

Potential of endothelin-1 and vasopressin antagonists for the treatment of congestive heart failure

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Abstract It is now becoming clear that two major systems namely the sympathetic nervous system and the renin-angiotensin system are activated in response to ischemic injury; these result in the elevation of plasma catecholamines and angiotensin II during the development of myocardial infarction as well as congestive heart failure. Although plasma levels of several other hormones including aldosterone, endothelin, vasopressin, natriuretic peptides, growth factors and inflammatory cytokines are also increased in heart failure, their relationship with changes in catecholamine and/or angiotensin levels as well as their significance for the induction of congestive heart failure are poorly understood. In this article we have examined the evidence regarding the role of endothelin and vasopressin in the pathogenesis of cardiac hypertrophy and congestive heart failure in addition to evaluating the significance of their antagonism by using their receptor blockade for treatment of congestive heart failure. Endothelin appears to maintain blood pressure by its vasoconstricting action whereas vasopressin primarily produces similar effect by retention of body fluid. Myocardium is also known to express both ET-A and ET-B receptors in addition to V_1 and V_2 receptors for vasopressin, which have been shown to induce cardiac remodeling. Out of various ET-1 receptor antagonists, which are available, a non-selective endothelin receptor antagonist, bosentan, as well as an ET-A receptor antagonist, BQ-123, seem most promising for the treatment of congestive heart failure. Likewise, vasopressin

antagonists such as a non-selective antagonist, conivaptan, as well as V_2 selective antagonist, tolvaptan, may prove highly valuable for the therapy of this condition. Since most of the existing interventions are helpful in treating patients with congestive heart failure only partially, there appears to be a real challenge for developing some combination therapy for the treatment of congestive heart failure.

Keywords Endothelin-1 · Vasopressin · Endothelin antagonists · Vasopressin antagonists · Congestive heart failure

Introduction

In the past two decades, congestive heart failure has emerged as a major public health hazard with grave implications. According to the Framingham Heart Study, the lifetime risk of congestive heart failure is 1 in 5 for both men and women [1]. Currently, 2.5% of the entire adult American population, approximately 5.3 million men and women, suffer from congestive heart failure and the total burden of heart failure in the United States is estimated to be \$35 billion to \$60 billion per year [2]. Even after devoting such high resources on the treatment of heart failure, the average rate of 5-year survival is about 50% [3]. Evidence based medicine has resulted in the acceptance of angiotensin converting enzyme inhibitors, angiotensin-receptor blockers, diuretics, β -adrenoreceptor blockers, digitalis glycosides and inotropic agents as the standard treatment by the American Heart Association [4]. These modalities have however failed to reduce the mortality and produce adequate results, as the average survival period from the time of diagnosis of congestive heart failure is

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about 1.7 years in men and 3.2 years in women [5]. Therefore, there is an urgent need to discover new modalities of treatment for heart failure but for this purpose it is important to understand the pathogenesis of ventricular remodeling, which is considered to be responsible for causing congestive heart failure.

Congestive heart failure and the activation of neurohumoral system

Congestive heart failure is a syndrome caused by inability of the heart to pump sufficient blood for the perfusion of various organs in the body. Despite sufficient filling of chambers of the heart, cardiac output decreases and the heart is unable to meet the metabolic needs of different organs and thus results in the activation of neurohumoral systems as well as development of apoptosis and adaptive changes in the myocardium at the cellular and molecular levels. Alterations in the ventricular size, shape, and function that occur over time in response to an insult on the heart are collectively called cardiac remodeling. The insult preceding the left ventricular remodeling could be myocardial infarction, valvular heart disease, uncontrolled hypertension, myocarditis, congenital heart disease, genetic mutation and hyperthyroidism. Earlier it was thought that an increase in body fluid and hemodynamic changes are responsible for congestive heart failure, but now the importance of systemic reactions such as neurohumoral activation and cardiomyocyte subcellular alterations are being appreciated. Neurohumoral systems are involved in maintaining the circulatory hemostasis by modulating various vascular reactions or by increasing inotropic and chronotropic responses of the failing myocardium. Various mediators, which either dilate or constrict blood vessels regulate the vascular tension in order to ensure blood flow through active organs while maintaining adequate perfusion pressure by vasoconstriction [6]. These mechanisms which are life saving in acute situations like myocardial infarction continue beyond the compensatory phase and contribute to ventricular remodeling as well as progression to congestive heart failure. Although the exact sequence of events following myocardial infarction is not known, the changes taking place at the cellular level in the myocardium and the activation of neurohormonal systems are discussed in the following sections.

Blockade of coronary flow by thrombosis, atherosclerosis or coronary spasm produces myocardial cell damage associated with a wide variety of arrhythmias. The acutely injured area of the heart becomes the site of myocardial infarct and sets in several mechanisms in motion leading to the activation of different neuroendocrine systems and restructuring of the viable myocardium. Within hours of an

acute myocardial infarction, different collagenases known as matrix metalloproteinases (MMPs) are activated and cause disruption of the collagen network in the extracellular matrix which is responsible for holding cardiomyocytes together [7]. The disruption of the collagen network results in slipping of cardiomyocytes and loss of their parallel alignment. This process results in thinning and dilatation of the myocardium at the infarct site. The dilatation of the cardiac muscle causes an increase in wall stress of the myocardium, which serves as a stimulus for cardiac hypertrophy in the non-infarcted portion of the ventricle [8].

After acute myocardial infarction, stimuli such as pain, anxiety and reflexes are carried through the afferent nerves from the ischemic myocardial area to the brain and cause activation of the sympathetic nervous system and release of catecholamines [9–11]. Stimulation of the sympathetic nervous system during myocardial infarction releases catecholamines from different organs including local release of catecholamines from the cardiac sympathetic nerve endings; however, contribution of the heart to the total norepinephrine release for raising the plasma level of catecholamines is about 3% [12]. It has been documented that there is a persistent sympathetic hyperactivity in patients after an acute myocardial infarction, which could last for 6 months; this hyperactivity was greater in patients with lower left ventricular ejection fraction [13]. Acute effects of the sympathetic activation include vasoconstriction, positive inotropy, positive chronotropy, and enhanced ventricular relaxation (lusitropism) [14]. Chronic effects of sympathetic stimulation result in intracellular calcium overload, ventricular hypertrophy and fibrosis [15, 16] and thus are considered to produce maladaptive changes in the heart during the development of myocardial infarction. These effects of sympathetic stimulation are mediated through beta-adrenoreceptors, which result in the activation of protein kinase A, as well as alpha receptors, which result in the activation of protein kinase C. These subcellular alterations in the heart lead to the activation of MAP kinase and expression of proto-oncogenes, transcription factor production and gene expression changes, cardiac hypertrophy and ventricular remodeling subsequent to the occurrence of myocardial infarction. Prolonged sympathetic activation is considered to result in heart failure by increasing metabolic demand of the infarcted heart or by decreasing myocardial oxygen supply and is also involved in the stimulation of renin release from the juxtaglomerular cells of kidney, which leads to the activation of renin-angiotensin-aldosterone system [17].

