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Article

Role of caveolin-eNOS platform and mitochondrial ATP-sensitive potassium channel in abrogated cardioprotective effect of ischemic preconditioning in postmenopausal women

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Caveolin, the protein of the caveolar membrane, interacts and binds with endothelial nitric oxide synthase (eNOS), forming a caveolin-eNOS complex leading to suppression of the eNOS activity. Caveolin, therefore, maintains eNOS in the inactivated state leading to reduced nitric oxide (NO) production. Ischemic preconditioning disrupts the caveolin-eNOS complex leading to activation of the eNOS and thus results in cardioprotection. During ischemic preconditioning, NO produces cardioprotection by the opening of the K_{ATP} channel, and the caveolin forms a suitable signalling platform facilitating the interaction of NO with the K_{ATP} channel. Estrogen deficiency has been reported to upregulate caveolin-1 expression. The article aims to review the various mechanisms that placed the women at the risk of coronary artery diseases after postmenopausal estrogen deficiency and their role in the cardioprotective effect of ischemic preconditioning.

Keywords: Caveolin. Nitric oxide. Mito K_{ATP}. Ischemic preconditioning. Postmenopause.

INTRODUCTION

Coronary artery disease (CAD) or ischemic heart disease is related to the stenosis of the coronary artery along with the arteriosclerosis. Sudden reperfusion of an ischemic heart induces a series of adverse events resulting in myocardial damage called as ischemia-reperfusion injury (I/R injury) (Collard, Gelman, 2001; Kloner, 1993). CAD is the leading cause of mortality in industrialised countries, and the major risk factors include family history, lack of exercise, obesity, diabetes, smoking, high blood pressure, and mental stress. Treatment can be done through percutaneous transluminal coronary angioplasty, cardiac valve replacement, and bypass-grafting of coronary artery and each of them could be treated according to the extent and health of the patients (Go *et al*., 2013). Despite improved surgery, ischemia and reperfusion remain a major cause of myocardial injury during cardiac surgery (Liu *et al*., 2012; Marczak *et al*., 2012). Reperfusion is necessary for the recovery of ischemic myocardium from infarction. Still, it also leads to irreversible myocardial damage, and thus the protection of the myocardium from ischemia-reperfusion injury during surgery remains significant (Han *et al*., 2013). Ischemic preconditioning (IPC) is one of the most effective ways of protecting the myocardium from ischemic attacks by various pathways (Murry, Jennings, Reimer, 1986; Snoeckx *et al*., 1993; Ferdinandy, Schulz, Baxter, 2007; Marina Prendes *et al*., 2007). However, the shielding effect of IPC has been proven to be assuaged under certain pathological conditions like hypertension,

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hyperlipidaemia, diabetes, aging and heart failure (Snoeckx *et al*., 1986; Abete *et al*., 1996; Ferdinandy, Szilvassy, Baxter, 1998; Yadav, Singh, Sharma, 2010a; 2010b; Ajmani *et al*., 2011). Interestingly, it has been seen that the likelihood of the incidence of CAD is higher in men than in women. Nevertheless, the incidence of CAD in women after menopause is the same as in men of the same age (Barrett-Connor, 1997; Clarkson *et al*., 1997). Therefore, in this review, we are focusing on the mechanisms responsible for putting the women at the risk of CAD after postmenopausal estrogen deficiency and their involvement in the cardioprotective effect of IPC.

METHODS

Appropriate studies were collected through Pubmed, Medline, Scopus, Google Scholar online searches. The terms "ischemia-reperfusion," "ischemia-reperfusion injury," or "ischemic preconditioning," along with "nitric oxide," "mito K_{ATP}," "caveolin," "postmenopause," "ovariectomized,"were used for searching. Besides, we looked for the bibliographies of relevant studies, reports, and editorial letters for writing this review.

Ischemic reperfusion injury

Myocardial ischemia occurs when the blood supply to the heart is inadequate (Gasser *et al*., 1994). Early restoration of blood flow, i.e., reperfusion, is necessary for the survival of ischemic heart (Anaya-Prado, 2002). However, reperfusion after a prolonged period of ischemia itself can elicit a cascade of adverse events that paradoxically causes tissue injury that is called I/R injury (Kloner, 1993; Collard, Gelman, 2001). Ischemia-reperfusion injury leads to myocardial stunning and microvascular injury, which leads to necrosis of myocardium (Ambrosio, Titto, 1999; Yellon, Baxter, 2000).

During ischemia as indicated in Figure 1, there is reduced oxidative phosphorylation, decreased ATP level, and subsequent increase in the concentration of ADP, AMP, and phosphate (Solaini, Harris, 2005; Powers *et al*., 2007). The decrease in ATP activates anaerobic respiration resulting in the reduction of intracellular pH and activation of Na^+/H^+ antiporter (Buja, 2005). The Na^+ that enters this route is normally pumped via Na^+/K^+ ATPase. Still, decreased ATP inhibits this efflux leading to the gradual rise in intracellular Na^+ and subsequent increase in the concentration of intracellular calcium ions (Piper, Abdallah, Schäfer, 2004).

