Dhalla et al. Scr Med. 2025 Jan-Feb;56(1):117-36. DOI:10.5937/scriptamed56-56443

REVIEW ARTICLE

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; Calium; Ca^{2+}-handling abnormalities; Metabolism; Metabolic defects; Remodelling, subcellular.

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Citation:
Dhalla NS, Elimban V, Adameova AD, Goyal RK. Molecular mechanisms for pathophysiology and therapy of cardiac dysfunction in heart failure. Scr Med. 2025 Jan-Feb;56(1):117-36.

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Received: 31 january 2025
Revision received: 22 February 2025
Accepted: 22 February 2025

Introduction

It is now well known that various cardiovascular diseases such as myocardial infarction, atherosclerosis, 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 aging 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 in 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 Ca^{2+}-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 HPpEF 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 HRrEF 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 HFpEF 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 modulators[67-69] 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-

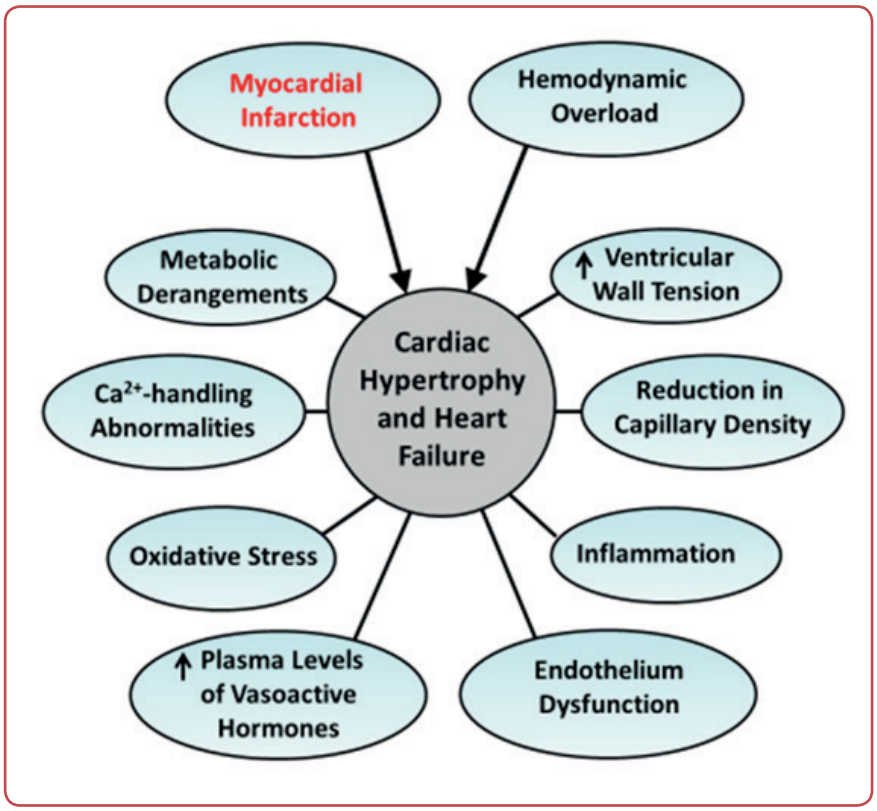

Figure 1: Various abnormalities associated with cardiac hypertrophy and heart failure due to myocardial infarction and haemodynamic overload

↑: 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 P*ubMed* 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

