Mechanisms for the Development of Heart Failure and Improvement of Cardiac Function by Angiotensin-Converting Enzyme Inhibitors

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Abstract

Angiotensin-converting enzyme (ACE) inhibitors, which prevent the conversion of angiotensin I to angiotensin II, are well-known for the treatments of cardiovascular diseases, such as heart failure, hypertension and acute coronary syndrome. Several of these inhibitors including captopril, enalapril, ramipril, zofenopril and imidapril attenuate vasoconstriction, cardiac hypertrophy and adverse cardiac remodeling, improve clinical outcomes in patients with cardiac dysfunction and decrease mortality. Extensive experimental and clinical research over the past 35 years has revealed that the beneficial effects of ACE inhibitors in heart failure are associated with full or partial prevention of adverse cardiac remodeling. Since cardiac function is mainly determined by coordinated activities of different subcellular organelles, including sarcolemma, sarcoplasmic reticulum, mitochondria and myofibrils, for regulating the intracellular concentration of Ca²⁺ and myocardial metabolism, there is ample evidence to suggest that adverse cardiac remodelling and cardiac dysfunction in the failing heart are the consequence of subcellular defects. In fact, the improvement of cardiac function by different ACE inhibitors has been demonstrated to be related to the attenuation of abnormalities in subcellular organelles for Ca²⁺-handling, metabolic alterations, signal transduction defects and gene expression changes in failing cardiomyocytes. Various ACE inhibitors have also been shown to delay the progression of heart failure by reducing the formation of angiotensin II, the development of oxidative stress, the level of inflammatory cytokines and the occurrence of subcellular defects. These observations support the view that ACE inhibitors improve cardiac function in the failing heart by multiple mechanisms including the reduction of oxidative stress, myocardial inflammation and Ca²⁺-handling abnormalities in cardiomyocytes.

Key words: ACE inhibitors; Adverse cardiac remodelling; Subcellular defects in myocardium; Cardiac dysfunction in failing heart; Ca²⁺-handling abnormalities; Oxidative stress and inflammation.

Introduction

Heart failure is a multifaceted syndrome/disease represented by the inability of the heart to pump sufficient blood to meet various needs of the body at rest or during exercise. Ranking among several public health hazards, this pathological entity is accompanied by marked changes in cardiac function and haemodynamic alterations; approximately more than 64 million people are affected globally. About 50% of patients with heart failure die as a consequence of sudden cardiac
death annually. This disease not only increases hospitalisation of patients but also imposes an enormous clinical, medical and economic burden worldwide.\textsuperscript{1-4} Several pathological conditions including atherosclerosis, hypertension, diabetes, severe anaemia and anti-cancer drug therapy are considered to be the major risk factors of heart failure. Among various stimuli such as pressure overload, volume overload or myocardial infarction (MI), ischemic heart disease is the most common cause (42.3\% cases globally) for the development of heart failure. While MI is estimated to affect more than 7 million people each year, this situation following heart attack often signals the onset of cardiac dysfunction and progresses to heart failure. In fact, most prevalent cardiovascular abnormalities at chronic stages invariably result in the development of heart failure.\textsuperscript{5-14} Regardless of the pathological stimulus, the common aetiology for different types of heart failure is the progressive development of morphological remodelling of the myocardium, which is associated with impaired contractile function and the inability of the heart to pump sufficient blood to the body.\textsuperscript{15-20} At initial stages of the pathological stimulus, there occurs a compensatory process for an increase in ventricular muscle mass to reflect cardiac hypertrophy, which shows either unaltered or augmented cardiac function and is characterised as physiological or adaptive cardiac remodelling (changes in size, shape, and structure of the myocardium). The hypertrophied myocardium at late stages of the pathological stimulus shows depressed cardiac function and is referred as adverse cardiac remodelling.

At early stages of pathological stimulus, the activation of neurohormonal systems, including the renin-angiotensin system (RAS), sympathetic nervous system and natriuretic hormonal system release various hormones such as angiotensin (Ang) II, norepinephrine, aldosterone, growth factors and antidiuretic peptides in the circulation. The elevated levels of these circulating hormones increase cardiac contractility, ventricular filling and peripheral vasoconstriction to maintain the perfusion of crucial organs, as well as blood pressure and cardiac function.\textsuperscript{21-26} However, continued activation of the neurohormonal systems and increased levels of circulating hormones for a prolonged period participate in inducing cardiac abnormalities and increasing the haemodynamic overload (both afterload and preload) on the left ventricle. Increases in heart rate, as well as alterations in myocardial extracellular matrix and development of fibrosis and apoptosis, are also considered to account for the progression of heart failure.\textsuperscript{27, 28} In this regard, various clinical signs including shortness of breath, lung congestion, fluid retention, exercise intolerance, weakness, fatigue and peripheral oedema have been identified and are used for the diagnoses of heart failure. It should be emphasised that a wide variety of mechanisms associated with prolonged neurohumoral activation, including changes in different cellular structures in the heart, cell to cell-interaction, subcellular organelles and Ca\textsuperscript{2+}-handling, substrate utilisation and energy metabolism, inflammatory cytokine activation, oxyradicals generation and oxidative stress, cellular growth and cell death, as well as diverse signal transduction pathways become effective at different times during the progression of adverse cardiac remodelling and cardiac dysfunction in heart failure.\textsuperscript{23-25, 29-41} Thus the pathogenesis of heart failure is considered to be of complex nature and none of the existing therapies is satisfactory in reducing its morbidity and mortality.

