalities during the development of cardiac dysfunction

↑: increase; ↓: decrease; MMPs: matrix metalloproteinases. This figure describes both the direct and indirect effects of oxidative stress, which is generated in different cardiovascular diseases leading to heart failure. The direct effects of oxidative stress include proteolysis of extracellular proteins due to the activation of MMPs and alterations in gene expression due to nuclear fragmentation. On the other hand, the indirect effects of oxidative stress occur due to elevated levels of intracellular Ca^{2+} . These effects include the activation of intracellular proteases such as calpain, development of apoptosis and necrosis and loss of cardiomyocytes as well as the occurrence of mitochondrial Ca^{2+} -overload and depression of energy stores. Both these defects result in changes in subcellular organelles and development of cardiac dysfunction.

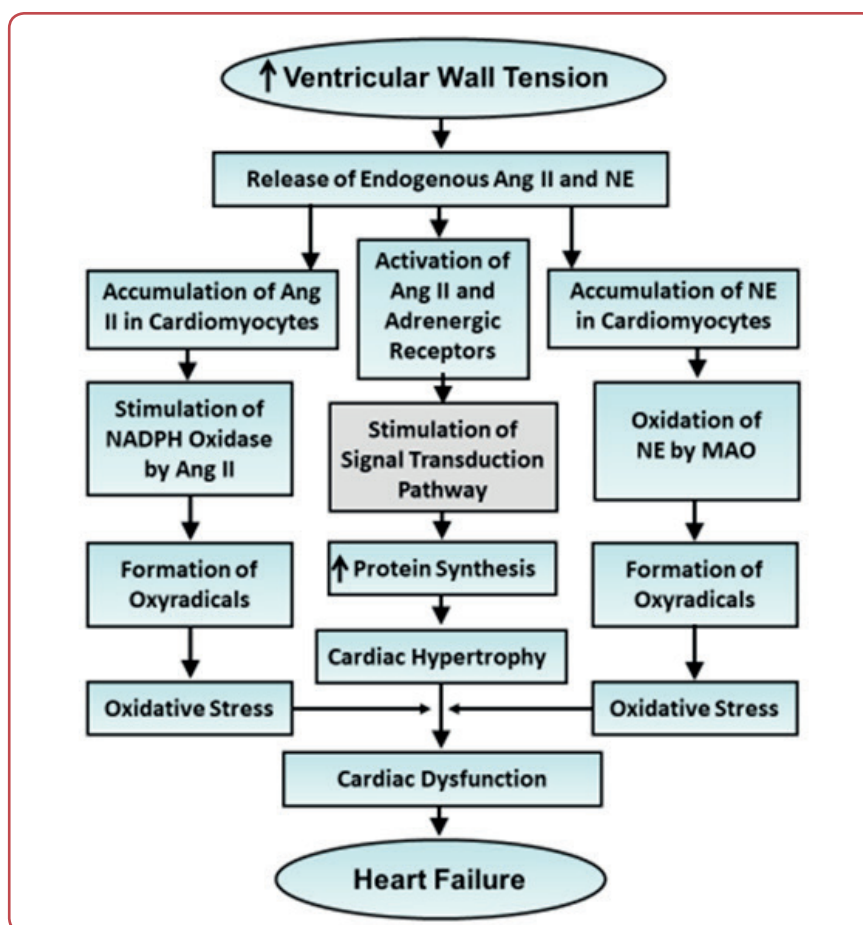


Figure 9: Role of increased ventricular wall tension in the induction of cardiac hypertrophy and oxidative stress during the development of heart failure

Ang II: angiotensin II; NE: norepinephrine; ↑: increase; MAO: monoamine oxidase. This figure describes the release of local hormones such as Ang II and NE due to increased ventricular wall tension as a consequence of haemodynamic overload. Both Ang II and NE produce cardiac hypertrophy due to activation of their respective receptor mediated signal transduction pathways. In addition, both Ang II and NE produce oxidative stress upon accumulation in cardiomyocytes by Ang II- induced stimulation of NADPH oxidase and oxidation of NE by MAO, respectively.

ment and progression of heart failure. Events involved in the pathogenesis of heart failure due to oxidative stress, increased ventricular wall tension and endothelial dysfunction are given in Figures 8, 9 and 10.^{11-13, 32-39, 41}

Since the generation of oxidative stress is increased in heart failure, it has been suggested that this pathogenic parameter may be involved in the progression of this disease.^{63, 64, 80-90} It should be mentioned that the development of oxidative stress is a result of excessive formation of oxyradicals as well as depression in the antioxidant systems depending upon the type and stage of heart failure. Although oxidative stress has been shown to promote inflammation by stimulating the formation of pro-inflammatory cytokines, inflammation has also been reported to generate oxidative stress in different cardiovascular diseases.^{7, 62, 65, 66, 78} Various

hormones have been shown to produce excessive amount of oxyradicals in heart failure due to the stimulation of NADPH oxidase by Ang II and endothelins as well as due to the oxidation of both catecholamines and serotonin by mono-amine oxidase. Furthermore, oxidative stress has been demonstrated to induce subcellular remodelling and subsequent Ca^{2+} -handling and myofibrillar abnormalities upon activating matrix metallo-proteinases as well as inducing nuclear fragmentation and changes in cardiac gene expression.^{7, 8, 13, 30, 31} In addition, oxidative stress is known to raise the intracellular concentration of Ca^{2+} and produce apoptosis and fibrosis by activating calpain and increasing the level of pro-inflammatory cytokines. Development of oxidative stress in the failing heart has also been reported to reduce ATP (energy) stores by producing mitochondrial Ca^{2+} -overload. All these alterations due to oxi-