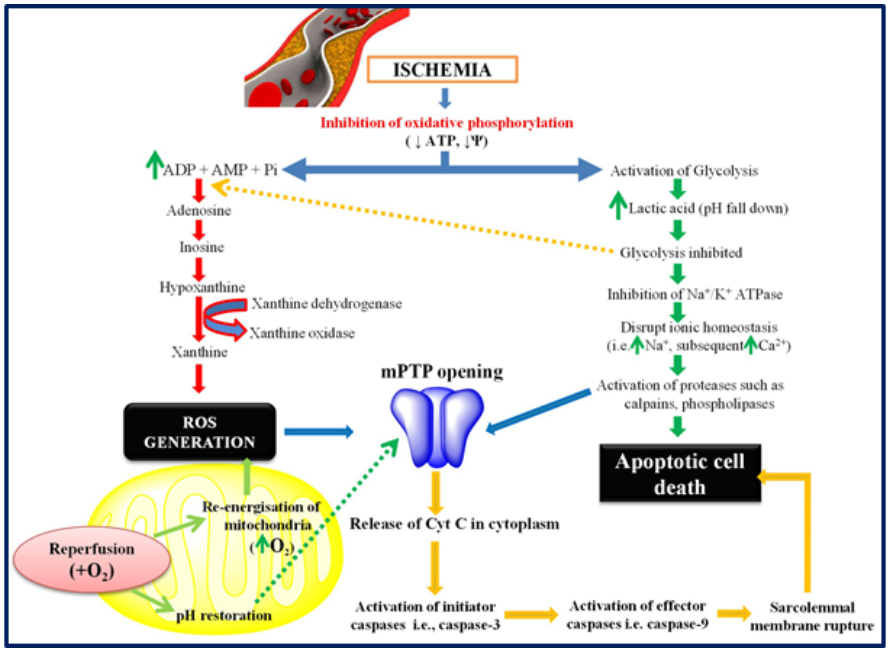

FIGURE 1 - Ischemic Reperfusion Injury.

AMP is converted to adenosine, which gets further converted into inosine and to hypoxanthine (Szocs, 2004). During reperfusion, hypoxanthine is oxidised by xanthine oxidase, which produces reactive oxygen species (ROS). Ischemia-reperfusion leads to the production of ROS from the mitochondria (Detmers *et al*., 1999; Elimadi *et al*., 2001; Becker, 2004) which is reported to damage the cell membranes by lipid peroxidation (Halestrap, Clarke, Javadov, 2004; Halestrap, 2006; Solaini, Harris, 2005). Moreover, in the first few minutes of reperfusion, oxidising agents such as superoxide anion, hydroxyl radical, and peroxynitrite are generated that cause marked damage to the myocardium (Bolli *et al*., 1989). $Ca^{++}$and elevated level of cytosolic ROS is known to open the mitochondrial permeability transition pore (mPTP) (Powers *et al*., 2007; Baines, 2009). mPTP are multiprotein complexes that form non-selective pores in the inner mitochondrial membrane (Powers *et al*., 2007, Baines, 2009) and their opening leads to release of cytochrome C into the cytoplasm and initiates the process of apoptosis through caspase 9 (Cardone *et al*., 1998) and caspase 3 (Zou *et al*., 1997; Weiland *et al*., 2000).

The opening of mPTP causes depolarisation of the inner mitochondrial membrane resulting in a decrease in ATP production, and even stored ATP gets consumed to maintain inner mitochondrial membrane potential (Honda, Korge, Weiss, 2005). Depletion of ATP and elevated Ca^{++} during ischemic insult activate the degradative enzymes such as phospholipases (PLA2) (Ford, 2002) and calcium-activated proteases (calpains) (Chen *et al*., 2002) with inhibition of ATP-dependent cytosolic repair processes due to lack of ATP, eventually resulting in the loss of cellular integrity (Murphy, Steenbergen, 2008).

It has been reported that persistently elevated level of calcium and ROS is responsible for membrane disruption, massive cell swelling, cell lysis (Hausenloy, Yellon, 2004) and ultimately contribute to necrotic cell death (Zong, Thompson, 2006). Necrosis results in rapid loss of plasma membrane integrity due to increased oxidative stress, cytosolic calcium level, and decreased level of ATP (Ermak, Davies, 2002; Bartosz, 2009).

Moreover, I/R injury has been well demonstrated to cause organ damage in the brain, heart, lungs, liver, kidneys, and skeletal muscle (Novgorodov, Gudz, 2009). Several therapeutic strategies such as controlled reperfusion, preconditioning, postconditioning, and several pharmacological interventions, for example, adenosine (Lozza *et al*., 1997; Moukarbel, Ayoub, Abchee, 2004), renin-angiotensin system antagonist (Paz *et al*., 1998), calcium antagonists (Segawa *et al*., 2000), antioxidants (Marczin *et al*., 2003), sodium-hydrogen exchange inhibitors (Hennan *et al*., 2006), iron chelators (Tang *et al*., 2008), N-methylated synthetic sphingolipid analog (Gundewar, Lefer, 2008), flavonoids (Yadav *et al*., 2015) and exenatide (Timmers *et al*., 2009) have shown to reduce ischemia-reperfusion-induced myocardial injury.

