Abstract

Heart failure (HF) is a major public health problem that is defined as a clinical syndrome that results when the heart is unable to provide sufficient blood flow to meet metabolic requirements or accommodate systemic venous return. Some systems participate as compensatory mechanisms, these include neurohumoral, Cellular immune activation and renin angiotensin system changes that lead to maladaptive condition. Several treatment strategies have been developed based upon the understanding of these compensatory mechanisms. In this paper, we review the general compensatory mechanisms, they lead to a maladaptive condition and the role that plays each component of renin angiotensin aldosterone system play in the development of heart failure.

Renin angiotensin system role on heart failure

During the past two decades we have witnessed the advances of knowledge over renin angiotensin system. Although originally perceived as a classical humoral system in which biologically active molecules are secreted from a dedicated gland to reach their target tissue via the bloodstream, a number of observations have indicated that local renin angiotensin systems are complete with respect to all the components of the enzymatic pathway, may reside within individual organs or tissues. This is due in part to the advent of molecular biological methods that for the first time, allowed unequivocal confirmation of local synthesis of the elements have demonstrated the importance of a RAS in the brain, heart, peripheral blood vessels, adrenal glands, and kidney.

Angiotensinogen

It has been shown that a marked increase of ventricular angiotensinogen mRNA levels in pressure overload-induced cardiac hypertrophy as well as in the heart after myocardial infarction have been interpreted as indicating that increased wall stress may represent a trigger for angiotensinogen gene expression. In rats with chronic pressure overload and in rats with left ventricular failure early after coronary artery ligation of following tachypacing, cardiac angiotensinogen gene expression is enhanced, suggesting that the local generation of angiotensinogen in the myocardium may become more important during cardiac hypertrophy and failure [1-3].

Renin

Although cardiac renin mRNA expression is extremely low, renin activity is readily detectable in the heart [4] but increased expression of renin mRNA has been detected in the border zone of the infarcted left ventricle in rats, indicating that cardiac renin expression may be induced under pathological conditions [5]. Also renin has been demonstrated in isolated ventricular myocytes using a specific renin antibody [6] suggesting that synthesis occurs in cardiomyocytes. Renin has been thought to have no direct biological action. The renin receptor is a 350-amino-acid protein with a single trans membrane domain that specifically binds both renin and prorenin. Binding induced the activation of the extracellular signal-related MAPKs (ERK1 and ERK2) associated with serine and tyrosine phosphorylation and a 4-fold increase in the catalytic conversion of AGT to AG I. The receptor was localized in the glomerular mesangium and the sub endothelial layer of both coronary and renal arteries, associated with vascular smooth muscle cells and colocalized with renin [7]. A direct functional role of the renin/prorenin receptor might contribute to the generation of tissue ANGs in the heart, kidney, and/or peripheral blood vessels.

Ang II

Ang II is produced by the conversion locally rather than blood-derived Ang I [8]. In addition of the effects of Ang II on vasoconstriction and hypertension, cardiac hypertrophy and remodeling, recent evidence suggests that Ang II can also affect cardiac energy metabolism in heart failure [9,10]; decreased cardiac efficiency can contribute to the severity of the energy deficit. It has shown that chronic elevations in Ang II alter the relationship between fatty acid and carbohydrate oxidation in the heart, resulting in a shift from carbohydrate oxidation towards fatty acid β-oxidation [11]. While glycolysis may be increased in heart failure, the subsequent oxidation of the pyruvate (glucose oxidation) can be decreased, a finding similar to what occurs following Ang II treatment. In support of this, a recent study in pigs with dilated cardiomyopathy due to rapid pacing showed that myocardial glucose oxidation rates were impaired [12]. Ang II mediated damage of mitochondrial respiratory enzymes might cause further production of ROS, resulting in the further damage to the mitochondria, then may eventually lead to the reduction of overall mitochondrial oxidative phosphorylation. In an Ang II induced hypertensive model, diastolic dysfunction precedes systolic dysfunction and is accompanied by mitochondrial damage [13]. Furthermore, perturbation in cardiac

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energy metabolism, accompanied by cardiac hypertrophy, precedes the development of diastolic dysfunction. In contrast, in Tacrolimus-induced hypertensive rats (TAC-induced hypertensive rats), diastolic dysfunction is not associated with mitochondrial dysfunction, and mitochondrial damage does not occur until the development of systolic dysfunction [14].