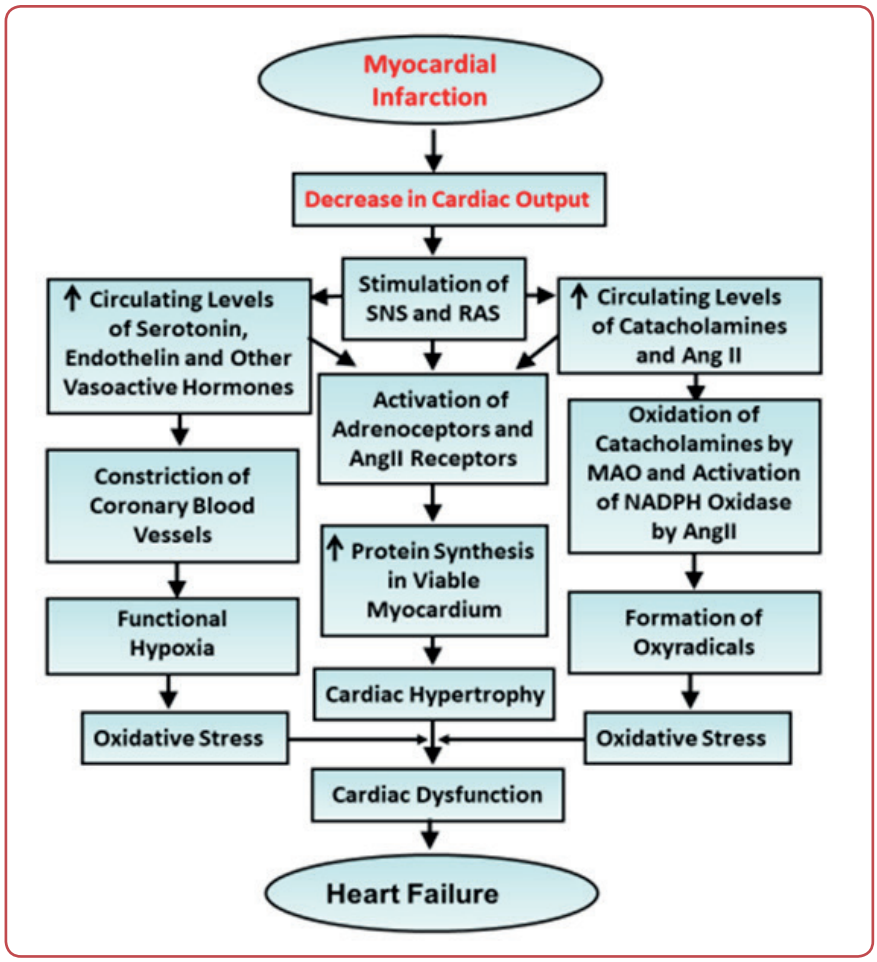

Figure 2: Involvement of some vasoactive hormones and other events during the development of cardiac hypertrophy and heart failure due to myocardial infarction

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.