Concept of preconditioning

In 1986, Murry and co-workers provided the strategy to prevent I/R injury. They found that short transient periods of sublethal ischemia accompanied by reperfusion protect the myocardial tissue from prolonged ischemic insult, which is known as "Ischemic preconditioning" (IPC) (Murry, Jennings, Reimer, 1986; Tomai *et al*., 1999). This potent cardioprotective strategy has been observed in all animal species examined to date, including mammals (Cohen, Liu, Downey, 1991). Ischemic preconditioning is a biphasic process, an early phase that begins within minutes and slowly decreases within 2-3 hours and called classical preconditioning (Downey, Cohen, 1997; Yellon, Downey, 2003). The other is a late phase that occurs after 12-24 hours of ischemic insult and lasts 3-4 days and called as late phase preconditioning or second window of protection (Kuzuya *et al*., 1993; Marber *et al*., 1993). The early phase IPC only protects from myocardial infarction, but the late phase IPC also protects from myocardial stunning (Bolli, 1996; Sisakiyan, 2008).

Many pharmacological agents have been shown a preconditioning-like effect, i.e., adenosine (Liu *et al*., 1991; Yao, Gross, 1994), bradykinin (Goto *et al*., 1995; Yoshida *et al*., 2005), protein kinase C activators (Ytrehus, Liu, Downey, 1994), ATP sensitive potassium channel openers (Parratt, Kane, 1994; Schulz, Rose, Heusch, 1994), opioids (Schultz *et al*., 1995), norepinephrine (Thornton *et al*., 1993), acetylcholine (Yao, Gross, 1993), α1 adrenergic receptors agonists (Banerjee *et al*., 1993),

estrogen (Lee *et al*., 2002), nitroglycerin (Du *et al*., 2004), sildenafil (Kukreja *et al*., 2005), ang (1-7) (Pachauri *et al*., 2017) atrial natriuretic peptide (ANP) (Charan *et al*., 2016) and heme oxygenase activator (Gupta *et al*., 2017) which is called as pharmacological preconditioning.

Moreover, a brief episode of ischemia followed by reperfusion to other organs produces protection against I/R injury on the heart, and it is known as remote preconditioning (RPC) (Przyklenk *et al*., 1993). Remote preconditioning has also been reported to occur in human beings (Kloner, Jennings, 2001; Walsh *et al*., 2007). Further, brief occlusion of the anterior mesenteric artery protects the heart against infarction is known as mesenteric preconditioning (Gho *et al*., 1996; Santos *et al*., 2008). The brief occlusion of the renal artery offers heart defense against infarction and known as renal preconditioning (Diwan *et al*., 2008). Similarly, brief episodes of aortic occlusion protect against infarction to the heart is known as remote aortic preconditioning (Khanna *et al*., 2008).

Brief episodes of occlusion and reperfusion of the left circumflex artery salvage the myocardium region from subsequent prolonged ischemia provided by the left anterior descending coronary artery. Paradoxically, the transfer of coronary effluent from the preconditioned heart to non-preconditioned heart limits infarct size in the latter against I/R injury, which is called as intracardiac preconditioning (Przyklenk *et al*., 2003; Galagudza *et al*., 2008).

Molecular mechanism of the cardioprotective effect of preconditioning

Preconditioning results in the generation of various endogenous ligands, i.e., adenosine (Liu *et al*., 1991), bradykinin (Goto *et al*., 1995; Cohen *et al*., 2007), opioids (Schultz *et al*., 1995) and norepinephrine (Banerjee *et al*., 1993), acetylcholine (Yao, Gross, 1993) as indicated in Figure 2.

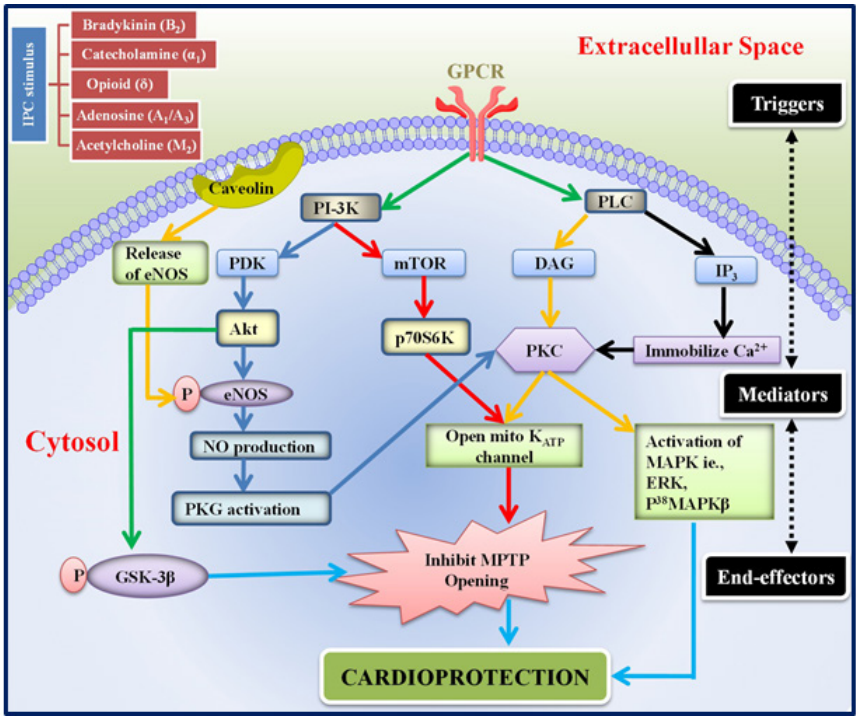

FIGURE 2 - Molecular Mechanism of Early Ischemic Preconditioning.