ACE

Myocardial expression of ACE is increased in rats with pressure overload ventricular hypertrophy and in the viable myocardium following experimental myocardial infarction [15-19]. Moreover ACE has been shown to be upregulated in the myocardium of patients with end stage heart failure [20]. Increased ACE activity has been detected in the left ventricular aneurysms of patients after myocardial infarction [21]. A report from the same group indicated that ACE was expressed in fibroblasts, macrophages and endothelial cells present in the scar tissue and in the cardiac myocytes in the region adjacent to the infarct scar [22]. On the other hand some studies have challenged the notion that ACE represents the mayor Ang II forming enzyme in the human heart. Urata and coworkers [23,24] demonstrated that ACE inhibitors could block only the 10-20 % of total Ang I to Ang II conversion in left heart. Meggs and coworkers [25] demonstrated that cardiac ACE inhibitor overexpression resulted in preservation of left ventricular global and regional function, indicating a beneficial role for the AT₂ receptor in volume-overload states, including post-myocardial infarction remodeling. Overexpression of the AT₂ receptor in cardiomyocytes was demonstrated to attenuate ANG II-induced cardiac interstitial fibrosis through BK/NO/cGMP pathway without effect on cardiomyocyte hypertrophy [45]. A very interesting information is that the AT₁ receptor and the BK₂ receptor can communicate directly with each other. These two receptors can physically associate to form stable heterodimers in the cell membrane, resulting in the increased activation of G proteins Gs and Gq, the major signaling proteins mediating AT₁ receptor responses [45]. The AT₁ and AT₂ receptors also have been shown to heterodimerize [46]. Thus, the AT₂ receptor binds directly to the AT₁ receptor, thereby antagonizing the signaling pathways and functions of the AT₁ receptor. The direct inhibition of the AT₁ receptor by the AT₂ receptor binding does not depend on ATP₂ receptor-stimulated G protein activation. Furthermore, increased AT₁/AT₂ receptor heterodimerization in myometrial cells of pregnant women correlated with decreased ANG II responsiveness. The results of these studies were consistent with the concept that the AT₁ receptor stabilizes AT₂ receptor structurally so that it can no longer undergo the requisite conformational changes to activate G proteins. Thus, it appears that the AT₂ receptor can be a direct AT₁ receptor-specific antagonist by heterodimerization [47]. The angiotensin AT₂ receptor is an AT₁ receptor antagonist.

