Role of renin angiotensin system in ischemic preconditioning

Vishal Kumar Vishwakarma[1,*], Ritesh Kumar Srivastav[2], Vivek Srivastava[3]

[1,3]Dept. of Pharmacology, Rajarshi Rananjay Sinh College of Pharmacy, Amethi, Uttar Pradesh, [2]Faculty of Pharmacy, Kamla Nehru Institute of Management & Technology, Sultanpur, Uttar Pradesh

***Corresponding Author:**
Email: vishal049uip@gmail.com

Abstract

Cardiovascular diseases are the leading cause of morbidity and mortality. Angiotensin has been noted down that enhance cardioprotection of ischemic preconditioning (IPC). Ischemia is a state of oxygen deprivation in tissues, whereas reperfusion is restoration of blood flow in ischemic tissues. Heart renin angiotensin system (RAS)plays an important role in the myocardial ischemia precondioning (IPC). Angiotensin(1-7) is responsible for vasodilation and angiotensin II for vasoconstriction. In IPC process upregulation of angiotensin II that leads to increased infarct size, which can be reduced by the use of ACE inhibitors, ACE2 activators and angiotensin II antagonist.Decreases the level of Angiotensin Converting Enzyme 2 (ACE 2) and increases the level of Angiotensin Converting Enzyme (ACE) is a negative regulator for cardioprotection of IPC.

Keyword: Ischemia preconditioning, ACE inhibitor,ACE2 activator, Angiotensin II antagonist.

Introduction

Coronary artery disease or ischemic heart disease is associated with the stenosis of the coronary artery along with the arteriosclerosis. The coronary lumen becomes narrower which lead to reduced blood supply to the heart that is the main cause of myocardial infarction. Coronary artery disease is the leading cause of mortality in industrialized countries.

Ischemic reperfusion injury

Coronary artery disease is major cause of mortality and morbidity (Hausenloy et al., 2005), this consequence leading cause of the myocardial infarction. Myocardial ischemic occurs due to insufficient-blood supply to the heart (Gasser et al., 1994), sudden or slowly starved of oxygen and other nutrients cause the death of effected cardiac muscle (Collard and Gelmen., 2001; Grunenfelder et al., 2001). Early restoration of blood flow i.e. reperfusion is necessary for survival of ischemic heart (Roberto and Prado, 2002) and Early reperfusion responsible for minimum damage cardiac cell (Napoli et al., 2002) while after a prolonged period of ischemia causes the injury to myocardium and know as ischemic-reperfusion injury (I-R) (Buckberg, 1981; Kloner, 1993).

Ischemic reperfusion injury has been well demonstrated to cause organ damage in the brain, heart, lung, liver, kidney and skeletal muscle (Novgorodov and Gudz, 2009). A number of therapeutic strategies such as controlled reperfusion, preconditioning and several pharmacological interventions, for example, adenosine (Lozza et al., 1997; Moukarbel et al., 2004), renin angiotensin system (Paz et al., 1998), calcium angiotensin (Segawa et al., 2000) have show to reduce ischemic reperfusion induced myocardial injury.

Concept of preconditioning

The strategy to prevent I-R injury was given by murry and coworkers in 1986. They showed that brief intermittent periods of sublethal ischemia followed by reperfusion have a protective effective on myocardial tissue against prolonged ischemic insult which is called "ischemic preconditioning" (IPC) (Murry et al., 1986; Tomai et al., 1999). This potent cardio protective strategy has been observed in all animal species examined to date including mammals (Cohen et al., 1991). Ischemic preconditioning is found to be a biphasic phenomenon, an early phase which starts within minutes and get wanes off gradually within 2-3 hours and called as classical preconditioning (Downey and Cohen, 1997; Yellow and Downey, 2003).