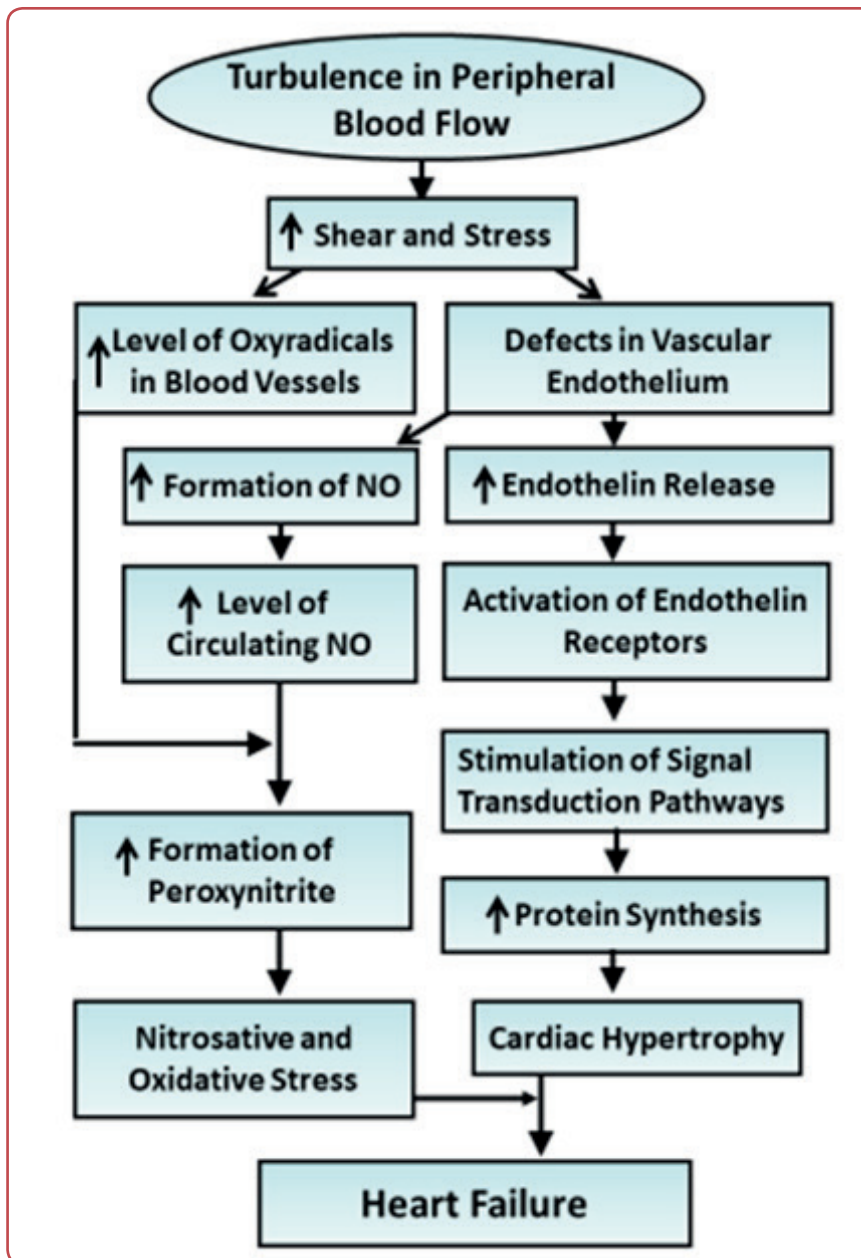


Figure 10: Role of peripheral blood flow turbulence and subsequent shear and stress in inducing endothelial defects and production of nitrosative and oxidative stress during the development of heart failure

NO: nitric oxide; ↑: increase. This figure describes the effects of increased shear and stress due to turbulence in blood flow on vascular smooth muscle and endothelium. The effect on vascular smooth muscle produces oxyradicals whereas that on endothelium induces the production of NO and release of endothelin. The combination of oxyradicals with NO results in the formation of peroxynitrite and nitrosative stress. On the other hand, elevated levels of endothelin produce cardiac hypertrophy upon the activation of its signal transduction pathway. These events result in the transition of cardiac hypertrophy into heart failure as a consequence of nitrosative stress.

datave stress are considered to result in cardiac dysfunction and heart failure. These events are depicted in Figure 8. It should be noted that various hormones in the circulation and haemodynamic overload not only increase ventricular wall tension^{4, 12, 13, 44} but also induce several changes in myocardial metabolism^{12, 13, 68, 69} and signal trans-

duction pathways^{70, 71, 91} for the occurrence of cardiac hypertrophy during the development of heart failure. In addition, the increased ventricular wall tension is also associated with release of norepinephrine and Ang II from the myocardial sympathetic nerve endings and endogenous cardiac RAS. Both these hormones act on their

respective receptors, stimulate protein synthesis and produce cellular growth as well as generate oxyradicals and oxidative stress upon accumulation in cardiomyocytes^{12, 13} for the occurrence of cardiac remodelling and cardiac dysfunction.^{32-37, 41} Thus, increased ventricular wall tension is considered to play a critical role in the development as well as progression of heart failure. These alterations due to increased ventricular wall tension are depicted in Figure 9.

It may also be mentioned that haemodynamic overload (both preload and afterload) and various hormones not only affect the myocardium but also produce marked turbulence in blood flow upon inducing vasoconstriction of the peripheral blood vessels.^{38, 39, 41, 92-94} Such alterations in the circulatory system for a prolonged period induce shear and stress on the blood vessels, produce defects in the endothelium and lead to the generation of oxyradicals as well as release of nitric oxide and endothelins.^{12, 13, 95-99} While endothelins will produce oxyradicals and cardiac hypertrophy, the combination of nitric oxide with oxyradicals is known to generate peroxynitrite and nitrosative stress. Thus, the occurrence of endothelial defects has been proposed to be one of the important mechanism for the progression cardiac dysfunction and heart failure. A schematic representation of events associated with endothelial defects in heart failure is depicted in Figure 10.

Mitochondrial defects, generation of oxidative stress and developments in the pathogenesis and therapy of heart failure

It is noteworthy that mitochondria are a major source of oxyradical production under pathological conditions which is associated with defects in electron transport system, occurrence of Ca^{2+} -overload and alteration in the activities of different enzymatic pathways in these organelles. It is also evident that oxidative stress generated by this source may impair oxidative phosphorylation for reducing energy production, open mitochondrial pores for producing cytotoxic effects

such as apoptosis and necrosis and induce abnormalities in other mitochondrial functions.¹⁰⁰⁻¹⁰⁶ In view of the critical role of oxidative stress for the induction of heart disease,^{83, 86-89} it is likely that the oxidative stress-induced mitochondrial dysfunction may be involved in the progression of heart failure. It is also emphasised that low concentrations of oxyradicals for a short duration are considered to be intimately involved in the generation of adaptive cardiac hypertrophy whereas high concentrations of oxyradicals for a prolonged period along with proinflammatory cytokines are involved in the development of maladaptive cardiac hypertrophy.^{13, 77, 88} Since, it is likely that different antioxidants may prove beneficial in attenuating the transition of adaptive hypertrophy into maladaptive as well as the progression of heart failure,^{82, 88, 107-109} there is a real challenge in developing both natural and synthetic antioxidants, which are safe and effective for the therapy of heart failure. Furthermore, in view of the modification of cardiac gene expression by oxidative stress,^{88, 108} extensive efforts are being made to develop gene-based and RNA-based therapies for the treatment of heart failure.¹¹⁰⁻¹¹⁸