ACE2

In the year 2000, ACE2 was discovered and was characterized as an enzyme similar to ACE [48]. Insight to the functional significance of ACE2 in the cardiac and intrarenal RAS has recently been provided using genetic approaches. The gene for ACE2 has been mapped to the X chromosome in humans, to the region that has previously shown to be a quantitative trait locus for several rat models of hypertension [49]. Indeed, ACE mRNA and protein levels were down-regulated in the kidneys of these rat models, indicating that ACE 2 may be a candidate gene for the quantitative trait locus on the X chromosome. The increase in cardiac and plasma ACE2 activity noted after experimental MI is consistent with studies in patients with heart failure, where both cardiac ACE2 gene [50] and protein are increased. ADAM 17 (metalloproteinase domain 17), also known as tumor necrosis factor-a-converting enzyme (TACE) is a major protease that cleaves ACE2 from the cellular membrane to allow its shedding as a fully active soluble glycoprotein [68], Donouge et al. reported that ACE gene ablation did not alter blood pressure, but severely impaired cardiac contractility and caused mild ventricular dilation and increased ANG II levels, suggesting that ACE2 may nullify the physiological actions of ACE. Ablation of both the ACE
and ACE2 genes completely prevented the cardiac abnormalities and the increase in ANG II production [49]. These observations suggest a direct effect of ANG II on cardiac function and indicate that ACE2 probably counterbalances the enzymatic actions of ACE because it provides a potential major pathway for ANG (1-7) production. ACE2 is highly efficient in the conversion of ANG II to ANG (1–7), over 400-fold greater than for the conversion of ANG I to ANG (1–9). The recent biosynthesis of a potent, selective ACE2 inhibitor will afford a means to determine the role of ACE2 in cardiovascular and renal function and disease [52]. On the other hand Xiao et al. [53] examined the sympathetic nervous effects in transgenic and wild type mice subjected to a chronic myocardial infarction and the subsequent development of CHF. While there were no major differences in cardiac function in both groups of mice, transgenic mice exhibited an improvement in arterial baroreflex function. Mice that overexpressed central ACE2 were able to suppress renal sympathetic nerve activity (RSNA) to zero during increases in blood pressure in contrast to wild type mice with CHF who could not lower RSNA in response to an increase in blood pressure. Examination of the spontaneous baroreflex control of heart rate also indicated an enhanced sympathetic inhibitory process in these mice. In a recent study by Zheng et al. [54] it was shown that viral overexpression of ACE2 reduced RSNA in a rat CHF model. This effect was apparently mediated by an increase in nitric oxide. Another component that opposite the axis of Angl-ACE-Angll-AT, receptor is the sACE2 (ACE2 soluble) that may provide a vasoprotective/antiplatelet mechanism resulting in the counter-regulation of the RAS [55]. The sACE2 was also implicated as a biomarker of definitive heart failure in animal models where absence of sACE2 caused severely impaired cardiac function. There is a wealth of information in human heart failure where myocardial sACE2 gene expression increased in patients with left ventricular dysfunction including thickening of the left ventricle and severe reduction in cardiac contractility. Burrell et al. observed an increase in sACE2 expression in failing human hearts independently of AT1R blockade [51]. There have been no reports on the combination of RAS blockade with either ACE2 overexpression or an ACE2 activator. Such studies are needed to test the hypothesis that augmentation of ACE2 over and above that due to cardiac injury itself would have further beneficial effects. Although there is great interest in this novel approach to cardiovascular diseases, further long-term studies are needed in experimental disease models as ACE2 overexpression may not always be beneficial. In ACE2 transgenic mice, there was a high incidence of sudden death that correlated with transgene expression levels and sustained overexpression of ACE2 in the heart of stroke-prone SHR mice which increased coronary blood flow by vascular dilation, thereby providing a potential positive inotropic activity [56,57]. The physiological effects of apelin are exerted through binding to its receptor APJ, a G protein–coupled receptor that shares significant homology with the angiotensin II type I receptor (AT1, receptor) [58,59].

Under pathological conditions, apelin signaling regulates cardiovascular functions including blood pressure, cardiac contractility, and fluid balance [60,61]. Apelin exerts load-independent positive inotropy and increases coronary blood flow by vascular dilation, thereby providing beneficial effects in failing hearts. In gene-targeting studies of apelin and APJ, Ashley EA, et al. and others have demonstrated that the endogenous apelin-APJ axis regulates heart contractility associated with aging, exercise, and pressure overload; in the absence of apelin or APJ expression, mutant mice show reduced contractile cardiac functions [62,63]. Ligand-independent but stretch-dependent APJ signaling has recently been shown to promote pathological cardiac hypertrophy [65–66]. However, the precise role of endogenous apelin signaling in heart function remained elusive.

**Ang (1–7)**

The ANG (1–7)heptapeptide fragment of ANG II was first discovered to have biological activity in 1988 [51]. Since that time, several studies have documented that ANG (1–7) is a major biologically active peptide product of the RAS. ANG (1–7) can be formed directly from ANG I by the action of several peptidases, including neutral-endopeptidase (NEP) 24.11 or prolyl-endopeptidase (PEP) or from ANG II via PEP or prolyl-carboxypeptidase. Current data suggest that NEP 24.11 plays a major role in both circulating and tissue ANG (1–7) formation [67]. The first Ang (1–7) analogue, AVE0091, can provide vasorelaxation, lower blood pressure, and attenuate remodeling in a post-infarction animal model. Similarly, Ang (1–7) peptide was shown to rescue systolic dysfunction in ACE2-null mice in a pressure-overloaded induced HF model [68]. It was shown that by Yamamoto et al. that the levels of Ang (1–7) increase so 25 times after inhibition with an ACE inhibitor or an ARB. ACE2 is particularly abundant in the coronary circulation, playing an important role in the generation of Ang (1–7) [67]. The actions of Ang (1–7) are mainly antiproliferative, inhibits protein synthesis, and amplify the vasodilator effect of bradykinin and nitric oxide signaling stimulates cGMP protein kinase G also acts as an antiarrhythmic agent and protects infarction of the consequences of cardiac reperfusion injury [69]. De Mello in 2004 [70], showed that angiotensin (1-7) activates the sodium pump, hyperpolarizes heart cells and restores the arrhythmias because of ischemia by reperfusion. Also has been reported that angiotensin (1–7) can inhibit oxidative stress, stimulating the tissue plasminogen activator 1 platelet aggregation and can act as an agent anti-inflammatory. Fulvia et al. evaluated the chronic cardiac effects of a formulation developed by including angiotensin Ang (1–7) in hydroxypropyl β-cyclodextrin (HPβCD), in infarcted rats. Myocardial infarction (MI) was induced by left coronary artery occlusion and found once-a-day oral HPβCD/Ang (1–7) administration improved the cardiac function and reduced the deleterious effects induced by MI on TGF-β and collagen type I expression, as well as on the velocity and displacement of myocardial fibers. These findings confirm cardioprotective effects of Ang (1–7) and indicate HPβCD/Ang (1–7) as a feasible formulation for long-term oral administration of this heptapeptide. HPβCD/Ang (1–7) was administered for 60 days (76 μg/Kg/once a day/gavage) starting immediately before infarction [71], in keeping with previous studies showing beneficial effects of chronic Ang (1–7) administration in different models of cardiovascular diseases [72]. Chronic Ang (1–7) administration improved LV function of Wistar rats [73] and of diabetic spontaneously hypertensive rats (SHRs) after global ischemia, attenuated the heart failure induced by MI, prevented the development of severe hypertension and end-organ damage in SHR treated with L-NAME, and reduced the cardiac remodeling in DOCA-salt and in