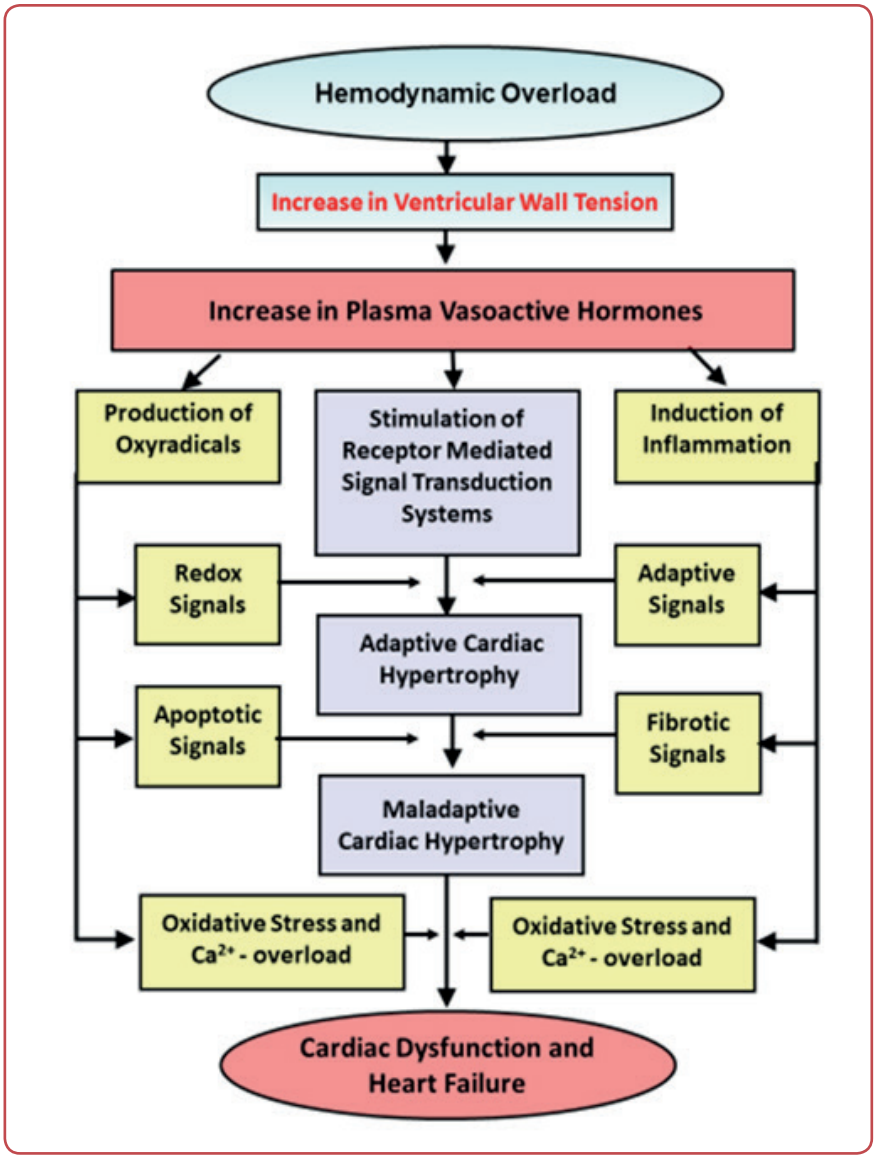

Figure 3: IInvolvement of some vasoactive hormones and signal transduction events during the development of cardiac hypertrophy and heart failure due to haemodynamic overload

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 peripheral 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

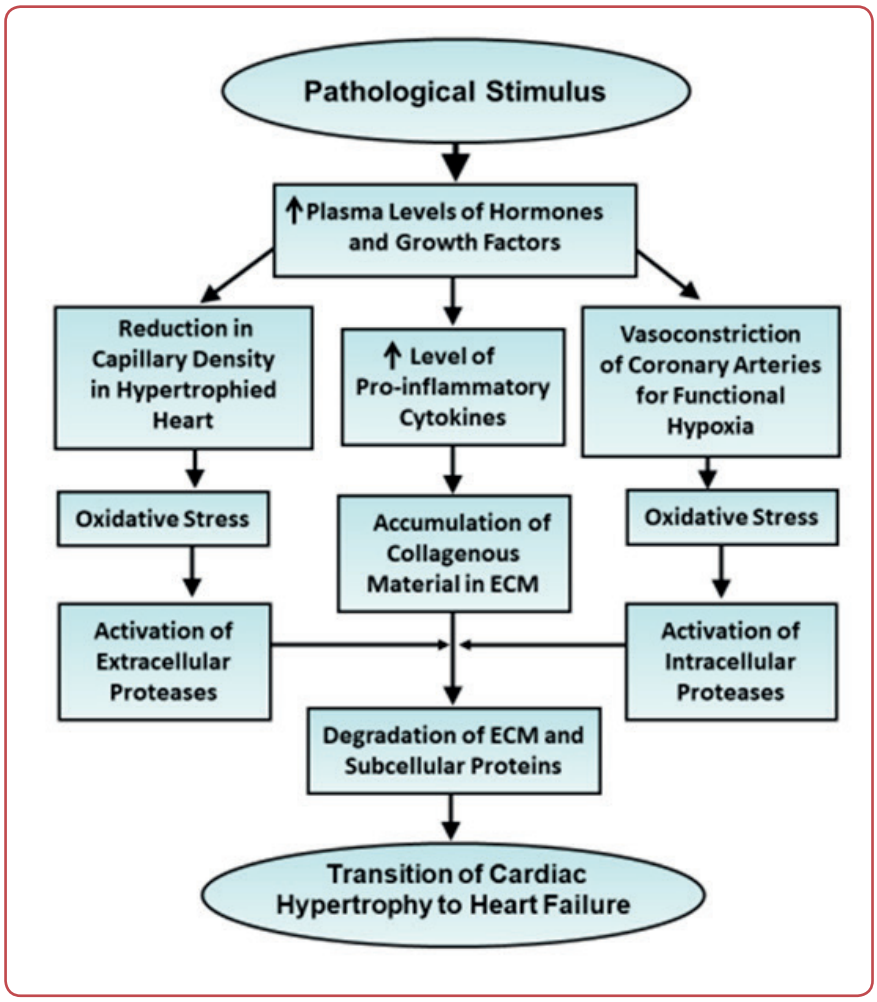

Figure 4: Role of some hormones and growth factors during the transition of cardiac hypertrophy to heart failure

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.