Several types of β -adrenoreceptor blocking agents and Ang II receptor inhibitors are commonly used for the treatment of HFrEF whereas therapy of HFpEF make use of different sodium-glucose cotransporter 2 inhibitors such as empagliflozin, dapagliflozin, canagliflozin and ertugliflozin.^{12, 13, 45, 48} However, various studies have now shown a new horizon for the pathogenesis and therapy of HFrEF and HFpEF. Some investigators have reported that sodium-glucose cotransporter-2 inhibitors are not only beneficial for the treatment of HFpEF^{42, 119, 120} but are also effective for the therapy of HFrEF.¹²¹⁻¹²⁵ Sodium-glucose cotransporter-2 inhibitors as well as Ang II receptor-neprilysin inhibitors, β -adrenoreceptor blockers and mineralocorticoids receptor antagonists have also been observed to be very promising for the outcome improvement of patients with mildly reduced and preserved ejection fraction.¹²⁶⁻¹³² Such studies indicate that a combination therapy using sodium-glucose cotransporter-2 inhibitors with Ang II receptor-neprilysin inhibitor, β -adrenoreceptor blocker or mineralocorticoid inhibitor may prove effective in the therapy of HFrEF for attenuating the morbidity and mortality.¹³³⁻¹³⁷ However, a great deal of both experimental and clinical work need to be carried out for making any meaningful conclusion as well as to identify the exact molecular target for improved therapy of heart failure.

Perspectives

In order to identify some new molecular targets for discovering novel drug therapy for heart failure, the existing literature was reviewed regarding the mechanisms of cardiac dysfunction in both ischaemic- and non-ischaemic cardiovascular diseases, which are known to result in the development of heart failure. Several drugs such as β -adrenoreceptor blockers, ACE inhibitors, Ang II receptor antagonists, vasodilators and some inotropic agents have been helpful in partially improving cardiac dysfunction as well as delaying the progression of heart failure; however, these agents are ineffective in reducing the morbidity or mortality associated with this disease. It should be mentioned that most of these new drugs were developed as receptor-antagonists for both catecholamines and Ang II as well as for reducing the elevated levels of Ang II. Furthermore, both catecholamines and Ang II have been shown to affect other sites as these hormones become accumulated in hypertrophied cardiomyocytes and produce oxyradicals and oxidative stress due to oxidation of catecholamines by mitochondrial monoamine oxidase as well as Ang II-induced activation of mitochondrial NADPH oxidase. In addition, different other vasoactive hormones including serotonin, endothelins and vasopressin are also elevated during the development of heart failure. Such observations seem to explain why β -adrenoreceptor or Ang II receptor blocking agents are not fully effective for the treatment of heart failure. Accordingly, it is suggested that development of an appropriate combination therapy for antagonising the adverse effects of different vasoactive hormones may prove more beneficial for the treatment of heart failure. In fact, in view of the recently discovered antioxidative, anti-inflammatory and anti-apoptotic properties of molecular hydrogen,¹³⁸⁻¹⁴² it appears that therapy of heart failure patients with molecular hydrogen may prove highly effective.

Conclusion

From the observations described in this article it is evident that the mechanisms of heart failure are of complex nature. In fact, a wide variety of abnormalities including metabolic derangements, subcellular defects and chang-

es in signal transduction pathways have been shown to occur in both cardiac and vascular systems during the development as well as progression of heart failure. Such alterations in the failing heart are considered to occur mainly as a consequence of both elevated levels of various vasoactive hormones and increases in haemodynamic overload (both preload and afterload) in diverse cardiovascular diseases. Both increased ventricular wall tension and turbulence of blood flow in the circulation have also been shown to involve adverse events in heart failure. Although such changes in heart failure are dependent upon the type and stage of cardiovascular disease, several pathogenic factors such as oxidative stress, inflammation, endothelial defects, Ca^{2+} -handling abnormalities and depletion of high energy phosphate stores are considered to play important role in the progression of cardiac dysfunction and heart failure. Accordingly, different events in the failing heart are indicated which may serve molecular targets for future drug development for the therapy of heart failure. Although, it is difficult to outline the explicit roadmap for future research directions and strategies for drug development for improving the treatment of heart failure, it is suggested that efforts should be made to develop a single intervention affecting multiple targets or a combination therapy for reducing the generation of oxidative stress, development of myocardial inflammation and occurrence of Ca^{2+} -handling abnormalities.

Ethics

This study was a secondary analysis based on the currently existing dataset and did not directly involve with human participants or experimental animals. Therefore, the ethics approval was not required in this paper.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

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References

1. Smith, WM. Epidemiology of congestive heart failure. *Am J Cardiol.* 1985;55(2):3A-8A. doi: 10.1016/0002-9149(85)90789-1.
2. Parmley, WW. Pathophysiology of congestive heart failure. *Am J Cardiol.* 1985;56(2):7A-11A. doi: 10.1016/0002-9149(85)91199-3.
3. Brophy, JM. Epidemiology of congestive heart failure. Canadian data from 1970 to 1989. *Can J Cardiol.* 1992; 8(5):495-8. PMID: 1617529.
4. 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(10):873-87. PMID: 8281476.
5. Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling--concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. Behalf of an International Forum on Cardiac Remodeling. *J Am Coll Cardiol.* 2000;35(3):569-82. doi: 10.1016/s0735-1097(99)00630-0.
6. Jessup M, Brozena S. Heart failure. *N Engl J Med.* 2003;348(20):2007-18. doi: 10.1056/NEJMra021498.
7. 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(1):31-45. doi: 10.1177/107424840601100103.
8. 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(4-5):671-81. doi: 10.1007/s10741-011-9278-7.
9. Francis GS. Development of arrhythmias in the patient with congestive heart failure: pathophysiology, prevalence and prognosis. *Am J Cardiol.* 1986;57(3):3B-7B. doi: 10.1016/0002-9149(86)90991-4.
10. Packer M. Neurohormonal interactions and adaptations in congestive heart failure. *Circulation.* 1988;77(4):721-30. doi: 10.1161/01.cir.77.4.721.
11. Dhalla NS, Elimban V, Shah AK, Nusier M. Mechanisms of cardiac dysfunction in heart failure due to myocardial infarction. *J Integ Cardiol Open Access.* 2019;2(4):2674-89. doi:10.31487/j.JICOA.2019.04.12.
12. Dhalla NS, Bhullar SK, Shah AK. Future scope and challenges for congestive heart failure: moving toward development of pharmacotherapy. *Can J Physiol Pharmacol.* 2022;100(9):834-47. doi: 10.1139/cjpp-2022-0154.
13. Dhalla NS, Mota KO, Elimban V, Shah AK, de Vasconcelos CML, Bhullar SK. Role of vasoactive hormone-induced signal transduction in cardiac hypertrophy and heart failure. *Cells.* 2024;13(10):856. doi: 10.3390/cells13100856.
14. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics--2012 update: a report from the American Heart Association. *Circulation.* 2012;125(1):e2-e220. doi: 10.1161/CIR.0b013e31823ac046.
15. Heidenreich PA, Albert NM, Allen LA, Bluemke DA, Butler J, Fonarow GC, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circ Heart Fail.* 2013;6(3):606-19. doi: 10.1161/HHF.0b013e318291329a.