In view of the pivotal role of prolonged activation of the RAS in the pathophysiology of heart failure, it has been well recognised that the angiotensin-converting enzyme (ACE) is a significant component of this system as it is responsible for converting angiotensin I (Ang I) to the main effector of this system, Ang II. Specifically, the interaction of this hormone with Ang II-type1 receptors (AT1R), is known to induce vasoconstriction and water retention effects for regulating the peripheral blood flow and blood pressure as well as for improving the cardiac function. Although these events are considered to reflect the role of RAS as a compensatory mechanism at initial stages, the increased activity of RAS (both systemically and locally) as well as the elevated levels of Ang II for a prolonged period are responsible for thickening of the vascular wall and aldosterone secretion. Hypertrophy of blood vessels, causes vasoconstriction whereas water retention by aldosterone increases the accumulation of fluid in the vascular system; both these situations augment the workload on the heart and promote fibrosis, left ventricular (LV) hypertrophy, adverse cardiac remodelling and defects in subcellular organelles, as well as worsen cardiac function in the heart failure patients.\textsuperscript{42-58} These AT1R-mediated effects of Ang II are antagonist by the activation of Ang type 2 receptors (AT2R) because the signalling mediated by AT2R induce vasodilatory, anti-fibrotic and antihypertrophic effects in heart fail-
Figure 1: A schematic representation of the renin-angiotensin system (RAS) involving ACE as well as the activities associated with different angiotensin receptors.

Different lines of evidence support the view that the blockade of RAS by ACE inhibitors prevents the vasoconstriction as well as reduce the all-cause mortality and cardiac death upon attenuating the development of heart failure in both animals and patients. In this context, it is noteworthy that inhibition of ACE has been shown to improve heart failure by decreasing the haemodynamic afterload and preload as well as systolic wall stress, thus increasing cardiac output without any change in heart rate. Apart from this, ACE inhibitors promote salt excretion by augmenting the renal blood flow and reducing the aldosterone and antidiuretic hormone production. Several clinical studies have demonstrated the ability of these inhibitors to reduce cardiac remodelling and mortality in patients with LV dysfunction in different types of heart failure including post MI. It should be mentioned that, ACE inhibitors also block bradykinin inactivation which promotes dry cough and angioedema; these side-effects occur more in women than men. However, reduced vagal tone and impaired baroreflex sensitivity in heart failure
patients are improved upon treatment with ACE inhibitors.\textsuperscript{103-107} Furthermore, the aldosterone facilitated retention of sodium and water as well as growth-promoting effects in patients with severe heart failure were attenuated by ACE inhibitors and aldosterone receptor blockers. In addition, renin antagonists have also been shown to improve cardiovascular function in heart failure.\textsuperscript{108-111} The importance of these aspects associated with the activation of RAS has been extensively documented elsewhere.\textsuperscript{50, 64, 71-73, 112} Accordingly, the present review is focused on describing the information related to ACE/Ang II–AT1R, pathway and its role in the pathogenesis of heart failure. Some observations regarding the effectiveness of ACE inhibitors with respect to different mechanisms for reducing oxidative stress and inflammation as well as improving cardiac function in heart failure are recorded. Since remodelling of subcellular organelles has been suggested to be intimately associated with the progression of heart failure, this article also outlines the beneficial effects of ACE inhibition in attenuating subcellular defects in myocardium and improving cardiac function in heart failure.\textsuperscript{26, 56, 113-124}

Mechanisms for the development of MI-induced heart failure

In order to understand the basis for the therapeutic use of ACE inhibitors for the treatment of heart failure, it is pertinent to briefly discuss its pathophysiology to identify appropriate molecular targets in the failing heart. It should be mentioned that heart failure due to MI (a manifestation of blockage of the coronary arteries) has been characterised as an entity due to a combination of pressure overload and volume overload, in which the myocardium experiences an excessive haemodynamic workload. The noticeable alterations in ventricular haemodynamics associated with cardiac dysfunction are low cardiac output, reduced ejection fraction, elevated end-diastolic pressure, increased ventricular wall stress, ventricular dilatation, ventricular hypertrophy and arrhythmias. These changes due to a large infarct size invariably lead to heart failure following MI. Some of the events associated with cardiac remodelling in heart failure due to MI involving the activation of RAS under both acute and chronic situations are represented in Figure 2. Abnormalities in Ca\textsuperscript{2+}-handling, defects in energy production and utilisation, developments of fibrosis, apoptosis and necrosis, as well as alterations in cardiac gene expression and subcellular defects have been examined in the failing heart.\textsuperscript{125-127} It is pointed out that the blockade of coronary blood flow leads to loss of myocardium, decrease in cardiac output and fall in blood pressure which result in the activation of RAS. During initial phase of this pathological stimulus, the elevated levels of Ang II induce adaptive changes such as cardiac hypertrophy and increased activities of subcellular organelles to stimulate cardiac function for maintaining cardiovascular homeostasis; however, chronic activation and increased plasma Ang II level for a prolonged period exert effects such as adverse cardiac remodelling and heart failure.\textsuperscript{40, 48, 49} Prolonged exposure of hypertrophied heart to elevated levels of Ang II enhances progressive ventricular dysfunction and stimulates the activities of various signalling transduction proteins, such as phospholipase C, protein kinase C, tyrosine kinases and mitogen-activated protein kinase. All these alterations affect cardiac contraction and relaxation processes, in addition to inducing defects in cardiac metabolism and intracellular Ca\textsuperscript{2+}-handling in cardiomyocyte. Marked changes also occur in cardiac interstitium where oncogenes and genes, that regulate the expression of different hypertrophic factors, including fibroblast growth factor, platelet-derived growth factor and transforming growth factor-β are stimulated and result in the accumulation of collagen and connective tissue in the heart. Thus adverse cardiac remodelling results in the development of cardiac dysfunction and progression of heart failure in a complex manner.\textsuperscript{89, 114, 128-135} It should also be noted that increased ANG II levels are associated with the activation of NADPH oxidase, production of reactive oxygen species and development of oxidative stress, which are considered to induce cardiomyocyte apoptosis and influence the expression and function of the excitation-contraction coupling proteins resulting in cardiac dysfunction and heart failure.\textsuperscript{63, 136-140}