They bind to their respective G-protein coupled receptors and initiates a cascade of signal transduction, which leads to activation of PI3K (Mocanu *et al*., 2002) and phospholipase C (Tyagi, Tayal, 2002). Activated

PI3K generates phosphatidyl-inositol 3,4,5-triphosphate (PIP3) from cell membrane lipid phosphatidylinositol 3,4-bisphosphate (PIP2) leading to activation of the phosphoinositide-dependent kinase (PDK1) and subsequent activation of protein kinase B (Akt) and p70S6-kinase (Jonassen, Mjos, Sack, 2004; Kis, Yellon, Baxter, 2003). PI3K activation reported to upstream of PKC (Tong *et al*., 2000), GSK3β (Tong *et al*., 2002), and activation of mitochondrial ATP-sensitive K channels (mito K_{ATP}) (Oldenburg *et al*., 2002; Garlid *et al*., 1997). The activated phospholipase C leads to the generation of two-second messengers, diacylglycerol (DAG) and inositol triphosphate (IP3), by hydrolysis of PIP2. The DAG activates protein kinase C by translocating it from cytosol to perinuclear membrane (Mitchell *et al*., 1995; Tong *et al*., 2004). ROS generation during preconditioning also activates PKC (Penna *et al*., 2009; Baines, Goto, Downey, 1997). PKC activation is important in the opening of mito K_{ATP} (Sato, O'Rourke, Marban, 1998; Murphy, 2004). PKC_{ε}, as well as PKCδ, has been demonstrated to mimic preconditioning due to the opening of mito K_{ATP} (Dreixler *et al*., 2008).

The opening of mito K_{ATP} channels can protect the mitochondria from Ca^{2+}overload and prevent cytochrome *c* loss (Garlid *et al*., 1997; Korge, Honda, Weiss, 2002). As potassium enters the mitochondria, it causes them to release free radicals, i.e., ROS (Downey, Cohen, 2006). Although a massive burst of ROS leads to cell damage, a moderate release of ROS during nonlethal short episodes of ischemia play a significant triggering role in the signal transduction pathways of IPC (Vanden *et al*., 1998). PKC_{ε} also forms a complex with mitochondrial permeability transition pore (mPTP) (Baines *et al*., 2003; Zoratti *et al*., 2009), which leads to decrease in the release of cytochrome C and apoptotic cell death (Kroemer, Dallaporta, Resche-Rigon, 1998; Hausenloy, Yellon, 2004).

Clinical aspects of ischemic preconditioning

Numerous studies have been well demonstrated the clinical potential of preconditioning in patients of ischemic heart disease. Various *in vivo* models of ischemic preconditioning in human myocardium have been shown including warm-up phenomenon, preinfarction angina, angioplasty studies, and other surgical studies (Yellon, Downey, 2003). The ischemic preconditioning phenomenon was well demonstrated in the human atrial muscle of patients undergoing coronary artery bypass graft surgery (CABG) (Walker *et al.,* 1994). Other invitro studies also indicated that the δ-opioid receptor as a trigger in human myocardium subjected to ischemic preconditioning (Bell *et al*., 2000). Myocardial biopsies were taken after 10min of cross-clamping exhibited significantly higher content of ATP and reduced release of troponin (Tomai *et al*., 1999; Ylitalo, Peuhkurinen, 2000). Pharmacological recruitment of protection using adenosine (Mentzer *et al*., 1997), volatile anesthetics, i.e., isoflurane (Belhomme *et al*., 1999; Riess, Stowe, Wartlier, 2004; Frassdorf *et al*., 2009) is another interesting alternative to provide preconditioning mediated cardioprotection in patients undergoing CABG (Tomai *et al*., 1999, Ylitalo, Peuhkurinen, 2000).

The Post-transluminal coronary angioplasty (PTCA) procedure involves repeated intracoronary balloon inflations with intervening periods of perfusion which was characterized by less anginal pain, less ST-segment shift, and lower mean pulmonary artery pressure, despite a reduction in cardiac vein flow and unchanged coronary wedge pressure during second balloon inflation (Yellon, Downey, 2003). Pre-treatment with Nicorandil, a mito K_{ATP} channel opener preconditions the myocardium by preventing the incidence of ventricular arrhythmias and myocardial dysfunction after coronary reperfusion (Kato *et al*., 2001).

Further, adenosine preconditioning decreases the severity of ischemia during the first balloon inflation, and that was significantly improved on subsequent balloon inflations during PTCA (Leesar*et al*., 2003). The warm-up phenomenon improves coronary blood flow and reduced myocardium oxygen consumption during the second period of exertion (Okazaki *et al*., 1993; Marber, Joy, Yellon, 1994). This endogenous adaptation has been studied during successive ergometer or walking tests and during repeated atrial and ventricular pacings (Joy, Cairns, Springings, 1987; Ylitalo, Peuhkurinen, 2000; Ylitalo *et al*., 2001). Patients with pre-infarct angina were found to have smaller creatine kinase output, less

arrhythmias, less stunning and heart failure and better in-hospital outcome after thrombolytic therapy than patients without pre-infarction angina (Anzai *et al*., 1995; Andreotti *et al*., 1996; Kloner *et al*., 1998; Skyschally*et al*., 2005; Yan *et al*., 2009). Pre-infarct angina may activate endogenous antithrombotic or fibrinolytic mechanisms, which gives more time for revascularization procedures (Haider *et al*., 1995; Tomoda, Aoki, 1999).

