Bhullar et al. Scr Med 2022 Mar;53(1):51-76. DOI:10.5937/scriptamed53-36256

REVIEW ARTICLE

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

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

1. Institute of Cardiovascular Sciences, St. Boniface Hospital Albrechtsen Research Centre and Department of Physiology and Pathophysiology, Max Rady College of Medicine, University of Manitoba, Winnipeg, Canada.
2. School of Kinesiology, Nutrition and Food Science, California State University, Los Angeles, CA, USA.

Correspondence:
NARANJAN S DHALLA
E: nsdhalla@sbrc.ca

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 Ca^{2+} 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 Ca^{2+}-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 Ca^{2+}-handling abnormalities in cardiomyocytes.

Key words: ACE inhibitors; Adverse cardiac remodelling; Subcellular defects in myocardium; Cardiac dysfunction in failing heart; Ca^{2+}-handling abnormalities; Oxidative stress and inflammation.

ARTICLE INFO

Received: 3 February 2022
Revision received: 8 March 2022
Accepted: 8 March 2022

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

This article should be cited as follows: Bhullar SK, Shah AK, Dhalla NS. Mechanisms for the development of heart failure and improvement of cardiac function by angiotensin-converting enzyme inhibitors. Scr Med 2022 Mar;53(1):51-76.

death annually. This disease not only increases hospitalisation of patients but also imposes an enormous clinical, medical and economic burden worldwide.[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.[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.[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.[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.[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^{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.[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.[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, antifibrotic and antihypertrophic effects in heart fail-

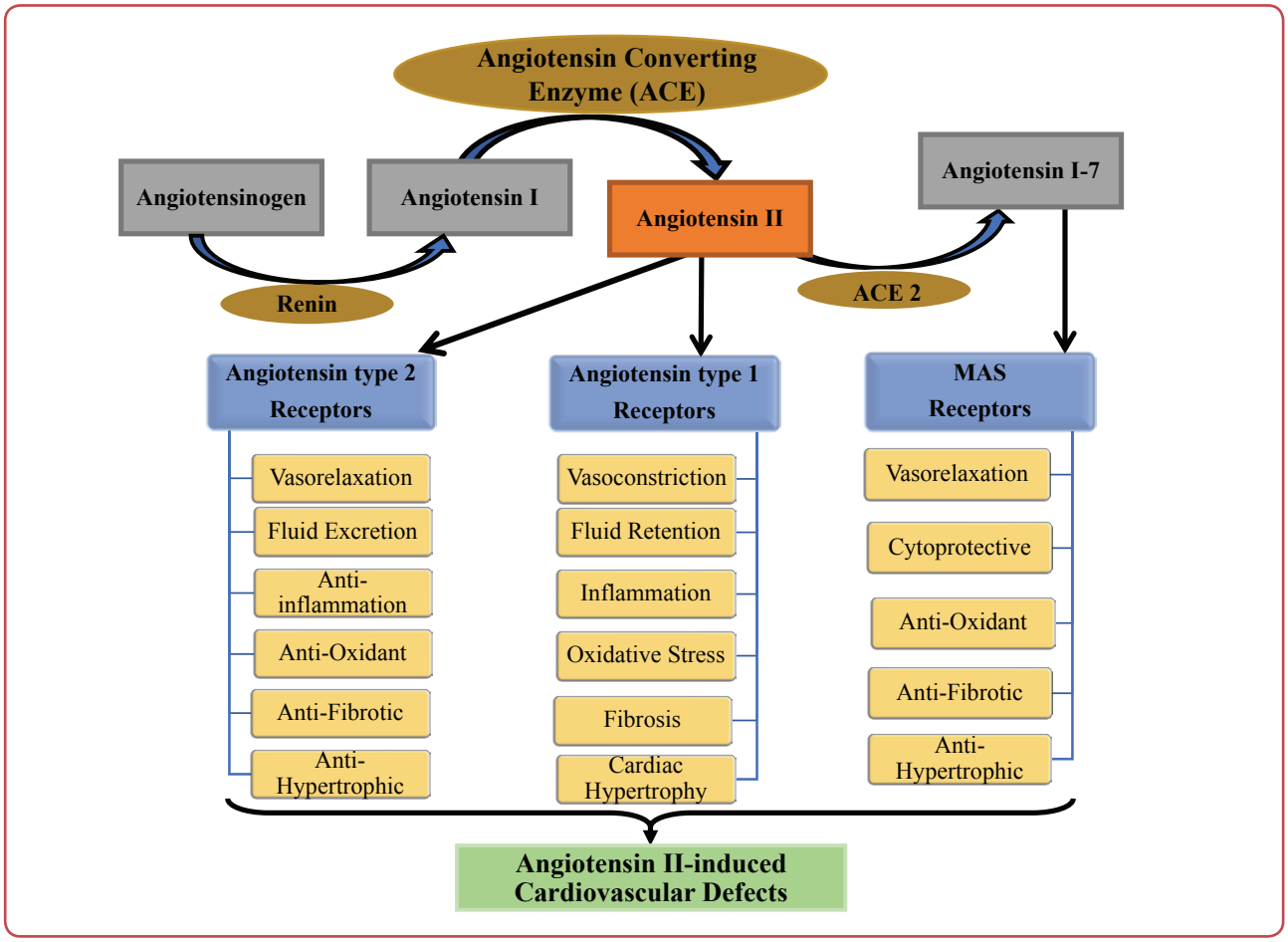

Figure 1: A schematic representation of the renin-angiotensin system (RAS) involving ACE as well as the activities associated with different angiotensin receptors.

ure.[59-62] Moreover, the homologue of ACE (ACE2) cleaves Ang I into a nonapeptide Ang 1-9 and Ang II into heptapeptide Ang 1-7; the activation of MAS receptors (MASR) by Ang 1-9 mediates signalling through (ACE2/Ang1–7/MASR pathway) to produce vasorelaxation, anti-inflammatory, anti-hypertrophic and cytoprotective effects, which also counteract with the pathophysiological effects induced by ACE/Ang II/AT1R pathway.[63-73] Thus an imbalance between the adverse actions of AT1R activation and the beneficial effects of AT2R activation as well as MASR activation leads to an acceleration of cardiovascular disease progression and cardiac dysfunction.[46, 63, 74, 75] A schematic representation of RAS pathway and the Ang II induced cardiovascular activities are given in Figure 1. It is difficult to speculate the contribution and significance of the deleterious and beneficial effects of Ang II in eliciting cardiac dysfunction during the progression of heart failure because the time-course information regarding these alterations needs to be obtained by employing AT1R-, AT2R- and MASR- knock-out mouse models.

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.[17, 76-97] 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.[98-102] However, reduced vagal tone and impaired baroreflex sensitivity in heart failure

patients are improved upon treatment with ACE inhibitors.[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.[108-111] The importance of these aspects associated with the activation of RAS has been extensively documented elsewhere.[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.[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^{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.[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.[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^{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.[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.[63, 136-140]

Because of the coordinated involvement of the activities of different subcellular organelles such as sarcolemma (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-

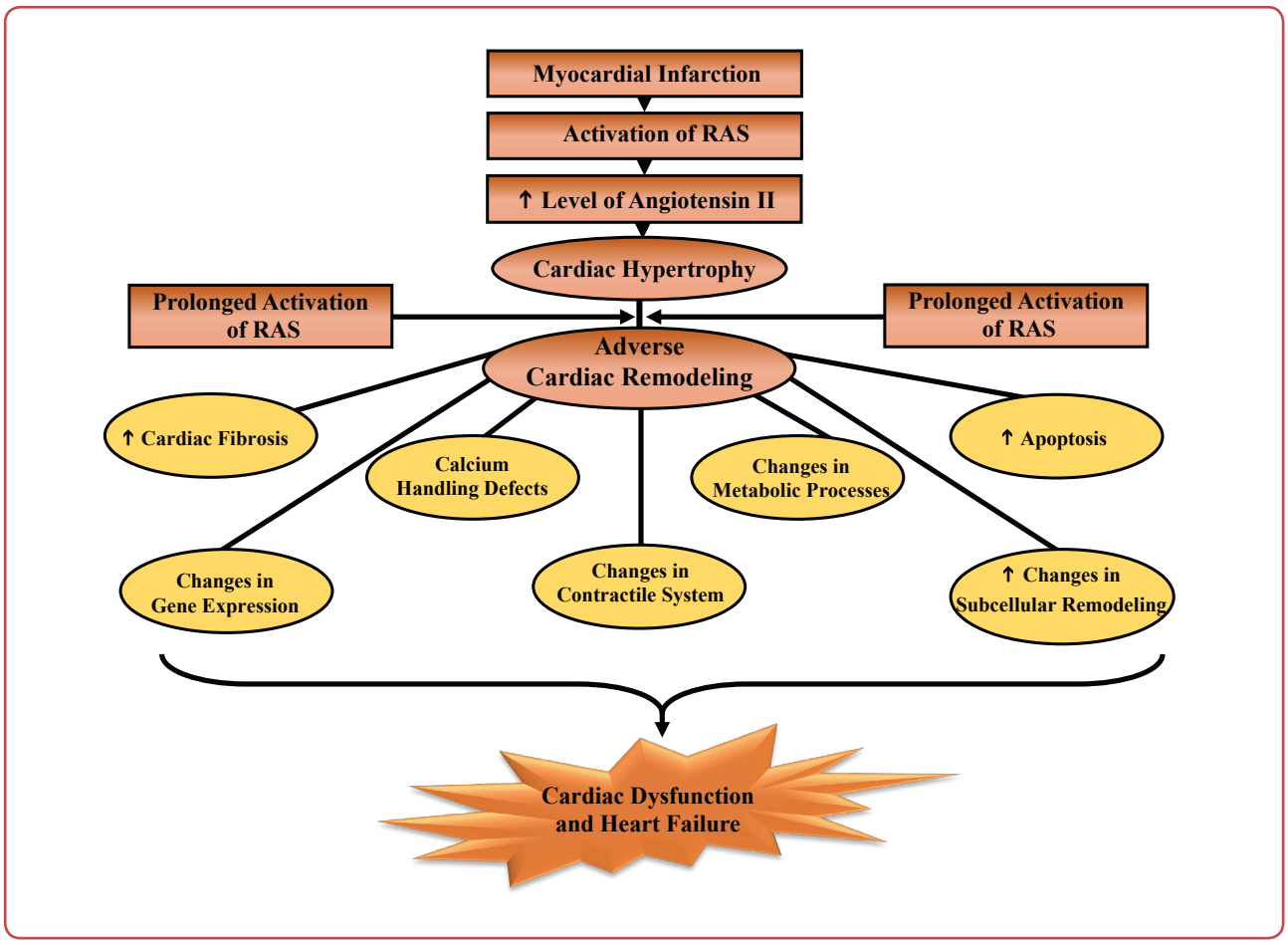

Figure 2: A schematic representation of events induced by myocardial infarction involving the acute and chronic activation of renin-angiotensin system (RAS). A wide variety of alterations have been shown to occur in the hypertrophied myocardium leading to the development of cardiac dysfunction and heart failure.

function and development of heart failure.[126, 127] 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.[141-150] 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.[151-159] 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, respectivley.[149, 152, 160-163] 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.[132, 164-169] Furthermore, the occurrence of changes in cardiomyocyte architecture and cardiac gene expression due to alterations in the extracellular matrix and nucleus, respectively,[96, 170-172] has been observed in addition to the degradation of extracellular matrix proteins in heart failure.[40, 41] 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.[119, 121, 132, 173-176] 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 in heart failure.[173-181] Furthermore, disorganisation of cellular structure has shown decreased mitochondrial mass, reduced efficacy 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

arterial and venous pressure for decreasing the preload and afterload on the heart.[239-240] Since ACE regulates the balance between the vasodilatory and natriuretic properties of bradykinin and the vasoconstrictive and salt-retentive properties of Ang II, ACE inhibitors alter the balance by decreasing the formation of Ang II and degradation of bradykinin.[241] Alterations in the formation and degradation of other vasoactive substances such as substance P by ACE have been demonstrated.[242] The increase in Ang II levels has also been shown to be caused by oxidised low-density lipoprotein-cholesterol as well as different neurohormones including endothelin, catecholamines and aldosterone.[231-233] Thus ACE inhibitors can be seen to attenuate vasoconstriction not only by suppressing Ang II formation and inhibiting bradykinin metabolism but also by modulating the effects of other factors. These changes by ACE inhibitors have been shown to improve cardiac output, decrease preload, induce vasodilation and promote natriuresis in heart failure.[243-245] By decreasing the destruction of bradykinin, ACE inhibitors may also augment the production of endothelium-derived factors, such as nitric oxide and prostacyclin and thus may improve haemodynamic changes and attenuate endothelial dysfunction. It has been reported that bradykinin enhances the status of high energy phosphates stores in the ischemic myocardium.[246-248]

ACE inhibitors have been shown to improve Ca^{2+}-handling in hypertrophied cardiomyocytes and thus play a significant role in preventing the transition of cardiac hypertrophy to heart failure.[249, 250] In addition, ACE inhibitors have been reported to improve the β-adrenergic receptor transduction by preventing depression in β1-adrenergic receptor density, decreased adenylyl cyclase activity and attenuated guanine nucleotide-binding protein changes in the failing heart.[175] 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.[104-107, 251] 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.[86, 252-259] 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.[98, 99, 260]

Improvement of cardiac function in MI-induced heart failure by various ACE inhibitors

Since the synthesis of captopril as the first antihypertensive drug,[261, 262] 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.[82, 263-267] 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.[268] Their beneficial effects on haemodynamic congestion,[269] acute and chronic MI,[270-272] cardiac remodeling;[90, 273] myocardial metabolism;[274] myeloid haematopoiesis, cardiac and vascular inflammation,[275] cardiac function at subcellular and molecular levels as well as mortality and morbidity of patients with heart failure are noteworthy.[90, 276-278] 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.[279] 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 upregulation 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, 274] prevent pathological hypertrophy,[320] and reduce the risk

of atrial fibrillation development.[321] Furthermore, enalapril suppressed aldosterone concentrations,[83] increased junctional conductance,[322] inhibited cardiac remodelling and improved cardiac function in heart failure patients.[323-326] Treatment with enalapril was also seen to decrease cardiovascular events[327-328] and mortality[329] as well as delay the progression of heart failure, decrease hospitalisation and increase the survival rate in heart failure patients.[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,[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.[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[338] and SL Na^+-K^+ ATPase activities[145] in failing hearts.