Heart rennin angiotensin system

The HRAS (Heart Renin-Angiotensin System) is intergrally involvement in the homeostasis of cardiovascular. The clinical application of the HRAS (Heart Renin Angiotensin System) is determine by the ACE inhibitors beneficial effect show, which block the conversion of Angiotensin I to Angiotensin II, in several pathological conditions. (Kenneth et al., 1992) and Angiotensinogen, Ang I (Angiotensin I), Ang II (Angiotensin II), ACE (Angiotensin Converting Enzyme), ACE II (Angiotensin Converting Enzyme II), Ang 1-7 (Angiotensin 1-7), Ang 1-9 (Angiotensin 1-9) andAng 1-5 (Angiotensin 1-5) is a parts of heart rennin Angiotensin system or present in the heart. Angiotensinogen convert in to the Ang I (Angiotensin I)by the rennin Rennin, a proteolytic enzyme, Ang I (Angiotensin I) convert in to the Ang II (Angiotensin II) with the help of ACE (Angiotensin converting enzyme) and Ang II (Angiotensin II) is the responsible for vasoconstriction and Ang I (Angiotensin I) convert in to the Angiotensin 1-9 with the help of ACE II

(Angiotensin Converting Enzyme II), Ang II (Angiotensin II) convert in to the Ang 1-7 (Angiotensin 1-7)with the help of ACE (Angiotensin Converting Enzyme), Angiotensin 1-9 convert in to the the Ang 1-7 (Angiotensin 1-7) and the Ang 1-7 (Angiotensin 1-7) is the responsible for vasodilation, Ang 1-7 (Angiotensin 1-7) convert in to the Ang 1-5 (Angiotensin 1-5) with the help ofACE (Angiotensin Converting Enzyme) and other conversion ofAng I (Angiotensin I) to Ang 1-7 (Angiotensin 1-7) by the NEP (Neprilysin Endopeptide) (Ryu et al., 2007).

Cardiacangiotensin

Cardiac angiotensin may negatively increase myocardial biotransformation and prove the ventricular arrhythmia during in the perfusion and ischemia induced cardiac muscle injury. Local Ang (Angiotensin) may activate the contractibility of heart and angiotensin may enhance the growth of cardiac myocytes and give to the developing of cardiac hypertrophy in hypertension (high blood pressure). Recently data define the pharmacologic inhibitors of heart ACE (Angiotensin Converting Enzyme) have an important role play in heart failure or hypertrophy and ischemia. Cardiac Angiotensin has been found in dog, (Lee et al., 1996) rat heart (Dostal et al., 1992) and human heart (Sawa et al., 1992) as well as in adult rat heart of fibroblast, myocytes and neonate (Sawa et al., 1992; Dostal et al., 1992)Angiotensin has been found in the adult human: Angiotensin low amount present in the cardiac atria and valves, Coronary vessels, moderate amount in Ventricles and high amount present in conductive system.

Cardiac angiotensin converting enzyme (ACE)

Cardiac ACE (Angiotensin converting enzyme) has been found in rat heart and human heart as well as in adult rat heart of fibroblast, myocytes. Angiotensin has been found in the adult human, Cardiac ACE (Angiotensin converting enzyme) high amount present in the cardiac atria, Fibroblasts and Cardiac ACE (Angiotensin converting enzyme) moderate amount in Ventricles and Cardiac ACE (Angiotensin converting enzyme) low amount present in cardiac Valves and conductive system. Angiotensin has been found in the adult rat, Cardiac ACE (Angiotensin converting enzyme) high amount present in cardiac atria, Valves, Coronary vessels, Myocytes and Cardiac ACE (Angiotensin converting enzyme) low amount present in Conduction system and moderate amount present in cardiac myocytes, Fibroblasts in neonate and Ventricles.(David et al., 1999)

Angiotensin converting enzyme 2 (ACE 2)

ACE 2 (Angiotensin converting enzyme 2) is a peptide that catalyzes the transformation of Ang I (Angiotensin I) to the non-apeptide Ang 1-9 (Angiotensin 1-9) (Walmor et al., 2000), or the change of Angiotensin II to Angiotensin 1-7 (Raman et al., 1995). ACE 2 has direct impacts on cardiovascular function, and is communicated overwhelmingly in endothelial vascular cells of the cardiac and the renal. (Brosnihan et al., 1999) and the Localization of ACE2 (Angiotensin converting enzyme 2) in arterial, venous endothelial cells and arterial smooth muscle cell in all organs studied and cardiac myocytes, myofibroblasts, smooth muscles cell of intramyocardial vessels, thoracic aorta, veins and carotid arteries. (Lawata et al., 2011; Hamming et al., 2004; Shi et al., 2010)