16. Felker GM, Thompson RE, Hare JM, Hruban RH, Clemetson DE, Howard DL, et al. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. *N Engl J Med*. 2000;342(15):1077-84. doi: 10.1056/NEJM200004133421502.
17. Levy D, Kenchaiah S, Larson MG, Benjamin EJ, Kupka MJ, Ho KK, et al. Long-term trends in the incidence of and survival with heart failure. *N Engl J Med*. 2002;347(18):1397-402. doi: 10.1056/NEJMoa020265.
18. McMurray JJ, Stewart S. Epidemiology, aetiology, and prognosis of heart failure. *Heart*. 2000;83(5):596-602. doi: 10.1136/heart.83.5.596.
19. Lloyd-Jones DM, Larson MG, Leip EP, Beiser A, D'Agostino RB, Kannel WB, Murabito JM, et al. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. *Circulation*. 2002;106(24):3068-72. doi: 10.1161/01.cir.0000039105.49749.6f.
20. Maillet M, van Berlo JH, Molkentin JD. Molecular basis of physiological heart growth: fundamental concepts and new players. *Nat Rev Mol Cell Biol*. 2013;14(1):38-48. doi: 10.1038/nrm3495.
21. Lyon RC, Zanella F, Omens JH, Sheikh F. Mechanotransduction in cardiac hypertrophy and failure. *Circ Res*. 2015;116(8):1462-76. doi: 10.1161/CIRCRESAHA.116.304937.
22. Bernardo BC, Weeks KL, Pretorius L, McMullen JR. Molecular distinction between physiological and pathological cardiac hypertrophy: experimental findings and therapeutic strategies. *Pharmacol Ther*. 2010;128(1):191-227. doi: 10.1016/j.pharmthera.2010.04.005.
23. Molkentin JD, Dorn GW 2nd. Cytoplasmic signaling pathways that regulate cardiac hypertrophy. *Annu Rev Physiol*. 2001;63:391-426. doi: 10.1146/annurev.physiol.63.1.391.
24. Shimizu I, Minamino T. Physiological and pathological cardiac hypertrophy. *J Mol Cell Cardiol*. 2016;97:245-62. doi: 10.1016/j.yjmcc.2016.06.001.
25. Wikman-Coffelt J, Parmley WW, Mason DT. The cardiac hypertrophy process. Analyses of factors determining pathological vs. physiological development. *Circ Res*. 1979;45(6):697-707. doi: 10.1161/01.res.45.6.697.
26. Dhalla NS, Heyliger CE, Beamish RE, Innes IR. Pathophysiological aspects of myocardial hypertrophy. *Can J Cardiol*. 1987;3(4):183-96. PMID: 3036324.
27. Heineke J, Molkentin JD. Regulation of cardiac hypertrophy by intracellular signalling pathways. *Nat Rev Mol Cell Biol*. 2006;7(8):589-600. doi: 10.1038/nrm1983.
28. Oldfield CJ, Duhamel TA, Dhalla NS. Mechanisms for the transition from physiological to pathological cardiac hypertrophy. *Can J Physiol Pharmacol*. 2020;98(2):74-84. doi: 10.1139/cjpp-2019-0566.
29. Olson RE. Myocardial metabolism in congestive heart failure. *J Chronic Dis*. 1959;9(5):442-64. doi: 10.1016/0021-9681(59)90172-9.
30. Dhalla NS, Saini-Chohan HK, Rodriguez-Leyva D, Elimban V, Dent MR, Tappia PS. Subcellular remodelling may induce cardiac dysfunction in congestive heart failure. *Cardiovasc Res*. 2009;81(3):429-38. doi: 10.1093/cvr/cvn281.
31. Dhalla NS, Das PK, Sharma GP. Subcellular basis of cardiac contractile failure. *J Mol Cell Cardiol*. 1978;10(4):363-85. doi: 10.1016/0022-2828(78)90384-x.
32. Pfeffer MA, Braunwald E. Ventricular remodeling after myocardial infarction. Experimental observations and clinical implications. *Circulation*. 1990;81(4):1161-72. doi: 10.1161/01.cir.81.4.1161.
33. Opie LH, Commerford PJ, Gersh BJ, Pfeffer MA. Controversies in ventricular remodelling. *Lancet*. 2006;367(9507):356-67. doi: 10.1016/S0140-6736(06)68074-4.
34. Machackova J, Barta J, Dhalla NS. Myofibrillar remodeling in cardiac hypertrophy, heart failure and cardiomyopathies. *Can J Cardiol*. 2006;22(11):953-68. doi: 10.1016/s0828-282x(06)70315-4.
35. Sabbah HN, Goldstein S. Ventricular remodelling: consequences and therapy. *Eur Heart J*. 1993;14 Suppl C:24-9. doi: 10.1093/eurheartj/14.suppl_c.24.
36. Mudd JO, Kass DA. Tackling heart failure in the twenty-first century. *Nature*. 2008;451(7181):919-28. doi: 10.1038/nature06798.
37. Burchfield JS, Xie M, Hill JA. Pathological ventricular remodeling: mechanisms: part 1 of 2. *Circulation*. 2013;128(4):388-400. doi: 10.1161/CIRCULATIONAHA.113.001878.
38. Gaasch WH. Diagnosis and treatment of heart failure based on left ventricular systolic or diastolic dysfunction. *JAMA*. 1994;271(16):1276-80. PMID: 8151903.
39. Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure--abnormalities in active relaxation and passive stiffness of the left ventricle. *N Engl J Med*. 2004;350(19):1953-9. doi: 10.1056/NEJMoa032566.
40. Zile MR, Gottdiener JS, Hetzel SJ, McMurray JJ, Komajda M, McKelvie R, et al. Prevalence and significance of alterations in cardiac structure and function in patients with heart failure and a preserved ejection fraction. *Circulation*. 2011;124(23):2491-501. doi: 10.1161/CIRCULATIONAHA.110.011031.
41. Zile MR, Kjellstrom B, Bennett T, Cho Y, Baicu CF, Aaron MF, et al. Effects of exercise on left ventricular systolic and diastolic properties in patients with heart failure and a preserved ejection fraction versus heart failure and a reduced ejection fraction. *Circ Heart Fail*. 2013;6(3):508-16. doi: 10.1161/CIRCHEARTFAILURE.112.000216.
42. Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. *Eur Heart J*. 2011;32(6):670-9. doi: 10.1093/eurheartj/ehq426.
43. Ho JE, Lyass A, Lee DS, Vasan RS, Kannel WB, Larson MG, Levy D. Predictors of new-onset heart failure: differences in preserved versus reduced ejection fraction. *Circ Heart Fail*. 2013;6(2):279-86. doi: 10.1161/CIRCHEARTFAILURE.112.972828.
44. Borbely A, van der Velden J, Papp Z, Bronzwaer JG, Edes I, Stienen GJ, Paulus WJ. Cardiomyocyte stiffness in diastolic heart failure. *Circulation*. 2005;111(6):774-81. doi: 10.1161/01.CIR.0000155257.33485.6D.
45. Upadhyay B, Haykowsky MJ, Kitzman DW. Therapy for heart failure with preserved ejection fraction: current status, unique challenges, and future directions. *Heart Fail Rev*. 2018;23(5):609-29. doi: 10.1007/s10741-018-9714-z.
46. Packer M. Drugs that ameliorate epicardial adipose tissue inflammation may have discordant effects in heart failure with a preserved ejection fraction as compared with a reduced ejection fraction. *J Card Fail*. 2019;25(12):986-1003. doi: 10.1016/j.cardfail.2019.09.002.

47. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med.* 2014;370(15):1383-92. doi: 10.1056/NEJMoa1313731.
48. Kjeldsen SE, von Lueder TG, Smiseth OA, Wachtell K, Mistry N, Westheim AS, et al. Medical therapies for heart failure with preserved ejection fraction. *Hypertension.* 2020;75(1):23-32. doi: 10.1161/HYPERTENSIONAHA.119.14057.
49. Vaduganathan M, Claggett BL, Desai AS, Anker SD, Perrone SV, Janssens S, et al. Prior heart failure hospitalization, clinical outcomes, and response to sacubitril/valsartan compared with valsartan in HFpEF. *J Am Coll Cardiol.* 2020;75(3):245-54. doi: 10.1016/j.jacc.2019.11.003.
50. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med.* 2021;385(16):1451-61. doi: 10.1056/NEJMoa2107038.
51. Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med.* 2021;384(2):117-28. doi: 10.1056/NEJMoa2030183.
52. Nassif ME, Windsor SL, Borlaug BA, Kitzman DW, Shah SJ, Tang F, et al. The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: a multicenter randomized trial. *Nat Med.* 2021;27(11):1954-60. doi: 10.1038/s41591-021-01536-x.
53. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med.* 2006;355(3):251-9. doi: 10.1056/NEJMoa052256.
54. 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(4):717-32. doi: 10.1586/14779072.3.4.717.
55. Ju H, Zhao S, Jassal DS, Dixon IM. Effect of AT1 receptor blockade on cardiac collagen remodeling after myocardial infarction. *Cardiovasc Res.* 1997;35(2):223-32. doi: 10.1016/s0008-6363(97)00130-2.
56. Rouleau JL. The neurohormonal hypothesis and the treatment of heart failure. *Can J Cardiol.* 1996; 12: 3F-8F.
57. Rehsia NS, Dhalla NS. Mechanisms of the beneficial effects of beta-adrenoceptor antagonists in congestive heart failure. *Exp Clin Cardiol.* 2010;15(4):e86-95. PMID: 21264074.
58. Sabbah HN, Shimoyama H, Kono T, Gupta RC, Sharov VG, Scicli G, et al. Effects of long-term monotherapy with enalapril, metoprolol, and digoxin on the progression of left ventricular dysfunction and dilation in dogs with reduced ejection fraction. *Circulation.* 1994;89(6):2852-9. doi: 10.1161/01.cir.89.6.2852.
59. Pandey AK, Dhingra NK, Hibino M, Gupta V, Verma S. Sodium-glucose cotransporter 2 inhibitors in heart failure with reduced or preserved ejection fraction: a meta-analysis. *ESC Heart Fail.* 2022;9(2):942-6. doi: 10.1002/ehf2.13805.
60. Spertus JA, Birmingham MC, Nassif M, Damaraju CV, Abbate A, Butler J, et al. The SGLT2 inhibitor canagliflozin in heart failure: the CHIEF-HF remote, patient-centered randomized trial. *Nat Med.* 2022;28(4):809-13. doi: 10.1038/s41591-022-01703-8.
61. Heath R, Johnsen H, Strain WD, Evans M. Emerging horizons in heart failure with preserved ejection fraction: the role of SGLT2 inhibitors. *Diabetes Ther.* 2022;13(2):241-50. doi: 10.1007/s13300-022-01204-4.
62. Neri M, Fineschi V, Di Paolo M, Pomara C, Riezzo I, Turillazzi E, Cerretani D. Cardiac oxidative stress and inflammatory cytokines response after myocardial infarction. *Curr Vasc Pharmacol.* 2015;13(1):26-36. doi: 10.2174/15701611113119990003.
63. van der Pol A, van Gilst WH, Voors AA, van der Meer P. Treating oxidative stress in heart failure: past, present and future. *Eur J Heart Fail.* 2019;21(4):425-35. doi: 10.1002/ehf.1320.
64. Sia YT, Lapointe N, Parker TG, Tsoporis JN, Deschepper CF, Calderone A, et al. Beneficial effects of long-term use of the antioxidant probucol in heart failure in the rat. *Circulation.* 2002;105(21):2549-55. doi: 10.1161/01.cir.0000016721.84535.00.
65. Ayoub KF, Pothineni NVK, Rutland J, Ding Z, Mehta JL. Immunity, inflammation, and oxidative stress in heart failure: emerging molecular targets. *Cardiovasc Drugs Ther.* 2017;31(5-6):593-608. doi: 10.1007/s10557-017-6752-z.
66. Milinković I, Polovina M, Simeunović DS, Ašanin M, Seferović PM. Oxidative stress and inflammation in heart failure: The best is yet to come. *Eur J Prev Cardiol.* 2020;27(5):490-3. doi: 10.1177/2047487319900294.
67. Rehsia NS, Dhalla NS. Potential of endothelin-1 and vasopressin antagonists for the treatment of congestive heart failure. *Heart Fail Rev.* 2010;15(1):85-101. doi: 10.1007/s10741-009-9152-z.
68. Lopaschuk GD, Ussher JR, Folmes CD, Jaswal JS, Stanley WC. Myocardial fatty acid metabolism in health and disease. *Physiol Rev.* 2010;90(1):207-58. doi: 10.1152/physrev.00015.2009.
69. Schmidt-Schweda S, Holubarsch C. First clinical trial with etomoxir in patients with chronic congestive heart failure. *Clin Sci (Lond).* 2000;99(1):27-35. doi: 10.1042/CS19990235.
70. English JM, Cobb MH. Pharmacological inhibitors of MAPK pathways. *Trends Pharmacol Sci.* 2002;23(1):40-5. doi: 10.1016/s0165-6147(00)01865-4.
71. Dhalla NS, Müller AL. Protein kinases as drug development targets for heart disease therapy. *Pharmaceuticals (Basel).* 2010;3(7):2111-45. doi: 10.3390/ph3072111.
72. Grossman W. Cardiac hypertrophy: useful adaptation or pathologic process? *Am J Med.* 1980;69(4):576-84. doi: 10.1016/0002-9343(80)90471-4.
73. Packer M. The neurohormonal hypothesis: a theory to explain the mechanism of disease progression in heart failure. *J Am Coll Cardiol.* 1992;20(1):248-54. doi: 10.1016/0735-1097(92)90167-l.
74. Weber KT, Sun Y, Guarda E. Structural remodeling in hypertensive heart disease and the role of hormones. *Hypertension.* 1994;23(6 Pt 2):869-77. doi: 10.1161/01.hyp.23.6.869.
75. Parmley WW. Neuroendocrine changes in heart failure and their clinical relevance. *Clin Cardiol.* 1995;18(8):440-5. doi: 10.1002/clc.4960180804.
76. Nicholls DP, Onuoha GN, McDowell G, Elborn JS, Riley MS, Nugent AM, et al. Neuroendocrine changes in chronic cardiac failure. *Basic Res Cardiol.* 1996;91 Suppl 1:13-20. doi: 10.1007/BF00810519.
77. Tarzami ST. Chemokines and inflammation in heart disease: adaptive or maladaptive? *Int J Clin Exp Med.* 2011;4(1):74-80. PMID: 21394288.