Several clinical studies have shown that ramipril is also an effective and well tolerated ACE inhibitor.[339, 340] This agent has been demonstrated to prevent cardiovascular diseases,[341-343] and produce beneficial effects on cardiovascular events in patients, who are at high risk of LV dysfunction or heart failure,[344-346] as well as in patients without any evidence of LV dysfunction.[347] Moreover, the therapeutic efficacy of ramipril alone or in combination with other treatments[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.[350-353] Beneficial effects of this ACE inhibitor for adverse ventricular remodeling,[354] LV hypertrophy,[355] and atrial fibrillation,[356] are associated with improving exercise performance[357] and cardiac function[358] in patients after acute MI.[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.[279, 359-362] Furthermore, ramipril treatment has been observed to reduce the risk of

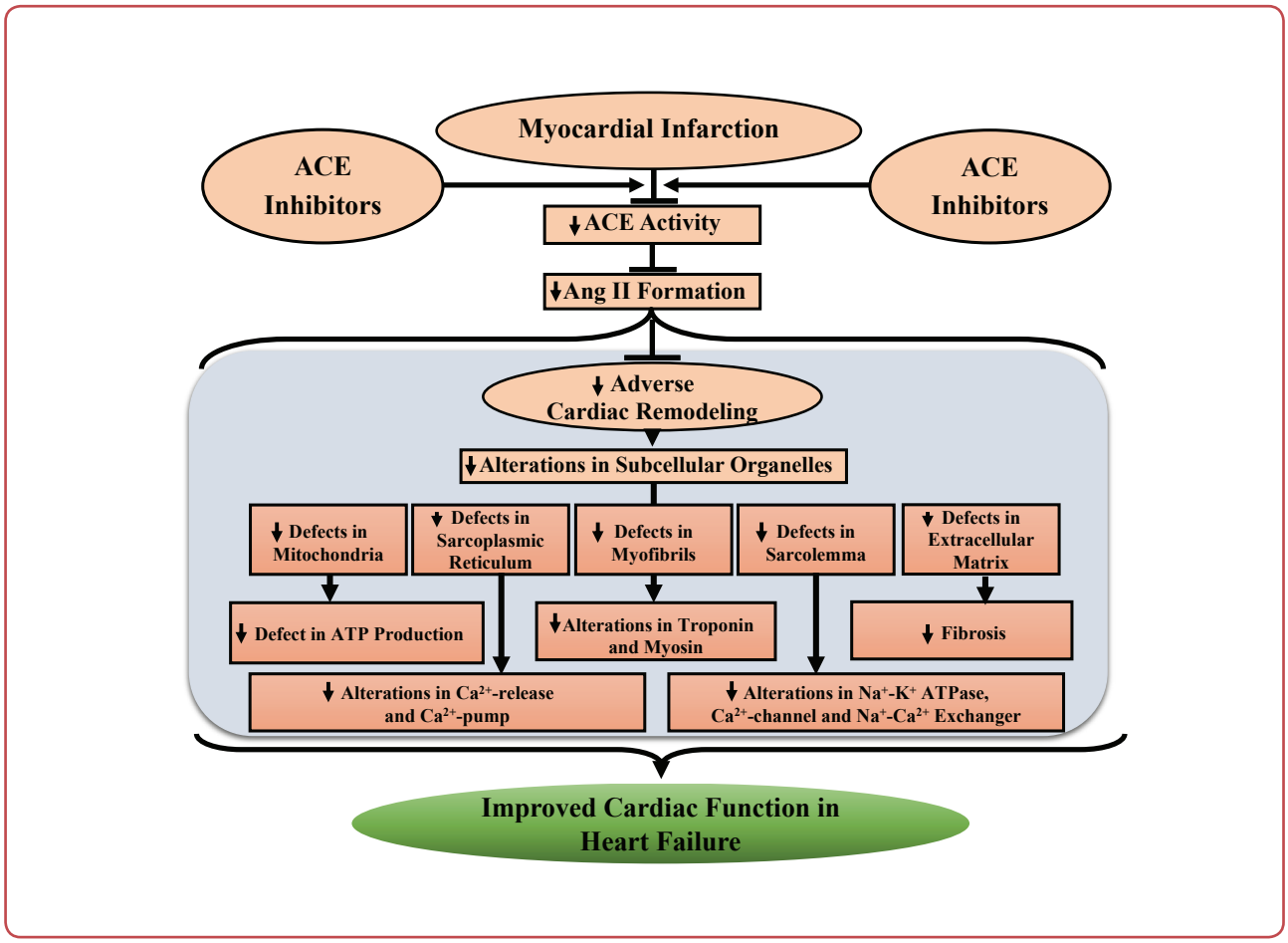

Figure 3: Modification of myocardial infarction induced changes in adverse cardiac remodelling and subcellular defects following treatment with ACE (angiotensin converting enzyme) inhibitors. ANG II, angiotensin II.

worsening angina and the occurrence of revascularisation,[363] the progression of heart failure and the all-cause mortality and morbidity following acute MI.[352, 364-366] In addition, ramipril treatment has been indicated to limit the decline of cardiac function in non-infarcted regions and prevent the circumferential shortening in the sub endocardium after MI.[345] Another ACE inhibitor, benazepril, has also been shown to exert several beneficial effects including increased survival time in congestive heart failure.[367-369] 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.[369] Long-term ACE inhibition with fosinopril was also observed to improve the depressed responsiveness to Ca^{2+} in myocytes from the aortic-banded rats.[249] 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.[370-373] 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.[374-376]

Various ACE inhibitors such as zofenopril, which contain sulfhydryl groups, have offered additional favourable effects for scavenging oxyradicals and reducing the reperfusion damage in heart failure.[377-381] 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.[349, 382,383] 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.[348,384] It needs to be emphasised that imidapril, a long-acting non-sulfhydryl ACE inhibitor, has been 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.[336, 385] Prevention of MI-induced haemodynamic changes and protection of the cardiovascular system by early treatment with imidapril have been demonstrated experimentally.[269 ,386] Other beneficial effects of this ACE inhibitor on LV hypertrophy,[387] exercise capacity in chronic heart failure,[388] LV remodeling in acute MI,[389] and subcellular organelle defects have also been reported in failing hearts.[198, 390-394] 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,[395, 396] 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,[397] myocardial energy metabolism,[80,177] SL PLC isoenzymes as well as SL Na^+-K^+-ATPase activities, protein content and mRNA levels in heart failure.[143-146, 398, 399] Furthermore, alterations in SR Ca^{2+} transport activities, Ca^{2+}-pump ATPase, phospholamban protein and gene expression,[142, 160, 196, 400] as well as myofibrillar ATPase activities,[198, 390] extracellular matrix,[401] cardiac gene expression and cardiac function[181, 184, 185, 196, 402] 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.[145] Enalapril, captopril and cilazapril have also been reported to affect SR remodelling in MI-induced heart failure.[338, 403, 404] 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.[198, 405] Imidapril, has shown the efficacy of partially preventing the altered PKC activities and its isoforms as well as phospholipase C and D activities,[146, 391] in addition to attenuating changes in Gi-proteins and adenylyl cyclase,[406] 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.

Parameters	Control	MI	MI + IMP
A. Cardiac functions:			
LV mass, mg	894 ± 16	981 ± 20*	898 ± 20†
LVEDP, mmHg	3.2 ± 0.8	14.2 ± 1.3*	4.6 ± 0.3†
LVSP, mmHg	144 ± 14	139 ± 3.3	135 ± 13
+ dP/dt, mmHg/s	9,450 ± 1,186	4,290 ± 618*	7,726 ± 648†
- dP/dt, mmHg/s	9,624 ± 1,068	4,064 ± 574*	7,840 ± 1,026†
B. RAS activity parameters:			
Plasma ANG II (fmol/ml)	7.6 ± 1.24	118 ± 5.8*	30 ± 3.4†
Plasma ACE activity (nmol/min/ml)	56 ± 3.7	74 ± 4.9*	50 ± 3.8†
LV ACE activity (nmol/min/mg protein)	0.50 ± 0.04	0.81 ± 0.03*	0.41 ± 0.02†
C. Oxidative stress levels:			
LV MDA (nmol/mg tissue lipids)	5.4 ± 0.3	16.7 ± 0.6*	39.8 ± 0.7†
LV GSH (µmol/g tissue)	72 ± 2.9	32 ± 3.6*	62 ± 2.4†
LV GSSH (µmol/g tissue)	16.3 ± 0.9	26.5 ± 1.8*	14.4 ± 1.2†

*Data are based on analysis of information in our paper[394] (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: H2637-2646). 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.*

failure.[392, 393, 395] Improvement of cardiac function in heart failure due to coronary occlusion[148, 398] 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 imidrapril 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^+-Ca^{2+} exchanger as well as N^+-K^+ ATPase in control and MI rats with or without IMP treatment for 4 weeks starting at 3 weeks after the induction of MI.

Parameters	Control	MI	MI + IMP
A. Sarcolemmal activities:			
Na^+-dependent Ca^{2+}-uptake (nmol/mg/2 sec)	460 ± 15.3	230 ± 30.6*	383.3 ± 15.3†
Na^+-Ca^{2+} exchanger protein content (% of control)	100	21.9 ± 4.7*	43.7 ± 6.2†
Na^+-Ca^{2+} exchanger mRNA (% of control)	100	43.3 ± 5.0*	81.7 ± 6.7†
Na^+-K^+ ATPase (µmol Pi/mg/hr)	61.1 ± 4.9	23.1 ± 13.2*	54.4 ± 11.5†
B. Na^+-K^+-ATPase isoform protein content: (% of control)			
α1	100	10.9 ± 1.7*	82.6 ± 3.5†
α2	100	4.7 ± 0.9*	41.3 ± 3.5 †
α3	100	150.0 ± 6.25*	96.9 ± 5.0†
β1	100	68.2 ± 5.0*	90.9 ± 4.5†
C. Na^+-K^+-ATPase isoform mRNA level (% of control)			
α1	100	53.3 ± 8.3*	86.7 ± 6.7†
α2	100	48.3 ± 10.3*	98.3 ± 6.9 †
α3	100	250.0 ± 4.2*	133.3 ± 8.3†
β1	100	43.1 ± 3.4*	82.75 ± 5.17†

*Data are based on analysis of information in our paper[144] (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 Ca^{2+}-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 imidrapril attenuated changes in the SL Na^+-Ca^{2+} 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 imidapril treatments on changes in MF Ca^{2+}-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 Ca^{2+} uptake and Ca^{2+} release activities as well as protein content and gene expressions, (except calsequestrin) in the failing hearts, were attenu-

Table 3: Myofibrillar ATPase activities, protein content and mRNA levels in control and MI rats with or without IMP treatment for 4 weeks starting at 3 weeks after the induction of MI.

Parameters	Control	MI	MI + IMP
A. Myofibrillar activities:			
Ca^{2+}-stimulated ATPase activity (µmol Pi/mg/h)	10.32 ± 0.58	6.83 ± 0.37*	8.3 ± 0.42†
Mg^{2+}-ATPase activity (µmol Pi /mg/h)	3.49 ± 0.19	3.87 ± 0.12	3.47 ± 0.2
B. Myosin heavy chain content (% of Total)			
Total MHC	100	102.67 ± 5.4	90.725 ± 7.9
α-MHC	94.63 ± 5.37	50.43 ± 5.9*	72.1 ± 4.6†
β-MHC	5.37 ± 0.3	49.57 ± 4*	27.93 ± 0.65†
C. Myosin heavy chain mRNA levels (Relative intensity)			
α-MHC	100	45.5 ± 11.25*	80.75 ± 13.0†
β-MHC	100	150.95 ± 4.5*	111.25 ± 11.25†

*Data are based on analysis of information in our paper[198] (Wang et al. J Mol Cell Cardiol 2002; 34: 847-857). Values are mean ± SE of 7 animals in each group. MHC: myosin heavy chain. *P < 0.05 compared with control; †P < 0.05 compared with MI group.*

ated by treatments with imidapril. These observations provide evidence that ACE inhibitors may improve cardiac dysfunction during the development of MI-induced heart failure by attenuating alterations in subcellular organelles.

Conclusion

From the foregoing discussion, it is evident that the activation of RAS and formation of Ang II due to pathological stimuli such as haemodynamic overload and heart attack (MI) play a critical role in the occurrence of cardiac hypertrophy and heart failure. At initial stages, the activation of RAS and release of Ang II increase myocardial muscle mass (adaptive cardiac remodelling or physiological cardiac hypertrophy) and blood pressure to maintain cardiovascular homeostasis. On the other hand, elevated levels of plasma Ang II for a prolonged period have been demonstrated to result in the development of cardiac dysfunction (pathological cardiac hypertrophy or adverse cardiac remodelling) and heart failure. A wide variety of defects in adverse cardiac remodelling including fibrosis, apoptosis, necrosis, inflammation, oxidative stress, Ca^{2+}-handling abnormalities, mitochondrial Ca^{2+}-overload and the loss of myofibril Ca^{2+}-sensitivity have been identified during the development of heart failure. However, 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 in the activation of both SL and MT NADPH oxidases by treatment with ACE inhibitors. Although the balance of opposing changes due to ACE treatments may be of a complex nature, the depression of oxidative stress and associated inflammation in the failing myocardium can be seen to attenuate subcellular alterations, Ca^{2+}-handling abnormalities as well as loss of myofilament Ca^{2+}-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.

Acknowledgements

The infrastructure support for the preparation of this article was provided by St. Boniface Hospital Albrechtsen Research Centre. Thanks, are also due to Ms. Andrea Opsima for typing this manuscript.

Conflict of interest

None.

Funding

Not Applicable.