Role of Heart Renin Angiotensin System in pathological conditions

In Diabetes: The expression of heart renin, ACE and Angiotensin II get increase during diabetes which leads to increase myocardial infarct size by several endogenous mechanisms including decreases the nitric oxide, increase the expression of caveolin, decrease the activity of heme oxygenase-1during diabetes (Frustaci et al., 2000; Schernthaner et al., 1984; Kakadiya et al., 2010; Tessari et al., 2010; Katyal et al., 2013; Chen et al., 2015). However, the recent discovery of a new element of RAAS, ACE2 (Angiotensin Converting Enzyme 2) and its peptide like Angiotensin(1-7) and Angiotensin(1-9) can expression get decreased which subsequently decrease the release of nitric oxide expression in diabetic myocardium which also lead to increase in myocardial infarct size during diabetes and ACE 2 activation increases the release of nitric oxide. (Patel et al., 2014; Kakadiya et al., 2010; Fraga-Silva et al., 2014)Moreover, it has been documented that ACE inhibitor, Angiotensin II antagonist and ACE 2 activator decrease the myocardial infarct size (Y et al., 2011; Martinez et al., 2003; Qi et al., 2013). The cardioprotective effects of ischemic preconditioning (IPC) get attenuate during in the diabetic heart which leads to myocardial injury (Ajmani et al., 2011). Angiotensin II Antagonist (Valsartan) and ACE inhibitor like zofenoprilat and enalaprilat both significantly increase of nitric oxide production and decrease the expression of caveolin (Maraghy et al., 2014; Ling et al., 2011; Bucci et al. 2008). So, ACE inhibitors, Angiotensin II antagonist and ACE 2 activators can be a promising approach to restore the cardio protective effect of ischemic preconditioning (IPC) during in the diabetic rat heart (Yang et al, 2009; Brown et al., 1998).

In Hypertension: It has been documented that the activity of Heart Renin Angiotensin System gets upregulated in hypertension (Richard et al., 2009). The expression of heart renin, ACE and Angiotensin II increase during hypertension which leads to increase myocardial infarct size by several endogenous mechanisms including decreases in nitric oxide, the expression of caveolin increase, and reduces the activity of heme oxygenase-1 during hypertension (Richard et al., 2009; Shiota et al., 1992; Mazzolai et al., 2000; Camilletti et al., 2001; Grayson et al., 2007; Elmarakby et al., 2012; Yamamoto et al., 1992; Harms et al., 2000).

However, the recent discovery of a new element of RAAS, ACE2 (angiotensin converting enzyme 2) and its peptide like Angiotensin(1-7) and Angiotensin(1-9) can expression get decreased which subsequently decrease the release of nitric oxide expression in hypertension myocardium which also lead to increase in myocardial infarct size during hypertension and ACE 2 activator the releases of nitric oxide increases. (Danilczyk et al., 2006; Camilletti et al., 2001; Yamamoto et al., 1992; Fraga-Silva et al., 2014) Moreover, it has been documented that ACE inhibitor, Angiotensin II antagonist and ACE 2 activator decrease the myocardial infarct size (Y et al., 2011; Martinez et al., 2003; Qi et al., 2013). The cardioprotective effects of ischemic preconditioning get attenuated in hypertension which leads to myocardial injury (Balakumar et al., 2009; Ravingerova et al., 2011; Yamamoto et al., 1992). Angiotensin II Antagonist (Valsartan) and ACE inhibitor like zofenoprilat and enalaprilat both significantly increase of nitric oxide production and decrease the expression of caveolin (Maraghy et al., 2014; Ling et al., 2011; Bucci et al. 2008) So, ACE inhibitors, Angiotensin II antagonist and ACE 2 activators can be a promising approach to restore the cardioprotective effect of ischemic preconditioning (IPC) in hypertension rat heart (Yang et al, 2009; Brown et al., 1998).