Depressed cardiac output due to loss of myocardium during the development of myocardial infarction is also considered to release renin from the kidney and promote the formation of angiotensin II. This peptide then binds

with type I angiotensin receptors and results in the activation of protein kinase C leading to growth of cardiomyocytes as a compensatory mechanism at initial stages [18, 19]. However, over a prolonged period angiotensin II has cytotoxic effects on cardiomyocytes causing necrosis, fibrosis and disruption of myocardial integrity. It also causes increase in coronary artery permeability resulting in diffusion of growth factors into the myocardial interstitium, which are responsible for enhanced collagen proliferation in the interstitium [20]. Such events lead to an increased myocardial stiffness and ventricular filling defects. It has been documented that the local production of angiotensin II in the heart is increased in cardiac hypertrophy as well as post myocardial infarction and contributes to ventricular remodeling [21]. Angiotensin II is also responsible for aldosterone secretion from the suprarenal glands; aldosterone not only causes sodium and water retention, which is detrimental in heart failure, but also exerts direct effects on heart function by inducing cardiac fibrosis because of the presence of mineralocorticoid receptors in the heart [22]. It is known that aldosterone is produced by heart tissue and is increased in congestive heart failure as is the activity of angiotensin converting enzyme (ACE) [23]. Aldosterone is involved in collagen deposition in the extracellular matrix post myocardial infarction, which can be prevented by spironolactone [24]. It also causes upregulation of ACE mRNA expression in heart and thus initiates a vicious circle resulting in ventricular remodeling [25].

Although plasma levels of several other hormones including endothelin, vasopressin, different cytokines, various peptides and growth factors are elevated in congestive heart failure due to myocardial infarction, the temporal relationship of their changes with activation of the sympathetic and renin angiotensin systems is poorly understood. Endothelin is secreted from the vascular endothelial layer in response to hypoxia, shear stress and other changes occurring as a consequence of myocardial infarction [26, 27]; its secretion is enhanced by angiotensin II [28]. Endothelin together with angiotensin and norepinephrine stimulate expression of different proteins and cause cardiomyocyte hypertrophy [29]. Endothelin has also been shown to cause increase in the activity of endothelial ACE, as well as secretion of aldosterone and thus has been proposed to play a major role in ventricular remodeling [30, 31]. Endothelin-1, angiotensin II, tumor necrosis factor- α (TNF- α) and catecholamines are probably associated with increase in MMPs [32]. There is inter-dependency between the endogenous endothelin and the renin-angiotensin system as angiotensin II increases tissue endothelin and induces vascular hypertrophy [28] while endogenous endothelin contributes to the cardiovascular and renal effects of angiotensin II [33]. Both endothelin and

angiotensin II activate the Na^+/H^+ exchange and couple ventricular stretch to cardiac hypertrophy [34].

In addition to endothelin, it should be noted that vasopressin secretion also takes place during the development of myocardial infarction and congestive heart failure. Vasopressin is released from the pituitary gland mainly through baroreceptors in the left atrium, aortic arch and carotid sinus in response to underfilling [35]. Vasopressin not only causes water retention but also causes increase in the protein synthesis and hypertrophy of cardiomyocytes [36]. It also causes increase in the collagen deposition and thus contributes to the ventricular remodeling [37]. Various studies have also shown the role of inflammatory cytokines like TNF- α and IL-1 in the pathogenesis of heart failure as these were observed to induce contractile dysfunction, ventricular dilation, apoptosis and cardiac cell hypertrophy [38, 39]. The circulating levels of two natriuretic hormones namely atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) have been shown to be elevated in heart failure. Both of these hormones are secreted by the heart in response to wall stretch and are also released by different agonists like catecholamines, endothelin, vasopressin and angiotensin II [40]. However, these hormones have a protective role in heart failure and cause smooth muscle relaxation and vasodilatation and they counteract the effects of sympathetic nervous system [41]. Thus there are a wide variety of hormones, the circulating levels of which are elevated during the development of congestive heart failure due to myocardial infarction. Some of these hormones, which are vasoconstrictor and produce cardiac hypertrophy, appear to be beneficial at initial stages of myocardial infarction but become harmful at chronic stages and thus participate in inducing heart dysfunction. On the other hand, hormones, peptides and growth factors, which do not produce vasoconstriction, are considered to play a compensatory role for the heart to adapt against the insult of myocardial infarction. In view of the vast information in the literature on several of these hormones such as angiotensin II, catecholamines and aldosterone in congestive heart failure and relatively scattered information available for other hormones including endothelin and vasopressin, we have chosen to discuss the role of endothelin and vasopressin in the development of heart failure in this article. Furthermore, we have attempted to analyze the evidence for the potential use of endothelin antagonists and vasopressin antagonists for the therapy of congestive heart failure.

Endothelin-1 and mode of its action

It is now well-known that the endothelium is not just a barrier between the blood and the vascular wall but it

releases a potent constricting factor [42]. After the discovery of endothelin-1 (ET-1, the constricting factor) in 1988 [43], it was found that it plays a major role in the pathogenesis of various cardiovascular diseases [44]. This led several investigators to work on the methods to control the endothelin activity and in fact pharmacological blockade of endothelin synthesis showed a great promise in this regard [45]. Blocking the endothelin receptors was also attempted to control the endothelin activity and this resulted in Bosentan becoming the first ET receptor antagonist to find clinical use [46]. But after the initial success of the ET receptor antagonist, results with other agents to attenuate the increased endothelin activity in congestive heart failure were not encouraging [47].

Endothelins are a family of three 21-amino acid peptides (ET-1, ET-2 and ET-3) out of which ET-1 is the principal cardiovascular isoform. Transcription of a gene on chromosome 6 generates mRNA encoding the 212 amino-acid peptide, prepro ET-1, which is stripped of its signal sequence and secreted into the cytoplasm as pro ET-1 [48]. Pro ET-1 is further cleaved by furin like endopeptidase to the 38 amino-acid precursor molecule big ET-1, which circulates in plasma at low concentrations [43]. Removal of a further 17 COOH terminal residues results in the formation of the 21 amino-acid ET-1 [49]; this reaction is mediated by a family of membrane bound zinc metalloproteases, from the neprilysin superfamily, termed endothelin converting enzyme (ECE) [50]. In addition to these proteases, other enzymes such as non-ECE metalloproteinase contribute to the final processing step [51]; this was evident in mice lacking both ECE-1 and ECE-2 where the level of mature endothelin peptides is reduced by one-third [52]. ET-1 is produced by vascular endothelial and smooth muscle cells as well as airway epithelial cells, macrophages, fibroblasts, cardiac myocytes, posterior pituitary, kidney and pancreatic islet [48, 53–55]. ET-1 is a unique peptide as it has a dual secretory pathway. It is continuously released from vascular endothelial cells by a constitutive pathway, thereby maintaining the endogenous vascular tone [56]. It is also secreted by the endothelial cell-specific storage granules in response to external pathophysiological stimuli, producing vasoconstriction [57]. The induction of prepro ET-1 mRNA in endothelial cells is augmented by several agents, such as thrombin, calcium ionophore, transforming growth factor, cytokines and shear stress [26, 27]. Generation of ET-1 is also increased by vasoactive hormones, hypoxia, lipoproteins, endotoxin, free radicals and cyclosporin. ET-1 synthesis is inhibited by nitric oxide, nitrovasodilators, natriuretic peptides, heparin and prostaglandins [55]. In this regard, it is pointed out that nitric oxide, which is also produced in the endothelium along with endothelin, may represent one of the

endogenous mechanism for the control of endothelin activity during the development of myocardial infarction.