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
ATPase = Adenosine triphosphate
MHC = Myosin heavy chain
mRNA = Messenger ribonucleic acid

References

1. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution. Eur Heart J 2021;42:3599–726.
2. Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, et al. Heart disease and stroke statistics—2021 update: a report from the American Heart Association. Circulation 2021;143:e254–e743.
3. Ziaeian B, Fonarow GC. Epidemiology and aetiology of heart failure. Nat Rev Cardiol 2016;13:368–78.
4. Lane RE, Cowie MR, Chow AWC. Prediction and prevention of sudden cardiac death in heart failure. Heart 2005;91:674–80.
5. Al-Mallah MH, Tleyjeh IM, Abdel-Latif AA, Weaver WD. Angiotensin-converting enzyme inhibitors in coronary artery disease and preserved left ventricular systolic function: a systematic review and meta-analysis of randomized controlled trials. J Am Coll Cardiol 2006;47:1576–83.
6. Cahill TJ, Kharbanda RK. Heart failure after myocardial infarction in the era of primary percutaneous coronary intervention: mechanisms, incidence and identification of patients at risk. World J Cardiol 2017;9:407-15.
7. Barnett R. Acute myocardial infarction. Lancet 2019 Jun 29;393(10191):2580. doi: 10.1016/S0140-6736(19)31419-9.
8. Anand I, McMurray JJ V, Whitmore J, Warren M, Pham A, McCamish MA, et al. Anemia and its relationship to clinical outcome in heart failure. Circulation 2004;110:149–54.
9. Shah AK, Dhalla NS. Effectiveness of some vitamins in the prevention of cardiovascular disease: A narrative review. Front Physiol 2021;12:72955. doi: 10.3389/fphys.2021.729255.
10. Stoltzfus, KC, Zhang Y, Sturgeon K, Sinoway LI, Trifiletti DM, Chinchilli VM, Zaorsky NG. Fatal heart disease among cancer patients. Nat Commun 2020;11:1–8.
11. Cardinale D, Colombo A, Bacchiani G, Tedeschi I, Meroni CA, Veglia F, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. Circulation 2015;131:1981–8.
12. Jenca D, Melenovský V, Stehlik J, Staněk V, Kettner J, Kautzner J, et al. Heart failure after myocardial infarction: incidence and predictors. ESC Heart Fail 2021;8:222-37.
13. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth universal definition of myocardial infarction (2018). Eur Heart J 2019;40:237–69.
14. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics—2016 update: a report from the American Heart Association. Circulation 2016;133:e38–360.
15. Johnson FL. Pathophysiology and etiology of heart failure. Cardiol Clin 2014;32:9–19.
16. Parmley WW. Pathophysiology of congestive heart failure. Am J Cardiol 1985;55: 9A–14A.
17. Pfeffer MA. Left ventricular remodeling after acute myocardial infarction. Annu Rev Med 1995;46:455–66.

18. Tanai E, Frantz S. Pathophysiology of heart failure. Compr Physiol 2011;6:187–214.
19. Schwinger RHG. Pathophysiology of heart failure. Cardiovasc Diagn Ther 2021;11:263-76.
20. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA). Eur Heart J 2016;37:2129–200.
21. Dhalla NS, Heyliger CE, Beamish RE, Innes IR. Pathophysiological aspects of myocardial hypertrophy. Can J Cardiol. 1987 May;3(4):183-96.
22. Hasenfuss G. Animal models of human cardiovascular disease, heart failure and hypertrophy. Cardiovasc Res 1998;39:60–76.
23. Packer M. Neurohormonal interactions and adaptations in congestive heart failure. Circulation 1988;77:721–30.
24. Francis GS. Neurohormonal control of heart failure. Cleve Clin J Med 2011;78:S75-9.
25. Hartupee J, Mann DL. Neurohormonal activation in heart failure with reduced ejection fraction. Nat Rev Cardiol 2017;14:30–8.
26. Dhalla N, Afzal N, Beamish RE, Naimark B, Takeda N, Nagano M. Pathophysiology of cardiac dysfunction in congestive heart failure. Can J Cardiol 1993;9:873–87.
27. Olivetti G, Abbi R, Quaini F, Kajstura J, Cheng W, Nitahara JA, et al. Apoptosis in the failing human heart. N Engl J Med 1997;336:1131–41.
28. Wagman G, Fudim M, Kosmas CE, Panni RE, Vittorio TJ. The neurohormonal network in the RAAS can bend before breaking. Curr Heart Fail Rep 2012;9:81–91.
29. Heineke J, Molkentin JD. Regulation of cardiac hypertrophy by intracellular signalling pathways. Nat Rev Mol Cell Biol 2006;7:589–600.
30. Dhalla NS, Das PK, Sharma GP. Subcellular basis of cardiac contractile failure. J Mol Cell Cardiol 1978;10:363–85.
31. Tarzami ST. Chemokines and inflammation in heart disease: adaptive or maladaptive? Int J Clin Exp Med 2011;4:74-80.
32. Adameova A, Abdellatif Y, Dhalla NS. Role of the excessive amounts of circulating catecholamines and glucocorticoids in stress-induced heart disease. Can J Physiol Pharmacol 2009;87:493–514.
33. Hill JA, Olson EN. Cardiac plasticity. N Engl J Med 2008;358:1370–80.
34. Segura AM, Frazier OH, Buja LM. Fibrosis and heart failure. Heart Fail Rev 2014;19:173–85.
35. Triposkiadis F, Butler J, Abboud FM, Armstrong PW, Adamopoulos S, Atherton JJ, et al. The continuous heart failure spectrum: moving beyond an ejection fraction classification. Eur Heart J 2019;40:2155–63.
36. Shah AK, Bhullar SK, Elimban V, Dhalla NS. Oxidative stress as a mechanism for functional alterations in cardiac hypertrophy and heart failure. Antioxidants 2021;10:1-19.
37. Tham YK, Bernardo BC, Ooi JY, Weeks KL, McMullen JR. Pathophysiology of cardiac hypertrophy and heart failure: Signaling pathways and novel therapeutic targets. Arch Toxicol 2015;89:1401–38.
38. Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling-concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. J Am Coll Cardiol 2000;35:569–82.
39. Ertl G, Brenner S, Angermann CE. Cardiac remodeling after myocardial infarction: Clinical practice update. Herz 2017;42:107–20.
40. Oldfield CJ, Duhamel TA, Dhalla NS. Mechanisms for the transition from physiological to pathological cardiac hypertrophy. Can J Physiol Pharmacol 2020;98:74–84.
41. Nakamura M, Sadoshima J. Mechanisms of physiological and pathological cardiac hypertrophy. Nat Rev Cardiol 2018;15:387–407.
42. Shao Q, Panagia V, Beamish RE, Dhalla NS. Role of renin-angiotensin system in cardiac hypertrophy and failure 1998;283–310.
43. Jin M, Wilhelm MJ, Lang RE, Unger T, Lindpaintner K, Ganten D. Endogenous tissue renin-angiotensin systems: from molecular biology to therapy. Am J Med 1988;84:28–36.
44. Dostal DE, Baker KM. The cardiac renin-angiotensin system: conceptual, or a regulator of cardiac function? Circ Res 1999;85:643–50.
45. Ohta K, Kim S, Wanibuchi H, Ganten D, Iwao H. Contribution of local renin-angiotensin system to cardiac hypertrophy, phenotypic modulation, and remodeling in TGR (mRen2) 27 transgenic rats. Circulation 1996;94(4):785–91.
46. Paul M, Mehr AP, Kreutz R. Physiology of local renin-angiotensin systems. Physiol Rev 2006;86:747–803.
47. Serneri GGN, Boddi M, Cecioni I, Vanni S, Coppo M, Papa ML, et al. Cardiac angiotensin II formation in the clinical course of heart failure and its relationship with left ventricular function. Circ Res 2001;88:961–8.
48. Ferrario CM. The renin-angiotensin system: Importance in physiology and pathology. J Cardiovasc Pharmacol 1990;15:S1–5.
49. Szczepanska-Sadowska E, Czarzasta K, Cudnoch-Jedrzejewska A. Dysregulation of the renin-angiotensin system and the vasopressinergic system interactions in cardiovascular disorders. Curr Hypertens Rep 2018;20:1–24.
50. Santos RA, Oudit GY, Verano-Braga T, Canta G, Steckelings UM, Bader M. The renin-angiotensin system: going beyond the classical paradigms. Am J Physiol Circ Physiol 2019;316:H958-70.
51. Kumar R, Singh VP, Baker KM. The intracellular renin–angiotensin system: implications in cardiovascular remodeling. Curr Opin Nephrol Hypertens 2008;17:168–73.
52. Crowley SD, Coffman TM. Recent advances involving the renin–angiotensin system. Exp Cell Res 2012;318:1049–56.
53. De Mello WC, Danser AH. Angiotensin II and the heart: on the intracrine renin-angiotensin system. Hypertension 2000;35:1183–8.
54. Raizada, MK, Phillips, MI, Sumners C. Cellular and molecular biology of the renin-angiotensin system. Boca Raton, Fla: CRC Press 1993:379-411.
55. De Mello WC. Local renin angiotensin aldosterone systems and cardiovascular diseases. Med Clin 2017;101:117–27.
56. Babick AP, Dhalla NS. Role of subcellular remodeling in cardiac dysfunction due to congestive heart failure. Med Princ Pract 2007;16:81–9.
57. Bhullar SK, Shah AK, Dhalla NS. Role of angiotensin II in

the development of subcellular remodeling in heart failure. Explor Med 2021;2:352–71.
58. Higuchi S, Ohtsu H, Suzuki H, Shirai H, Frank GD, Eguchi S. Angiotensin II signal transduction through the AT1 receptor: novel insights into mechanisms and pathophysiology. Clin Sci 2007;112:417–28.
59. Matsubara H. Pathophysiological role of angiotensin II type 2 receptor in cardiovascular and renal diseases. Circ Res 1998;83:1182–91.
60. Steckelings UM, Paulis L, Namsolleck P, Unger T. AT2 receptor agonists: hypertension and beyond. Curr Opin Nephrol Hypertens 2012;21:142–6.
61. Wang Y, Del Borgo M, Lee HW, Baraldi D, Hirmiz B, Gaspari TA, et al. Anti-fibrotic potential of AT2 receptor agonists. Front Pharmacol 2017;8:564. doi: 10.3389/fphar.2017.00564.
62. Rompe F, Artuc M, Hallberg A, Alterman M, Ströder K, Thöne-Reineke C, et al. Direct angiotensin II type 2 receptor stimulation acts anti-inflammatory through epoxyeicosatrienoic acid and inhibition of nuclear factor κB. Hypertension 2010;55:924–31.
63. Forrester SJ, Booz GW, Sigmund CD, Coffman TM, Kawai T, Rizzo V, et al. Angiotensin II signal transduction: An update on mechanisms of physiology and pathophysiology. Physiol Rev 2018;98:1627–738.
64. Patel VB, Zhong J-C, Grant MB, Oudit GY. Role of the ACE2/angiotensin 1–7 axis of the renin–angiotensin system in heart failure. Circ Res 2016;118:1313–26.
65. Simoes Silva AC, Silveira KD, Ferreira AJ, Teixeira MM. ACE2, angiotensin-(1-7) and M as receptor axis in inflammation and fibrosis. Br J Pharmacol 2013;169:477–92.
66. Santos RA, Sampaio WO, Alzamora AC, Motta-Santos D, Alenina N, Bader M, et al. The ACE2/angiotensin-(1–7)/MAS axis of the renin-angiotensin system: focus on angiotensin-(1–7). Physiol Rev 2018;98:505-53.
67. Jiang F, Yang J, Zhang Yf, Dong M, Wang S, Zhang Q, et al. Angiotensin-converting enzyme 2 and angiotensin 1–7: novel therapeutic targets. Nat Rev Cardiol 2014;11:413–26.
68. Mercure C, Yogi A, Callera GE, Aranha AB, Bader M, Ferreira AJ, et al. Angiotensin (1-7) blunts hypertensive cardiac remodeling by a direct effect on the heart. Circ Res 2008;103:1319–26.
69. Namsolleck P, Recarti C, Foulquier S, Steckelings UM, Unger T. AT 2 receptor and tissue injury: therapeutic implications. Curr Hypertens Rep 2014;16:1-10.
70. Steckelings UM, de Kloet A, Sumners C. Centrally mediated cardiovascular actions of the angiotensin II type 2 receptor. Trends Endocrinol Metab 2017;28:684–93.
71. Donoghue M, Hsieh F, Baronas E, Godbout K, Gosselin M, Stagliano N, et al. A novel angiotensin-converting enzyme-related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1-9. Circ Res 2000;87:E1–E9.
72. Santos RA, Simoes e Silva AC, Maric C, Silva DMR, Machado RP, De Buhr I, et al. Angiotensin-(1-7) is an endogenous ligand for the G protein-coupled receptor Mas. Proc Natl Acad Sci U S A. 2003;100:8258–63.
73. Kriszta G, Kriszta Z, Váncsa S, Hegyi PJ, Frim L, Erőss B, et al. Effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on angiotensin-converting enzyme 2 levels: A comprehensive analysis based on animal studies. Front Pharmacol 2021;12:619524. doi: 10.3389/fphar.2021.619524.
74. Touyz RM, Schiffrin EL. Signal transduction mechanisms mediating the physiological and pathophysiological actions of angiotensin II in vascular smooth muscle cells. Pharmacol Rev 2000;52:639–72.
75. Ferrario CM, Ahmad S, Nagata S, Simington SW, Varagic J, Kon N, et al. An evolving story of angiotensin-II-forming pathways in rodents and humans. Clin Sci 2014;126:461–9.
76. Dzau VJ, Colucci WS, Williams GH, Curfman G, Meggs L, Hollenberg NK. Sustained effectiveness of converting-enzyme inhibition in patients with severe congestive heart failure. N Engl J Med 1980;302:1373–9.
77. Gavras H, Faxon DP, Berkoben J, Brunner HR, Ryan TJ. Angiotensin converting enzyme inhibition in patients with congestive heart failure. Circulation 1978;58:770–6.
78. Ambrosioni E, Borghi C, Magnani B. The effect of the angiotensin-converting–enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction. N Engl J Med 1995;332:80–5.
79. Dasgupta C, Zhang L. Angiotensin II receptors and drug discovery in cardiovascular disease. Drug Discov Today 2011;16:22–34.
80. Sanbe A, Tanonaka K, Kobayashi R, Takeo S. Effects of long-term therapy with ACE inhibitors, captopril, enalapril and trandolapril, on myocardial energy metabolism in rats with heart failure following myocardial infarction. J Mol Cell Cardiol 1995;27:2209–22.
81. Tipnis SR, Hooper NM, Hyde R, Karran E, Christie G, Turner AJ. A human homolog of angiotensin-converting enzyme: Cloning and functional expression as a captopril-insensitive carboxypeptidase. J Biol Chem 2000;275:33238–43.
82. De Backer G, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J, et al. European guidelines on cardiovascular disease prevention in clinical practice; third joint task force of European and other societies on cardiovascular disease prevention in clinical practice. Eur J Prev Cardiol 2003;10:S1–10.
83. Cleland JG, Dargie HJ, Ball SG, Gillen G, Hodsman GP, Morton JJ, et al. Effects of enalapril in heart failure: a double blind study of effects on exercise performance, renal function, hormones, and metabolic state. Heart 1985;54:305–12.
84. Hsieh C, Li C, Hsu C, Chen H, Chen Y, Liu Y, et al. Mitochondrial protection by simvastatin against angiotensin II-mediated heart failure. Br J Pharmacol 2019;176:3791–804.
85. Dzau VJ. Implications of local angiotensin production in cardiovascular physiology and pharmacology. Am J Cardiol 1987;59:A59–65.
86. Ferrario CM. Role of angiotensin II in cardiovascular disease-therapeutic implications of more than a century of research. J Renin Angiotensin Aldosterone Syst 2006;7:3–14.
87. Gradman AH, Papademetriou V. Combined renin-angiotensin-aldosterone system inhibition in patients with chronic heart failure secondary to left ventricular systolic dysfunction. Am Heart J 2009;157:S17–23.
88. Ma TK, Kam KK, Yan BP, Lam YY. Renin-angiotensin-aldosterone system blockade for cardiovascular diseases: Current status. Br J Pharmacol 2010;160:1273–92.
89. Bader M. Tissue renin-angiotensin-aldosterone systems: targets for pharmacological therapy. Annu Rev Pharmacol Toxicol 2010;50:439–65.