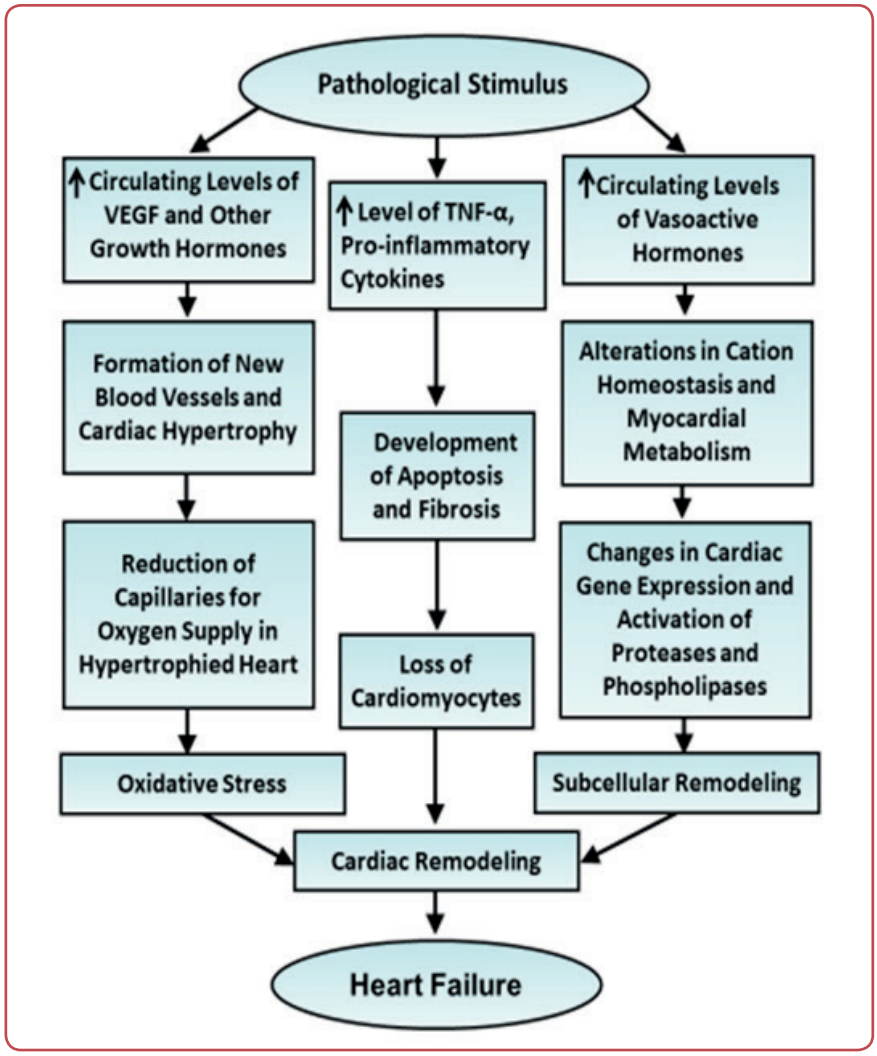

Figure 5: Role of vasoactive hormones, growth factors and pro-inflammatory cytokines in the development of oxidative stress and subcellular remodelling during the development of heart failure

VEGF: Vascular endothelium growth factor; TNF-α: tumour necrosis factor- α; ↑, 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 remodelling and subsequent heart failure (Figure 5).