78. Zhang H, Dhalla NS. The role of pro-inflammatory cytokines in the pathogenesis of cardiovascular disease. *Int J Mol Sci.* 2024;25(2):1082. doi: 10.3390/ijms25021082.
79. Sawyer DB, Siwik DA, Xiao L, Pimentel DR, Singh K, Colucci WS. Role of oxidative stress in myocardial hypertrophy and failure. *J Mol Cell Cardiol.* 2002;34(4):379-88. doi: 10.1006/jmcc.2002.1526.
80. Keith M, Geranmayegan A, Sole MJ, Kurian R, Robinson A, Omran AS, Jeejeebhoy KN. Increased oxidative stress in patients with congestive heart failure. *J Am Coll Cardiol.* 1998;31(6):1352-6. doi: 10.1016/s0735-1097(98)00101-6.
81. Dhalla NS, Elmoselhi AB, Hata T, Makino N. Status of myocardial antioxidants in ischemia-reperfusion injury. *Cardiovasc Res.* 2000;47(3):446-56. doi: 10.1016/s0008-6363(00)00078-x.
82. Dhalla NS, Temsah RM, Netticadan T. Role of oxidative stress in cardiovascular diseases. *J Hypertens.* 2000;18(6):655-73. doi: 10.1097/00004872-200018060-00002.
83. Mialet-Perez J, Santin Y, Parini A. Monoamine oxidase-A, serotonin and norepinephrine: synergistic players in cardiac physiology and pathology. *J Neural Transm (Vienna).* 2018;125(11):1627-34. doi: 10.1007/s00702-018-1908-y.
84. Looi YH, Grieve DJ, Siva A, Walker SJ, Anilkumar N, Cave AC, et al. Involvement of Nox2 NADPH oxidase in adverse cardiac remodeling after myocardial infarction. *Hypertension.* 2008;51(2):319-25. doi: 10.1161/HYPERTENSIONAHA.107.101980.
85. Murdoch CE, Zhang M, Cave AC, Shah AM. NADPH oxidase-dependent redox signalling in cardiac hypertrophy, remodelling and failure. *Cardiovasc Res.* 2006;71(2):208-15. doi: 10.1016/j.cardiores.2006.03.016.
86. Lassègue B, San Martín A, Griendling KK. Biochemistry, physiology, and pathophysiology of NADPH oxidases in the cardiovascular system. *Circ Res.* 2012;110(10):1364-90. doi: 10.1161/CIRCRESA-HA.111.243972.
87. Shah AK, Bhullar SK, Elimban V, Dhalla NS. Oxidative stress as a mechanism for functional alterations in cardiac hypertrophy and heart failure. *Antioxidants (Basel).* 2021;10(6):931. doi: 10.3390/antiox10060931.
88. Umbarkar P, Singh S, Arkat S, Bodhankar SL, Lohidasan S, Sitasawad SL. Monoamine oxidase-A is an important source of oxidative stress and promotes cardiac dysfunction, apoptosis, and fibrosis in diabetic cardiomyopathy. *Free Radic Biol Med.* 2015;87:263-73. doi: 10.1016/j.freeradbiomed.2015.06.025.
89. Dammanahalli KJ, Sun Z. Endothelins and NADPH oxidases in the cardiovascular system. *Clin Exp Pharmacol Physiol.* 2008;35(1):2-6. doi: 10.1111/j.1440-1681.2007.04830.x.
90. Backs J, Backs T, Neef S, Kreusser MM, Lehmann LH, Patrick DM, et al. The delta isoform of CaM kinase II is required for pathological cardiac hypertrophy and remodeling after pressure overload. *Proc Natl Acad Sci U S A.* 2009;106(7):2342-7. doi: 10.1073/pnas.0813013106.
91. van Heerebeek L, Borbély A, Niessen HW, Bronzwaer JG, van der Velden J, Stienen GJ, et al. Myocardial structure and function differ in systolic and diastolic heart failure. *Circulation.* 2006;113(16):1966-73. doi: 10.1161/CIRCULATIONAHA.105.587519.
92. Selby DE, Palmer BM, LeWinter MM, Meyer M. Tachycardia-induced diastolic dysfunction and resting tone in myocardium from patients with a normal ejection fraction. *J Am Coll Cardiol.* 2011;58(2):147-54. doi: 10.1016/j.jacc.2010.10.069.
93. Shimizu I, Minamino T, Toko H, Okada S, Ikeda H, Yasuda N, et al. Excessive cardiac insulin signaling exacerbates systolic dysfunction induced by pressure overload in rodents. *J Clin Invest.* 2010;120(5):1506-14. doi: 10.1172/JCI40096.
94. Parodi EM, Kuhn B. Signalling between microvascular endothelium and cardiomyocytes through neuregulin. *Cardiovasc Res.* 2014;102(2):194-204. doi: 10.1093/cvr/cvu021.
95. Ruetten H, Dimmeler S, Gehring D, Ihling C, Zeiher AM. Concentric left ventricular remodeling in endothelial nitric oxide synthase knockout mice by chronic pressure overload. *Cardiovasc Res.* 2005;66(3):444-53. doi: 10.1016/j.cardiores.2005.01.021.
96. Agapitov AV, Haynes WG. Role of endothelin in cardiovascular disease. *J Renin Angiotensin Aldosterone Syst.* 2002;3(1):1-15. doi: 10.3317/jraas.2002.001.
97. Davenport AP, Hyndman KA, Dhaun N, Southan C, Kohan DE, Pollock JS, et al. Endothelin. *Pharmacol Rev.* 2016;68(2):357-418. doi: 10.1124/pr.115.011833.
98. Margulies KB, Hildebrand FL Jr, Lerman A, Perrella MA, Burnett JC Jr. Increased endothelin in experimental heart failure. *Circulation.* 1990;82(6):2226-30. doi: 10.1161/01.cir.82.6.2226.
99. Wu C, Zhang Z, Zhang W, Liu X. Mitochondrial dysfunction and mitochondrial therapies in heart failure. *Pharmacol Res.* 2022;175:106038. doi: 10.1016/j.phrs.2021.106038.
100. Zhou B, Tian R. Mitochondrial dysfunction in pathophysiology of heart failure. *J Clin Invest.* 2018;128(9):3716-26. doi: 10.1172/JCI120849.
101. Keshavarz-Bahaghighat H, Darwesh AM, Sosnowski DK, Seubert JM. Mitochondrial dysfunction and inflammation in heart failure: novel roles of CYP-derived epoxy lipids. *Cells.* 2020;9(7):1565. doi: 10.3390/cells9071565.
102. Kumar AA, Kelly DP, Chirinos JA. Mitochondrial dysfunction in heart failure with preserved ejection fraction. *Circulation.* 2019;139(11):1435-50. doi: 10.1161/CIRCULATIONAHA.118.036259.
103. Hinton A Jr, Claypool SM, Neikirk K, Senoo N, Wanjalla CN, Kirabo A, Williams CR. Mitochondrial structure and function in human heart failure. *Circ Res.* 2024;135(2):372-96. doi: 10.1161/CIRCRESAHA.124.323800.
104. Bhattarai N, Scott I. In the heart and beyond: Mitochondrial dysfunction in heart failure with preserved ejection fraction (HFpEF). *Curr Opin Pharmacol.* 2024;76:102461. doi: 10.1016/j.coph.2024.102461.
105. Bhullar SK, Dhalla NS. Status of mitochondrial oxidative phosphorylation during the development of heart failure. *Antioxidants (Basel).* 2023;12(11):1941. doi: 10.3390/antiox12111941.
106. Mongirdienė A, Liuzė A, Karčiauskaitė D, Mazgelytė E, Liekis A, Sadauskienė I. Relationship between oxidative stress and left ventricle markers in patients with chronic heart failure. *Cells.* 2023;12(5):803. doi: 10.3390/cells12050803.