In Heart Failure: It has been documented that the activity of heart renin angiotensin system gets upregulated in diabetes (Barluchhi et al., 2001). The expression of heart Angiotensin II get increase during heart failure which leads to increase myocardial infarct size by several endogenous mechanisms including decreases in nitric oxide, increase the expression of caveolin, decrease the activity of heme oxygenase-1 during heart failure (Plokker et al., 2006; Shavadia et al., 2015; Uray et al., 2003; Arnal et al., 1998; Grebellus et al., 2002; Ding et al., 2008). However, the recent discovery of a new element of RAAS, ACE2 (Angiotensin converting enzyme 2) and its peptide like Angiotensin$^{(1-7)}$ and Angiotensin$^{(1-9)}$ can expression get decreased which subsequently decrease the release of nitric oxide expression in heart failure myocardium which also lead to increase in myocardial infarct size during heart failure and ACE 2 activation increases the release of nitric oxide. (Wang et al., 2015; Arnal et al., 1998; Shavadia et al., 2015; Fraga-Silva et al., 2014) Moreover, it has been documented that ACE inhibitor, Angiotensin II antagonist and ACE 2 activator decrease the myocardial infarct size (Y et al., 2011; Martinez et al., 2003; Qi et al., 2013). The cardioprotective effects of ischemic preconditioning get attenuated in heart failure which leads to myocardial injury (Seeger et al., 2011). Angiotensin II Antagonist (Valsartan) and ACE inhibitor like zofenoprilat and enalaprilat both significantly increase of nitric oxide production and decrease the expression of caveolin (Maraghy et al., 2014; Ling et al., 2011; Bucci et al. 2008) So, ACE inhibitors, Angiotensin II antagonist and ACE 2 activators can be a promising approach to restore the cardio protective effect of ischemic preconditioning (IPC) in heart failure (Yang et al, 2009; Brown et al., 1998).

Reference

1. Ajmani P, Yadav H.N, Singh M, Sharma P.L. "Possible involvement of caveolin in attenuation of cardioprotective effect of ischemic preconditioning in diabetic rat heart". *BMC Cardiovascular Disorders* (2011) 11:43.
2. Baker K.M, Booz G.W, Dostal D.E. "Cardiac Action Of Angiotensin II: Role Of An Intracardiac Renin Angiotensin System". *Annu Rev Physiol.* (1992) 54: 227-41.
3. Baker K.M, Campanile M.P, Trachte G.J, Peach M.J. "Identification and characterization of the rabbit angiotensin II myocardial receptor". *Circ Res.* (1984) 54:286–293.
4. Balakumar P, Singh H, Singh M, Srivastava A. "The impairment of preconditioning-mediated cardioprotective in pathological conditions". *Pharmacological Research.* (2009) 60:18-23.
5. Barlucchi L, Leri A, Dostal D.E, Fiodaliso F, Tada H, Hintze T.H, Kajstura J, Nadal-Ginard B, Anversa P. " Canine Ventricular Myocytes Possess a Renin-Angiotensin System That Is Upregulated With heart failure". *Circulation Research.* (2001) 88:298-304.
6. Brosnihan K.B, Senanayake P.S, Li P. and Ferrario C.M. "Bi-directional actions of estrogen on the renin-angiotensin system". *Brazilian Journal of Medical and Biological Research* (1999) 32:373-381.
7. Brown N.J, Vaughan, D.E. "Angiotensin-Converting Enzyme Inhibitors". *Circulation*. (1998) 97:1411-1420.
8. Camilletti A, Moretti N, Giachetti G, Faloria E, Martarelli D, Mantero F and Mazzanti L. Decreased nitric oxide levels and increased calcium content in platelets of hypertensive patients. *Am J Hypertension.* 2001; 14(4):382-6.
9. Chen QY, Wang GG, Li W, Jiang YX, Lu XH, and Zhou PP. Heme Oxygenase-1 Promotes Delayed Wound Healing in Diabetic Rats. *Journal of Diabetes Research.* 2016; 9726503; 10.
10. Chiu A.T, Herblin W.F, McCall D.E, Ardecky R.J, Carini D.J, Duncia J.V, Pease L.J, Wong P.C, Wexler R.R, Johnson A.L, Timmermans P. "Identification of angiotensin II receptor subtypes". *Biochem Biophys Res Commun*. (1989) 165:196–203.
11. Danilczyk U, Penninger J.M. "Angiotensin-Converting Enzyme II in the Heart and the Kidney". *Circ Res.* (2006) 98:463-471.
12. Danilczyk, U., Sarao, R., Remy, C., Stange, G., Richter, A. "Essential role for collection in renal amino acid transport, Nature" (2006), vol. 444, 1088-191.
13. Danser A.H.J, van Kesteren C.A.M, Bax W.A, Tavenier M, Derkx F.H.M, Saxena P.R, Schalekamp M.A.D.H. "Prorenin, renin, angiotensinogen, and angiotensin converting enzyme in normal and failing hearts: evidence for renin binding". *Circulation.* (1997). 96:220–226.
14. David E. Dostal, Kenneth M. Baker "The Cardiac Renin-Angiotensin System Conceptual, or a Regulator of Cardiac Function?" *Circ Res.* (1999) 85:643-650.
15. Derkx F.H, Steunkel C, Schalekamp M.P, Visser W, Huisveld I.H, Schalekamp M.A. "Immunoreactive renin, prorenin, and enzymatically active renin in plasma during pregnancy and in women taking oral contraceptives". *J Clin Endocrinol Metab*. (1986) 63:1008–1015.
16. Dervim E., Erguder IB., Ozbek H., Durak I. High-cholesterol diet increases xanthine oxidase and decreases