90. Meune C, Wahbi K, Duboc D, Weber S. Meta-analysis of Renin-angiotensin-aldosterone blockade for heart failure in presence of preserved left ventricular function. J Cardiovasc Pharmacol Ther 2011;16:368–75.
91. Emdin CA, Callender T, Cao J, McMurray JJ, Rahimi K. Meta-analysis of large-scale randomized trials to determine the effectiveness of inhibition of the renin-angiotensin aldosterone system in heart failure. Am J Cardiol 2015;116:155–61.
92. Ferrario CM, Mullick AE. Renin angiotensin aldosterone inhibition in the treatment of cardiovascular disease. Pharmacol Res 2017;125:57–71.
93. Ames MK, Atkins CE, Pitt B. The renin-angiotensin-aldosterone system and its suppression. J Vet Intern Med 2019;33:363–82.
94. Bakogiannis C, Theofilogiannakos E, Papadopoulos C, Lazaridis C, Bikakis I, Tzikas S, et al. A translational approach to the renin-angiotensin-aldosterone system in heart failure. Ann Res Hosp 2019;3:1-11.
95. Nadir MA, Wei L, Elder DHJ, Libianto R, Lim TK, Pauriah M, et al. Impact of renin-angiotensin system blockade therapy on outcome in aortic stenosis. J Am Coll Cardiol 2011;58:570–6.
96. Guo X, Saini HK, Wang J, Gupta SK, Goyal RK, Dhalla NS. Prevention of remodeling in congestive heart failure due to myocardial infarction by blockade of the renin–angiotensin system. Expert Rev Cardiovasc Ther 2005;3:717–32.
97. Flather MD, Yusuf S, Køber L, Pfeffer M, Hall A, Murray G, et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. Lancet 2000;355:1575–81.
98. Pinargote P, Guillen D, Guarderas JC. ACE inhibitors: upper respiratory symptoms. BMJ Case Reports 2014;1-3:bcr2014205462. doi: 10.1136/bcr-2014-205462.
99. Israili ZH, Hall WD. Cough and angioneurotic edema associated with angiotensin-converting enzyme inhibitor therapy: a review of the literature and pathophysiology. Ann Intern Med 1992;117:234–42.
100. Os I, Bratland B, Dahlöf B, Gisholt K, Syvertsen J. Female sex as an important determinant of lisinopril-induced cough. Lancet 1992;339:372. doi: 10.1016/0140-6736(92)91694-4.
101. Brown NJ, Ray WA, Snowden M, Griffin MR. Black Americans have an increased rate of angiotensin converting enzyme inhibitor-associated angioedema. Clin Pharmacol Ther 1996;60:8–13.
102. Liau Y, Chua I, Kennedy MA, Maggo S. Pharmacogenetics of angiotensin-converting enzyme inhibitor-induced angioedema. Clin Exp Allergy 2019;49:142–54.
103. Eckberg DL, Drabinsky M, Braunwald E. Defective cardiac parasympathetic control in patients with heart disease. N Engl J Med 1971;285:877–83.
104. DiCarlo LA, Libbus I, Kumar HU, Mittal S, Premchand RK, Amurthur B, et al. Autonomic regulation therapy to enhance myocardial function in heart failure patients: the ANTHEM-HFpEF study. ESC Heart Fail 2018;5:95–100.
105. Osterziel KJ, Hänlein D, Dietz R. Interactions between the renin-angiotensin system and the parasympathetic nervous system in heart failure. J Cardiovasc Pharmacol 1994;24:S70-4.
106. Guo GB, Abboud FM. Angiotensin II attenuates baroreflex control of heart rate and sympathetic activity. Am J Physiol Circ Physiol 1984;246:H80–9.
107. Iovino M, Lisco G, Giagulli VA, Vanacore A, Pesce A, Guastamacchia E, et al. Angiotensin II-vasopressin interactions in the regulation of cardiovascular functions. evidence for an impaired hormonal sympathetic reflex in hypertension and congestive heart failure. Endocr Metab Immune Disord Drug Targets 2021;2:1830-4.
108. Sepehrdad R, Frishman WH, Stier Jr CT, Sica DA. Direct inhibition of renin as a cardiovascular pharmacotherapy: focus on aliskiren. Cardiol Rev 2007;15:242–56.
109. Seed A, Gardner R, McMurray J, Hillier C, Murdoch D, MacFadyen R, et al. Neurohumoral effects of the new orally active renin inhibitor, aliskiren, in chronic heart failure. Eur J Heart Fail 2007;9:1120–7.
110. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med 1999;341:709–17.
111. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 2003;348:1309–21.
112. Dang Z, Su S, Jin G, Nan X, Ma L, Li Z, et al. Tsantan Sumtang attenuated chronic hypoxia-induced right ventricular structure remodeling and fibrosis by equilibrating local ACE-AngII-AT1R/ACE2-Ang1-7-Mas axis in rat. J Ethnopharmacol 2020;250:112470. doi: 10.1016/j.jep.2019.112470.
113. Dhalla NS, Ziegelhoffer A, Harrow JAC. Regulatory role of membrane systems in heart function. Can J Physiol Pharmacol 1977;55:1211–34.
114. 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; 81:429–38.
115. Duhamel TA, Dhalla NS. New insights into the causes of heart failure. Drug Discov Today Dis Mech 2007;4:175–84.
116. Dhalla NS, Dent MR, Tappia PS, Sethi R, Barta J, Goyal RK. Subcellular remodeling as a viable target for the treatment of congestive heart failure. J Cardiovasc Pharmacol Ther 2006;11:31- 45.
117. Dhalla NS, Liu X, Panagia V, Takeda N. Subcellular remodeling and heart dysfunction in chronic diabetes. Cardiovasc Res 1998;40:239–47.
118. Dhalla NS, Saini HK, Tappia PS, Sethi R, Mengi SA, Gupta SK. Potential role and mechanisms of subcellular remodeling in cardiac dysfunction due to ischemic heart disease. J Cardiovasc Med 2007;8:238–50.
119. Dhalla NS, Rangi S, Babick AP, Zieroth S, Elimban V. Cardiac remodeling and subcellular defects in heart failure due to myocardial infarction and aging. Heart Fail Rev 2012;17:671–81.
120. Dhalla NS, Shah AK, Tappia PS. Role of oxidative stress in metabolic and subcellular abnormalities in diabetic cardiomyopathy. Int J Mol Sci 2020;21:2413. doi: 10.3390/ijms21072413.
121. Mudd JO, Kass DA. Tackling heart failure in the twenty-first century. Nature 2008;451:919–28.
122. Val-Blasco A, Gil-Fernández M, Rueda A, Pereira L, Delgado C, Smani T, et al. Ca2+ mishandling in heart fail-

ure: potential targets. Acta Physiol 2021;e13691. doi: 10.1111/apha.13691.
123. Gorski PA, Ceholski DK, Hajjar RJ. Altered myocardial calcium cycling and energetics in heart failure—a rational approach for disease treatment. Cell Metab 2015;21:183–94.
124. Kho C, Lee A, Hajjar RJ. Altered sarcoplasmic reticulum calcium cycling—targets for heart failure therapy. Nat Rev Cardiol 2012;9:717–33.
125. Pfeffer MA, Braunwald E. Ventricular remodeling after myocardial infarction. Experimental observations and clinical implications. Circulation 1990;81:1161–72.
126. Dhalla NS, Shao Q, Panagia V. Remodeling of cardiac membranes during the development of congestive heart failure. Heart Fail Rev 1998;2:261–72.
127. Pagani ED, Alousi AA, Grant AM, Older TM, Dziuban Jr SW, Allen PD. Changes in myofibrillar content and Mg-ATPase activity in ventricular tissues from patients with heart failure caused by coronary artery disease, cardiomyopathy, or mitral valve insufficiency. Circ Res 1988;63:380–5.
128. Mehta PK, Griendling KK. Angiotensin II cell signaling: physiological and pathological effects in the cardiovascular system. Am J Physiol Physiol 2007;292:C82–97.
129. Dostal DE. The cardiac renin–angiotensin system: novel signaling mechanisms related to cardiac growth and function. Regul Pept 2000;91:1–11.
130. Rasini E, Cosentino M, Marino F, Legnaro M, Ferrari M, Guasti L, et al. Angiotensin II type 1 receptor expression on human leukocyte subsets: a flow cytometric and RT-PCR study. Regul Pept 2006;134:69–74.
131. Deschamps AM, Spinale FG. Pathways of matrix metalloproteinase induction in heart failure: bioactive molecules and transcriptional regulation. Cardiovasc Res 2006;69:666–76.
132. Hasenfuss G. Alterations of calcium-regulatory proteins in heart failure. Cardiovasc Res 1998;37:279–89.
133. Morano I, Hädicke K, Haase H, Böhm M, Erdmann E, Schaub MC. Changes in essential myosin light chain isoform expression provide a molecular basis for isometric force regulation in the failing human heart. J Mol Cell Cardiol 1997;29:1177–87.
134. Guimarães PB, Alvarenga ÉC, Siqueira PD, Paredes-Gamero EJ, Sabatini RA, Morais RLT, et al. Angiotensin II binding to angiotensin I-converting enzyme triggers calcium signaling. Hypertension 2011;57:965–72.
135. Nusier M, Ozcelikay AT, Shah AK, Dhalla NS. Role of intracellular Ca2+-overload in cardiac dysfunction in heart disease. Clin Cardiol Cardiovasc Interv 2020;3:419–2641.
136. Steinberg SF. Oxidative stress and sarcomeric proteins. Circ Res 2013;112:393–405.
137. Brixius K, Reuter H, Bloch W, Schwinger RHG. Altered hetero-and homeometric autoregulation in the terminally failing human heart. Eur J Heart Fail 2005;7:29–35.
138. Schwinger RH, Böhm M, Koch A, Schmidt U, Morano I, Eissner H-J, et al. The failing human heart is unable to use the Frank-Starling mechanism. Circ Res 1994;74:959–69.
139. Sag CM, Wagner S, Maier LS. Role of oxidants on calcium and sodium movement in healthy and diseased cardiac myocytes. Free Radic Biol Med 2013;63:338–49.
140. Wang X, Yuan B, Dong W, Yang B, Yang Y, Lin X, et al. Humid heat exposure induced oxidative stress and apoptosis in cardiomyocytes through the angiotensin II signaling pathway. Heart Vessels 2015;30:396–405.
141. Pieske B, Maier LS, Schmidt-Schweda S. Sarcoplasmic reticulum Ca2+load in human heart failure. Basic Res Cardiol 2002;97:I63–71.
142. Schwinger RHG, Bundgaard H, Müller-Ehmsen J, Kjeldsen K. The Na, K-ATPase in the failing human heart. Cardiovasc Res 2003;57:913–20.
143. Dixon IM, Hata T, Dhalla NS. Sarcolemmal Na+-K+-ATPase activity in congestive heart failure due to myocardial infarction. Am J Physiol Physiol 1992;262:C664–71.
144. Shao Q, Ren B, Elimban V, Tappia PS, Takeda N, Dhalla NS. Modification of sarcolemmal Na+-K+-ATPase and Na +/Ca2+ exchanger expression in heart failure by blockade of renin-angiotensin system. Am J Physiol - Heart Circ Physiol 2005;288:H2637–46.
145. Guo X, Wang J, Elimban V, Dhalla NS. Both enalapril and losartan attenuate sarcolemmal Na+-K+-ATPase remodeling in failing rat heart due to myocardial infarction. Can J Physiol Pharmacol 2008;86:139–47.
146. Yu C-H, Panagia V, Tappia PS, Liu S-Y, Takeda N, Dhalla NS. Alterations of sarcolemmal phospholipase D and phosphatidate phosphohydrolase in congestive heart failure. Biochim Biophys Acta (BBA)-Molecular Cell Biol Lipids 2002;1584:65–72.
147. Tappia PS, Liu S-Y, Shatadal S, Takeda N, Dhalla NS, Panagia V. Changes in sarcolemmal PLC isoenzymes in postinfarct congestive heart failure: partial correction by imidapril. Am J Physiol Circ Physiol 1999;277:H40–9.
148. Dixon IM, Hata T, Dhalla NS. Sarcolemmal calcium transport in congestive heart failure due to myocardial infarction in rats. Am J Physiol Circ Physiol 1992;262:H1387–94.
149. Weisser-Thomas J, Kubo H, Hefner CA, Gaughan JP, McGowan BS, Ross R, et al. The Na+/Ca2+ exchanger/SR Ca2+ ATPase transport capacity regulates the contractility of normal and hypertrophied feline ventricular myocytes. J Card Fail 2005;11:380–7.
150. Camors E, Charue D, Trouvé P, Monceau V, Loyer X, Russo-Marie F, et al. Association of annexin A5 with Na+/Ca2+ exchanger and caveolin-3 in non-failing and failing human heart. J Mol Cell Cardiol 2006;40:47–55.
151. Setterberg IE, Le C, Frisk M, Li J, Louch WE. The physiology and pathophysiology of t-tubules in the heart. Front Physiol 2021;12:1-21.
152. Cannell MB, Crossman DJ, Soeller C. Effect of changes in action potential spike configuration, junctional sarcoplasmic reticulum micro-architecture and altered t-tubule structure in human heart failure. J Muscle Res Cell Motil 2006;27:297–306.
153. Pinali C, Malik N, Davenport JB, Allan LJ, Murfitt L, Iqbal MM, et al. Post-myocardial infarction t-tubules form enlarged branched structures with dysregulation of junctophilin-2 and bridging integrator 1 (BIN-1). J Am Heart Assoc 2017;6:e004834. doi: 10.1161/JAHA.116.004834.
154. Hoydal MA, Kirkeby-Garstad I, Karevold A, Wiseth R, Haaverstad R, Wahba A, et al. Human cardiomyocyte calcium handling and transverse tubules in mid-stage of post-myocardial-infarction heart failure. ESC Heart Fail 2018;5:332–42.

