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Impact of hypoglycemic agents on myocardial ischemic preconditioning

Rosa Maria Rahmi Garcia, Paulo Cury Rezende, Whady Hueb

Rosa Maria Rahmi Garcia, Paulo Cury Rezende, Whady Hueb, MASS Study Group, Heart Institute of the University of São Paulo, São Paulo 05403-000, Brazil
Author contributions: All the authors contribute equally to this work.
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Correspondence to: Whady Hueb, MD, PhD, MASS Study Group, Heart Institute of the University of São Paulo, Av. Dr. Eneas de Carvalho Aguiar, 44, AB, Sala 114, Cerqueira Cesar, São Paulo 05403-000, Brazil. mass@incor.usp.br
Telephone: +55-11-26615032 Fax: +55-11-26615352
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Abstract

Murry *et al* in 1986 discovered the intrinsic mechanism of profound protection called ischemic preconditioning. The complex cellular signaling cascades underlying this phenomenon remain controversial and are only partially understood. However, evidence suggests that adenosine, released during the initial ischemic insult, activates a variety of G protein-coupled agonists, such as opioids, bradykinin, and catecholamines, resulting in the activation of protein kinases, especially protein kinase C (PKC). This leads to the translocation of PKC from the cytoplasm to the sarcolemma, where it stimulates the opening of the ATP-sensitive K^+ channel, which confers resistance to ischemia. It is known that a range of different hypoglycemic agents that activate the same signaling cascades at various cellular levels can interfere with protection from ischemic preconditioning. This review examines the effects of several hypoglycemic agents on myocardial ischemic preconditioning in animal studies and clinical trials.

Key words: Ischemic preconditioning; Myocardial ischemia; Coronary artery disease; Hypoglycemic agents; Diabetes mellitus

INTRODUCTION

In the last 3 decades, the prevalence of diabetes mellitus in adults 18 years and older has increased 2-fold[1]. Approximately 50%-60% of patients with diabetes die from cardiovascular disease (CVD)[2]. Among various CVDs, acute myocardial infarction (AMI) has a high rate of mortality, and infarct size is a primary determinant of prognosis in these patients[3-5]. Furthermore, patients with diabetes are more likely than patients without diabetes to develop heart failure after AMI[6]. Thus, the development of new cardioprotective strategies capable of protecting the myocardium are imperative in order to improve clinical outcomes in diabetic patients with coronary heart disease. Moreover, hyperglycemia is an important risk factor for coronary artery disease and death; however, the use of some medications to achieve glycemic control is controversial, as their use has not consistently been shown to reduce mortality. The University Group Diabetes Program (UGDP) in 1970 showed that the administration of tolbutamide, a first-generation sulfonylurea, may increase the risk of cardiovascular death[7].

As a cardioprotective strategy, ischemic preconditioning (IPC) has received much attention for its powerful infarct size-limiting effect. This intrinsic mechanism of profound protection was suggested by Murry *et al*[8] in 1986 who found in a canine model that 4 consecutive periods of coronary occlusion of 5 min were able to reduce
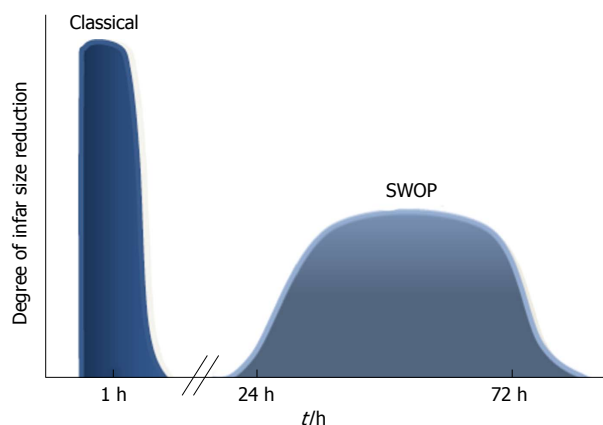
Figure 1 Diagrammatic representation of the temporal nature of the 2 windows of preconditioning (adapted from Baxter *et al*[9]). SWOP: Second window of protection.

the infarct size by as much as 75%, after induction by a subsequent period of occlusion for 40 min. For the first time, it was demonstrated that limitation of infarct size was theoretically possible.

IPC causes 2 phases of protection: "early" or "first window" and "second window of protection" (SWOP). The first window protects the heart for about 2 h and then wanes; the SWOP appears 24 h after the initiation of the IPC protocol and can last for 3 d (Figure 1)[9].

Although IPC was initially referred to as the ability of short periods of ischemia to limit infarct size, some investigators extended this definition to include a beneficial effect on reperfusion-induced arrhythmias[10] and on myocardial stunning[11].

Experimental findings on IPC cannot be directly extrapolated to humans, because of obvious ethical restrictions and because its mechanisms are different from those of other animal species. IPC in human hearts has been demonstrated by results of *in vitro* experiments using human ventricular myocytes[12] and atrial trabeculae[13]. In addition, surrogate clinical endpoints have also been used, including contractile function, electrocardiographic ischemic changes, or biochemical evidence of cell damage.