The findings from many preclinical studies in which cardioprotection has been seen in healthy animal hearts might not be reproducible in the human myocardium due to several factors such as old age, the presence of comorbid disease such as diabetes, hypertension, hypercholesterolemia (Goyal, Agrawal, 2017; Varshney *et al*., 2017). Moreover, the timing and duration of myocardial ischemia, use of pharmacological agents such as oral sulfonylurea drugs or cyclooxygenase 2 inhibitors and practical constraints may complicate preconditioning protocol and limit the benefits of these drugs under such clinical conditions (Schulman, Latchman, Yellon, 2001; Riess, Stowe, Wartlier, 2004).

Role of nitric oxide (NO) in preconditioning

It has been demonstrated that NO is involved in preconditioning induced PKC_{ϵ} translocation (Ping *et al*., 1999). Because inhibition of PI3K leads to the reduction in the generation of NO, it can be concluded that PI3K activates PKC_{ϵ} via eNOS mediated mechanism (Tong *et al*., 2000). Akt also directly activates eNOS (Fulton *et al*., 1999; Dimmeler *et al*., 1999), and NO generated by eNOS is proposed to initiate preconditioning (Ping *et al*., 1999). It has been demonstrated that NO generated during preconditioning is a trigger for late PC (Ping *et al*., 1999), but the role of NO in early PC is controversial (Woolfson *et al*., 1995). The mechanism by which NO activates PKC_{ϵ} is still to be elucidated. Because the antioxidant mercaptopropionyl glycine blocks NO-donor induced late PC (Takano *et al*., 1998), it can be postulated that NO-derived reactive species ($ONOO^-$) may activate PKC_{ϵ} either by direct oxidative modification or via activation of phospholipases (Ping *et al*., 1999). eNOS generates NO, which results in activation of guanylyl cyclase, which via protein kinase G is reported to activate a mitochondrial PKC_{ϵ}, which results in the opening of the mito K_{ATP} channel (Costa *et al*., 2005).

Biology of caveolae

The term Caveolae was coined by Yamada in 1955 to reflect their appearance as "little caves", which is 50-100 nm in diameter (Roth, Porter, 1964). Caveolae are plasma membrane invaginations on the surface of endothelial cells (Palade, 1953). Glenney in 1989 first identified caveolin as a 21-22KDa tyrosine-phosphorylated substrate in chick fibroblasts. Caveolae are the specialized membrane domains, triton insoluble, cholesterol and sphingolipids enriched protein (Garcia-Cardena *et al*., 1997) which form lipid raft with caveolins (Williams, Lisanti, 2004) that serves as organizing centers for cellular signal transduction (Shaul, Anderson, 1998; Patel, Murray, Insel, 2008). Caveolin also possesses a scaffolding domain that facilitates the interaction and organization of signaling molecules to provide coordinated and efficient signal transduction (Okamoto *et al*., 1998).

The caveolin gene family consists of three members that differ in their pattern of expression in different cell types. Caveolin-1 (cav-1) and caveolin-2 (cav-2) are co-expressed in many cell types including adipocytes, endothelial cells, epithelial cells and fibroblast (Scherer *et al*., 1994; Scherer *et al*., 1997) whereas Caveolin-3 (cav-3) is restricted to the skeleton and smooth muscles including cardiac myocytes (Scherer *et al*., 1994; Song *et al*., 1996; Minetti *et al*., 1998; Galbiati *et al*., 2001). It is also found in a variety of other cells, including the immune and nervous system. Cav-1 is a specific marker of caveolae and is up-regulated by oxidized LDL, estrogen deficiency, and hyperglycemia (Sharma, Singh, Sharma, 2011). It serves as a cholesterol-binding protein and helps cholesterol to move from endoplasmic reticulum through the golgi apparatus to the plasma membrane of endothelial cells (Fulton, Gratton, Sessa, 2001). Caveolin is a negative regulator of eNOS as its interaction, and binding suppresses the activity of eNOS by making a caveolin-eNOS complex (Minshall *et al*., 2002; Feron, Balligand, 2006; Koneru *et al*., 2007). Alterations in caveolin/eNOS interaction influence various mechanisms of diseases such as atherosclerosis, diabetes, cirrhosis

(Spieker, Lüscher, Noll, 2001; Elçioglu *et al*., 2010; Xu *et al*., 2008; Ajmani *et al*., 2011).

Various signaling molecules have been shown to localize within caveolae. These include SCR family, tyrosine kinase, GPCR, members of Ras-MAPK cascade, and nitric oxide synthase (Ostrom, Insel, 2004; Insel *et al*., 2005). It has been documented that phosphatidylinositol-3 kinase/protein kinase B (PI-3K/AKT) pathway, PKC and PKA in caveolae interact with caveolin and modulate the opening of ATP-dependent K^+ channels and regulate the survival of cell facilitating the interaction of NO with K_{ATP} channel by forming a suitable signaling platform (Razani, Lisanti, 2001). Caveolins (cav-1 and cav-3) maintains eNOS in the inactivated state, which leads to a decrease in NO production (Quinlan *et al*., 2008; Garcia-Cardena *et al*., 1997; Maniatis *et al*., 2006). Increased disruption of the caveolin/eNOS complex by calcium/calmodulin-binding to eNOS leads to an increase in the activity of eNOS (Feron, Balligand, 2006). It has been reported that activation of PKA and Ras-p42/44 MAPK downregulates cav-1 expression (Engelman *et al*., 1999). Moreover, overexpression of cav-3 in myocardium has been reported to mimic preconditioning by activating PI-3K (Tsutsumi *et al*., 2008).