155. Lyon AR, MacLeod KT, Zhang Y, Garcia E, Kanda GK, Korchev YE, et al. Loss of t-tubules and other changes to surface topography in ventricular myocytes from failing human and rat heart. Proc Natl Acad Sci 2009;106:6854–9.
156. Feiner EC, Chung P, Jasmin JF, Zhang J, Whitaker-Menezes D, Myers V, et al. Left ventricular dysfunction in murine models of heart failure and in failing human heart is associated with a selective decrease in the expression of caveolin-3. J Card Fail 2011;17:253–63.
157. Bryant SM, Kong CHT, Watson JJ, Gadeberg HC, Roth DM, Patel HH, et al. Caveolin-3 KO disrupts t-tubule structure and decreases t-tubular I Ca density in mouse ventricular myocytes. Am J Physiol Circ Physiol 2018;315:H1101–11.
158. Pinali C, Bennett HJ, Davenport JB, Caldwell JL, Starborg T, Trafford AW, et al. Three-dimensional structure of the intercalated disc reveals plicate domain and gap junction remodeling in heart failure. Biophys J 2015;108:498–507.
159. Ortega A, Tarazon E, Gil-Cayuela C, García-Manzanares M, Martínez-Dolz L, Lago F, et al. Intercalated disc in failing hearts from patients with dilated cardiomyopathy: Its role in the depressed left ventricular function. PLoS One 2017;12:e0185062. doi: 10.1371/journal.pone.0185062.
160. Afzal N, Dhalla NS. Differential changes in left and right ventricular SR calcium transport in congestive heart failure. Am J Physiol Circ Physiol 1992;262:H868–74.
161. Pinali C, Bennett H, Davenport JB, Trafford AW, Kitmitto A. Three-dimensional reconstruction of cardiac sarcoplasmic reticulum reveals a continuous network linking transverse-tubules: this organization is perturbed in heart failure. Circ Res 2013;113:1219–30.
162. Marks AR. Calcium cycling proteins and heart failure: mechanisms and therapeutics. J Clin Invest 2013;123:46–52.
163. Luo M, Anderson ME. Mechanisms of altered Ca2+ handling in heart failure. Circ Res 2013;113:690–708.
164. Machackova J, Barta J, Dhalla NS. Myofibrillar remodelling in cardiac hypertrophy, heart failure and cardiomyopathies. Can J Cardiol 2006;22:953–68.
165. O'Brien PJ, Ianuzzo CD, Moe GW, Stopps TP, Armstrong PW. Rapid ventricular pacing of dogs to heart failure: biochemical and physiological studies. Can J Physiol Pharmacol 1990;68:34–9.
166. Neagoe C, Kulke M, del Monte F, Gwathmey JK, de Tombe PP, Hajjar RJ, et al. Titin isoform switch in ischemic human heart disease. Circulation 2002;106:1333–41.
167. Hajjar RJ, Schwinger RG, Schmidt U, Kim CS, Lebeche D, Doye AA, et al. Myofilament calcium regulation in human myocardium. Circulation 2000;101:1679–85.
168. Dhalla NS, Wang X, Beamish RE. Intracellular calcium handling in normal and failing hearts. Exp Clin Cardiol 1996;1:7–20.
169. Davies CH, Harding SE, Poole-Wilson PA. Cellular mechanisms of contractile dysfunction in human heart failure. Eur Heart J 1996;17:189–98.
170. Spinale FG. Myocardial matrix remodeling and the matrix metalloproteinases: influence on cardiac form and function. Physiol Rev 2007;87:1285–342.
171. Rysa J, Leskinen H, Ilves M, Ruskoaho H. Distinct upregulation of extracellular matrix genes in transition from hypertrophy to hypertensive heart failure. Hypertension 2005;45:927–33.
172. Li YY, McTiernan CF, Feldman AM. Proinflammatory cytokines regulate tissue inhibitors of metalloproteinases and disintegrin metalloproteinase in cardiac cells. Cardiovasc Res 1999;42:162–72.
173. Tappia P, Singal T, Dent M, Asemu G, Mangat R, Dhalla NS. Phospholipid-mediated signaling in diseased myocardium. Future Lipidol 2006;1:701–17.
174. Singh RB, Dandekar SP, Elimban V, Gupta SK, Dhalla NS. Role of proteases in the pathophysiology of cardiac disease. Mol Cell Biochem 2004;263:241–56.
175. Dhalla NS, Wang X, Sethi R, Das PK, Beamish RE. β-adrenergic linked signal transduction mechanisms in failing hearts. Heart Fail Rev 1997;2:55–65.
176. Kubalova Z, Terentyev D, Viatchenko-Karpinski S, Nishijima Y, Györke I, Terentyeva R, et al. Abnormal intrastore calcium signaling in chronic heart failure. Proc Natl Acad Sci 2005;102:14104–9.
177. Ventura-Clapier R, Garnier A, Veksler V. Energy metabolism in heart failure. J Physiol 2004;555:1–13.
178. Bertero E, Maack C. Metabolic remodelling in heart failure. Nat Rev Cardiol 2018;15:457–70.
179. Moos WH, Faller D V, Glavas IP, Harpp DN, Kamperi N, Kanara I, et al. Pathogenic mitochondrial dysfunction and metabolic abnormalities. Biochem Pharmacol 2021;193:114809. doi: 10.1016/j.bcp.2021.114809.
180. O'Rourke B, Cortassa S, Akar F, Aon M. Mitochondrial ion channels in cardiac function and dysfunction. Novartis Foundation Symp 2007;287:140-51.
181. Zhou B, Tian R. Mitochondrial dysfunction in pathophysiology of heart failure. J Clin Invest 2018;128:3716–26.
182. Griffiths EJ, Balaska D, Cheng WHY. The ups and downs of mitochondrial calcium signalling in the heart. Biochim Biophys Acta (BBA)-Bioenergetics 2010;1797:856–64.
183. Lai L, Qiu H. The physiological and pathological roles of mitochondrial calcium uptake in heart. Int J Mol Sci 2020;21:7689. doi: 10.3390/ijms21207689.
184. Kwong JQ. The mitochondrial calcium uniporter in the heart: energetics and beyond. J Physiol 2017;595:3743–51.
185. Finkel T, Menazza S, Holmström KM, Parks RJ, Liu J, Sun J, et al. The ins and outs of mitochondrial calcium. Circ Res 2015;116:1810–9.
186. Williams GSB, Boyman L, Lederer WJ. Mitochondrial calcium and the regulation of metabolism in the heart. J Mol Cell Cardiol 2015;78:35–45.
187. Rosca MG, Tandler B, Hoppel CL. Mitochondria in cardiac hypertrophy and heart failure. J Mol Cell Cardiol 2013;55:31–41.
188. Gustafsson ÅB, Gottlieb RA. Heart mitochondria: gates of life and death. Cardiovasc Res 2008;77:334–43.
189. Holmström KM, Pan X, Liu JC, Menazza S, Liu J, Nguyen TT, et al. Assessment of cardiac function in mice lacking the mitochondrial calcium uniporter. J Mol Cell Cardiol 2015;85:178–82.
190. Hersel J, Jung S, Mohacsi P, Hullin R. Expression of the L-type calcium channel in human heart failure. Basic Res Cardiol 2002;97:I4–10.
191. Zima A V, Bovo E, Mazurek SR, Rochira JA, Li W, Terentyev D. Ca handling during excitation–contraction coupling in heart failure. Pflügers Arch J Physiol 2014;466:1129–37.

192. Kolwicz Jr SC, Purohit S, Tian R. Cardiac metabolism and its interactions with contraction, growth, and survival of cardiomyocytes. Circ Res 2013;113:603–16.
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.
194. Catterall WA. Structure and regulation of voltage-gated Ca2+ channels. Annu Rev Cell Dev Biol 2000;16:521–55.
195. Meissner G. Ryanodine receptor/ Ca2+ release channels and their regulation by endogenous effectors. Annu Rev Physiol 1994;56:485–508.
196. Fabiato A. Calcium-induced release of calcium from the cardiac sarcoplasmic reticulum. Am J Physiol Physiol 1983;245:C1–14.
197. Andersson DC, Betzenhauser MJ, Reiken S, Meli AC, Umanskaya A, Xie W, et al. Ryanodine receptor oxidation causes intracellular calcium leak and muscle weakness in aging. Cell Metab 2011;14:196–207.
198. Wang J, Liu X, Ren B, Rupp H, Takeda N, Dhalla NS. Modification of myosin gene expression by imidapril in failing heart due to myocardial infarction. J Mol Cell Cardiol 2002;34:847–57.
199. Bers DM. Cardiac excitation–contraction coupling. Nature 2002;415:198–205.
200. de Tombe PP. Cardiac myofilaments: mechanics and regulation. J Biomech 2003;36:721–30.
201. Marston SB, de Tombe PP. Troponin phosphorylation and myofilament Ca2+-sensitivity in heart failure: increased or decreased? J Mol Cell Cardiol 2008;45:603–7.
202. Bublitz M, Musgaard M, Poulsen H, Thogersen L, Olesen C, Schiøtt B, et al. Ion pathways in the sarcoplasmic reticulum Ca2+-ATPase. J Biol Chem 2013;288:10759–65.
203. Simmerman HKB, Jones LR. Phospholamban: protein structure, mechanism of action, and role in cardiac function. Physiol Rev 1998;78:921–47.
204. MacLennan DH, Kranias EG. Phospholamban: a crucial regulator of cardiac contractility. Nat Rev Mol cell Biol 2003;4:566–77.
205. Lee S-H, Hadipour-Lakmehsari S, Murthy HR, Gibb N, Miyake T, Teng ACT, et al. REEP5 depletion causes sarco-endoplasmic reticulum vacuolization and cardiac functional defects. Nat Commun 2020;11:1–20.
206. Egger M, Niggli E. Regulatory function of Na-Ca exchange in the heart: milestones and outlook. J Membr Biol 1999;168:107–30.
207. Zhihao L, Jingyu N, Lan L, Michael S, Rui G, Xiyun B, et al. SERCA2a: a key protein in the Ca2+cycle of the heart failure. Heart Fail Rev 2020;25:523–35.
208. Eisner D, Caldwell J, Trafford A. Sarcoplasmic reticulum Ca-ATPase and heart failure 20 years later. Circ Res 2013;113:958–61.
209. Morgan JP. Abnormal intracellular modulation of calcium as a major cause of cardiac contractile dysfunction. N Engl J Med 1991;325:625–32.
210. Denniss AL, Dashwood AM, Molenaar P, Beard NA. Sarcoplasmic reticulum calcium mishandling: central tenet in heart failure? Biophys Rev 2020;12:865–78.
211. Lou Q, Janardhan A, Efimov IR. Remodeling of calcium handling in human heart failure. Calcium Signal 2012;1145–74.
212. Nakao K, Minobe W, Roden R, Bristow MR, Leinwand LA. Myosin heavy chain gene expression in human heart failure. J Clin Invest 1997;100:2362–70.
213. Anderson PA, Malouf NN, Oakeley AE, Pagani ED, Allen PD. Troponin T isoform expression in humans. A comparison among normal and failing adult heart, fetal heart, and adult and fetal skeletal muscle. Circ Res 1991;69:1226–33.
214. Wolff MR, Buck SH, Stoker SW, Greaser ML, Mentzer RM. Myofibrillar calcium sensitivity of isometric tension is increased in human dilated cardiomyopathies: role of altered beta-adrenergically mediated protein phosphorylation. J Clin Invest 1996;98:167–76.
215. Smith GL, Eisner DA. Calcium buffering in the heart in health and disease. Circulation 2019;139:2358–71.
216. Skeggs Jr LT, Kahn JR, Shumway NP. The preparation and function of the hypertensin-converting enzyme. J Exp Med 1956;103:295-9.
217. Bernstein KE, Ong FS, Blackwell WLB, Shah KH, Giani JF, Gonzalez-Villalobos RA, et al. A modern understanding of the traditional and nontraditional biological functions of angiotensin-converting enzyme. Pharmacol Rev 2013;65:1–46.
218. Takeda Y, Miyamori I, Yoneda T, Iki K, Hatakeyama H, Blair IA, et al. Production of aldosterone in isolated rat blood vessels. Hypertension 1995;25:170–3.
219. De Mello W, Frohlich ED. Clinical perspectives and fundamental aspects of local cardiovascular and renal renin-angiotensin systems. Front Endocrinol (Lausanne) 2014;5:16. doi: 10.3389/fendo.2014.00016.
220. Bader M, Ganten D. Update on tissue renin–angiotensin systems. J Mol Med 2008;86:615-21.
221. Dzau VJ, Re RN. Evidence for the existence of renin in the heart. Circulation 1987;75:I134-6.
222. Kumar R, Boim MA. Diversity of pathways for intracellular angiotensin II synthesis. Curr Opin Nephrol Hypertens 2009;18:33–9.
223. Davis JO. Freeman RH. Mechanisms regulating renin release. Physiol Rev 1976;56:2–44.
224. Azevedo PS, Polegato BF, Minicucci MF, Paiva SAR, Zornoff LAM. Cardiac remodeling: concepts, clinical impact, pathophysiological mechanisms and pharmacologic treatment. Arq Bras Cardiol 2016;106:62–9.
225. Silva Jr SD, Jara ZP, Peres R, Lima LS, Scavone C, Montezano AC, et al. Temporal changes in cardiac oxidative stress, inflammation and remodeling induced by exercise in hypertension: Role for local angiotensin II reduction. PLoS One 2017;12:e0189535. doi: 10.1371/journal.pone.0189535.
226. Danilov SM, Faerman AI, Printseva OY, Martynov A V, Sakharov IY, Trakht IN. Immunohistochemical study of angiotensin-converting enzyme in human tissues using monoclonal antibodies. Histochemistry 1987;87:487–90.
227. Schunkert H, Dzau VJ, Tang SS, Hirsch AT, Apstein CS, Lorell BH. Increased rat cardiac angiotensin converting enzyme activity and mRNA expression in pressure overload left ventricular hypertrophy. Effects on coronary resistance, contractility, and relaxation. J Clin Invest 1990;86:1913–20.
228. Urata H, Boehm KD, Philip A, Kinoshita A, Gabrovsek J, Bumpus FM, et al. Cellular localization and regional distribution of an angiotensin II-forming chymase in the heart. J Clin Invest 1993; 91:1269–81.
229. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Dra-