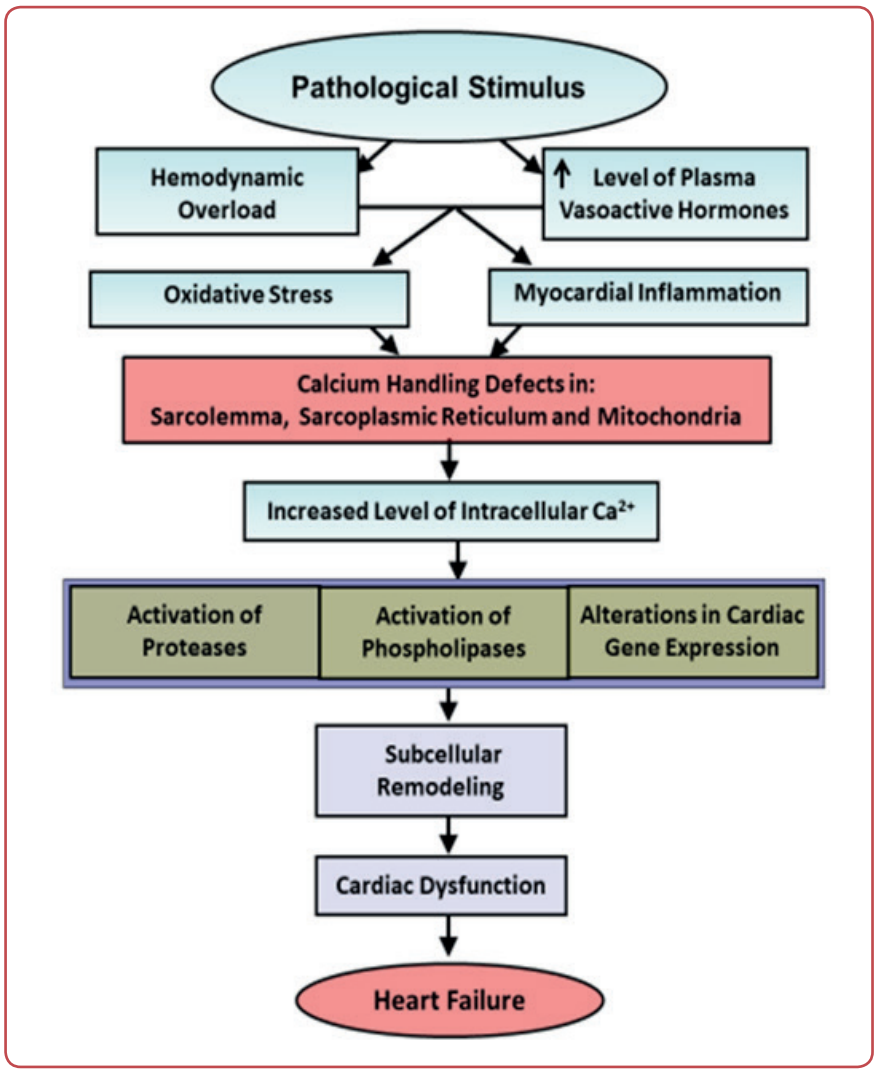

Figure 6: Role of oxidative stress and myocardial inflammation in Ca^{2+}-handling defects and subcellular abnormalities during the development of cardiac dysfunction and heart failure

↑: 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+}-handing 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 concentration 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 remodelling 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