In humans, two G protein coupled endothelin receptors (ET-A and ET-B) have been identified, which have seven hydrophobic membrane-spanning domains [58]. ET-A receptor binds ET-1 and ET-2 with greater affinity than that for ET-3 whereas ET-B receptor binds all three isoforms with similar affinity [59]. The ET-A is the primary vasoconstrictor and growth promoting receptor, while the ET-B receptor inhibits vasoconstriction and cell growth. ET-B also functions as a clearance receptor, which is particularly important in the lung, which clears about 80% of circulating ET-1 [60]. These receptors are expressed in a variety of human tissues. For example vascular smooth muscle cells express both ET-A and ET-B while the endothelial cells typically express only ET-B. Furthermore, in the human heart, cardiomyocytes and fibroblasts predominantly express ET-A, whereas the cardiac conducting tissue, express ET-B [61]. Electron microscopic autoradiography of ET-A and ET-B receptors in human coronary arteries has revealed that both receptors are located on the cell membrane and plasmalemmal vesicles of vascular smooth cells but neither receptor was observed on endothelial cell [62]. Non ET-A/ET-B receptors for ET-1 are also present [63]. There are many factors, which regulate the expression of endothelin receptors; ischemia and cyclosporin increase the number of endothelin receptors, angiotensin II, phorbol esters and endothelin-1 decrease the number of these receptors [64–67].

Endothelin-1 is considered to play a major role in pathogenesis of cardiovascular disease by its direct effects on cardiomyocytes and vascular smooth muscle cells. The mechanism of action of endothelin include interaction with endothelin receptors on the cell surface, activation of phospholipase C through G-proteins, and increase in intracellular concentration of Ca^{2+} through the increase in phosphoinositol turnover. Different endothelins were observed to exert no effects on the sarcolemmal Na^+/K^+ ATPase, Na^+-Ca^{2+} exchange and Ca^{2+} -pump systems nor on the sarcoplasmic reticular Ca^{2+} pump and myofibrillar ATPase activities in rat heart [68]. However, endothelins have two major effects on cardiomyocytes; they affect the contractile properties and they stimulate the myocyte growth and myofibrillogenesis, thereby causing cardiac hypertrophy. These changes are produced by the modulation of the intracellular signaling pathways because ET-1 binds to the ET-A receptor on the cell surface and stimulates hydrolysis of phosphatidylinositol 4',5'-biphosphate to diacylglycerol and inositol 1,4,5-triphosphate (IP_3). Diacylglycerol causes the translocation of the delta and epsilon isoforms of protein kinase C to the membrane and results in activation of the small G-protein Ras and of the extracellular signal regulated kinase 1/2 (ERK1/2) cascade. As the signals

originating from the ET-A receptors are transmitted through these protein kinase pathways, other signaling molecules become phosphorylated and change their biological activity. These molecules include nuclear transcription factors, protein kinases, and ion channels and are responsible for the effects of endothelins on cardiomyocytes [69]. The signal transduction pathway for endothelin action on cardiomyocytes leading to the development of cardiac hypertrophy is given in a schematic sketch (Fig. 1).

The activity of endothelin-1 is normally inhibited by endothelin receptor antagonists and there are three categories of antagonists depending on their relative affinity for the endothelin receptor, ET-A selective, ET-B selective, and mixed ET-A/ET-B antagonists. Among the mixed or non-selective antagonists are Bosentan, Tezosentan and Enrasentan. It is important to keep in consideration that these antagonist do not have an equal affinity for both receptors. The difference between ET-A selective and the non-selective antagonist is that selective antagonists display more than 100 times selectivity for ET-A receptor than that by the non-selective antagonists. ET-A selective antagonist are BQ123 (highest selectivity), darusentan, ambrisentan, atrasentan, sitaxsentan and FR 139317 whereas ET-B selective antagonists are BQ788, IRL2500 and RES7011 [58]. The effects of endothelin can also be inhibited by ECE inhibitors, which decrease the production of endothelin. Intra-arterial administration of phophoramidon, an ECE inhibitor, reversed the effects of endothelin and caused vasodilation [56]. There is also evidence that ECE-1 is overexpressed in certain cardiovascular diseases like atherosclerosis [70]. There is a theoretical advantage in

using ECE inhibitors because by decreasing ET-1 concentration, these agents will inhibit both ET-A and ET-B mediated actions. However, there has been little progress in the development of drugs in this category and the ongoing efforts seem to be in the direction of dual inhibition of ECE and ACE by a single agent [71].

Role of endothelin in cardiovascular dysfunction

Endothelin-1 has been shown to be involved in pathophysiology of myocardial infarction and congestive cardiac failure. This view is based on observations that ET-1 causes vasoconstriction of coronary vessels resulting in myocardial ischemia and ventricular arrhythmias when injected in the porcine coronary circulation [72]. Furthermore, blocking the endothelin activity by administering BQ-123, an ET-A selective antagonist, decreased the infarct size by 40% in dogs upon inducing myocardial infarction [73]. In humans there is a fivefold increase in ET-1 levels within few hours of myocardial infarction [74]. It was also documented that ET-1 maintained the basal coronary vasoconstrictor tone by its action on ET-A receptors because ET-A receptor antagonist BQ-123, when administered directly in coronary arteries, results in their dilatation in humans [75].

In some studies ET-1 was found to act as a potent survival factor against apoptosis. In neonatal cardiomyocytes, administration of ET-1 blocked the isoproterenol-induced apoptosis; this effect of ET-1 is prevented by an ET-A receptor antagonist, FR139317 but not by an ET-B receptor antagonist, BQ788 [76]. Accordingly, it was suggested that the anti-apoptotic effect of ET-1 is mediated through ET-A receptors. The anti-apoptotic effect of ET-1 on cardiomyocytes was neutralized by an MEK1 specific inhibitor, PD098059, indicating that the anti-apoptotic effect requires MEK-ERK pathway. It was also found that the anti-apoptotic effect of ET-1 was abolished by rapamycin (an immunosuppressant) by blocking mTOR pathway and by wortmannin (a fungal metabolite) by blocking P13 K-Akt pathway [76]. It has been shown that ET-1 activates S6 K in MEK-dependent manner in adult cardiomyocytes [77]. Those observations indicate that all three signaling pathways, P13-kinase, mTOR and MEK1-ERK1/2, converge into activation of S6 K, which may be involved in inducing translational changes in cardiomyocytes. In another study, a selective ET-A antagonist was observed to reduce the hypoxia-induced apoptosis in primary cultured neonatal rat cardiomyocytes suggesting the role of ET-1 in apoptosis through ET-A receptors [78]. Thus there are conflicting reports with respect to the action of endothelin on cardiac apoptosis but it is possible that such actions of endothelin may depend on the type of endothelin receptors, which may