zner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. Circulation 2013;128:e147–239.
230. Riegger GA. ACE inhibitors in early stages of heart failure. Circulation 1993;87:117-9.
231. No authors listed. Comparative Study Angiotensin II receptor antagonists and heart failure: angiotensin-converting-enzyme inhibitors remain the first-line option. Prescrire Int 2005;14:180-6.
232. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: The task force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). Eur Heart J 2020;41:407–77.
233. Ward JL, Chou Y, Yuan L, Dorman KS, Mochel JP. Retrospective evaluation of a dose-dependent effect of angiotensin-converting enzyme inhibitors on long-term outcome in dogs with cardiac disease. J Vet Intern Med 2021;35:2102–11.
234. Struthers AD. The clinical pharmacology of angiotensin converting enzyme inhibitors in chronic heart failure. Pharmacol Ther 1992;53:187–97.
235. Kiowski W, Sütsch G, Dössegger L. Clinical benefit of angiotensin-converting enzyme inhibitors in chronic heart failure. J Cardiovasc Pharmacol 1996;27:19–24.
236. Arendse LB, Danser AHJ, Poglitsch M, Touyz RM, Burnett JC, Llorens-Cortes C, et al. Novel therapeutic approaches targeting the renin-angiotensin system and associated peptides in hypertension and heart failure. Pharmacol Rev 2019;71:539–70.
237. Gromotowicz-Poplawska A, Szoka P, Kolodziejczyk P, Kramkowski K, Wojewodzka-Zelezniakowicz M, Chabielska E. New agents modulating the renin-angiotensin-aldosterone system—Will there be a new therapeutic option? Exp Biol Med 2016;241:1888–99.
238. Hebert PR, Foody JM, Hennekens CH. The renin-angiotensin system: the role of inhibitors, blockers, and genetic polymorphisms in the treatment and prevention of heart failure. Curr Vasc Pharmacol 2003;1:33–9.
239. Folkow B, Johansson B, Mellander S. The comparative effects of angiotensin and noradrenaline on consecutive vascular sections. Acta Physiol Scand 1961;53:99–104.
240. Bell L, Madri JA. Influence of the angiotensin system on endothelial and smooth muscle cell migration. Am J Pathol 1990;137:7-12.
241. Timmermans PBMWM, Wong PC, Chiu AT, Herblin WF, Benfield P, Carini DJ, et al. Angiotensin II receptors and angiotensin II receptor antagonists. Pharmacol Rev 1993;45:205–51.
242. Cascieri MA, Bull HG, Mumford RA, Patchett AA, Thornberry NA, Liang T. Carboxyl-terminal tripeptidyl hydrolysis of substance P by purified rabbit lung angiotensin-converting enzyme and the potentiation of substance P activity in vivo by captopril and MK-422. Mol Pharmacol 1984;25:287–93.
243. Dzau VJ. Evolving concepts of the renin-angiotensin system: focus on renal and vascular mechanisms. Am J Hypertens 1988;1:S334-7.
244. Gibbons GH. Autocrine-paracrine factors and vascular remodeling in hypertension. Curr Opin Nephrol Hypertens 1993;2:291–8.
245. Griendling KK, Tsuda T, Berk BC, Alexander RW. Angiotensin II stimulation of vascular smooth muscle. J Cardiovasc Pharmacol 1989;14:S27-33.
246. Bicket DP. Using ACE inhibitors appropriately. Am Fam Physician 2002 Aug 1;66(3):461-8.
247. Anderson TJ. Assessment and treatment of endothelial dysfunction in humans. J Am Coll Cardiol 1999;34:631–8.
248. Parmley WW. Evolution of angiotensin-converting enzyme inhibition in hypertension, heart failure, and vascular protection. Am J Med 1998;105:27S-31S.
249. Kagaya Y, Hajjar RJ, Gwathmey JK, Barry WH, Lorell BH. Long-term angiotensin-converting enzyme inhibition with fosinopril improves depressed responsiveness to Ca2+ in myocytes from aortic-banded rats. Circulation 1996;94:2915–22.
250. Doggrell SA, Hancox JC. Is timing everything? Therapeutic potential of modulators of cardiac Na+ transporters. Expert Opin Investig Drugs 2003;12:1123–42.
251. Sadoshima J, Xu Y, Slayter HS, Izumo S. Autocrine release of angiotensin II mediates stretch-induced hypertrophy of cardiac myocytes in vitro. Cell 1993;75:977–84.
252. Litwin SE, Katz SE, Weinberg EO, Lorell BH, Aurigemma GP, Douglas PS. Serial echocardiographic-Doppler assessment of left ventricular geometry and function in rats with pressure-overload hypertrophy: chronic angiotensin-converting enzyme inhibition attenuates the transition to heart failure. Circulation 1995;91:2642–54.
253. Düsing R. Pharmacological interventions into the renin–angiotensin system with ACE inhibitors and angiotensin II receptor antagonists: effects beyond blood pressure lowering. Ther Adv Cardiovasc Dis 2016;10:151–61.
254. Swedberg K, Eneroth P, Kjekshus J, Wilhelmsen L. Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality. CONSENSUS Trial Study Group. Circulation 1990;82:1730–6.
255. Khattar RS. Effects of ACE-inhibitors and beta-blockers on left ventricular remodeling in chronic heart failure. Minerva Cardioangiol 2003;51:143–54.
256. Strauss MH, Hall AS, Narkiewicz K. The combination of beta-blockers and ACE inhibitors across the spectrum of cardiovascular diseases. Cardiovasc Drugs Ther 2021;1–14.
257. Lim S, Choo EH, Choi IJ, Ihm S-H, Kim H-Y, Ahn Y, et al. Angiotensin receptor blockers as an alternative to angiotensin-converting enzyme inhibitors in patients with acute myocardial infarction undergoing percutaneous coronary intervention. J Korean Med Sci 2019;34:1-13.
258. Ghanem FA, Movahed A. Should angiotensin receptor blockers be added to angiotensin-converting enzyme inhibitors in the treatment of heart failure? Rev Cardiovasc Med 1900;6:206–13.
259. Ferrario CM. Cardiac remodelling and RAS inhibition. Ther Adv Cardiovasc Dis 2016;10:162–71.
260. Pitt B. ACE inhibitors in heart failure: prospects and limitations. Cardiovasc Drugs Ther 1997;11:285–90.
261. Ferguson R, Brunner H, Turini G, Gavras H, Mckinstry

D. A specific orally active inhibitor of angiotensin-converting enzyme in man. Lancet 1977;309:775–8.
262. Gavras H, Brunner HR, Turini GA, Kershaw GR, Tifft CP, Cuttelod S, et al. Antihypertensive effect of the oral angiotensin converting-enzyme inhibitor SQ 14225 in man. N Engl J Med 1978;298:991–5.
263. Sauer WH, Baer JT, Berlin JA, Kimmel SE. Class effect of angiotensin-converting enzyme inhibitors on prevention of myocardial infarction. Am J Cardiol 2004;94:1171–3.
264. White CM. Angiotensin-converting-enzyme inhibition in heart failure or after myocardial infarction. Am J Health Syst Pharm 2000;57:S18–25.
265. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Eur Heart J 2016;37:2129-200.
266. Mielniczuk L, Stevenson LW. Angiotensin-converting enzyme inhibitors and angiotensin II type I receptor blockers in the management of congestive heart failure patients: what have we learned from recent clinical trials? Curr Opin Cardiol 2005;20:250–5.
267. Gremmler B, Kunert M, Schleiting H, Ulbricht LJ. Improvement of cardiac output in patients with severe heart failure by use of ACE-inhibitors combined with the AT1-antagonist eprosartan. Eur J Heart Fail 200;2:183-7.
268. Tai C, Gan T, Zou L, Sun Y, Zhang Y, Chen W, et al. Effect of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on cardiovascular events in patients with heart failure: a meta-analysis of randomized controlled trials. BMC Cardiovasc Disord 2017;17:1–12.
269. Jobs A, Abdin A, de Waha-Thiele S, Eitel I, Thiele H, de Wit C, et al. Angiotensin-converting-enzyme inhibitors in hemodynamic congestion: a meta-analysis of early studies. Clin Res Cardiol 2019;108:1240–8.
270. Cudnoch-Jedrzejewska A, Czarzasta K, Puchalska L, Dobruch J, Borowik O, Pachucki J, et al. Angiotensin converting enzyme inhibition reduces cardiovascular responses to acute stress in myocardially infarcted and chronically stressed rats. Biomed Res Int 2014;2014:1-9.
271. Olivares EL, Costa-e-Sousa RH, Werneck-de-Castro JPS, Pinho-Ribeiro V, Silva MG, Ribeiro KC, et al. Cellular cardiomyoplasty in large myocardial infarction: Can the beneficial effect be enhanced by ACE-inhibitor therapy? Eur J Heart Fail 2007;9:558–67.
272. Hrebenyk MV, Bidovanets LY. Impact of different angiotensin-converting inhibitors on outcomes of post-myocardial infarction patients. Wiad Lek (Warsaw, Pol 1960) 2020;73:555–60.
273. Frigerio M, Roubina E. Drugs for left ventricular remodeling in heart failure. Am J Cardiol 2005;96:10–8.
274. Fukuzawa S, Ozawa S, Inagaki M, Sugioka J, Daimon M, Kushida S. Angiotensin-converting enzyme inhibitor therapy affects myocardial fatty acid metabolism after acute myocardial infarction. J Nucl Cardiol 2000;7:23–8.
275. Rudi W-S, Molitor M, Garlapati V, Finger S, Wild J, Münzel T, et al. ACE inhibition modulates myeloid hematopoiesis after acute myocardial infarction and reduces cardiac and vascular inflammation in ischemic heart failure. Antioxidants 2021;10:396. doi: 10.3390/antiox10030396.
276. Arnold JMO, Yusuf S, Young J, Mathew J, Johnstone D, Avezum A, et al. Prevention of heart failure in patients in the Heart Outcomes Prevention Evaluation (HOPE) study. Circulation 2003;107:1284–90.
277. Garg R, Yusuf S, Bussmann WD, Sleight P, Uprichard A, Massie B, et al. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. JAMA 1995;273:1450–6.
278. Brown, NJ, Vaughan DE. Angiotensin-converting enzyme inhibitors. Circulation 1998;97:1411–20.
279. Van Griensven JT, Schoemaker RC, Cohen AF, Luus HG, Seibert-Grafe M, Röthig H-J. Pharmacokinetics, pharmacodynamics and bioavailability of the ACE inhibitor ramipril. Eur J Clin Pharmacol 1995;47:513–8.
280. Pfeffer MA, Braunwald E, Moyé LA, Basta L, Brown Jr EJ, Cuddy TE, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and Ventricular Enlargement Trial. N Engl J Med 1992;327(10):669–77.
281. Pfeffer JM, Pfeffer MA, Braunwald E. Hemodynamic benefits and prolonged survival with long-term captopril therapy in rats with myocardial infarction and heart failure. Circulation 1987;75:I149-55.
282. ISIS-4 Collaborative Group. Fourth International Study of Infarct Survival: Protocol for a large simple study of the effects of oral mononitrate, of oral captopril, and of intravenous magnesium. Am J Cardiol 1991;68:87–100.
283. Collins R, Peto R, Flather M, Parish S, Sleight P, Conway M, et al. ISIS-4-A randomised factorial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial-infarction. Lancet 1995;345:669–85.
284. Oldroyd KG, Pye MP, Ray SG, Christie J, Ford I, Cobbe SM, et al. Effects of early captopril administration on infarct expansion, left ventricular remodeling and exercise capacity after acute myocardial infarction. Am J Cardiol 1991;68:713–8.
285. Litwin SE, Katz SE, Morgan JP, Douglas PS. Long-term captopril treatment improves diastolic filling more than systolic performance in rats with large myocardial infarction. J Am Coll Cardiol 1996;28:773–81.
286. Martínez LA, Villalobos-Molina R. Early and chronic captopril or losartan therapy reduces infarct size and avoids congestive heart failure after myocardial infarction in rats. Arch Med Res 2003;34:357–61.
287. Moller JE, Dahlström U, Gøtzsche O, Lahiri A, Skagen K, Andersen GS, et al. Effects of losartan and captopril on left ventricular systolic and diastolic function after acute myocardial infarction: results of the optimal trial in myocardial infarction with angiotensin II antagonist losartan (OPTIMAAL) echocardiographic substudy. Am Heart J 2004;147:494–501.
288. Litwin SE, Litwin CM, Raya TE, Warner AL, Goldman S. Contractility and stiffness of noninfarcted myocardium after coronary ligation in rats. Effects of chronic angiotensin converting enzyme inhibition. Circulation 1991;83:1028–37.
289. Schoemaker RG, Debets JM, Struyker-Boudier HAJ, Smits JFM. Delayed but not immediate captopril thera-

