

## Role of renin angiotensin system in ischemic preconditioning

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### 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 preconditioning (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 renin 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) and Ang 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 of ACE (Angiotensin Converting Enzyme) and other conversion of Ang I (Angiotensin I) to Ang 1-7 (Angiotensin 1-7) by the NEP (Neprilysin Endopeptide) (Ryu et al., 2007).

### Cardiac angiotensin

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-peptide 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-1 during diabetes (Frustraci 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<sup>(1-7)</sup> and Angiotensin<sup>(1-9)</sup> 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).

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