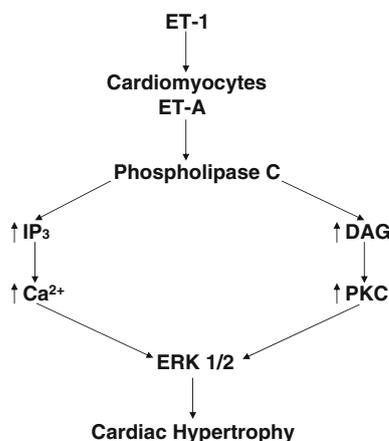


Fig. 1 Signaling pathway of ET-1. It binds to the ET-A receptors on cardiac cells and cause hydrolysis of phospholipase C to inositol triphosphate (IP₃) and diacylglycerol (DAG). DAG causes translocation of delta and epsilon isoforms of protein kinase C which result in activation of extracellular signal regulated kinase 1/2 (ERK 1/2). IP₃ causes increase in the intracellular calcium concentration. These changes result in cardiac hypertrophy which may lead to the development of congestive heart failure over time

be participating in inducing opposite changes in the myocardium. This view is supported by the observations that, another pathway activated by ET-A receptors is calcium-calceinurin signaling [79] and in fact ET-1 has been demonstrated to increase the intracellular level of calcium that activates calcineurin [80]. It should be noted that calcineurin is involved in the transcriptional pathways that modulate cardiac hypertrophy [81] and ET-1 receptor antagonists, bosentan and BQ123, were observed to prevent remodeling of the heart and improve survival following myocardial infarction [82]. It is likely that ET-1 is also involved in causing heart failure independent of cardiac cell apoptosis because it may decrease the intracellular level of cAMP and thereby may decrease the systolic function of the heart [83].

On the basis of the beneficial effects of some ET-1 antagonists, it has been suggested that ET-1 may be involved in causing hypertension as well as atherosclerosis [84, 85]. In this regard, it is noteworthy that both ET-A and ET-B receptors are highly expressed in smooth muscle cells as well as foamy macrophages in atherosclerotic animals [86]. Since ET-1 is a proinflammatory hormone, it has been indicated to promote the development of atherosclerosis [87]. Blockade of endothelin receptors was also observed to result in a marked reduction of atherosclerosis in LDL receptor deficient mice [88]. In addition to their actions on smooth muscle, both ET-1 and ET-3 were found to exert positive inotropic and chronotropic effects on rat atria; the inotropic action of ET-1 was greater than that of ET-3 whereas the chronotropic action of ET-1 was equipotent to that of ET-3 [89]. This suggests the possibility that the ET receptors mediating the chronotropic response are different from that mediating the inotropic response. It is pointed out that the inotropic response to ET-1 in ventricles is weak compared with that in atria.

In order to appreciate the role of endothelin in congestive heart failure, it is important to understand their actions on organs other than the heart. Endothelin has been reported to cause contraction of afferent as well as efferent arterioles resulting in reduction of both renal flow and glomerular filtration rate [90, 91]. There is also evidence which shows that ET-1 is produced by renal medullary collecting duct cells and there is a high concentration of ET-B receptors in renal tubular epithelial cells [92, 93]. The local production of ET-1 in kidneys is believed to play a role in regulating the transport of salt and water in the terminal nephrons, resulting in natriuresis and diuresis by their action on ET-B receptors [55]. Endothelin, like other vasoconstrictor hormones such as angiotensin II, vasopressin and noradrenaline, was found to inhibit renin release by increasing the intracellular concentration of calcium [94]. Clinically, a selective ET-A receptor antagonist BQ 123 was seen to lower the systemic blood pressure, increase the renal blood flow and reduce the renal vascular resistance in patients

with chronic renal failure [95]. Endogenous ET-1 also plays an important role in the central autonomic control of circulation and respiration because ET-1 deficient mice, produced by gene targeting, were observed to show elevated arterial blood pressure and attenuated reflex control of respiration [96]. It has also been reported that chronic intracerebro-ventricular infusion of endothelin results in increase in arterial blood pressure in rats [97] possibly due to its function as a neuromodulator or as a hormone that functions either locally in an autocrine or paracrine manner. Topical application of endothelin at carotid bifurcation inhibits baroreceptor responses and stimulates chemoreceptor responses in cats [98]. The intravenously administered ET-1 did not cross blood brain barrier but when applied directly, it was localized in hypothalamus, thalamus, lateral ventricle region, globus pallidum and caudate putamen [99]. It should be noted that apart from its interaction with ACE, rennin and angiotensin; endothelin also affects aldosterone and atrial natriuretic peptide (ANP) because the secretion of both these hormones is increased by endothelin [31, 100]. ET-1 also stimulates the release of catecholamines from adrenal chromaffin cells [101]. It is thus possible that ET-1 may induce congestive heart failure by acting directly on cardiomyocytes or indirectly through the release of different hormones in the body. The events associated with opposing actions of endothelin on vascular smooth muscle and endothelial cells for the resultant changes in blood pressure and subsequent development of

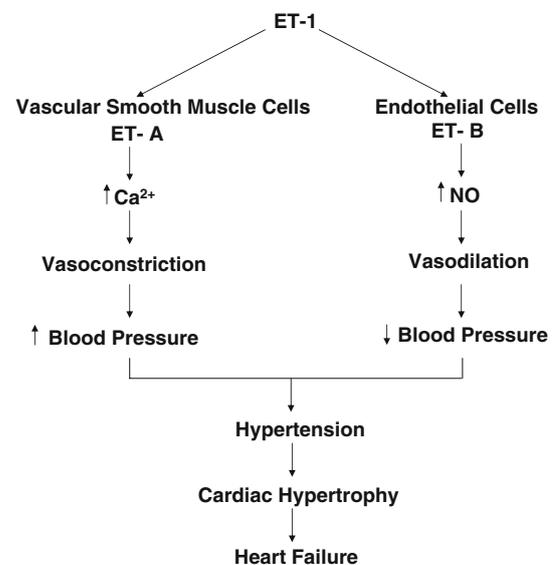


Fig. 2 Effect of ET-1 on cardiac function through different receptors. Vascular smooth muscle cells express ET-A receptors which may cause vasoconstriction and increase the blood pressure. On the other hand endothelial cells express only ET-B receptors which increase nitric oxide and thus result in vasodilation and decrease in blood pressure. The net result of these changes is an increase in blood pressure which may cause cardiac hypertrophy and heart failure

cardiac hypertrophy and heart failure are given in Fig. 2. Such effects of endothelin may be occurring in addition to the direct effects of this hormone on the myocardium.