Because of the coordinated involvement of the activities of different subcellular organelles such as sarcolemna (SL), sarcoplasmic reticulum (SR), myofibrils (MF), mitochondria (MT) and extracellular matrix (ECM) in determining the status of cardiac function, a defect in any activities of these organelles can be seen to produce disturbance in cardiac contractile cycle leading to cardiac dys-
Figure 2: A schematic representation of events induced by myocardial infarction involving the acute and chronic activation of renin-angiotensin system (RAS). A wide variety of alterations have been shown to occur in the hypertrophied myocardium leading to the development of cardiac dysfunction and heart failure.


function and development of heart failure. In this regard, remodelling of the SL membrane has been shown to induce alterations in myocardial cation composition and signal transduction pathways due to changes in membrane receptor proteins, cation channels and cation transporters. As well as alterations in the SL microdomains, such as t-tubular network, caveolae and intercalated disc, the loss of SL viability may cause cell death, arrhythmias and contractile dysfunction in heart failure. While Ca\(^{2+}\)-handling abnormalities in cardiomyocytes are mostly associated with defects in SR Ca\(^{2+}\)-cycling proteins, changes in SR Ca\(^{2+}\)-uptake and release activities are considered to explain impaired contraction and relaxation processes in the failing heart, respectively. Likewise, MF remodelling as a consequence of alterations in both contractile and regulatory proteins is also considered to produce alterations in cardiac contraction and relaxation due to modifications in their sensitivity to Ca\(^{2+}\) in the failing heart. Furthermore, the occurrence of changes in cardiomyocyte architecture and cardiac gene expression due to alterations in the extracellular matrix and nucleus, respectively, has been observed in addition to the degradation of extracellular matrix proteins in heart failure. Alterations in these organelles in failing hearts have been explained on the basis of the activation of various proteases and phospholipases as well as changes in different receptor-mediated signal transduction mechanisms. Since heart failure is associated with alterations in energy transfer, production and utilisation, defects in MT function with respect of oxidative phosphorylation have been recognised as a significant contributor for the genesis of heart failure. Furthermore, disorganisation of cellular structure has shown decreased mitochondrial mass, reduced efficiency of direct adenine nucleotide channelling and alterations of the creatine kinase shuttle associated energetic deficiency; all these subcellular abnormalities lead to the development of cardiac dysfunction in the failing heart. It is also noteworthy that MT-produced defects in redox status...
in the failing heart due to alterations in electron transport system and oxidative phosphorylation have been shown to generate oxidative stress,120, 182-190 a most critical pathogenic factor for inducing cardiac dysfunction.

There is ample evidence to show that the development of cardiac contractile force is initiated as a consequence of increase in the cytosolic free Ca\(^{2+}\) concentration ([Ca\(^{2+}\)]\(_i\)) due to excessive Ca\(^{2+}\)-entry through the SL Ca\(^{2+}\)-channels as well as opening of the SR Ca\(^{2+}\)-release channels (ryanodine receptor type 2, RyR2).191-197 The binding of this Ca\(^{2+}\) with Troponin C (TnC) relieves its inhibitory effect on tropomyosin, promotes the interaction of myosin and actin filaments for the occurrence of the cardiac contraction.198-204 On the other hand, cardiac relaxation occurs upon sequestration of [Ca\(^{2+}\)]\(_i\) and dissociation of myosin filaments from actin filaments; Ca\(^{2+}\) sequestration is mainly affected by the SR Ca\(^{2+}\)-pump ATPase (SERCA2a) and SL Na\(^+\)-Ca\(^{2+}\) exchanger.190, 199, 205-208 Thus dysregulation of different processes for Ca\(^{2+}\) handling in cardiomyocytes in failing hearts is considered to result in impaired cardiac function.209-211 A reduction in the maximal force-generating capacity of myofilaments in heart failure is also associated with suppression of α-myosin heavy chain expression, troponin T isoforms switching, decreased cyclic adenosine monophosphate (cAMP)-dependent phosphorylation and other alterations in the contractile apparatus.199, 212-214 It should be mentioned that MT serve as Ca\(^{2+}\)-buffer because cardiomyocytes encounter an excessive level of [Ca\(^{2+}\)]\(_i\) during the development of heart failure.168, 215 When these organelles become overloaded with Ca\(^{2+}\), their function for producing ATP becomes impaired and this defect is also considered to result in cardiac dysfunction in the failing heart.184, 186