Role of caveolin in ischemic preconditioning

It has been documented that there is the involvement of caveolins and caveolae in protecting the heart from ischemia/reperfusion injury (Gratton, Bernatchez, Sessa, 2004; Ajmani *et al.,* 2011). Caveolae disruption in cardiac myocytes abolished cardiac protection (Patel *et al*., 2007). Signaling molecules, as shown in Figure 3 involved in cardiac protection, include GPCRs and the protein tyrosine kinase Src, which compartmentalize within caveolae and interact with the scaffolding domain of caveolin (Krajewska, Maslowska, 2004). Various GPCRs such as opioids and adenosine promote cardiac protection as well as post-receptor components that can enhance protection localize to caveolae and co-immunoprecipitate with caveolins (Head *et al*., 2005). Further, it has been reported that the infusion of the caveolin scaffolding domain (CSD) peptide of cav-1 into ischemic/reperfused hearts results in the recovery of cardiac function (Young, Ikeda, Lefer, 2001). Further, treatment with isoflurane modifies cardiac myocytes sarcolemmal structure and composition leads to activation of Src kinase and phosphorylation of cav-1 contributes to cardiac protection (Patel *et al*., 2007). It is documented that calmodulin disrupts the heterotrimeric complex formed between eNOS and caveolin in a calcium-dependent manner (Michel *et al*., 1997).

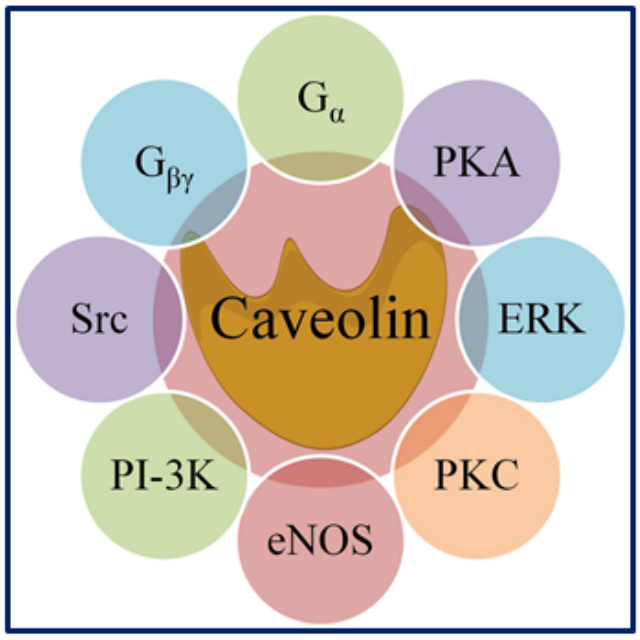

FIGURE 3 - Caveolin Binding with Signaling Molecules.

Moreover, caveolin (cav-1 and cav-3) maintains eNOS in inactivated state and thereby limits NO production (Maniatis *et al*., 2006), but agonist stimulation leads to activation of eNOS through the increase in calcium and disruption of caveolin/eNOS heterocomplex (Feron, Balligand, 2006). It has been reported that activation of PKA and Ras-p42/44 MAPK downregulates cav-1 expression (Engelman *et al*., 1999). Moreover, overexpression of cav-3 in myocardium has been reported to mimic preconditioning by activating PI3K (Tsutsumi *et al*., 2008). Ischemic preconditioning induces the translocation of eNOS and GLUT-4 to and from the plasma membrane, which is essential for cardioprotection (Koneru *et al.,* 2007). However, preconditioning with angiotensin II improves post-ischemic ventricular recovery, reduces myocardial infarction and decreases cardiomyocyte apoptosis (Das, Das, Das, 2007) which is

due to decrease association of p38MAPKβ and ERK1/2, i.e., anti-death signalling components with caveolin and increased association with p38MAPKα and JNK, i.e., death signaling components generate survival signal as demonstrated by increased phosphorylation of Akt and enhanced induction of expression of Bcl-2 in the heart (Das, Das, Das, 2007). Moreover, Pharmacological Preconditioning with bradykinin induces the formation of a caveolar signaling platform (signalosomes) that contains the enzymes of the signaling pathway which interact with mitochondria to induce the opening of mito K_{ATP} channel (Quinlan *et al*., 2008).

Mitochondrial K_{ATP} and ischemic preconditioning

ATP-Sensitive K^+ Channel was first identified in 1983 in the myocardium (Noma, 1983). Two subtypes of K_{ATP} channels have been documented, one is sarcolemmal K_{ATP} channel (sarc K_{ATP}) which is present on the cell membrane (Aguilar-Bryan *et al.*, 1998) while other is located in the inner membrane of the mitochondria and known as mitochondrial ATP sensitive potassium channels (mito K_{ATP}) (Yokoshiki *et al*., 1998). The K_{ATP} channels belong to the ATP-binding cassette transporter superfamily. Sarcolemmal K_{ATP} channel is composed of an octameric complex of two types of subunits, the Kir6.2 and the SUR2A subunit whereas mito K_{ATP} channel is comprised of two subunits one is a pore-forming, inward-rectifying potassium channel subunit (Kir), and other is regulatory sulfonylurea receptor (SUR) (Mccully, Levitsky, 2003; Mironova *et al*., 2004).