**APELIN**

Apelin is a second catalytic substrate for ACE2 and functions as an inotropic and cardioprotective peptide. While an antagonistic relationship between the RAS and apelin has been proposed, such functional interplay remains elusive. It was found that ACE2 was downregulated in apelin-deficient mice. Apelin is an endogenous peptide with a potent positive inotropic activity [56,57]. The physiological effects of apelin are exerted through binding to its receptor APJ, a G protein–coupled receptor that shares significant homology with the angiotensin II type I receptor (AT1, receptor) [58,59].
Ang II-infused rats. In addition, an antifibrotic effect was observed in transgenic animals, which chronically present an increased plasma Ang (1–7) levels [74]. In 2007, Chappel describes the signaling pathway of Ang (1–7) according to the effects it produces. Ang (1–7) participates in oxidative stress by inhibiting NADPH oxidase (NOX) which is the main enzyme generating reactive oxygen species such as superoxide anion 
[74-97]. Also inhibits the mitogen activated protein kinases (MAPK) (ERK 1 and 2), which promotes cell proliferation. More recently, several studies have shown that the counter-regulatory ACE2/Ang (1–7)/Mas axis may also influence inflammatory responses. Indeed, there is now much evidence demonstrating that Ang (1–7) modulates negatively leukocyte migration, cytokine expression and release, and fibrogenic pathways [97-106]. For example, studies by Sukumaran and co-workers have shown that the ACE2/Ang (1–7)/Mas axis is activated and is relevant for the anti-inflammatory effects of the ARBs Telmisartan and Olmesartan in a rat model of autoimmune myocarditis. ARBs increased ACE2, Ang (1–7) and Mas expression in line with reduction of pro-inflammatory cytokines as TNF-α, INF-γ, IL-1β, IL-6 and increase of the anti-inflammatory cytokine, IL-10 [76]. These anti-inflammatory effects were associated with less myocardial fibrosis and down-regulation of PI3K, phospho-Akt, phospho-p38 MAPK, phospho-JNK, phospho-ERK and phospho-MAPK-2, but formal demonstration of the role of the ACE2/Ang (1–7)/Mas axis was not provided. The anti-proliferative and anti-fibrotic effect of Mas activation in the heart may also involve modulation of several extracellular matrix proteins. Neonatal and adult Mas-deficient mice showed significantly higher levels of collagen types I and III and fibronectin and reduced levels of collagen IV in both right ventricle and AV valves. In mice lacking the angiotensin receptors, Ang (1–7) reduced mean arterial pressure, suggesting that the AT2R may not be responsible for the vasodepressor effect of Ang (1–7) [77]. As well as cardioprotective effects with regards to fibrosis and hypertrophy, Ang (1–7) has recently been shown to promote angiogenesis in infarcted rat hearts in a Mas-dependent manner via the up-regulation of VEGF-D (vascular endothelial growth factor D) and MMP-9 (matrixmetalloproteinase-9) (78). Ang (1–7) has also been demonstrated to reduce the production of cardiac ROS (reactive oxygen species) in response to cardiac injury, as well as increased NO production, thus further providing a cardioprotective effect [79]. Beneficial functional effects of Ang (1–7) were also observed in ACE2-knockout mice in pressure-overload-induced heart failure. Ang (1–7)-infused animals showed normalization of fractional shortening, LVEDPs (LV end-diastolic pressures) and + dP/dt max. This was accompanied by normalization of heart weight and hypertrophy marker expression levels, as well as attenuated NADPH oxidase activation. Moreover, the benefits observed were comparable with those observed in animals treated with the AT1R blocker irbesartan [80]. Many studies on the electrical properties of Ang (1–7) on the heart have been performed using ex vivo whole-heart Langendorff preparations, where anti-arrhythmogenic effects inischaemia/reperfusion injury has been clearly demonstrated [70,81,82]. Ang (1–7) delivered via an osmotic mini-pump in a dog pacing model of AF (atrial fibrillation) reduced interstitial fibrosis and, as a result, showed reduced susceptibility to and duration of induced AF. Again, this effect was believed to be mediated by a reduction in ERK1/2 signaling. In this model, Ang-(1–7) also attenuated the decrease in action potential duration, characteristically observed in atrial myocytes during AF, as well as preventing the decrease in expression of ICaL (L-type calcium channel) and ITO (outward potassium channel) observed in the model; however, the mechanism by which this occurs remains to be clarified [83-86]. This demonstrates that Ang (1–7) not only has potential benefits for cardiac function through anti structural remodeling, but also that it has the potential to alter ion channel and calcium-handling protein expression, resulting in modulation of cardiac function (Figure 1).