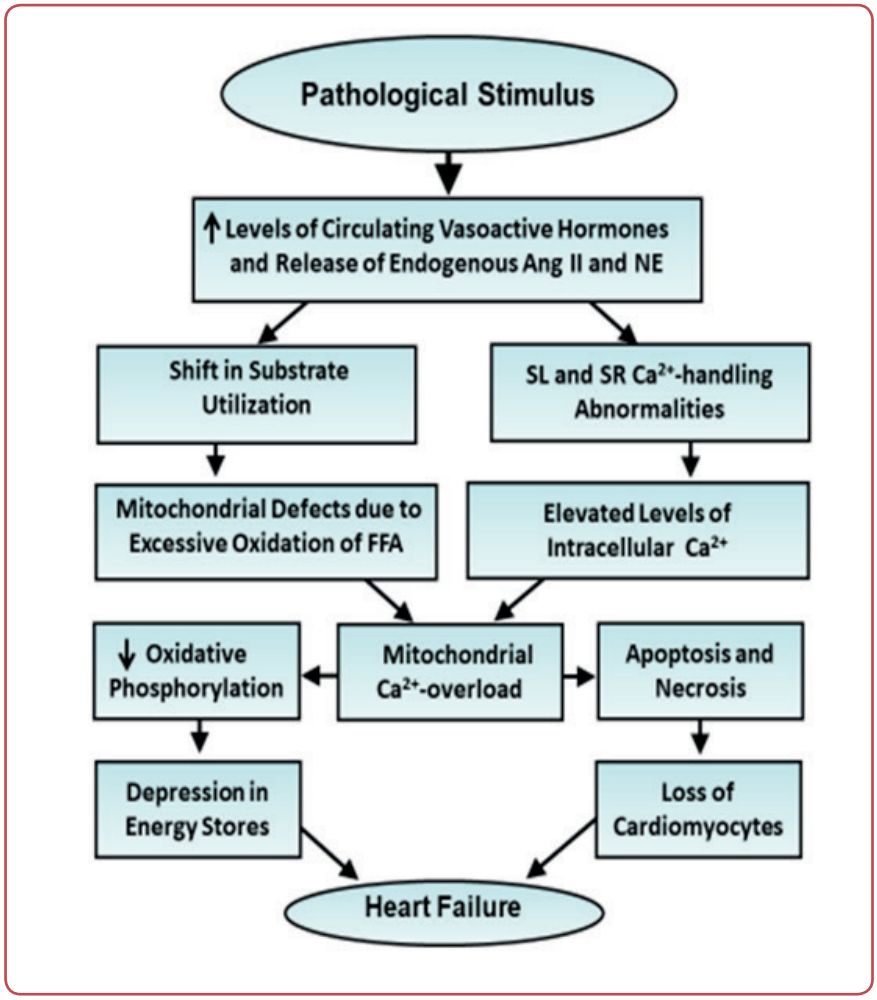

Figure 7: Role of circulating and cardiac vasoactive hormones in the occurrence of mitochondrial Ca^{2+}-overload during the development of heart failure

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 Ca^{2+} - handling abnormalities in the heart due to elevated levels of circulating vasoactive hormones under various pathological conditions. These alterations produce mitochondrial Ca^{2+} - 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 subcellular Ca^{2+}-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 Ca^{2+}-handling result in the occurrence of mitochondrial defect as well as mitochondrial Ca^{2+}-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-