Mito K_{ATP} channel acts as the trigger, as well as the end effector of ischemic preconditioning mediated cardioprotection (Gross, Peart, 2003). Moreover, the opening of mito K_{ATP} channel leads to an influx of K^+ in the mitochondrial matrix (da Silva *et al.*, 2003) resulting in depolarised inner mitochondrial membrane and reduced mitochondrial calcium entry into the mitochondria resulting in inhibition of opening of mPTP (Costa *et al.*, 2006; Zoratti *et al.*, 2009) consequently decrease in the release of cytochrome C and reduction of apoptotic cell death (Kroemer, Dallaporta, Resche-Rigon, 1998; Javadov *et al*., 2003; Hausenloy, Duchen, Yellon, 2003; Hausenloy, Yellon, 2004). The influx of K^+ facilitates the entry of weak acids into the mitochondrial matrix and accelerates the process of oxidative phosphorylation (Tanonaka *et al*., 1999). In addition, the opening of mito K_{ATP} channels has been shown to cause partial alkalinization, and a small reduction of transmembrane potential leading to the production of ROS (Penna *et al*., 2007) which mediate the cardioprotective effect of ischemic preconditioning by activation of PKC (Bouwman *et al*., 2004; Andrukhiv *et al*., 2006). Several potassium channel openers such as cromakalim (Grover *et al*., 1995), bimakalim (Puddu *et al*., 2006), diazoxide (Lawrence *et al*., 2001; Dröse, Brandt, Hanley, 2006), have been reported to produce cardioprotection against ischemia reperfusion-induced injury. A specific blocker of mito K_{ATP} channel, i.e., 5-hydroxy decanoate (Hide, Thiemermann, 1996; Yang *et al*., 2009), has been shown to block the protective effects of ischemic preconditioning in the heart. On the other hand, HMR 1098, a specific blocker of sarc K_{ATP} channel, has been demonstrated to abolish the protective effects of ischemic preconditioning (Suzuki *et al*., 2002).

Ischemic preconditioning in postmenopausal heart

It has been reported that men are more susceptible than women to hypertension and cardiovascular diseases (Barrett-Connor, 1997). However, after menopause in women, the risk of ischemic heart disease reaches to the same level as in men of the same age (Clarkson *et al*., 1997; Barrett-Connor, 1997), which indicates that the female sex hormones, particularly estrogen plays a crucial role in reducing the risk of ischemic heart diseases (Sullivan *et al*., 1998; Stampfer, 1995). The dramatic increase in the ischemic heart disease is the leading cause of death in postmenopausal women (Bush *et al*., 1988) and the estrogen replacement therapy lowers the incidence of cardiovascular events (Stampfer *et al*., 1985; Bush *et al*., 1987). However, several clinical studies failed to demonstrate any cardioprotection from such estrogen replacement therapy (Barrett-Connor, Stuenk el, 1999; Rossouw *et al*., 2002). Rossouw *et al*., 2002 has been reported that the incidence of ischemic heart disease was increased in women receiving estrogen as compared to those receiving placebo.

Cardiomyocytes from female hearts are more resistant to ischemia-reperfusion-induced injury as a

comparison of male hearts (Ranki *et al*., 2001). It has been documented that an increased level of phosphorylated Akt and PKCε are responsible for cardioprotection against I-R induced injury in female hearts (Bae, Zhang, 2005).

Estrogen deficiency is associated with increased TNF-α level, which may lead to increased myocardial injury after menopause (Liao, Chen, Chen, 2002). In another study, it has been reported that decreased mitochondrial respiration and increased mPTP opening with aging are responsible for necrotic cell death associated with ischemia/reperfusion injury in postmenopausal women (Machikas *et al*., 2018).

Shinmura and coworkers demonstrated that the cardioprotective effect of IPC is lost in ovariectomized rats, which is partly due to impaired phosphorylation and translocation of PKCε to the membrane. Moreover, estrogen replacement or selective activation of PKCε-mediated signaling restores the cardioprotective effect of IPC (Shinmura *et al*., 2008).

Montalcini *et al*. (2007) found that the development of cardiovascular diseases after menopause is not only due to a decrease in estrogen but also due to a decrease in androgen. Furthermore, it has been reported that testosterone enhances estradiol's cardioprotection in ovariectomized rats, estradiol and testosterone combination protects cardiomyocytes against I-R injury (Liu *et al*., 2011). It has been well documented that ovariectomy (surgical menopause) reduces the protein expression of eNOS and increases the cav-1 expression subsequently decrease the activation of mito K_{ATP} channels in cardiac tissue which is also the main cause of abrogated cardioprotective effect of IPC (Figure 4; Pelligrino *et al*., 2000; Goyal, Semwal, Yadav, 2016) but the chronic estrogen treatment or phytoestrogens like daidzein accompanies restoration of the normal activity of myocardial eNOS (Wang *et al*., 2002; Goyal, Semwal, Yadav, 2016).