Role of ACE in MI-induced heart failure

ACE (a zinc metallopeptidase) was discovered in mid-1950s in plasma as well as kidney extract and was found to convert Ang I to Ang II.216, 217 This enzyme was established to play a critical role in the RAS pathway, which exerts direct effects on vital organs such as the heart, kidneys, brain, blood vessels, adrenal glands and adipose tissues.218-220 Several biochemical and molecular studies concerning the expression of renin, angiotensinogen and ACE genes as well as the distribution of ACE in the heart have also revealed the existence of cardiac RAS indicating that some Ang II is also generated in the heart.221, 222 The contribution of systemic and tissue (local) RAS in elevating the circulating levels of Ang II during the development of heart failure remains to be established. The upregulation of ACE and increased production of Ang II under various pathological conditions associated with cardiac remodelling provide further evidence of its involvement in deteriorating cardiac function during the development of heart failure.216, 223-227 It is pointed out that chymase, which has been shown to be present in endothelial cells and cardiac interstitium, may also contribute in the formation of Ang II in the failing heart.228 It is noteworthy that the inhibition of ACE has been reported to produce beneficial effects by improving ventricular dilation, cardiac output as well as coronary circulation in addition to reducing ventricular wall stress in different types of failing hearts induced by MI, pressure overload or volume overload.229-235 The inhibition of ACE has also been reported to improve cardiac function or delay the development of cardiac dysfunction by reducing the incidence of events associated with cardiac hypertrophy, cardiac remodelling, apoptosis, fibrosis, endothelial dysfunction and subcellular defects.116, 181, 236-238

Although the exact mechanisms of ACE inhibitors are not fully understood, various ACE inhibitors interfere with RAS, but their effects may not only be related alterations in the of Renin-Ang pathway in the blood. Since ACE not only converts Ang I to Ang II but also degrades bradykinin, the mode of action of ACE inhibitors may be of complex nature and may involve both blocking of ACE that reduces vasoconstriction and decreasing the breakdown of bradykinin that causes vasodilation. It should be noted that Ang II induces direct vasoconstriction of the precapillary arterioles and postcapillary venules, restricts the reuptake of norepinephrine, promotes the release of catecholamines from the adrenal medulla, decreases the urinary excretion of sodium and water, facilitates the synthesis and release of aldosterone and stimulates the growth of both vascular smooth muscle cells and cardiac myocytes. In fact, decreased production of Ang II by ACE inhibitors has been reported to enhance natriuresis, drop blood pressure, inhibit remodelling of smooth muscle and cardiac myocytes, as well as depress...
Improvement of cardiac function in MI-induced heart failure by various ACE inhibitors

ACE inhibitors have been shown to improve Ca²⁺-handling in hypertrophied cardiomyocytes and thus play a significant role in preventing the transition of cardiac hypertrophy to heart failure. In addition, ACE inhibitors have been reported to improve the β-adrenergic receptor transduction by preventing depression in β1-adrenergic receptor density, decreased adenyl cyclase activity and attenuated guanine nucleotide-binding protein changes in the failing heart. Since the impaired cardiac dysfunction in the failing heart is associated with reduced myosin chain content, myosin isoform shift and altered myosin gene expression, improvement of cardiac function by ACE inhibition has been suggested to be associated with an increase in myosin heavy chain content and normalisation of myosin isoform shift. Such beneficial effects of the ACE inhibition are considered to be due to protection of sulfhydryl groups and antioxidant properties of ACE inhibitors. Although several agents exerting ACE inhibition have been shown to protect changes in myocardial energy metabolism in the failing heart, it has been indicated that the possible mechanism by which ACE inhibitors improve myocardial metabolism is via bradykinin (instead of Ang II inhibition) which is known to improve myocardial oxygen consumption by increasing the accumulation of nitric oxide. Furthermore, ACE inhibitors have been shown to exert vagomimetic action and increase the baroreflex sensitivity in patients with heart failure. These agents also down-regulate the sympathetic activity by modifying the effects of Ang II on the release of norepinephrine from the adrenergic nerve endings and improve variations in the heart rate. Thus, treatments with ACE inhibitors have been demonstrated to improve cardiac function and delay the development of end-stage heart failure by diverse multiple mechanisms. However, the disadvantage of the ACE inhibitor treatment is its effects on non-ACE pathways as well as increase in the levels of bradykinin causing side effects such as dry cough and angioedema.

Since the synthesis of captopril as the first antihypertensive drug, various ACE inhibitors have been developed and their effects in heart failure have been extensively investigated both experimentally and clinically, either alone or in combination with other therapies. In this regard, ACE inhibitors including captopril, enalapril, ramipril, benazepril, zofenopril, lisinopril, fosinopril, perindopril and imidapril have been increasingly helpful in advancing therapeutic potentials for attenuating cardiovascular events in heart failure. Their beneficial effects on haemodynamic congestion, acute and chronic MI, cardiac remodeling, myocardial metabolism, myeloid haematopoiesis, cardiac and vascular inflammation, cardiac function at subcellular and molecular levels as well as mortality and morbidity of patients with heart failure are noteworthy. It has been indicated that ACE inhibitors differ from each other in terms of their half-lives, bioavailability, lipophilicity, tissue distribution, bradykinin site selectivity and routes of elimination. Nonetheless, the dis-
crepancy of observations in their effects seems to occur due to the time of administration and doses of ACE inhibitors given to heart failure patients.42 Although it would be desirable to discuss the clinical significance of different ACE inhibitors in terms of their dosages and dose-schedules for the therapy of heart failure, these aspects are beyond the scope of this article. Nonetheless, the beneficial effects of some of these agents including captopril, enalapril, lisinopril and ramipril specifically for the treatment of MI-induced heart failure are outlined in the following discussion.