nitric oxide synthase activities in erythrocytes from rats. *Nature Research.* 2008; 28(3):212-5.

17. Dostal D.E, Rothblum K.C, and Baker K.M. "An improved method for absolute quantification of mRNA using multiplex polymerase chain reaction: determination of renin and angiotensinogen mRNA levels in various tissues". *Anal Biochem.* (1994). 223:239–250.
18. Dostal DE, Rothblum KC, Chernin MI, Cooper GR, and Baker KM. "Intracardiac detection of angiotensinogen and renin: a localized renin-angiotensin system in neonatal rat heart". *American J Physiol.* (1992). 263:C838–C863.
19. Dostal, D.E., Baker, K.M. "The Cardiac Renin-Angiotensin System Conceptual or a Regulator of Cardiac Function". *Circ Res.*, (1999).85, 643-650.
20. Ekholm M, Kahan T, Jorneskog G, Broijersen A, Wallen N. H. "The infusion of angiotensin ii increases fibrinolysis in healthy individuals but not in patient with familial combined hyperlipidemia". *Blood Coagulation & Fibrinolysis*. (2016) 27:113-116.
21. Elhemely M.A, Omar H.A, Ain-shoka A.A, Abd El-Latif H.A, Abo-youssef A.M, El Sherbiny G.A. "Rosuvastation and ellagic acid protect against isoproterenol-induced myocardial infarction in hyperlipidemia rats". *Beni-Suef University Journal Of Basic and Applied Sciences*. (2014) 3:239-246.
22. Elmarakby AA, Faulkner J, Baban B, and Sullivan JC. Induction of Hemeoxygenase-1 Reduces Renal Oxidative Stress and Inflammation in Diabetic Spontaneously Hypertensive Rats. *International Journal of Hypertension.* 2012; 957235: 11.
23. Endo-Mochizuki Y, Mochizuki N, Sawa H, Takada A, Okamoto H, Kawaguchi H, Nagashima K, Kitabatake A. "Expression of renin and angiotensin-converting enzyme in human hearts". *Heart Vessels.* (1995). 10:285–293.
24. Feron O., Dessy C., Moniotte S., Desager JP. Baligand JL. Hypercholesterolemia decreases nitric oxide production by promoting the interaction of caveolin and endothelial nitric oxide synthase. *J Clin Invest.* 1999; 103(6):897-905.
25. Fraga-Silva R A., Costa Fraga FP., Montecucco F., Sturny M., Faye Y., Mach F., Pelli G., Shenoy V., Rafaela F., Silva D., Raizada MK., Santos RAS., Stergiopulos N. Diminazene protect corpus cavernosum against hypercholesterolemia-induced injury. *Journal of sexual medicine*. 2014:26852848.
26. Gordon D.B. "The Role of Renin Substrate in Hypertension". *Hypertension.*(1983) 5:353-362.
27. Goyal A, Semwal B.C, Yadav H.N. "Abrogated cardioprotective effect of ischemic preconditioning in ovariectomized rat heart". *Hum Exp Toxicol*. 2015 Aug 11. pii: 0960327115597980.
28. Grayson TH, Ohms SJ, Brackenbury TD, Meaney KR, Peng K, Pittelkow YE, Wilson SR, Sandow SL and Hill CE. Vascular microarray profiling in two models of hypertension identifies caveolin-1, Rgs2 and Rgs5 as antihypertensive targets. *BMC Genomics* 2007, 8:404.
29. Hamming I., Timens, W., Bulthuis, M.L., Lely, A.T., Navis, G. (2004).Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol.*, 203(2):6317.
30. Hamming, I., Timens, W., Bulthuis, M.L., Lely, A.T., Navis, G. "Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis". *J Pathol,* (2004). 203(2) 6317.
31. Harm H, Wiegand F, Megow D, Prass K, Einhaupl K.M, Dirnagl U. "Acute treatment of hypertension increases infarct sizes in spontaneously hypertension rats". *Neuroreport*. (2000) 7:355-9.