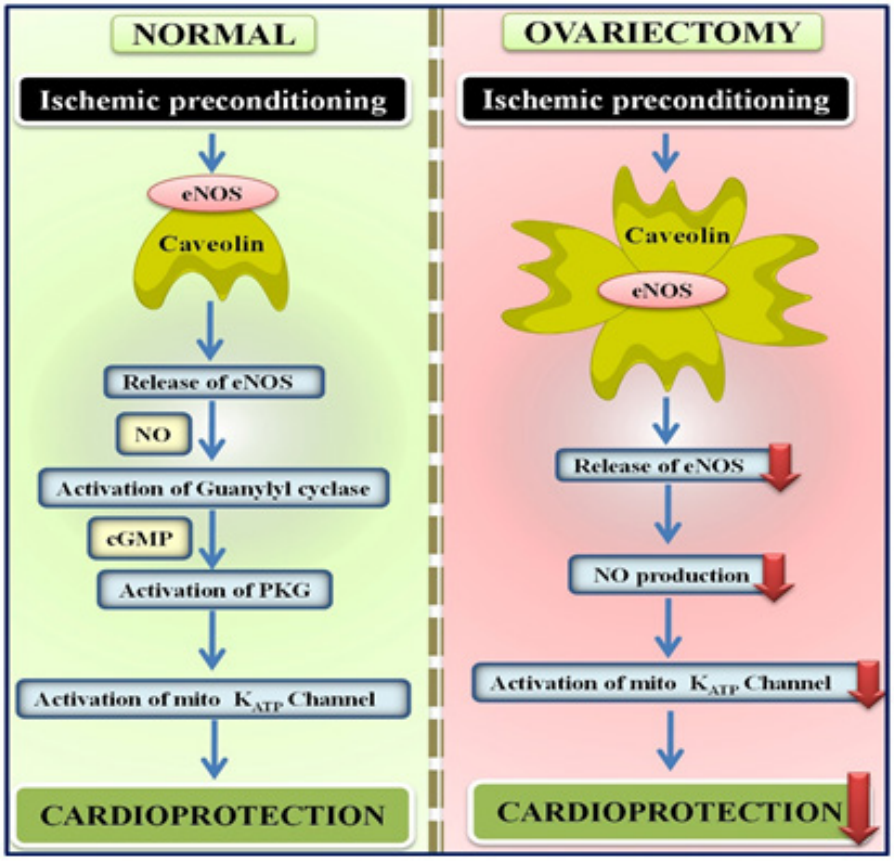

FIGURE 4 - Role of Caveolin-eNOS and mito-K_{ATP} in Normal and Estrogen Deficient Condition.

Endogenous and exogenous estrogen in premenopausal and postmenopausal women, respectively, protects against cardiovascular disease (Stampfer *et al*., 1991; Grady *et al*., 1992). Estrogen acts as a vasoprotective molecule by increasing the bioavailability of nitric oxide (Best *et al*., 1998; Levin, 2005). Estrogen upregulates eNOS and downregulates its inhibitory protein cav-1 (Hishikawa *et al*., 1995). The cardioprotective effects of estrogen are, in part, mediated by the regulation of TNFα levels in the ischemic heart (Xu *et al*., 2006). The effect of estrogen on eNOS expression is mediated via estrogen receptors α (ERα) and β (ERβ), which are present on endothelial cells (Gavin *et al*., 2009).

Activation of eNOS by estrogen has been reported to occur through ERK-1/2 (Chen *et al*., 1999) pathway as well as via the phosphatidylinositol 3-kinase (PI3K)/protein kinase (Akt) pathway (Simoncini *et al*., 2000; Hisamoto *et al*., 2001; Haynes *et al*., 2000). The recruitment of the latter cascade depends on the ligand-dependent association of ERα with PI3K (Simoncini *et al*., 2000). Akt can be activated by estrogen (Camper-Kirby *et al*., 2001), which further activates eNOS by phosphorylating it at serine 1177 residue (Fulton *et al*., 1999; Dimmeler *et al*., 1999). This phosphorylation not only activates eNOS but also increases the efficiency of activation by Ca^{++}/calmadulin (McCabe *et al*., 2000). Thus, estrogen increases the bioavailability of NO and thus results in a decrease in myocardial injury. In addition, 17β-estradiol has been shown to reduce myocardial necrosis in rabbits after ischemia and reperfusion (Hale, Birnbaum, Kloner, 1996) and improve recovery of mechanical function following global ischemia in isolated rat hearts (Kolodgie *et al*., 1997; Fraser *et al*., 1999).

CONCLUSION

The cardioprotective potential of IPC is lost in estrogen deficiency. In this condition, the outcome of I/R injury worsens, and the infarct size limiting effect of IPC is blunted due to the upregulation of caveolin and downregulation of nitric oxide as well as inhibition of mito K_{ATP} channel. This may affect the clinical application of IPC in patients with estrogen deficiency or postmenopausal women undergoing cardiac surgery. Therefore, we can say that by adopting the approaches like inhibiting caveolin, upregulating nitric oxide, and the opening of mito K_{ATP} can help in regaining the cardioprotective effect of IPC in postmenopausal or estrogen-deficient condition.

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CONFLICT OF INTEREST

All authors have no conflict of interest to declare.

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