Captopril has been reported to the improve survival and reduce the mortality and morbidity as well as both the fatal and non-fatal cardiovascular events in MI-induced heart failure.42, 280-283 Since the infarct size and cardiac stiffness are important factors which influence the post-infarction process and the progression of heart failure, captopril alone or with combination of other therapies has been shown to reduce the infarct expansion significantly. It has been suggested that this reduction of the infarct size may be due to increased collateral blood flow to the areas of infarction at risk. Reduced myocardial infarct size during the early-phase (within 72 hours post-MI) was associated with increased exercise capacity, improved diastolic function and attenuated left ventricular remodeling,284-287 whereas reduction of myocardial stiffness in the infarcted and non-infarcted myocardium,288 was observed to delay the occurrence of cardiac dysfunction in patients after MI.289-292 Treatment of MI-patients with captopril has shown that this ACE inhibitor attenuated the progressive LV enlargement and improved the LV ejection fraction.293 The beneficial effects of this drug against ischaemia-reperfusion induced cardiac injury have also been reported.294 Cardiac remodelling accompanied changes in membranes, contractile proteins and extracellular matrix, as well as intracellular calcium handling defects were improved with captopril treatment in MI-induced heart failure.295, 296 As Ang II is considered to be a stress hormone,297 the administration of captopril has been shown to reduce cardiovascular responses to acute stress in the post-infarction heart failure as well as in the chronically stressed infarcted animals.270 Furthermore, captopril has been observed to improve cardiac function, reduce collagen levels and decrease artery media thickness,298 as well as produce long-term haemodynamic benefits in patients with MI-induced heart failure.281

Since the hyperactivity of brain RAS is associated with the progression of diastolic dysfunction and heart failure after MI, the intracerebral therapy with captopril was found to reduce LV dilatation and improve LV filling, increase brain blood flow during moderate-intensity physical activity and delay the development of cardiac dysfunction in heart failure.299, 300 Because cardiac apoptosis induced cell death has been shown to play a critical role in the transition from compensated to non-compensated cardiac hypertrophy for the progression of heart failure due to increased circulatory levels of Ang II,301-305 captopril has been reported to exert the protective effects on cardiac apoptosis due to the inhibition of Wnt3a/β-catenin signalling pathway, attenuate myocardial hypertrophy via the suppression of Jak2/Stat3 pathway and markedly improve cardiac function.306 Furthermore, because MI-activated RAS and up-regulation of mineralocorticoid receptors facilitate the production of aldosterone for ventricular remodelling and increase reactive fibrosis in the myocardium during the development of heart failure, captopril treatment has been reported to normalise cardiac mineralocorticoid receptors protein and mRNA expression. These results support the view that ACE inhibitors diminish the reactive fibrosis by reducing Ang II production and attenuating the aldosterone-signalling pathways by decreasing the expression of mineralocorticoid receptors.307 Captopril treatment has also been shown to suppress the expression of protein kinases in the Ang II-mediated mitogen-activated protein kinase signalling pathway which modulates gene expression in the vascular smooth muscle, prevents myosin targeting subunit isoform switching to preserve normal blood flow due to nitric oxide-mediated vasodilatation and attenuates the depression in LV function.308, 309 In addition, the beneficial effects of captopril on energy metabolism have been reported upon the treatment of MI-induced heart failure.80

The efficacy of another ACE inhibitor, enalapril, in improving cardiac function has been established in both experimental animals and patients with heart failure.83, 310-313 Alone or in combination with other therapies, enalapril was observed to produce beneficial effects in patients with reduced LV ejection fraction,314-317 in addition to improving exercise performance,83, 318 and heart rate variability.319 This therapy was found to restore normal autonomic tone in the heart, enhance myocardial fatty acid metabolism,83, 278 prevent pathological hypertrophy,320 and reduce the risk
of atrial fibrillation development.\textsuperscript{321} Furthermore, enalapril suppressed aldosterone concentrations,\textsuperscript{83} increased junctional conductance,\textsuperscript{322} inhibited cardiac remodelling and improved cardiac function in heart failure patients.\textsuperscript{323-326} Treatment with enalapril was also seen to decrease cardiovascular events\textsuperscript{327-328} and mortality\textsuperscript{329} as well as delay the progression of heart failure, decrease hospitalisation and increase the survival rate in heart failure patients.\textsuperscript{330-335} It has been noted that the administration of enalapril started within 24 hours of the onset of acute MI in patients did not show any improvement in survival\textsuperscript{317} whereas the benefits of enalapril in heart failure patients are most probably due to its actions on both bradykinin metabolism and Ang II production.\textsuperscript{336, 337} Enalapril treatment has been observed to improve Ang II-induced defects in subcellular organelles and attenuate cardiac dysfunction during the progression of MI-induced heart failure by partially preventing changes in SR gene expression\textsuperscript{338} and SL Na$^+$$\cdot$K$^+$ ATPase activities\textsuperscript{145} in failing hearts.