32. Hein L. "Genetic deletion and overexpression of angiotensin II receptors". *J Mol Med*. (1998) 76:756–763.
33. Hoshi, F.R., Nakamoto, H., Imai, H., Kanno, Y., Ishida Y., Suzuki, H. "Estrogen and Angiotensin II Interactions Determine Cardio-Renal Damage in Dahl Salt-Sensitive Rats with Heart Failure". *Am J Nephrol,* (2008) 28:413–423?
34. Jesmin S, Mowa C, Thompson M, Zaedi S and Miyauchi T. "Endothelin Angiotensin reverses Upregulated Renin Angiotensin System in the hypertrophy heart of stroke prone spontaneously hypertrophy rat". The FASEB Journal. (2007) 21: 710-09.
35. Katyal T and Budhiraja RJD. Combination of daidzein and hemin halts the progression of development of experimental diabetic nephropathy in rats. *Der Pharmacia Lettre*, 2013, 5 (4):326-334.
36. Kokkonen J.O, Saarinen J, Kovanen P.T. "Regulation of local angiotensin II formation in the human heart in the presence of inhibition of chymase by protease inhibitors of interstitial fluid and ofangiotensin-converting enzyme by Ang-(1–9) formed by heart carboxypeptidase a-like activity". *Circulation*. (1997) 95:1455–1463.
37. Koyanagi S, Eastham C.L, Harrison D.G, and Marcus M.L. "Increased Size of Myocardial Infarction in Dogs with Chronic Hypertension and Left Ventricular Hypertrophy". *Circ Res* (1982)50: 55-62.
38. Lee YA, Liang CS, Lee MA, Lindpaintner K. "Local stress, not systemic factors, regulates gene expression of the cardiac renin-angiotensin system in vivo: a comprehensive study of all its components in the dog". *Proc Natl Acad Sci UfSf*A. (1996) 93:11035–11040.
39. Lindpaintner D, Lu W, Niedermajer J, Schieffer B, Just H, Ganten D, Drexler H. "Selective activation of cardiac angiotensinogen gene expression in post-infarction ventricular remodeling in the rat". *J Mol Cell Cardiol.* (1993). 25:133–143.
40. Lindsey, S.H., Cohen, J.A.,Brosnihan, K.B., Gallagher, P.E.,and Chappell, M.C. Chronic Treatment with the G Protein-Coupled Receptor 30 Agonist G-1 Decreases Blood Pressure in Ovariectomized mRen2.Lewis Rats. *Endocrinology*, (2009) 150(8):3753–3758.
41. Lwai N, Shimoike H, Kinoshita M. "Cardiac Renin-Angiotrnsin system in the hypertrophy heart". *American Heart association.* (1995) 92: 520-21.
42. Lwata M., Cowling, R.T., Yeo, S.J., and Greenberg, B. (2011). Targeting the ACE2-Ang-(1–7) Pathway in Cardiac Fibroblasts to treat cardiac remodeling and heart failure. *J Mol Cell Cardiol*. 51(4): 542–547.
43. Martnez L.A, Molina R.V. "Early and chronic captopril or losarten therapy reduce infarct size and avoids congestive heart failure after myocardial infarction in rats". *Science Direct* (2003) 34:357-361.
44. Mazzolai L, Nussberger J, Jean-Francois A, Brunner DB, Gabbiani G, Brunner HR, Pedrazzini T. "Blood pressure-independent cardiac hypertrophy induced by locally activated renin-angiotensin system". *Hypertension*. (1998) 31:1324–1330.
45. Mazzolai L, Pedrazzini T, Nicoud F, Gabbiani G, Brunner H.R, Nussberger J. "Increased Cardiac Angiotensin II Levels Induce Right and Left Ventricular Hypertrophy in Normotensive Mice". *Hypertension*. (2000) 35:985-991.
46. Minicucci M.F, Azevedo P.S, Polegato B.F, Paiva S.A.R, Zornoff L.A.M." Heart Failure After Myocardial Infarction: Clinical Implications and Treatment". *Clin. Cardiol.* (2011) 34:410–414.