Endothelin receptor blockade in heart failure

There is considerable experimental and clinical data available on the effects of different endothelin antagonists in congestive heart failure in both humans and animals (Tables 1, 2) [102–116] as described below:

Human trials

Various reports have shown beneficial effects of endothelin antagonists in heart failure. Nonselective endothelin receptor antagonist, tezosentan, improved cardiac index and reduced systemic and pulmonary vascular resistance and capillary wedge pressure in patients with severe chronic heart failure as well as in patients with acute heart failure [94]. Similarly, another nonselective endothelin antagonist, Bosentan 500 mg given twice daily in patients with heart failure of NYHA class III–IV increased the likelihood of clinical improvement, and reduced the combined endpoint of death and worsening of congestive heart failure after 6 months of treatment, but this was accompanied by an asymptomatic increase in liver enzymes [117]. This led to a trial of bosentan 125 mg twice daily in patients with severe congestive heart failure which, showed that there were only minor increases in liver enzymes but no benefits in cardiac failure [118].

In the Enrasentan Clinical Outcomes Randomised (ENCORE) Study, effects of enrasentan were compared to placebo and a high dose of an ACE inhibitor for 9 months in patients with NYHA class II/III heart failure. Enrasentan was associated with worsening heart failure, increased mortality and increased rate of withdrawal for adverse events [104]. Then another trial, the Endothelin-A Receptor Antagonist Trial in Heart Failure (EARTH), showed no effect of darusentan on the incidence of death, hospitalizations related to congestive heart failure or worsening heart failure [119]. This study was a multicentre trial in patients in NYHA class II–IV heart failure who were on standard treatment. At baseline, patients had an average LV ejection fraction of 26%, LV end-diastolic volume of 249 ml. Although there was a trend of reduction of LV end-diastolic volume in the darusentan group with dosage more than 50 mg per day, this effect was statistically not significant. Similarly, the Randomized Intravenous Tezosentan (RITZ)-4 Study did not show any significant improvement in worsening heart failure, recurrent or new MI or clinical end point of death [105]. Earlier study with the same agent had demonstrated significant improvement in cardiac index and a reduction in pulmonary capillary wedge pressure at 6 h compared with placebo [104].

Animal experiments

In a study, an infusion of BQ-123, a selective ET-A receptor antagonist, when started 10 days after myocardial infarction in rats and maintained for 12 weeks, improved

Table 1 Effects of some non-selective endothelin antagonists on experimental and clinical congestive heart failure

Endothelin-1 antagonist	Effects	Reference
Tezosentan	No improvement in symptoms or clinical outcome but evidence of improved hemodynamics in acute heart failure	John et al. [102]
Tezosentan	No change in dyspnoea	Coletta et al. [103]
Tezosentan	Improvement in cardiac index and reduction in pulmonary capillary wedge pressure	Louis et al. [104]
Tezosentan	No improvement in heart failure or deaths in patients	O'Connor et al. [105]
Tezosentan	In patients with congestive heart failure, low dose had a better outcome while the patients on high dose had worse outcome	Kaluski et al. [106]
Tezosentan	Administration first day after MI, increased long term survival and improved hemodynamics	Clozel et al. [107]
Bosentan	Improved survival rates in rats with chronic heart failure	Breu et al. [108]
Bosentan	In humans with heart failure, increased symptoms in first month but decreased during fourth to sixth months	Packer et al. [109]
Bosentan	Attenuation of progressive ventricular dilatation and improvement in cardiac function in rats with MI	Fraccarollo et al. [110]
Enrasentan	Adverse ventricular remodeling in chronic heart failure, despite an increase in resting cardiac index	Parsad et al. [111]
LU-420627	Reduced survival and promoted LV dilatation and dysfunction whether started early or late after MI	Nguyen et al. [112]

The selectivity of agents is based on their effects on ET-A and ET-B receptors; *MI* myocardial infarction, *LV* left ventricle

Table 2 Effects of some selective endothelin receptor antagonists on clinical and experimental congestive heart failure

Endothelin-1 antagonist	Effects	Reference
Darusentan selective ET-A	Safe and effective in resistant hypertension in humans	Epstein et al. [113]
YM-598 selective ET-A	Improved exercise tolerance and cardiac function in rats with chronic heart failure	Miyauchi et al. [114]
BQ-123 selective ET-A	Improved survival and LV function, reduced cardiac filling pressure and remodeling	Sakai et al. [81]
ABT-627 selective ET-A	Modest improvement in LV function and prevent tissue damage in cardiomyopathic hamsters	Nishida et al. [115]
A-192621 selective ET-B	Degeneration of cardiomyocytes despite improving hemodynamic parameters in cardiomyopathic hamsters	Nishida et al. [115]
BQ-123 selective ET-A	Causes systemic vasodilatation without any change in plasma ET-1 level	Cowburn et al. [116]
BQ-788 selective ET-B	Causes systemic vasoconstriction and increases plasma ET-1 level	Cowburn et al. [116]

survival and cardiac function [81]. Similarly, it was observed that bosentan, a non-selective antagonist, started immediately or 7 days after MI in rats, attenuated progressive ventricular dilatation and improved cardiac function [110]. Even in chronic heart failure, oral bosentan improved survival rates in rats [108] and it was demonstrated that a selective ET-A receptor antagonist, YM598, improved exercise tolerance and cardiac function in rats with chronic heart failure [114]. In another study, effects of a selective ET-A antagonist, ABT-627, and a selective ET-B antagonist, A-192621, were studied in cardiomyopathic hamsters. It was found that ABT-627 decreased the ET-1 level as well as NADPH diaphorase activity and resulted in modest improvement of LV function in addition to preventing tissue damage. On the other hand, A-192621 had no effect on ET-1 levels and it worsened the degeneration of cardiomyocytes despite improving the hemodynamic parameters [115]. In a similar study, BQ-123, a selective ET-A antagonist, caused no change in plasma ET-1, but caused systemic vasodilation, while a selective ET-B antagonist, BQ-788, resulted in systemic vasoconstriction and increase in ET-1 level [116]. It has also been observed that LV dilatation was aggravated by the use of an ET-A receptor antagonist early after MI [120] but in another study, timing of the therapy was found to have no effect on the outcome because LU-420627, a nonselective ET-A and ET-B antagonist, reduced survival and promoted LV dilatation and dysfunction whether it was started early or late after MI [112]. On the contrary, tezosentan, a dual receptor antagonist, given on the first day after MI increased long term survival and improved hemodynamic conditions [107]. It was also shown to have protective effects on myocardial injury induced by ischemia–reperfusion [121]. Even a selective ET-A receptor blocker in acute setting has been documented to be superior to chronic blockade in attenuating ischemia/reperfusion injury in failing hearts [122]. A detailed analysis of data with different ET- receptor antagonists (Tables 1, 2) reveal that a non-selective agent bosentan, and an ET-A receptor

antagonist, BQ-123, show a great promise for use in the treatment of congestive heart failure.