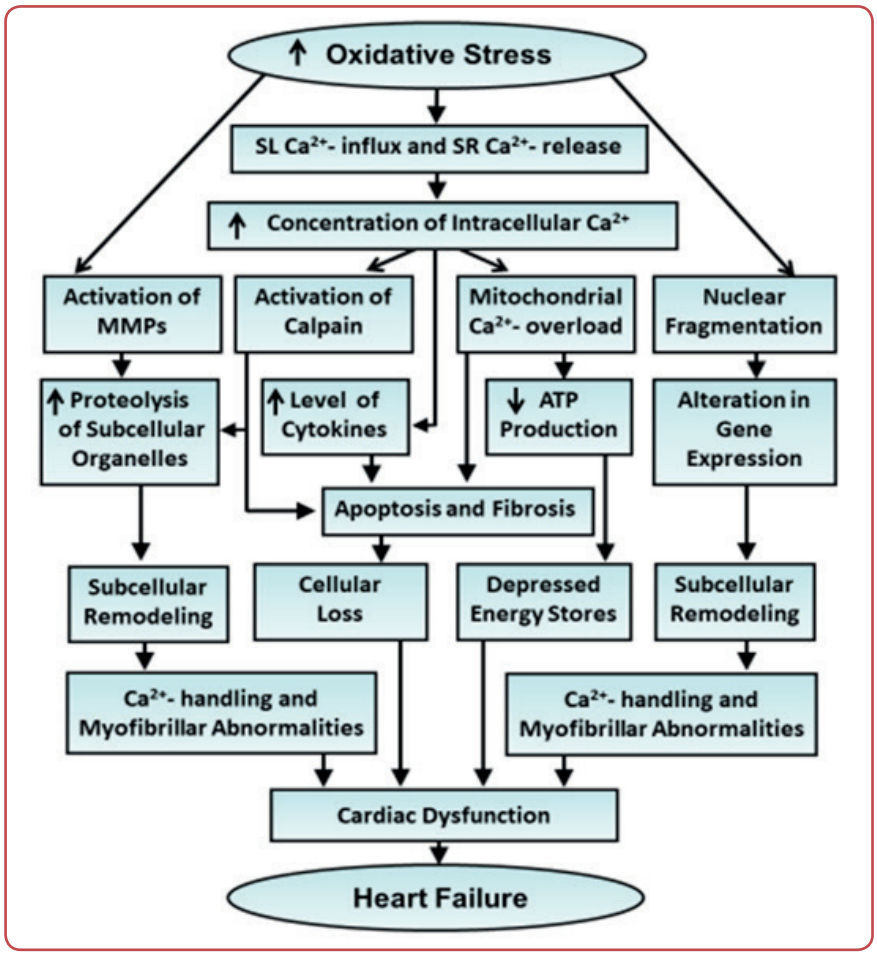

Figure 8: Role of oxidative stress in myocardial alterations and Ca^{2+}-handling abnormalities during the development of cardiac dysfunction

↑: 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.

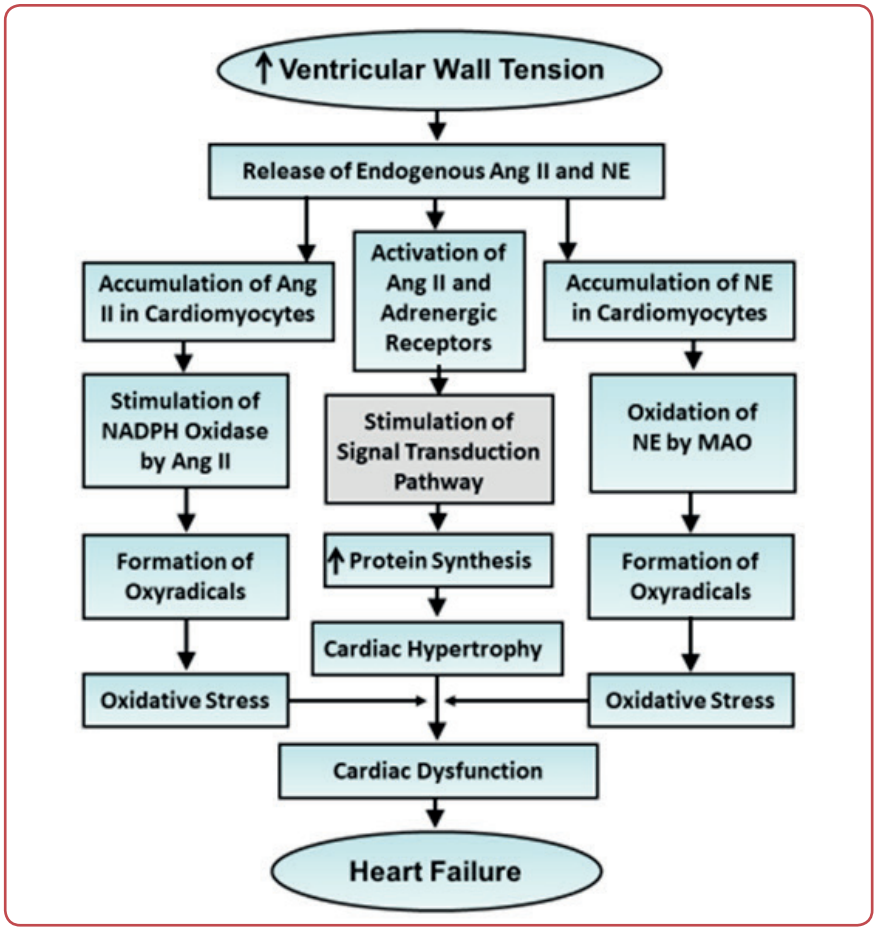

Figure 9: Role of increased ventricular wall tension in the induction of cardiac hypertrophy and oxidative stress during the development of heart failure

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 metalloproteinases 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-