47. Nickenig G. "Should Angiotensin II Receptor Blockers and Statins Be Combined". *Circulation*. (2004)110:1013-1020.
48. Obercyger M.H., Graeve L, and Madar Z. A high-cholesterol diet increases the association between caveolae and insulin receptors in rat liver. J. Lipid Res. 2009. 50:98–107.
49. Patel V.K, Parajuli N, and Oudit G.Y, "Role of angiotensin-converting enzyme 2 (ACE2) in diabetic cardiovascular complications". *Clinical Science* (2014) 126, 471–482.
50. Paul, M., Poyan, M.A., Kreutz, R. "Physiology of local rennin-angiotensin system". *Physiol. Rev*. (2006) 86(3):747-803.
51. Qi Y.F, Zhang J, Cole-Jeffrey C.T, Shenoy V, Espejo A, Hanna M, Song C, Pepine C.J, Katovich M.J, Raizada M.K. "Diminazene Aceturate Enhances Angiotensin-Converting Enzyme 2 Activity and Attenuates Ischemia-Induced Cardiac Pathophysiology". *Hypertension.* (2013) 62:746-752.
52. Raman V.K, Lee Y.A, Lindpaintner K. "The cardiac renin-angiotensin-aldosterone system and hypertensive cardiac hypertrophy. "Am J Cardiol. (1995):76(13):18D-23D.
53. Ravingerova T, Bernatova I, Matejikova J, Ledvenyiova V, Nemcekova M, Pechanova O, Tribulova N, Slezak J. "Impaired cardiac ischemic tolerance in spontaneously hypertensive rats is attenuated by adaptation to chronic and acute stress". *Exp Clin Cardiol*. (2011) 16:23-29.
54. Re R.N. "Obesity-Related Hypertension". *The Ochsner Journal*. (2009)9:133–136.
55. Rioux F, Park W.F, Regoli D. "Characterization of angiotensin receptors in rabbit isolated atria". *J Physiol Pharmacol*. (*1975*) *54:229*–237.
56. Sawa H, Tokuchi F, Mochizuki N, Endo Y, Furuta Y, Shinohara T, Takada A, Kawaguchi H, Yasuda H, Nagashima K. "Expression of the angiotensinogen gene and localization of its protein in the human heart". *Circulation.* (1992)86:138–146.
57. Schernthaner G, Schwarzer C.H, Kuzmits R, Muller M.M, Klemen U, Freyler H. "Increased angiotensin-converting enzyme activities in diabetes mellitus: analysis of diabetes type, state of metabolic control and occurrence of diabetic vascular disease". *J Clin Pathol* (1984) 37:307-312.
58. Seeger J.PH, Benda N.MM, Riksen N.P, Dijk A.P.J.V, Bellersen L, Hopman M.TE, Cable N.T, Thijssen D. HJ. "Heart failure is associated with exaggerated endothelial ischemia-reperfusion injury and attenuated effect of ischemia preconditioning". *European journal of preventive cardiology*. (2016) 23:133-40.
59. Shavadia J, Zheng Y, Maleki N.D, Huber K, Halvorsen S, Goldstein P, Gershlick A.H, Wilcox R, Werf F.V.D, Armstrong P.W. "Infarct Size, Shock, and Heart Failure: Does Reperfusion Strategy Matter in Early Presenting Patients With ST-Segment Elevation Myocardial Infarction?". *J Am Heart Assoc.* (2015) 4:10-1161.
60. Shi L., Mao. C., Xu, Z. and Zhang, L. (2010). Angiotensin-converting enzymes and drug discovery in cardiovascular diseases. Drug Discov Today. 15(9-10): 332–341. *Drug Discov Today*. 15(9-10): 332–341.
61. Shiota N, Miyazaki M, Okunishi H. "Increase of angiotensin converting enzyme gene expression in the hypertensive aorta". *Hypertension*. (1992) 20:168-74.