Vasopressin and mode of its action

Vasopressin is a nonapeptide neurohormone with a six member disulfide ring and a three member tail with an amidated terminal carboxyl group [123, 124]. This antidiuretic hormone is increased in patients with chronic heart failure as well as acute decompensated heart failure [125–128]. The secretion of vasopressin takes place in response to the activation of osmotic and non-osmotic receptors; osmotic secretion is controlled by osmoreceptors sensing change in sodium concentration whereas non-osmotic release takes place through baroreceptors in left atrium, aortic arch and carotid sinus in response to underfilling [33]. Vasopressin results in retention of water but not sodium and thus predisposing to hyponatremia [129] and the activation of receptors on vascular smooth muscle cells leads to vasoconstriction and increased responsiveness to sympathetic nervous system.

Vasopressin is produced in the supraoptic and the paraventricular nuclei of the hypothalamus, from where it migrates down the axons and is stored in the posterior pituitary. The secretion is regulated through osmoreceptors in the hypothalamus, which detect even small changes in plasma osmolality and stimulate or inhibit vasopressin secretion, thus maintaining a tight control of serum sodium and plasma osmolality [130]. Other pathway for its release is through mechanoreceptors in the carotid sinus, aortic arch and left ventricle. Arterial underfilling resulting from a decrease in cardiac output or peripheral vascular resistance stimulates mechanoreceptors to activate sympathetic central nervous system causing vasopressin production [131]. It has also been documented that there is de novo synthesis of vasopressin in the heart in response to acute pressure overload or NO, which may have local or systemic effects [132]. In the setting of low cardiac output state such as

heart failure, the nonosmotic mechanisms have a greater influence than osmoreceptors on controlling vasopressin release, thus leading to water retention in an already overloaded state [133]. Endogenous angiotensin II also plays a role in the control of vasopressin secretion [134].

There are three vasopressin receptors, which belong to a family of rhodopsin-like G-protein coupled receptors [135]. The two major receptors are V_1 receptor (also called V_{1a}) and the V_2 receptor. The third receptor, which is pituitary-specific is named as V_3 receptor (also called V_{1b}) [136, 137]. V_2 receptors are mainly located on the basolateral membrane of the collecting ducts in the renal medulla, and are responsible for the antidiuretic action of vasopressin [138]. This can lead to water retention, which is detrimental in heart failure. There is also evidence of their presence on endothelial cells where they are involved in the secretion of von Willebrand factor [139]. V_{1a} receptors are located on the vascular smooth muscle and cardiomyocytes and the stimulation of these receptors cause vasoconstriction and a positive inotropic effect [140]; these receptors are also responsible for causing hypertrophy of the cardiac cells [141]. Therefore, vasopressin is considered to increase the systemic vascular resistance and cause cardiac hypertrophy, which result in the development of congestive heart failure.

Vasopressin binds to V_1 receptors and activates the G_q -phospholipase C pathway; this results in an increase in intracellular IP_3 and diacylglycerol levels and the subsequent increase in intracellular Ca^{2+} levels [137]. The increase in intracellular IP_3 leads to the activation of protein kinase C, which results in vasoconstriction, platelet aggregation and growth of smooth muscle cells. Some of the effects of V_1 receptor activation are mediated by stimulation of small G proteins as well as activation of phospholipase D and phospholipase A_2 [142]. On the other hand, V_2 receptors are coupled to G_s proteins and thus cause stimulation of adenylyl cyclase activity and result in an increase in the cellular cyclic AMP [137]. Intracellular cAMP elevation activates protein kinase A, which triggers an increased rate of insertion of water channel containing vesicles into the apical membrane and a decreased rate of endocytosis of these vesicles from the apical membrane [143]. Since the apical membrane compartment has higher concentration of water channel containing vesicles than the cytosolic compartment, these vesicles contain functional water channels (aquaporin 2), resulting in increased water permeability of the apical membrane [138]. The effects of vasopressin on smooth muscles, cardiomyocytes and renal function are described in Fig. 3 to show their involvement in the pathogenesis of congestive heart failure.

Many cyclic and linear peptide vasopressin antagonists, that have varying degrees of selectivity for vasopressin receptors, have been synthesized [144]. These peptide

antagonists are effective in animals, but human studies with the same agents have shown partial agonist actions [145, 146]. This could be due to marked species-differences, short biological half-life and poor oral bioavailability. The first discovered nonpeptide vasopressin antagonist, OPC-31260, has different properties than the peptide antagonists. It does not have V_2 receptor agonist effects in human and is orally bioavailable having a longer half-life than most of the peptides. However, being lipophilic, it passes the blood brain barrier and can have central nervous system side effects [147]. Vasopressin antagonists currently under investigation for heart failure are OPC-31260 (mozavaptan), OPC-41061 (tolvaptan), VPA-985 (lixivaptan) and SR-121463 (satavaptan), which are selective V_2 receptor antagonist and YM-087 (conivaptan), which is a non-selective antagonist [148].

Role of vasopressin in heart failure

During the development of heart failure, vasopressin is secreted in response to stimulation of the baroreceptors by reduction in the arterial pressure [130]. This reduction in the arterial pressure detected by the sinoaortic baroreceptor outweighs the hypothalamic osmoreceptor response to a small decrease in the plasma osmolality seen in such subjects [149]; therefore a net increase in vasopressin release

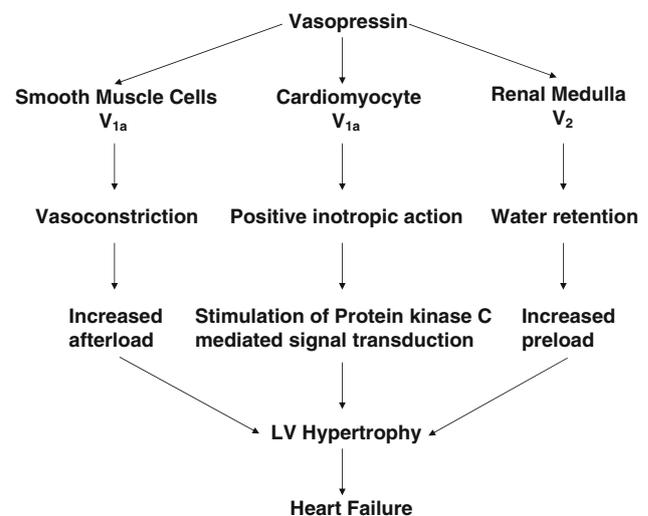


Fig. 3 Effect of vasopressin on cardiac function through different receptors. Vasopressin binds to V_{1a} receptors in smooth muscle cells and causes vasoconstriction resulting in increased afterload, cardiac hypertrophy and heart failure. Vasopressin has been shown to act on V_{1a} receptors on the cardiomyocytes resulting in protein kinase C mediated signal transduction to cause heart failure. Vasopressin also acts on V_2 receptors in renal medulla causing water retention and increased afterload, which has detrimental effect leading to the development of heart failure

is seen in patients with heart failure, even though there is reduced plasma osmolality as compared to normal humans. The increase in vasopressin results in impaired excretion of free water in patients with heart failure due to an increase in the number of AQ2 water channels in the collecting duct [138]. This not only results in abnormal water retention, but also causes hyponatremia [149]. The water retention is a detrimental event in heart failure as it results in increased congestion. Likewise, the hyponatremia caused by vasopressin is also associated with increased mortality in patients with heart failure [150].