py improves cardiac function in conscious rats, following myocardial infarction. J Mol Cell Cardiol 1991;23:187–97.
290. Van Gilst WH, Herre Kingma J, Peels KH, Dambrink J-HE, Sutton MSJ. Which patient benefits from early angiotensin-converting enzyme inhibition after myocardial infarction? Results of one-year serial echocardiographic follow-up from the Captopril and Thrombolysis Study (CATS). J Am Coll Cardiol 1996;28:114–21.
291. Pfeffer MA, McMurray JJ V, Velazquez EJ, Rouleau J-L, Køber L, Maggioni AP, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med 2003;349:1893–906.
292. Liu L. Long-term mortality in patients with myocardial infarction: impact of early treatment with captopril for 4 weeks. Chin Med J 2001;114:115–8.
293. Solomon SD, Skali H, Anavekar NS, Bourgoun M, Barvik S, Ghali JK, et al. Changes in ventricular size and function in patients treated with valsartan, captopril, or both after myocardial infarction. Circulation 2005;111:3411–9.
294. Parlakpinar H, Ozer MK, Acet A. Effects of captopril and angiotensin II receptor blockers (AT1, AT2) on myocardial ischemia–reperfusion induced infarct size. Cytokine 2011;56:688–94.
295. Litwin SE, Morgan JP. Captopril enhances intracellular calcium handling and beta-adrenergic responsiveness of myocardium from rats with postinfarction failure. Circ Res 1992;71:797–807.
296. Shao Q, Ren B, Zarain-Herzberg A, Ganguly PK, Dhalla NS. Captopril treatment improves the sarcoplasmic reticular Ca2+ transport in heart failure due to myocardial infarction. J Mol Cell Cardiol 1999;31:1663–72.
297. Yang G, Xi Z-X, Wan Y, Wang H, Bi G. Changes in circulating and tissue angiotensin II during acute and chronic stress. Neurosignals 1993;2:166–72.
298. Kramer CM, Ferrari VA, Rogers WJ, Theobald TM, Nance ML, Axel L, et al. Angiotensin-converting enzyme inhibition limits dysfunction in adjacent noninfarcted regions during left ventricular remodeling. J Am Coll Cardiol 1996;27:211–7.
299. Butenas ALE, Colburn TD, Baumfalk DR, Ade CJ, Hageman KS, Copp SW, et al. Angiotensin converting enzyme inhibition improves cerebrovascular control during exercise in male rats with heart failure. Respir Physiol Neurobiol 2021;286:103613. doi: 10.1016/j.resp.2020.103613.
300. Araujo IG, Trindade DC, Mecawi AS, Sonoda-Côrtes R, Werneck-de-Castro JP, Costa-e-Sousa RH, et al. Inhibition of brain renin-angiotensin system improves diastolic cardiac function following myocardial infarction in rats. Clin Exp Pharmacol Physiol 2009;36:803–9.
301. Majno G, Joris I. Apoptosis, oncosis, and necrosis. An overview of cell death. Am J Pathol 1995;146:3.
302. Whelan RS, Kaplinskiy V, Kitsis RN. Cell death in the pathogenesis of heart disease: mechanisms and significance. Annu Rev Physiol 2010;72:19–44.
303. Gao X, Liu W, Huang L, Zhang T, Mei Z, Wang X, et al. HSP70 inhibits stress-induced cardiomyocyte apoptosis by competitively binding to FAF1. Cell Stress Chaperones 2015;20:653–61.
304. Pan S, Zhao X, Wang X, Tian X, Wang Y, Fan R, et al. Sfrp1 attenuates TAC-induced cardiac dysfunction by inhibiting Wnt signaling pathway-mediated myocardial apoptosis in mice. Lipids Health Dis 2018;17:1–6.
305. Palomeque J, Delbridge L, Petroff MV. Angiotensin II: a regulator of cardiomyocyte function and survival. Front Biosci 2009;14:5118–33.
306. Zhang Y, Zhang L, Fan X, Yang W, Yu B, Kou J, et al. Captopril attenuates TAC-induced heart failure via inhibiting Wnt3a/β-catenin and Jak2/Stat3 pathways. Biomed Pharmacother 2019;113:108780. doi: 10.1016/j.biopha.2019.108780.
307. de Resende MM, Kauser K, Mill JG. Regulation of cardiac and renal mineralocorticoid receptor expression by captopril following myocardial infarction in rats. Life Sci 2006;78:3066–73.
308. Chen FC, Brozovich F V. Gene expression profiles of vascular smooth muscle show differential expression of mitogen-activated protein kinase pathways during captopril therapy of heart failure. J Vasc Res 2008;45:445–54.
309. Chen FC, Ogut O, Rhee AY, Hoit BD, Brozovich F V. Captopril prevents myosin light chain phosphatase isoform switching to preserve normal cGMP-mediated vasodilatation. J Mol Cell Cardiol 2006;41:488–95.
310. Woodfield JA. Controlled clinical evaluation of enalapril in dogs with heart failure: results of the cooperative veterinary enalapril study group the cove study group. J Vet Intern Med 1995;9:243–52.
311. Cleary JD, Taylor JW. Enalapril: a new angiotensin converting enzyme inhibitor. Drug Intell Clin Pharm 1986;20:177–86.
312. Sharpe DN, Murphy J, Coxon R, Hannan SF. Enalapril in patients with chronic heart failure: a placebo-controlled, randomized, double-blind study. Circulation 1984;70:271–8.
313. Packer M, Califf RM, Konstam MA, Krum H, McMurray JJ, Rouleau J-L, et al. Comparison of omapatrilat and enalapril in patients with chronic heart failure: the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE). Circulation 2002;106:920–6.
314. SOLVD Investigators, Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med 1992;327:685–91.
315. Yusuf S, Pepine CJ, Garces C, Pouleur H, Rousseau M, Salem D, et al. Effect of enalapril on myocardial infarction and unstable angina in patients with low ejection fractions. Lancet 1992;340:1173–8.
316. SOLVD Investigators, Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325:293–302.
317. Swedberg K, Held P, Kjekshus J, Rasmussen K, Rydén L, Wedel H. Effects of the early administration of enalapril on mortality in patients with acute myocardial infarction: results of the cooperative new scandinavian enalapril survival study II (CONSENSUS II). N Engl J Med 1992;327:678–84.
318. Dickstein K, Chang P, Willenheimer R, Haunso S, Remes J, Hall C, et al. Comparison of the effects of losartan and enalapril on clinical status and exercise performance in patients with moderate or severe chronic heart failure. J Am Coll Cardiol 1995;26:438–45.

319. Ooie T, Saikawa T, Hara M, Takakura T, Sato Y, Sakata T. Beneficial effects of long-term treatment with enalapril on cardiac function and heart rate variability in patients with old myocardial infarction. J Card Fail 1999;5:292–9.
320. Pitt B, Reichek N, Willenbrock R, Zannad F, Phillips RA, Roniker B, et al. Effects of eplerenone, enalapril, and eplerenone/enalapril in patients with essential hypertension and left ventricular hypertrophy: the 4E–left ventricular hypertrophy study. Circulation 2003;108:1831–8.
321. Vermes E, Tardif J-C, Bourassa MG, Racine N, Levesque S, White M, et al. Enalapril decreases the incidence of atrial fibrillation in patients with left ventricular dysfunction: insight from the studies of left ventricular dysfunction (SOLVD) trials. Circulation 2003;107:2926–31.
322. De Mello WC, Altieri P. Enalapril, an inhibitor of angiotensin converting enzyme, increases the junctional conductance in isolated heart cell pairs. J Cardiovasc Pharmacol 1991;18:643–6.
323. Onodera H, Matsunaga T, Tamura Y, Maeda N, Higuma T, Sasaki S, et al. Enalapril suppresses ventricular remodeling more effectively than losartan in patients with acute myocardial infarction. Am Heart J 2005;150:689-e11.
324. McKelvie RS, Yusuf S, Pericak D, Avezum A, Burns RJ, Probstfield J, et al. Comparison of candesartan, enalapril, and their combination in congestive heart failure: randomized evaluation of strategies for left ventricular dysfunction (RESOLVD) pilot study: the RESOLVD Pilot Study Investigators. Circulation 1999;100:1056–64.
325. Maia LN, Nicolau JC, Vítola J V, Santos M, Brandi JM, Joaquim MR, et al. Prospective evaluation comparing the effects of enalapril and losartan in left ventricular remodeling after acute myocardial infarction. Am Heart J 2003 Jun;145(6):E21. doi: 10.1016/S0002-8703(03)00109-1.
326. Rastogi S, Sharov VG, Mishra S, Gupta RC, Blackburn B, Belardinelli L, et al. Ranolazine combined with enalapril or metoprolol prevents progressive LV dysfunction and remodeling in dogs with moderate heart failure. Am J Physiol Circ Physiol 2008;295:H2149–55.
327. Funck-Brentano C, van Veldhuisen DJ, van de Ven LL, Follath F, Goulder M, Willenheimer R. CIBIS-III investigators, Influence of order and type of drug (bisoprolol vs. enalapril) on outcome and adverse events in patients with chronic heart failure: a post hoc analysis of the CIBIS-III trial. Eup J Hear Fail 2011;13:765–72.
328. Krum H, Van Veldhuisen DJ, Funck-Brentano C, Vanoli E, Silke B, Erdmann E, et al. Effect on mode of death of heart failure treatment started with bisoprolol followed by Enalapril, compared to the opposite order: results of the randomized CIBIS III trial. Cardiovasc Ther 2011;29:89–98.
329. Consensus Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. N Engl J Med 1987;316:1429–35.
330. Swedberg K, Idanpaan Heikila U, Remes J. CONSENSUS trial study group: Effects of enalapril on mortality in severe congestive heart failure. Results of the cooperative north scandinavian enalapril survival study (CONSENSUS). N Engl J Med 1987;316:1429–35.
331. Ettinger SJ, Benitz AM, Ericsson GF, Cifelli S, Jernigan AD, Longhofer SL, et al. Effects of enalapril maleate on survival of dogs with naturally acquired heart failure. The long-term investigation of veterinary enalapril (LIVE) Study Group. J Am Vet Med Assoc 1998;213:1573–7.
332. Konstam MA, Rousseau MF, Kronenberg MW, Udelson JE, Melin J, Stewart D, et al. Effects of the angiotensin converting enzyme inhibitor enalapril on the long-term progression of left ventricular dysfunction in patients with heart failure. SOLVD Investigators. Circulation 1992;86:431–8.
333. Konstam MA, Kronenberg MW, Rousseau MF, Udelson JE, Melin J, Stewart D, et al. Effects of the angiotensin converting enzyme inhibitor enalapril on the long-term progression of left ventricular dilatation in patients with asymptomatic systolic dysfunction. SOLVD (Studies of Left Ventricular Dysfunction) Investigators. Circulation 1993;88:2277–83.
334. Swedberg K, Kjekshus J, Group CTS. Effects of enalapril on mortality in severe congestive heart failure: results of the cooperative north Scandinavian enalapril survival study (CONSENSUS). Am J Cardiol 1988;62:60A-66A.
335. Kiss K, Fekete V, Pálóczi J, Sárközy M, Murlasits Z, Pipis J, et al. Renin-angiotensin-aldosterone signaling inhibitors-losartan, enalapril, and cardosten-prevent infarction-induced heart failure development in rats. Altern Ther Health Med 2016;22:10-7.
336. Saruta T, Arakawa K, Imura O. A multicenter comparative study of imidapril and enalapril on usefulness, and incidence of cough. J New Remedies Clin 1998;47:249–82.
337. Fröhlich H, Henning F, Täger T, Schellberg D, Grundtvig M, Goode K, et al. Comparative effectiveness of enalapril, lisinopril, and ramipril in the treatment of patients with chronic heart failure: a propensity score-matched cohort study. Eur Heart J Cardiovasc Pharmacother 2018;4:82–92.
338. Guo X, Chapman D, Dhalla NS. Partial prevention of changes in SR gene expression in congestive heart failure due to myocardial infarction by enalapril or losartan. Mol Cell Biochem 2003;254:163–72.
339. Meisel S, Shamiss A, Rosenthal T. Clinical pharmacokinetics of ramipril. Clin Pharmacokinet 1994;26:7–15.
340. Beermann B, Nyquist O, Hoglund C, Jacobsson K-A, Näslund U, Jensen-Urstad M. Acute haemodynamic effects and pharmacokinetics of ramipril in patients with heart failure. Eur J Clin Pharmacol 1993;45:241–6.
341. Vuong AD, Annis LG. Ramipril for the prevention and treatment of cardiovascular disease. Ann Pharmacother 2003;37:412–9.
342. Warner GT, Perry CM. Ramipril. Drugs 2002;62:1381–405.
343. Todd PA, Benfield P. Ramipril. Drugs 1990;39:110–35.
344. Yusuf S, Sleight P, Pogue J ft, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med 2000;342:145–53.
345. Dagenais GR, Yusuf S, Bourassa MG, Yi Q, Bosch J, Lonn EM, et al. Effects of ramipril on coronary events in high-risk persons: results of the heart outcomes prevention evaluation study. Circulation 2001;104: 522–6.