Several clinical studies have shown that ramipril is also an effective and well tolerated ACE inhibitor.\textsuperscript{339, 340} This agent has been demonstrated to prevent cardiovascular diseases,\textsuperscript{341-343} and produce beneficial effects on cardiovascular events in patients, who are at high risk of LV dysfunction or heart failure,\textsuperscript{344-346} as well as in patients without any evidence of LV dysfunction.\textsuperscript{347} Moreover, the therapeutic efficacy of ramipril alone or in combination with other treatments\textsuperscript{343, 348, 349} has revealed significant reduction of the risk for fatal and nonfatal arrhythmic events in high-risk patients without clinical heart failure or LV dysfunction.\textsuperscript{350-353} Beneficial effects of this ACE inhibitor for adverse ventricular remodeling,\textsuperscript{354} LV hypertrophy,\textsuperscript{355} and atrial fibrillation,\textsuperscript{356} are associated with improving exercise performance\textsuperscript{257} and cardiac function\textsuperscript{358} in patients after acute MI.\textsuperscript{337} It has also been demonstrated that ramipril, by decreasing the vasopressor activity, aldosterone secretion, and bradykinin degradation, improves different haemodynamic, thrombotic and inflammatory events.\textsuperscript{279, 359-362} Furthermore, ramipril treatment has been observed to reduce the risk of

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**Figure 3:** Modification of myocardial infarction induced changes in adverse cardiac remodelling and subcellular defects following treatment with ACE (angiotensin converting enzyme) inhibitors. ANG II, angiotensin II.
worsening angina and the occurrence of revascularisation, the progression of heart failure and the all-cause mortality and morbidity following acute MI. In addition, ramipril treatment has been shown to limit the decline of cardiac function in non-infarcted regions and prevent the circumferential shortening in the sub endocardium after MI. Another ACE inhibitor, benazepril, has also been shown to exert several beneficial effects including increased survival time in congestive heart failure. The use of the benazepril in combination of spironolactone results in delaying the recurrence of heart failure and its associated clinical signs as well as reducing the death rate. Long-term ACE inhibition with fosinopril was also observed to improve the depressed responsiveness to Ca$^{2+}$ in myocytes from the aortic-banded rats. Additionally, the inhibition of ACE with perindopril has been shown to exert a reduction in the cardiovascular mortality and a significant decrease in the non-fatal MI in both preclinical and clinical settings.

The benefits of perindopril are evident during its long-term efficacy and tolerability for reducing cardiac events while achieving the targeted heart rate and blood pressure levels.

Various ACE inhibitors such as zofenopril, which contain sulphydryl groups, have offered additional favourable effects for scavenging oxyradicals and reducing the reperfusion damage in heart failure. By providing high lipophilicity, long-lasting tissue penetration and good efficacy, zofenopril has been shown to reverse cardiac remodelling in congestive heart failure and decrease the short-term and long-term mortality in MI patients. Administration of zofenopril was found to produce cardiac-specific effects and modulation of gene expression involved in the pathophysiology of myocardial ischaemia and heart failure, in addition to increasing the resistance to ischaemia. It needs to be emphasised that imidapril, a long-acting non-sulphydryl ACE inhibitor, has shown to improve the prognosis of MI in mild, moderate and severe cases of heart failure with a lower incidence of dry cough as compared to other ACE inhibitors. Prevention of MI-induced haemodynamic changes and protection of the cardiovascular system by early treatment with imidapril have been demonstrated experimentally. Other beneficial effects of this ACE inhibitor on LV hypertrophy, exercise capacity in chronic heart failure, LV remodeling in acute MI, and subcellular organelle defects have also been reported in failing hearts. A schematic representation of the beneficial effects of ACE inhibitors at different subcellular targets for improving heart function and preventing heart failure due to MI is shown in Figure 3.