Intravenous infusion of vasopressin in heart failure patients increases systemic vascular resistance and pulmonary capillary wedge pressure and decreases cardiac output and stroke volume. These changes were seen without any significant alteration in blood pressure or heart rate [151] and could be caused by an increase in the afterload because of stimulation of V_{1a} receptors and resulting vasoconstriction [152]. At the same time, stimulation of V_2 receptors causing water retention results in an increase in venous blood volume; this in turn leads to increased preload and pulmonary capillary wedge pressure. There is also ample evidence that vasopressin stimulates cardiac cell hypertrophy by enhancing protein synthesis and cellular growth without affecting cell division in neonatal rat cardiomyocytes as well as adult rat heart [34, 141, 153]. It has also been documented that activation of V_{1a} receptors is associated with left ventricular hypertrophy and collagen deposition in spontaneously hypertensive rats; these changes were attenuated with a V_{1a} receptor antagonist [35].

Vasopressin blockade in heart failure

Treatment of heart failure with loop diuretics to get rid of the excess water can result in worsening of hyponatremia; even mild hyponatremia in patients with heart failure indicates a worse prognosis [154]. Vasopressin antagonists, which cause the loss of free water and conserve sodium, seem to be an ideal choice for such patients. Several studies have been conducted in both humans and animals to find if these agents are beneficial in congestive heart failure (Tables 3, 4) [155–165] and following is the analysis of these data:

Human trials

The ACTIV (Acute and Chronic Therapeutic Impact of a Vasopressin) trial evaluated the short-term and intermediate-term effects of tolvaptan in patients hospitalized with heart failure. Patients, with signs and symptoms of congestive heart failure and left ventricular ejection fraction less than 40%, were given 30, 60, or 90 mg/day of tolvaptan for 60 days in addition to the standard therapy. The treatment group showed an increase in the net fluid loss resulting in decreased body weight as compared to the standard therapy group; there was improvement in the survival rate and hyponatremia [155]. However, no reduction in the rate of worsening of heart failure was evident but at the same time, there were no adverse effects like changes in blood pressure, heart rate and electrolytes [155].

Table 3 Effect of some V_2 selective vasopressin antagonists in congestive heart failure

Vasopressin antagonist	Effects	Reference
Tolvaptan	Improvement in survival rates, Na^+ and fluid loss in humans. No reduction in worsening of heart failure after discharge	Gheorghiade et al. [155]
Tolvaptan	Improvement in dyspnoea, body wt, edema, Na^+ , JVP and chest rales in humans. No change in clinical status, morbidity and mortality	Gheorghiade et al. [156], Konstam et al. [157]
Tolvaptan	Decreased mortality and hospital admissions with 1 year treatment, but no reductions in LV volumes in patients	Udelson et al. [158]
Lixivaptan	Increased urine output in heart failure patients	Abraham et al. [159]
Tolvaptan	Tolvaptan compared to furosemide in heart failure in rats. It produced free water loss with no renin or aldosterone activation	Veeraveedu et al. [160]
OPC-31260	In dogs with pacing induced heart failure. Increased urine output, Na^+ , renin and vasopressin levels. No improvement in hemodynamics. Combined therapy resulted in supra-additive hemodynamic, renal and metabolic effects	Naitoh et al. [161]
OPC-31260	Post MI induced heart failure in rats. Increased urine output, vasopressin levels. No activation of RAS and no long-term survival benefits	Burrell et al. [162]
OPC-31260	Rats in heart failure induced by aortocaval shunt. Decrease in wt. of right ventricle, right ventricular systolic pressure, LVEDP and ANP	Nishikimi et al. [163]

The selectivity of agents is based on their effects on V_2 and V_1 receptors; JVP jugular venous pressure, LV left ventricle, MI myocardial infarction, RAS renin angiotensin system, LVEDP left ventricular end diastolic pressure, ANP atrial natriuretic peptide

Table 4 Effects of some V_1 selective and non-selective vasopressin antagonists in congestive heart failure

Vasopressin antagonist	Effects	Reference
Conivaptan non-selective	Reduction in PCWP, right atrial pressure in humans. Increase in urine output. No change in hemodynamics	Udelson et al. [164]
Conivaptan non-selective	In dogs with pacing induced heart failure, significant increase in LVP, CO, urine output. Decrease in LVEDP, PVR	Yatsu et al. [165]
OPC-21268 V_1 selective	In dogs with pacing induced heart failure, improvement in CO and renal function	Naitoh et al. [161]
OPC-21268 V_1 selective	Rats in heart failure induced by aortocaval shunt. No change in hemodynamics, wt. of right ventricle and ANP	Nishikimi et al. [163]

CO cardiac output; PCWP pulmonary capillary wedge pressure, LVP left ventricular pressure, LVEDP left ventricular end diastolic pressure, ANP atrial natriuretic peptide, PVR peripheral vascular resistance

The EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan) trial was conducted to evaluate the short-term and long-term effects of tolvaptan added to standard therapy within 48 h of hospital admission for heart failure [156]. This treatment for 60 days revealed that oral tolvaptan, in addition to the standard therapy including diuretics, improved many signs and symptoms of heart failure without any serious side effects. There was improvement in body weight, peripheral edema and patient-assessed dyspnoea on day 1 and day 7 of the tolvaptan treatment but there was no significant change in the patient-assessed global clinical status. A greater correction of hyponatremia was observed in the tolvaptan group and improvement in physician-assessed dyspnoea, orthopnoea, fatigue, jugular venous distension and rales was also seen [156]. The long-term follow-up of tolvaptan treated patients over a median period of 9.9 months did not show any significant change in long-term mortality or heart failure related morbidity. However there were no excess adverse effects like changes in heart rate, blood pressure, renal function or potassium levels [157].

For another clinical trial, 142 patients with symptomatic heart failure having dyspnoea of NYHA class III, were randomized to double blind, short-term treatment with conivaptan, a non-selective vasopressin antagonist, or a placebo [158]. It was observed that the treatment group had a significant reduction in pulmonary capillary wedge pressure and right atrial pressure during 3–6 h interval after intravenous administration of conivaptan. Urine output also increased significantly but there was no significant change in cardiac index, systemic and pulmonary vascular resistance, blood pressure or heart rate [158]. In a multicenter, randomized, double blind, placebo controlled study, it was observed that conivaptan significantly increased the urine output and decreased the body weight but failed to improve the clinical status of patients [166]. Another multicenter, randomized, double blind study showed that 1-year treatment with tolvaptan did not reduce the LV volume significantly but the mortality and hospital admissions were

reduced significantly [158]. Selective V_2 receptor blocker, lixivaptan, was studied to examine the renal effects in heart failure. The results confirmed the role of vasopressin in renal water retention associated with heart failure as significant dose related increase in the urine output was seen with lixivaptan administration [159].