**Ang (1-9)**

Ang (1-9) is the product of the Ang I metabolism by ACE2. The first evidence to suggest that Ang (1–9) elicits independent biological effects in the heart was reported by Ocaranza et al. [87], using a rat

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**Figure 1.** Renin Angiotensin System and its regulation through the evolution of Myocardial infarction (MI) until Heart Failure (HF)

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coronary artery ligation model of MI, where cardiac hypertrophy and dysfunction are present at 8 weeks, and in which they assessed peptide and enzyme levels. It was found that, 1 week post-MI, circulating levels of Ang (1–9), along with levels of AngII, ACE, and ACE2, were increased compared with control animals; however, at 8 weeks, only AngII and ACE remained high, with circulating levels of ACE2 and Ang (1–9) diminishing to levels lower than the control group. Treatment of the animals with the ACE inhibitor enalapril prevented the changes observed at 8 weeks, suggesting the generation of Ang (1–9) via ACE2 is able to counter-regulate Ang II-mediated actions. Chronic infusion of Ang (1–9) has been demonstrated by echocardiography to prevent LV wall thickening, LVESV (LV end-systolic volume) and LVEDV (LV end-diastolic volume) in comparison with the MI animals [88]. However, there was no change observed in cardiac function between MI and Ang (1–9)-infused MI animals as measured via LVEF (LV ejection fraction) and LVFS (LV fractional shortening). Ang (1–9) has also been reported to indirectly contribute to improved vascular function by stimulating bradykinin release in endothelial cells and enhancing the effects of bradykinin by augmenting NO and arachidonic acid release. Although Ang II is largely accepted to be pro-thrombotic and Ang (1–7) anti-thrombotic, evidence for Ang (1–9) is inconclusive. Flores-Munoz et al. [89] provided the first evidence to suggest a direct beneficial effect of Ang (1–9) in vascular function. Ang (1–9) infusion in the SHRSP improved aortic vasorelaxation and NO bioavailability via the AT2R (117). Although the mechanisms involved are currently unknown, it is possible that Ang (1–9) may increase NO bioavailability by stimulating bradykinin release, as described previously in cardiac endothelial cells, or by enhancing the activity of eNOS, as has been shown for Ang (1–7). Additionally, Ang (1–9) infusion and AT1 receptor stimulation resulted in an increase in aortic expression of NOX4 (NADPH oxidase 4), which has been demonstrated previously to promote vasodilation via the production of H2O2. However, this protective effect of NOX4 is vascular-bed-specific and therefore further investigation is required to fully assess the involvement of increased NOX4 levels in the aorta in response to Ang (1–9) infusion [90].

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