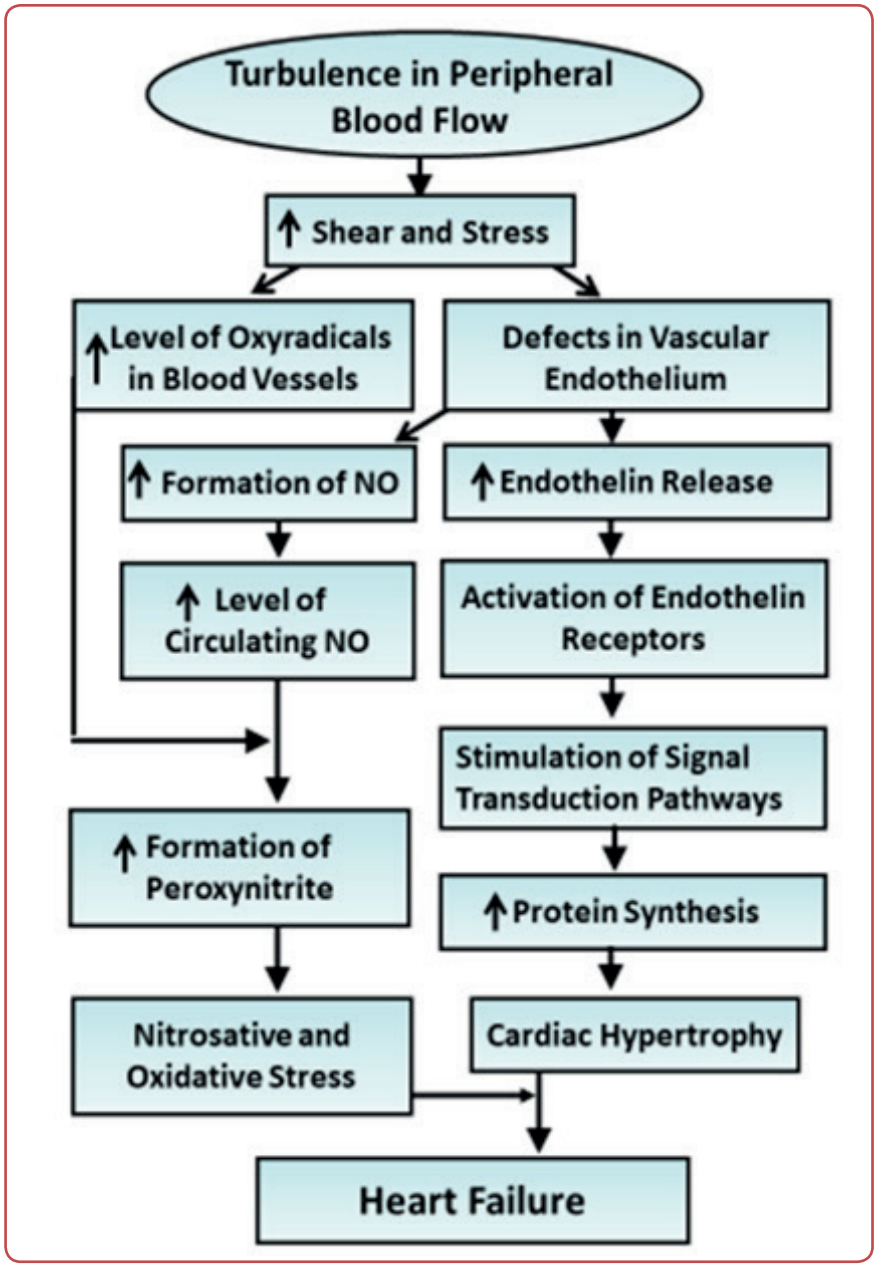

Figure 10: Role of peripheral blood flow turbulence and subsequent shear and stress in inducing endothelial defects and production of nitrosative and oxidative stress during the development of heart failure

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.

dative 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 transduction 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 HRrEF 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 changes 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.

Acknowledgement

The infrastructure for the preparation of this article was provided by St. Boniface Hospital Research Centre, Winnipeg, Canada. Thanks are due to Khushman Kaur for helping to prepare the manuscript.

Conflicts of interest

The authors declare that there is no conflict of interest.

Funding

This study was supported by a Foundation grant from the Canadian Institutes for Health Research.

Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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