62. Singh V.P, Le B, Khode R, Baker K.M, and Kumar R. "Intracellular Angiotensin II Production in Diabetic Rats Is Correlated With Cardiomyocyte Apoptosis, Oxidative Stress, and Cardiac Fibrosis". *Diabetes* (2008) 57:08-0805.
63. Stamler J. "The INTERSALT study: background, methods, figures, and implications". *Am J Clin Natr*. 65:626-642.
64. Stygar D., Sawczyn T., Skrzep-Poloczek B., Poloczek J., Kłosok M., Karcz-Socha I., Fink J.M., Skonieczna M., Elsner M., Doleżych B., Żwirska-Korczala K., and Karcz W.K. Metabolic surgery in Zucker rats influenced miRNA, caveolin-1 expression and lipid metabolism. *Open Life Sci*. 2015;10:451–460.
65. Tsutomu, Y., Issei, K., and Yoshio, Y., "Role of the renin-angiotensin system in cardiac hypertrophy". *The American Journal of Cardiology*(1999). Volume 83, Issue 12, Supplement 1, Pages 53–57
66. Van de wal R.M, Plokker H.W, Lok D.J, Boomsma F, Van der Horst F.A, Van Veldhuisen D.J, Van Gilst W.H, Voors A.A. "Determination of increases angiotensin ii level in severe chronic heart failure patient despite ACE inhibition". *Int J Cardial.* (2006) 26:106(3):367-72.
67. Victor J. Dzau, "Cardiac renin-angiotensin system". The American journal of medicine. (1988). volume 84, issue 3, supplement 1, page 22-27.
68. Victor J. Dzau, "Cardiac renin-angiotensin system". The American journal of medicine. (1988). volume 84, issue 3, supplement 1, page 22-27.
69. Walmor C. De Mello, A.H. Jan Danser. "Angiotensin II and the Heart on the Intracrine Renin-Angiotensin System". *Hypertension*. (2000)35:1183-1188.
70. Wang H, Jessup J.A, and Groban L. "Characterization of the Cardiac Renin Angiotensin System in Oophorectomized and Estrogen-Replete mRen2.Lewis Rats". *Plos one* (2013) 8:10-1371.
71. Wang J, Li N, Gao F, Song R, Zhu S, Geng Z. " Balance between angiotensin converting enzymes 2 in patient with chronic heart failure". *J Renin Angiotensin Aldosterone Syst.* (2015) 16:553-8.
72. Yadav H.N, Singh M, Sharma P.L. "Modulation of the cardioprotective effect of ischemia preconditioning in hypertension rat heart". *European Journal of pharmacology*. (2010) 643:78-83.
73. Yamamota S, Golanov E.V, Berger S.B, Reis D.J. "Inhibition of nitric oxide synthesis increases focal ischemia infarction in rat. *J Blood Flow Metab* (1992) 12:717-726.
74. Yang J, Jiang H, Yang J, Ding J.W, Chen L.H, Li S, Zhang X.D. "Valsartan preconditioning protect against myocardial ischemia reperfusion injury through TLR4/NF-kappaB signaling pathway". *Mol Cell Biochem.* (2009) 330:39-46.
75. Ye Y, Qian J, Castillo A.C, Perez-Polo J.R, Birnbaum, Y. "Aliskiren and Valsartan reduce myocardial AT1 receptor expression and limit myocardial infarct size in diabetes mice. *Journal article* (2011) 25:505-515.
76. Zhang G., Li M., Xu Y., Peng L., Yang C., Zhou Y., Zhang J. Antioxidation effect of simvastatin in aorta and hippocampus: A rabbit model fed high-cholesterol diet. Oxidative Medicine and Cellular Longevity 2016; 6929306:8.
77. Zhang X, Dostal D.E, Reiss K, Cheng W, Kajstura J, Li P, Huang H, Sonnenblick E.H, Meggs L.G, Baker K.M, Anversa P. "Identification and activation of autocrine renin-angiotensin system in adult ventricular myocytes". *Am J Physiol.* (1995). 269:H1791–H1802.