Animal experiments

Various animal studies have demonstrated the role of vasopressin antagonists in the treatment of heart failure. In an experiment on conscious dogs, heart failure was induced, by rapid right ventricular pacing [161]. It was observed that, oral administration of a selective V_1 receptor antagonist, OPC-21268, significantly improved the cardiac output and renal functions. On the other hand, OPC-31260, a selective V_2 receptor antagonist, given orally, induced marked diuresis, increase in sodium levels, plasma renin and vasopressin levels but there was no improvement in the hemodynamics [161]. The combined administration of these two agents resulted in supra-additive hemodynamic response like prolonged decrease in mean arterial pressure and increase in cardiac output as well as renal and metabolic responses [161]. In a similar study, conivaptan was given intravenously to dogs with pacing induced heart failure. It resulted in significant increase in left ventricular pressure and cardiac output [165]. A significant decrease in the left ventricular end-diastolic pressure and total peripheral vascular resistance was seen with conivaptan which also caused increased urine output and decreased urine osmolality [165]. Another study was carried out to assess the long-term effects of V_2 antagonism in heart failure in rats [162]. Chronic V_2 antagonism in rats with postinfarction-induced heart failure resulted in increased urine output and decreased urine osmolality. This study did not show any improvement in the long-term survival but affirmed the role of V_2 antagonist in management of water retention in heart failure [162]. V_2 antagonism has also been shown to alter the hemodynamics of heart due to its

affect on water retention. In this trial chronic administration of a V_2 receptor antagonist, OPC-31260, in rats with heart failure induced by aortocaval fistula, significantly reduced weight of the right ventricle, right ventricle systolic pressure, left ventricular end-diastolic pressure and plasma concentration of ANP [163]. Chronic administration of a V_1 receptor antagonist, OPC-21268; however, did not alter hemodynamics, weight of right ventricle or ANP. This showed that vasopressin affected the heart indirectly, by its action on V_2 receptors causing water retention [163].

In a comparison of the effects of tolvaptan on congestive heart failure in rats with those of furosemide, it was found that the diuretic effects of tolvaptan at 3 and 10 mg/kg were almost equal to that of furosemide at 30 and 100 mg/kg, respectively [160]. However, tolvaptan produced a free water loss while furosemide resulted in the loss of potassium and sodium in urine. Furosemide also resulted in the activation of renin and aldosterone but no such activity was seen in the tolvaptan group. It was observed that furosemide, unlike tolvaptan, had adverse effect on glomerular filtration rate [160]. It was also documented that the diuretic therapy resulted in activation of renin, and the plasma concentrations of norepinephrine, atrial natriuretic peptide as well as vasopressin were significantly higher in patients with left ventricular dysfunction; these neuroendocrine factors had even higher values in patients with overt heart failure [125]. In an interesting study, the effects of a selective vasopressin antagonist, an angiotensin II antagonist or dual blockade were studied in congestive heart failure in which three groups of pigs with pacing-induced heart failure were treated with, either a V_{1a} blocker, SR49059, an AT_1 blocker, irbesartan, or with both the blockers [167]. It was observed that left ventricular end-diastolic dimension and peak wall stress were reduced in all the groups. However, left ventricular fractional shortening and the basal left ventricle myocyte percent shortening were increased in the dual blockade group [167].

Summary and concluding remarks

From the foregoing discussion it is evident that vasopressin and endothelin are increased in congestive heart failure and play an important part in the cascade of events that take place after the initiating insult is inflicted on the heart. The essential task is to control these protective mechanisms so that they do not overshoot. For example, in the event of acute ischemia with hypotension and arterial underfilling, both endothelin and vasopressin cause vasoconstriction to maintain blood pressure and thus perfusion to important organs. Vasopressin in addition also causes water retention to maintain the blood pressure and ET-1 is known to have a role in preventing apoptosis in early stages of congestive

heart failure. However, at later stages, both endothelin and vasopressin are responsible for cardiac hypertrophy and fibrosis. Therefore the timing of the therapy with their antagonists is of utmost importance. Although it was shown that endothelin protect cardiomyocytes in acute phase after myocardial infarction and yet tezosentan was found to improve hemodynamics in acute heart failure. On the other hand, LU-420627, a nonselective ET-A and ET-B antagonist, reduced survival and promoted LV dilatation and dysfunction whether it was started early or late after myocardial infarction [112]. Such disparities are hard to explain as both of these agents are non-selective endothelin antagonists.

Vasopressin and endothelin act through different receptors, which at times have opposite effects on congestive heart failure. Endothelin for instance causes natriuresis and diuresis through ET-B receptors whereas vasopressin causes water retention through V_2 receptors. For their antagonist therapy to be successful, regular monitoring of hemodynamics and other factors is required to adjust the dose of various drugs accordingly. For instance, when the patient with congestive heart failure is overloaded with fluid in association with hyponatremia, it would be prudent to use a V_2 selective antagonist but sodium concentration and water status should be monitored and the dosage should be adjusted in an appropriate manner. For preventing the adverse effects of cardiac hypertrophy, long-term selective V_{1a} antagonists may be tried but there appears to be some hindrance to this approach, because antagonism of V_{1a} receptors could lead to increased plasma vasopressin concentration, which can act on V_2 receptors to cause water retention.

Another important point which needs to be emphasized is that, most of the studies have focused on the effects of vasopressin antagonists on heart failure patients who were already on diuretics and thus the results are difficult to interpret. Accordingly, new studies are required to directly compare the effects of diuretics with those of vasopressin antagonists. It is also noted that bosentan, a non-selective endothelin antagonist has showed consistent results in rats with congestive heart failure but in humans the results were seen at a higher dose, which resulted in raising the liver enzymes. It is therefore necessary to carry out studies with appropriately adjusted dose of bosentan. Another issue is to monitor the central effects of endothelin antagonists carefully in addition to their renal effects. Since ET-1 is produced locally in kidney and this can be seen to cause natriuresis and diuresis, blockade of this effect can be detrimental in patient with heart failure.

It seems appropriate to point out that congestive heart failure is not a one-time event but a progressively changing process with episodes of ischemia, inflammation, pressure overload, volume overload and the associated neurohumoral

activation. There are numerous factors, like sympathetic nervous system, renin angiotensin system, vasopressin, aldosterone, natriuretic peptides and endothelins, which play a complex and yet well coordinated role in the development of cardiac dysfunction in this morbid syndrome. Other disease entities such as hypertension, atherosclerosis and diabetes also affect the genesis of cardiac dysfunction in congestive heart failure. Accordingly, it is not surprising that no single drug has proven satisfactory for the treatment of heart failure. Extensive studies using a combination of drugs that block various neurohumoral pathways involved in the pathogenesis of congestive heart failure are the need of the day. As endothelin and vasopressin seem to act through a number of pathways and have different effects on various systems of the body, newer agents which may affect multiple sites to antagonize their actions in various tissues should be developed for the treatment of heart failure. The timing of starting the administration of endothelin and vasopressin antagonists is also crucial for obtaining maximal beneficial effects as these hormones are essential to maintain the cardiac structure early after myocardial infarction, but may contribute to pathological cardiac hypertrophy, fibrosis and chronic dilatation at later stages. Therefore, new studies are needed that are started not too late in the process of cardiac remodeling but also not started too early in the post-infarct compensatory stage.

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