107. Dhalla NS, Elimban V, Bartekova M, Adameova A. Involvement of oxidative stress in the development of subcellular defects and heart disease. *Biomedicines*. 2022;10(2):393. doi: 10.3390/biomedicines10020393.
108. Barteková M, Adameová A, Görbe A, Ferenczyová K, Pechánová O, Lazou A, et al. Natural and synthetic antioxidants targeting cardiac oxidative stress and redox signaling in cardiometabolic diseases. *Free Radic Biol Med*. 2021;169:446-77. doi: 10.1016/j.freeradbiomed.2021.03.045.
109. Argirò A, Ding J, Adler E. Gene therapy for heart failure and cardiomyopathies. *Rev Esp Cardiol (Engl Ed)*. 2023;76(12):1042-54. English, Spanish. doi: 10.1016/j.rec.2023.06.009.
110. Greenberg B. Gene therapy for heart failure. *J Cardiol*. 2015;66(3):195-200. doi: 10.1016/j.jjcc.2015.02.006.
111. Korpela H, Järveläinen N, Siimes S, Lampela J, Airaksinen J, Valli K, et al. Gene therapy for ischaemic heart disease and heart failure. *J Intern Med*. 2021;290(3):567-82. doi: 10.1111/joim.13308.
112. Gabisonia K, Recchia FA. Gene therapy for heart failure: new perspectives. *Curr Heart Fail Rep*. 2018;15(6):340-9. doi: 10.1007/s11897-018-0410-z.
113. Wang J, Shi Q, Wang Y, Dawson LW, Ciampa G, Zhao W, et al. Gene therapy with the N-terminus of junctophilin-2 improves heart failure in mice. *Circ Res*. 2022;130(9):1306-17. doi: 10.1161/CIRCRESAHA.121.320680.
114. Hsu A, Duan Q, Day DS, Luo X, McMahon S, Huang Y, et al. Targeting transcription in heart failure via CDK7/12/13 inhibition. *Nat Commun*. 2022;13(1):4345. doi: 10.1038/s41467-022-31541-8.
115. Lucas T, Bonauer A, Dimmeler S. RNA therapeutics in cardiovascular disease. *Circ Res*. 2018;123(2):205-20. doi: 10.1161/CIRCRESAHA.117.311311.
116. Saddique MN, Qadri M, Ain NU, Farhan E, Shahid F, Benyamin J, et al. Safety and effectiveness of interference RNA (RNAi) based therapeutics in cardiac failure: A systematic review. *Heart Lung*. 2024;68:298-304. doi: 10.1016/j.hrtlng.2024.08.015.
117. Dave P, Anand P, Kothawala A, Srikanth P, Shastri D, Uddin A, et al. RNA interference therapeutics for hereditary amyloidosis: A narrative review of clinical trial outcomes and future directions. *Cureus*. 2024;16(6):e62981. doi: 10.7759/cureus.62981.
118. Packer M, Butler J, Zannad F, Filippatos G, Ferreira JP, Pocock SJ, et al. Effect of empagliflozin on worsening heart failure events in patients with heart failure and preserved ejection fraction: EMPEROR-Preserved Trial. *Circulation*. 2021;144(16):1284-94. doi: 10.1161/CIRCULATIONAHA.121.056824.
119. Omote K, Verbrugge FH, Borlaug BA. Heart failure with preserved ejection fraction: mechanisms and treatment strategies. *Annu Rev Med*. 2022;73:321-37. doi: 10.1146/annurev-med-042220-022745.
120. Omar M, Jensen J, Ali M, Frederiksen PH, Kistorp C, Videbæk L, et al. Associations of empagliflozin with left ventricular volumes, mass, and function in patients with heart failure and reduced ejection fraction: A sub-study of the EMPEROR-HF randomized clinical trial. *JAMA Cardiol*. 2021;6(7):836-40. doi: 10.1001/jamacardio.2020.6827.
121. Vaduganathan M, Docherty KF, Claggett BL, Jhund PS, de Boer RA, Hernandez AF, et al. SGLT-2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials. *Lancet*. 2022;400(10354):757-67. doi: 10.1016/S0140-6736(22)01429-5.
122. Das US, Paul A, Banerjee S. SGLT2 inhibitors in heart failure with reduced ejection fraction. *Egypt Heart J*. 2021;73(1):93. doi: 10.1186/s43044-021-00218-w.
123. Tomasoni D, Fonarow GC, Adamo M, Anker SD, Butler J, Coats AJS, et al. Sodium-glucose co-transporter 2 inhibitors as an early, first-line therapy in patients with heart failure and reduced ejection fraction. *Eur J Heart Fail*. 2022;24(3):431-41. doi: 10.1002/ehf.2397.
124. Zannad F, Macari S. Drug treatment with empagliflozin lowered risk for hospitalization in people with heart failure with reduced ejection fraction: plain language summary of the EMPEROR-Reduced study. *Future Cardiol*. 2023;19(13):625-30. doi: 10.2217/fca-2023-0090.
125. Solomon SD, de Boer RA, DeMets D, Hernandez AF, Inzucchi SE, Kosiborod MN, et al. Dapagliflozin in heart failure with preserved and mildly reduced ejection fraction: rationale and design of the DELIVER trial. *Eur J Heart Fail*. 2021;23(7):1217-25. doi: 10.1002/ehf.2249.
126. Wang Y, Gao T, Meng C, Li S, Bi L, Geng Y, Zhang P. Sodium-glucose co-transporter 2 inhibitors in heart failure with mildly reduced or preserved ejection fraction: an updated systematic review and meta-analysis. *Eur J Med Res*. 2022;27(1):314. doi: 10.1186/s40001-022-00945-z.
127. Shang Z, Wang X, Gao W. Heart failure with mildly reduced ejection fraction: emerging frontiers in clinical characteristics, prognosis, and treatment. *Rev Cardiovasc Med*. 2022;23(1):30. doi: 10.31083/j.rcm2301030.
128. Talha KM, Butler J. Breakthroughs in the treatment of heart failure with mildly reduced and preserved ejection fraction. *Clin Cardiol*. 2022;45 Suppl 1(Suppl 1):S31-S39. doi: 10.1002/clc.23846.
129. Xiang B, Zhang R, Wu X, Zhou X. Optimal pharmacologic treatment of heart failure with preserved and mildly reduced ejection fraction: A Meta-analysis. *JAMA Netw Open*. 2022;5(9):e2231963. doi: 10.1001/jamanetworkopen.2022.31963.
130. Arnold SV, Silverman DN, Gosch K, Nassif ME, Infeld M, Litwin S, et al. Beta-blocker use and heart failure outcomes in mildly reduced and preserved ejection fraction. *JACC Heart Fail*. 2023;11(8 Pt 1):893-900. doi: 10.1016/j.jchf.2023.03.017.
131. Vaduganathan M, Mentz RJ, Claggett BL, Miao ZM, Kurlac IJ, Ward JH, et al. Sacubitril/valsartan in heart failure with mildly reduced or preserved ejection fraction: a pre-specified participant-level pooled analysis of PARAGLIDE-HF and PARAGON-HF. *Eur Heart J*. 2023;44(31):2982-93. doi: 10.1093/eurheartj/ehad344.
132. Packer M, McMurray JJV. Rapid evidence-based sequencing of foundational drugs for heart failure and a reduced ejection fraction. *Eur J Heart Fail*. 2021;23(6):882-94. doi: 10.1002/ehf.2149.
133. Lin Y, Zhang H, Zhao S, Chen L, Li J, Wang X, Tian W. The efficacy and safety of the combined therapy of sodium-glucose co-transporter-2 inhibitors and angiotensin receptor-neprilysin inhibitor in patients with heart failure with reduced ejection fraction: A meta-analysis of the EMPEROR-reduced and DAPA-HF sub-analysis. *Front Cardiovasc Med*. 2022;9:882089. doi: 10.3389/fcvm.2022.882089.