**Modification of subcellular defects in MI-induced heart failure by ACE inhibitors**

Although the activation of RAS and elevated levels of Ang II are known to produce cardiac dysfunction in MI-induced heart failure and different ACE inhibitors have been reported to prevent or delay the progression of heart failure, the mechanisms of their action for improving cardiac function are not fully understood. Various ACE inhibitors have shown to produce beneficial effects on changes on collagen expression, myocardial energy metabolism, SL PLC isoenzymes as well as SL Na$^+$-K$^+$-ATPase activities, protein content and mRNA levels in heart failure. Furthermore, alterations in SR Ca$^{2+}$ transport activities, Ca$^{2+}$-pump ATPase, phospholamban protein and gene expression, as well as myofibrillar ATPase activities, extracellular matrix, cardiac gene expression and cardiac function were observed to be attenuated by ACE inhibitors in MI-induced heart failure. Enalapril treatment was found to partially or fully prevent the MI-induced SL remodelling, and changes in protein content and mRNA levels for different isoforms of Na$^+$-K$^+$ ATPase. Enalapril, captopril and cilazapril have also been reported to affect SR remodelling in MI-induced heart failure. Alterations in MF Ca$^{2+}$-stimulated ATPase activities, myosin gene expression and protein content induced by MI were attenuated by the treatments of infarcted rats with agents such as imidapril and trandolapril. Imidapril, has shown the efficacy of partially preventing the altered PKC activities and its isoforms as well as phospholipase C and D activities, in addition to attenuating changes in Gi-proteins and adenylyl cyclase, and improving cardiac function in MI-induced heart failure. It should also be mentioned that imidapril has been reported to improve haemodynamic parameters and morbidity as well as reduce mortality in MI-induced heart
Table 1: Cardiac function, status of RAS and oxidative stress in control and MI rats with or without IMP treatment for 4 weeks starting at 3 weeks after the induction of MI.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control</th>
<th>MI</th>
<th>MI + IMP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Cardiac functions:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV mass, mg</td>
<td>894 ± 16</td>
<td>981 ± 20*</td>
<td>898 ± 20†</td>
</tr>
<tr>
<td>LVEDP, mmHg</td>
<td>3.2 ± 0.8</td>
<td>14.2 ± 1.3*</td>
<td>4.6 ± 0.3†</td>
</tr>
<tr>
<td>LVSP, mmHg</td>
<td>144 ± 14</td>
<td>139 ± 3.3</td>
<td>135 ± 13</td>
</tr>
<tr>
<td>+ dP/dt, mmHg/s</td>
<td>9,450 ± 1,168</td>
<td>4,290 ± 618*</td>
<td>7,726 ± 648†</td>
</tr>
<tr>
<td>- dP/dt, mmHg/s</td>
<td>9,624 ± 1,068</td>
<td>4,064 ± 574*</td>
<td>7,840 ± 1,026†</td>
</tr>
<tr>
<td><strong>B. Oxidative stress levels:</strong></td>
<td></td>
<td></td>
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<tr>
<td>Plasma ANG II (nmol/ml)</td>
<td>7.6 ± 1.24</td>
<td>118 ± 5.8*</td>
<td>30 ± 3.4†</td>
</tr>
<tr>
<td>Plasma ACE activity (nmol/min/ml)</td>
<td>56 ± 3.7</td>
<td>74 ± 4.9*</td>
<td>50 ± 3.8†</td>
</tr>
<tr>
<td>LV ACE activity (nmol/min/mg protein)</td>
<td>0.50 ± 0.04</td>
<td>0.81 ± 0.03*</td>
<td>0.41 ± 0.02†</td>
</tr>
<tr>
<td>LV MDA (nmol/mg tissue lipids)</td>
<td>5.4 ± 0.3</td>
<td>16.7 ± 0.6*</td>
<td>39.8 ± 0.7†</td>
</tr>
<tr>
<td>LV GSSH (μmol/g tissue)</td>
<td>72 ± 2.9</td>
<td>32 ± 3.6*</td>
<td>62 ± 2.4†</td>
</tr>
<tr>
<td>LV GSSG (μmol/g tissue)</td>
<td>16.3 ± 0.9</td>
<td>26.5 ± 1.8*</td>
<td>14.4 ± 1.2†</td>
</tr>
</tbody>
</table>

Data are based on analysis of information in our paper144 (Shao et al. Am J Physiol Heart Circ Physiol 2005; 288: H1674-H1682) as well as from our paper144 (Shao et al. Am J Physiol Heart Circ Physiol 2005; 288: H2637-H2646). Values are mean ± SE of 6 animals in each group. IMP: Imidapril (1 mg/kg/day); MI, myocardial infarction; LV, left ventricle; LVEDP, LV end diastolic pressure; LVSP, LV systolic pressure; + dP/dt: maximal rate of pressure development; -dP/dt: maximal rate of pressure decay; RAS, renin-angiotensin system; ANG II, angiotensin II; ACE, angiotensin-converting enzyme; MDA, malondialdehyde, GSH, reduced glutathione, GSSG, oxidised glutathione. *P < 0.05 compared with respective control; †P < 0.05 compared with respective MI group.

Improvement of cardiac function in heart failure due to coronary occlusion by imidrapil treatment has been suggested to be due to reduction in the Ang II-induced subcellular defects.144, 394 This view is based on our observations that treatment of infarcted animals with imidrapil attenuated the elevated LV end-diastolic pressure as well as depressions in both contraction and relaxation rates (+dP/dt) in the failing hearts (Table 1). The improved cardiac function upon imidrapil treatment was associated with reductions in the MI-induced increases in RAS activities as reflected by changes in plasma Ang II, plasma ACE and LV ACE levels (Table 1). The imidrapil-treated MI animals also showed depressed content of malondialdehyde, conjugated dienes, and oxidised glutathione, as well as increased content of reduced glutathione (Table 1), indicating depression in oxidative stress parameters in the failing heart. These findings provide evidence that ACE inhibitors exert beneficial effects by decreasing oxidative stress during the development of MI-induced heart failure.144, 394

Table 2: Sarcolemmal activities, protein content and mRNA levels for Na+-Ca2+-exchanger as well as Na+-K+ ATPase in control and MI rats with or without IMP treatment for 4 weeks starting at 3 weeks after the induction of MI.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control</th>
<th>MI</th>
<th>MI + IMP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Sarcolemmal activities:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na+-dependent Ca2+-uptake (nmol/mg/2 sec)</td>
<td>460 ± 15.3</td>
<td>230 ± 30.6*</td>
<td>383.3 ± 15.3†</td>
</tr>
<tr>
<td>Na+-Ca2+ exchanger protein content (% of control)</td>
<td>100</td>
<td>21.9 ± 4.7*</td>
<td>43.7 ± 6.2†</td>
</tr>
<tr>
<td>Na+-Ca2+ exchanger mRNA (% of control)</td>
<td>100</td>
<td>43.3 ± 5.0*</td>
<td>81.7 ± 6.7†</td>
</tr>
<tr>
<td>Na+-K+ ATPase (μmol Pi/mg/hr)</td>
<td>61.1 ± 4.9</td>
<td>23.1 ± 13.2*</td>
<td>54.4 ± 11.5†</td>
</tr>
<tr>
<td><strong>B. Na+-K+ATPase isoform protein content:</strong></td>
<td>(%) of control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>α1</td>
<td>100</td>
<td>10.9 ± 1.7*</td>
<td>82.6 ± 3.5†</td>
</tr>
<tr>
<td>α2</td>
<td>100</td>
<td>4.7 ± 0.9*</td>
<td>41.3 ± 3.5†</td>
</tr>
<tr>
<td>α3</td>
<td>100</td>
<td>150.0 ± 6.25*</td>
<td>96.9 ± 5.0†</td>
</tr>
<tr>
<td>β1</td>
<td>100</td>
<td>68.2 ± 5.0*</td>
<td>90.9 ± 4.5†</td>
</tr>
</tbody>
</table>