346. Yusuf, S., Sleight, P., Pogue, J., Bosch, J., Davies, R., Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med 2000;342:145–53.
347. Kjøller-Hansen L, Steffensen R, Grande P. Beneficial effects of ramipril on left ventricular end-diastolic and end-systolic volume indexes after uncomplicated invasive revascularization are associated with a reduction in cardiac events in patients with moderately impaired left ventricular functio. J Am Coll Cardiol 2001;37:1214–20.
348. Borghi C, Omboni S, Novo S, Vinereanu D, Ambrosio G, Ambrosioni E. Efficacy and safety of zofenopril versus ramipril in the treatment of myocardial infarction and heart failure: a review of the published and unpublished data of the randomized double-blind SMILE-4 study. Adv Ther 2018;35:604–18.
349. Borghi C, Omboni S, Cicero AFG, Bacchelli S, Degli Esposti D, Novo S, et al. Randomised comparison of zofenopril and ramipril plus acetylsalicylic acid in postmyocardial infarction patients with left ventricular systolic dysfunction: a post hoc analysis of the SMILE-4 Study in patients according to levels of left ventricular eject. Open Heart 2015 Aug 3;2(1):e000195. doi: 10.1136/openhrt-2014-000195.
350. Teo KK, Mitchell LB, Pogue J, Bosch J, Dagenais G, Yusuf S. Effect of ramipril in reducing sudden deaths and nonfatal cardiac arrests in high-risk individuals without heart failure or left ventricular dysfunction. Circulation 2004;110:1413–7.
351. Lonn E, Roccaforte R, Yi Q, Dagenais G, Sleight P, Bosch J, et al. Effect of long-term therapy with ramipril in high-risk women. J Am Coll Cardiol 2002;40:693–702.
352. Kongstad-Rasmussen O, Blomstrand P, Broqvist M, Dahlström U, Wranne B. Treatment with ramipril improves systolic function even in patients with mild systolic dysfunction and symptoms of heart failure after acute myocardial infarction. Clin Cardiol 1998;21:807–11.
353. Spargias KS, Lindsay SJ, Hall AS, Cowan JC, Ball SG. Ramipril reduces QT dispersion in patients with acute myocardial infarction and heart failure. Am J Cardiol 1999;83:969–71.
354. Wei Q, Liu H, Liu M, Yang C, Yang J, Liu Z, et al. Ramipril attenuates left ventricular remodeling by regulating the expression of activin A-follistatin in a rat model of heart failure. Sci Rep 2016;6:1–10.
355. Cacciapuoti F, Capasso A, Mirra G, De Nicola A, Minicucci F, Gentile S. Prevention of left ventricular hypertrophy by ACE-inhibitor, ramipril in comparison with calcium-channel antagonist, felodipine. Int J Cardiol 1998;63:175–8.
356. Salehian O, Healey J, Stambler B, Alnemer K, Almerri K, Grover J, et al. Impact of ramipril on the incidence of atrial fibrillation: results of the Heart Outcomes Prevention Evaluation study. Am Heart J 2007;154:448–53.
357. Willenheimer R, Rydberg E, Oberg L, Juul-Möller S, Erhardt L. ACE inhibition with ramipril improves left ventricular function at rest and post exercise in patients with stable ischaemic heart disease and preserved left ventricular systolic function. Eur Heart J 1999;20:1647–56.
358. Tao Z, Huang Y, Xia Q, Xu Q-W. Combined effects of ramipril and angiotensin II receptor blocker TCV116 on rat congestive heart failure after myocardial infarction. Chin Med J (Engl) 2005;118:146–54.
359. Santi RGL, Valeff EC, Duymovich CR, Mazziotta D, Mijailovsky NE, Filippa GC, et al. Effects of an angiotensin-converting enzyme inhibitor (ramipril) on inflammatory markers in secondary prevention patients: RAICES Study. Coron Artery Dis 2005;16:423–9.
360. Amann K, Gassmann P, Buzello M, Orth SR, Törnig J, Gross ML, et al. Effects of ACE inhibition and bradykinin antagonism on cardiovascular changes in uremic rats. Kidney Int 2000;58:153–61.
361. Crozier IG, Ikram H, Nicholls MG, Jans S. Global and regional hemodynamic effects of ramipril in congestive heart failure. J Cardiovasc Pharmacol 1989;14:688–93.
362. Schölkens BA, Martorana PA, Göbel H, Gehring D. Cardiovascular effects of the converting enzyme inhibitor ramipril (HOE 498) in anesthetized dogs with acute ischemic left ventricular failure. Clin Exp Hypertens Part A Theory Pract 1986;8:1033–48.
363. Kjøller-Hansen L, Steffensen R, Grande P. The angiotensin converting enzyme inhibition post revascularization study (APRES): Effects of ramipril in patients with reduced left ventricular function. rationale, design, methods, baseline characteristics and first-year experience. Scand Cardiovasc J 1998;32:225–32.
364. Spargias KS, Ball SG. Clinical implications for the acute infarction ramipril efficacy extension (AIREX) Study. Int J Clin Pract Suppl 1998;94:32–6.
365. Study TAIREA. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. Lancet 1993;342:821–8.
366. Anderson VR, Perry CM, Robinson DM. Ramipril. Am J Cardiovasc Drugs 2006;6:417–32.
367. Mochel JP, Peyrou M, Fink M, Strehlau G, Mohamed R, Giraudel JM, et al. Capturing the dynamics of systemic renin-angiotensin-aldosterone system (RAAS) peptides heightens the understanding of the effect of benazepril in dogs. J Vet Pharmacol Ther 2013;36:174–80.
368. The BENCH Study Group. The effect of benazepril on survival times and clinical signs of dogs with congestive heart failure: Results of a multicenter, prospective, randomized, double-blinded, placebo-controlled, long-term clinical trial. J Vet Cardiol 1999;1:7–18.
369. Coffman M, Guillot E, Blondel T, Garelli-Paar C, Feng S, Heartsill S, et al. Clinical efficacy of a benazepril and spironolactone combination in dogs with congestive heart failure due to myxomatous mitral valve disease: The benazepril spironolactone study (BESST). J Vet Intern Med 2021;35:1673-87.
370. Fox KM. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, doubleblind, placebo-controlled, multicentre trial (the EUROPA study). Lancet 2003;362:782–8.
371. Ferrari R. Angiotensin-converting enzyme inhibition in cardiovascular disease: Evidence with perindopril. Expert Rev Cardiovasc Ther 2005;3:15–29.
372. Fox K. Contribution of perindopril to cardiology: 20 years of success. Eur Hear J Suppl 2007;9: E10–9.
373. Ferrari R, Pasanisi G, Notarstefano P, Campo G, Gardini E, Ceconi C. Specific properties and effect of perindo-

pril in controlling the renin–angiotensin system. Am J Hypertens 2005;18:S142-54.
374. Dahlöf B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian cardiac outcomes trial-blood pressure lowering arm (ASCOT-BPLA): a multicentre randomised controlled trial. Lancet 2005;366:895–906.
375. Bertrand ME, Ferrari R, Remme WJ, Simoons ML, Fox KM. Perindopril and β-blocker for the prevention of cardiac events and mortality in stable coronary artery disease patients: A European trial on reduction of cardiac events with perindopril in stable coronary artery disease (EUROPA) subanalysis. Am Heart J 2015;170:1092–8.
376. Brugts JJ, Bertrand M, Remme W, Ferrari R, Fox K, MacMahon S, et al. The treatment effect of an ACE-inhibitor based regimen with perindopril in relation to beta-blocker use in 29,463 patients with vascular disease: a combined analysis of individual data of ADVANCE, EUROPA and PROGRESS trials. Cardiovasc Drugs Ther 2017;31:391–400.
377. DeForrest JM, Waldron TL, Krapcho J, Turk C, Rubin B, Powell JR, et al. Preclinical pharmacology of zofenopril, an inhibitor of angiotensin I converting enzyme. J Cardiovasc Pharmacol 1989;13:887–94.
378. Borghi C, Omboni S. Angiotensin-converting enzyme inhibition: beyond blood pressure control—The role of zofenopril. Adv Ther 2020;1–18.
379. Borghi C, Bacchelli S, Degli Esposti D. Long-term clinical experience with zofenopril. Expert Rev Cardiovasc Ther 2012;10:973–82.
380. Evangelista S, Manzini S. Antioxidant and cardioprotective properties of the sulphydryl angiotensin-converting enzyme inhibitor zofenopril. J Int Med Res 2005;33:42–54.
381. Donnarumma E, Ali MJ, Rushing AM, Scarborough AL, Bradley JM, Organ CL, et al. Zofenopril protects against myocardial ischemia–reperfusion injury by increasing nitric oxide and hydrogen sulfide bioavailability. J Am Heart Assoc 2016;5:e003531. doi: 10.1161/JAHA.116.003531.
382. Borghi C, Bacchelli S, Degli Esposti D, Ambrosioni E. A review of the angiotensin-converting enzyme inhibitor, zofenopril, in the treatment of cardiovascular diseases. Expert Opin Pharmacother 2004;5:1965–77.
383. Borghi C, Cosentino ER, Rinaldi ER, Cicero AFG. Effect of zofenopril and ramipril on cardiovascular mortality in patients with chronic heart failure. Am J Cardiol 2013;112:90–3.
384. Carnicelli V, Frascarelli S, Zucchi R. Effect of acute and chronic zofenopril administration on cardiac gene expression. Mol Cell Biochem 2011;352:301–7.
385. Omboni S, Borghi C. Zofenopril and incidence of cough: a review of published and unpublished data. Ther Clin Risk Manag 2011;7:459-71.
386. Shao Q, Takeda N, Temsah R, Dhalla KS, Dhalla NS. Prevention of hemodynamic changes due to myocardial infarction by early treatment of rats with imidapril. Cardiovasc Pathobiol 1996;1:180–6.
387. Sabharwal NK, Swinburn J, Lahiri A, Senior R. Effect of imidapril and nifedipine on left ventricular hypertrophy in untreated hypertension. Clin Drug Investig 2005;25:367–75.
388. Kitaoka H, Takata J, Hitomi N, Furuno T, Seo H, Chikamori T, et al. Effect of angiotensin-converting enzyme inhibitor (enalapril or imidapril) on ventilation during exercise in patients with chronic heart failure secondary to idiopathic dilated cardiomyopathy. Am J Cardiol 2000;85:658–60.
389. Yoshitomi Y, Kojima S, Yano M, Sugi T, Matsumoto Y, Kuramochi M. Long-term effects of bisoprolol compared with imidapril on left ventricular remodeling after reperfusion in acute myocardial infarction: An angiographic study in patients with maintained vessel patency. Am Heart J 2000;140:5A-11A.
390. Zalvidea S, Andre L, Loyer X, Cassan C, Sainte-Marie Y, Thireau J, et al. ACE inhibition prevents diastolic Ca2+ overload and loss of myofilament Ca2+ sensitivity after myocardial infarction. Curr Mol Med 2012;12:206–17.
391. Wang J, Liu X, Sentex E, Takeda N, Dhalla NS. Increased expression of protein kinase C isoforms in heart failure due to myocardial infarction. Am J Physiol Circ Physiol 2003;284:H2277–87.
392. Ren B, Lukas A, Shao Q, Guo M, Takeda N, Aitken RM, et al. Electrocardiographic changes and mortality due to myocardial infarction in rats with or without imidapril treatment. J Cardiovasc Pharmacol Ther 1998;3:11–21.
393. Ren B, Shao Q, Ganguly PK, Tappia PS, Takeda N, Dhalla NS. Influence of long-term treatment of imidapril on mortality, cardiac function, and gene expression in congestive heart failure due to myocardial infarction. Can J Physiol Pharmacol 2004;82:1118–27.
394. Shao Q, Ren B, Saini HK, Netticadan T, Takeda N, Dhalla NS. Sarcoplasmic reticulum Ca2+ transport and gene expression in congestive heart failure are modified by imidapril treatment. Am J Physiol Circ Physiol 2005;288:H1674–82.
395. Hunyady L, Catt KJ. Pleiotropic AT1 receptor signaling pathways mediating physiological and pathogenic actions of angiotensin II. Mol Endocrinol 2006;20:953–70.
396. Wu CH, Mohammadmoradi S, Chen JZ, Sawada H, Daugherty A, Lu HS. Renin-angiotensin system and cardiovascular functions. Arterioscler Thromb Vasc Biol 2018;38:E108–16.
397. Dixon IM, Ju H, Jassal DS, Peterson DJ. Effect of ramipril and losartan on collagen expression in right and left heart after myocardial infarction. Mol Cell Biochem 1996;165:31–45.
398. Dixon IM, Lee S-L, Dhalla NS. Nitrendipine binding in congestive heart failure due to myocardial infarction. Circ Res 1990;66:782–8.
399. Frank KF, Bölck B, Brixius K, Kranias EG, Schwinger RHG. Modulation of SERCA: implications for the failing human heart. Basic Res Cardiol 2002;97:I72–8.
400. Prestle J, Quinn FR, Smith GL. Ca2+-handling proteins and heart failure: novel molecular targets? Curr Med Chem 2003;10:967–81.
401. Huang H, Joseph LC, Gurin MI, Thorp EB, Morrow JP. Extracellular signal-regulated kinase activation during cardiac hypertrophy reduces sarcoplasmic/endoplasmic reticulum calcium ATPase 2 (SERCA2) transcription. J Mol Cell Cardiol 2014;75:58–63.
402. Movsesian MA, Schwinger RHG. Calcium sequestration by the sarcoplasmic reticulum in heart failure. Cardiovasc Res 1998;37:352–9.

403. Awwad ZM, El-Ganainy SO, ElMallah AI, Khattab MM, El-Khatib AS. Telmisartan and captopril ameliorate pregabalin-induced heart failure in rats. Toxicology 2019;428:152310. doi: 10.1016/j.tox.2019.152310.
404. Yoshiyama M, Takeuchi K, Hanatani A, Shimada T, Takemoto Y, Shimizu N, et al. Effect of cilazapril on ventricular remodeling assessed by Doppler-echocardiographic assessment and cardiac gene expression. Cardiovasc drugs Ther 1998;12:57–70.
405. Yamaguchi F, Sanbe A, Takeo S. Effects of long-term treatment with trandolapril on sarcoplasmic reticulum function of cardiac muscle in rats with chronic heart failure following myocardial infarction. Br J Pharmacol 1998;123:326–34.
406. Sethi R, Shao Q, Takeda N, Dhalla NS. Attenuation of changes in Gi-proteins and adenylyl cyclase in heart failure by an ACE inhibitor, imidapril. J Cell Mol Med 2003;7:277–86.