134. Bozkurt B. Contemporary pharmacological treatment and management of heart failure. *Nat Rev Cardiol*. 2024;21(8):545-55. doi: 10.1038/s41569-024-00997-0.
135. Cotter G, Davison BA, Mebazaa A, Takagi K, Novosadova M, Freund Y, et al. Medical therapy of heart failure with reduced ejection fraction-A call for comparative research. *J Clin Med*. 2021;10(9):1803. doi: 10.3390/jcm10091803.
136. Narayan SI, Terre GV, Amin R, Shanghavi KV, Chandrashekar G, Ghouse F, et al. The pathophysiology and new advancements in the pharmacologic and exercise-based management of heart failure with reduced ejection fraction: A narrative review. *Cureus*. 2023;15(9):e45719. doi: 10.7759/cureus.45719.
137. Murphy SP, Ibrahim NE, Januzzi JL Jr. Heart failure with reduced ejection fraction: A review. *JAMA*. 2020;324(5):488-504. doi: 10.1001/jama.2020.10262.
138. Kura B, Bagchi AK, Singal PK, Barancik M, LeBaron TW, Valachova K, et al. Molecular hydrogen: potential in mitigating oxidative-stress-induced radiation injury. *Can J Physiol Pharmacol*. 2019;97(4):287-92. doi: 10.1139/cjpp-2018-0604.
139. Slezak J, Kura B, LeBaron TW, Singal PK, Buday J, Barancik M. Oxidative stress and pathways of molecular hydrogen effects in medicine. *Curr Pharm Des*. 2021;27(5):610-25. doi: 10.2174/1381612826666200821114016.
140. LeBaron TW, Kura B, Kalocayova B, Tribulova N, Slezak J. A new approach for the prevention and treatment of cardiovascular disorders. Molecular hydrogen significantly reduces the effects of oxidative stress. *Molecules*. 2019;24(11):2076. doi: 10.3390/molecules24112076.
141. Singh RB, Sumbalova Z, Fatima G, Mojto V, Fedacko J, Tarnava A, et al. Effects of molecular hydrogen in the pathophysiology and management of cardiovascular and metabolic diseases. *Rev Cardiovasc Med*. 2024;25(1):33. doi: 10.31083/j.rcm2501033.
142. Kura B, Slezak J. The protective role of molecular hydrogen in ischemia/reperfusion injury. *Int J Mol Sci*. 2024;25(14):7884. doi: 10.3390/ijms25147884.