Data are based on analysis of information in our paper144 (Shao et al. Am J Physiol Heart Circ Physiol 2005; 288: H1674-H1682) as well as from our paper144 (Shao et al. Am J Physiol Heart Circ Physiol 2005; 288: H2637-H2646). Values are mean ± SE of 6 animals in each group. IMP: Imidapril (1 mg/kg/day); MI, myocardial infarction. *P < 0.05 compared with respective control; †P < 0.05 compared with respective MI group.

Because cardiac dysfunction in heart failure is related to remodelling of subcellular organelles and Ca2+-handling abnormalities,114, 116, 119 the effects of imidrapil on SL, MF and SR changes in the infarcted animals were also examined. The results in Table 2 show that treatment of MI-induced animals with imidrapil attenuated changes in the SL Na+-Ca2+ exchange activity, mRNA levels and protein content in the failing heart. In addition, alterations in SL Na+-K+ ATPase activity as well as mRNA levels and protein content of different isoforms were fully or partially prevented in the failing hearts by imidrapil treatment (Table 2). The beneficial effects of imidrapil treatments on changes in MF Ca2+-stimulated ATPase and MHC isoforms and mRNA levels in the failing hearts are shown in Table 3. Furthermore, the data in Table 4 indicate that marked alterations in SR Ca2+ uptake and Ca2+ release activities as well as protein content and gene expressions, (except calsequestrin) in the failing hearts, were attenu-
contrast, the exact contribution of these alterations for explaining pathogenesis of cardiac dysfunction due to elevated levels of Ang II for a prolonged period is not clearly understood. Nonetheless, both experimental and clinical studies have revealed that blocking the formation of Ang II by different ACE inhibitors or preventing the actions of Ang II by various AT1R antagonists produce beneficial effects for improving heart function as well as delaying the progression of heart failure. In this review we have attempted to analyse the existing information regarding the effects of various ACE inhibitors to understand the role of Ang II as well as the mechanisms of its action for inducing cardiac dysfunction and heart failure.

Since ACE inhibitors not only attenuate the formation of Ang II by preventing the conversion of Ang I to Ang II but also interfere with the breakdown of bradykinin, the beneficial effects of these agents in heart failure are considered to be due to both the reduction of Ang II levels as well as the accumulation of bradykinin. However, it should be noted that the accumulation of bradykinin upon the administration of ACE inhibitors has also been suggested to account for their side effects such as dry cough and angioedema. Furthermore, the reduction in the level of Ang II by ACE would attenuate the beneficial effects of AT2R activation as well as that of the MASR activation because the formation of Ang 1-7 will be decreased. On the other hand, the formation of oxyradicals and subsequent development of oxidative stress will be reduced due to depression of oxidative stress and associated inflammation in the failing myocardium can be seen to attenuate subcellular alterations, Ca²⁺-handling abnormalities as well as loss of myofilament Ca²⁺-sensitivity. These observations support the view that the modification of all these subcellular defects upon the reduction of oxidative stress in cardiomyocytes due to treatment with ACE inhibitors results in improving cardiac function and delaying the progression of heart failure. It is emphasised that it is not the authors’ intention to exclude other Ang II-induced mechanisms for partially or fully preventing metabolic abnormalities and diverse signal transduction defects in eliciting the beneficial effects of ACE inhibitors in heart failure.
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Conflict of interest

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Authors Contribution

All authors have contributed in preparing and editing this manuscript and have approved its submission for publication.

List of abbreviation

MI = Myocardial infarction
RAS = Renin-angiotensin system
Ang = Angiotensin
AT1R = Ang II-type1 receptors
AT2R = Ang II-type 2 receptors
LV = Left ventricle
ACE =Angiotensin-converting enzyme
MASR =MAS receptor
MT =Mitochondria
SR =Sarcoplasmic reticular
SL = Sarcolemma
MF = Myofibrils
ECM=Extracellular matrix
SERCA = Sarcoplasmic reticulum calcium pump
ATPase = Adenosine triphosphate
MHC = Myosin heavy chain
mRNA = Messenger ribonucleic acid

References

42. Shao Q, Panagia V, Beamish RE, Dhalla NS. Role of renin-angiotensin system in cardiac hypertrophy and failure 1998;283–310.
57. Bhullar SK, Shah AK, Dhalla NS. Role of angiotensin II in...


134. Guimarães PB, Alvarenga ÉC, Siqueira PD, Pare –


193. Fabiato A, Fabiato F. Use of chlorotetracycline fluorescence to demonstrate Ca2+-induced release of Ca2+ from the sarcoplasmic reticulum of skinned cardiac cells. Nature 1979;281:146–8.


196. Fabiato A. Calcium-induced release of calcium from the cardiac sarcoplasmic reticulum. Am J Physiol 1983;245:C1–14.


226. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Dra-


289. Schoemaker RG, Debets JM, Struyker-Boudier HAJ, Smits JFM. Delayed but not immediate captopril thera-