CELLULAR MECHANISMS OF CLASSICAL PRECONDITIONING

The cellular mechanisms that confer resistance to ischemia have been extensively studied. However, these pathways remain controversial and are only partially understood[14,15]. It has been proposed that endogenous adenosine released during the brief ischemia of the IPC protocol enhances the release of G-protein coupled receptor (GPCR) agonists, such as opioids, adenosine, bradykinin, or catecholamines[16-18]. These GPCR agonists appear to work simultaneously and in parallel to provide redundancy to the preconditioning stimulus. Although these 3 receptors trigger signaling through divergent pathways, this signaling activates prosurvival kinase or reperfusion injury salvage kinase paths, including phosphatidylinositol

3-kinase, protein kinase B, and protein kinase C[14,15]. In turn, it leads to the translocation of protein kinases from the cytoplasm to sarcolemmal receptors[19] and mitochondrial membranes[20], where it phosphorylates a substrate protein, the ATP-sensitive K^+ (KATP) channel[21]. Marinovic *et al*[22] demonstrated in mouse cardiac myocyte cells that the opening of the sarcolemmal KATP channels plays an important role in the prevention of cardiomyocyte apoptosis during metabolic stress, and may interact with mitochondrial channels. Thus, opening of KATP channels are strongly involved in the protection provided by preconditioning[23-26].

Due to the growing knowledge about the cellular pathways of this important protective mechanism, we must consider whether IPC can be applied as a cardioprotective therapy in ischemic heart disease patients.

PHARMACOLOGICAL INTERACTIONS

Pharmacological agents have the capacity to either interfere with signaling or trigger protection. The use of agents capable of mimicking the protective effects of preconditioning, besides brief ischemia, may offer a more benign approach for eliciting cardioprotection. Agents commonly used in coronary disease may interfere with the protection of IPC pathways. Penson *et al*[27] demonstrated in rat-isolated atria and ventricles that activation of beta-adrenoceptors mimics preconditioning. However, β-adrenoceptor blockers impair cardioprotection in animals[28]. Other agents such as Ca^{2+} channel blockers[29] and nonsteroidal anti-inflammatories may interfere with protection by IPC pathways[30,31]. Liu *et al*[16] reported that an adenosine receptor antagonist could block IPC protection and that adenosine or the A1-selective agonist adenosine, instead of brief ischemia, could duplicate IPC protection. Other potential candidates currently in clinical use include nicorandil or diazoxide[32,33]. These drugs have been shown to open KATP channels in ischemic cardiomyocytes, and might act as pharmacological imitators of the preconditioning phenomenon.

HYPOGLYCEMIC DRUGS AND IPC

Hyperglycemia is an important risk factor for coronary artery disease and death. However, the use of some hypoglycemic medications is controversial, because they have not been shown to reduce mortality. Indeed, physicians face challenges regarding the use of new agents in patients with diabetes who are at high cardiovascular risk. Several factors contribute to this concern, and among these is IPC. As described above, the UGDP raised concerns that the administration of tolbutamide may increase the risk of cardiovascular death, but this result remained unexplained until data were reported suggesting deleterious effects of some sulfonylureas (glyburide), specifically in the mechanisms of IPC[23,24].

Insulin secretagogues stimulate insulin secretion by the shutdown of the KATP channel in pancreatic β

cells[34]. KATP channels are composed of 2 types of subunits, inwardly rectifying K^+ channels (Kir6.x) and sulfonylurea receptors (SURx), arranged as tetradimeric complexes (Kir6.x/SURx)[35]. Closure of the KATP channel results in membrane depolarization and influx of calcium (Ca^{2+}) into the β cell. The increase in intracellular Ca^{2+} causes release of insulin from β cell secretory granules. KATP channels are also abundant in both cardiomyocytes[36,37] and arterial smooth muscle cells[38].

The β cell and cardiac muscle KATP channels have been shown to possess a common pore-forming subunit (Kir6.2) but different sulfonylurea receptor subunits (SUR1 and SUR2A, respectively). Although the roles of KATP channel in extrapancreatic tissues are less well characterized, it is likely that they open in response to metabolic stress, such as during cardiac ischemia[39]. Thus, the ideal sulfonylurea for treatment of type 2 diabetes would be one that interacts only with the β cell KATP channel.

EFFECT OF SULFONYLUREAS ON IPC

There is concern about the effect of sulfonylureas on preconditioning protection. Unfortunately, little is known about the ability of the clinically used insulin secretagogues to interfere with IPC. To evaluate studies on the effects of sulfonylureas on IPC, it is important to assess their selectivity for SUR receptor subtypes. These drugs have a range of affinities for KATP channels with different SUR isoform composition, resulting in different abilities to stimulate the KATP channel activity. Tolbutamide has a high affinity for SUR 1 receptors in β cells, but a very low affinity for SUR 2A receptors in the myocardium[40,41]. Glibenclamide (glyburide) inhibits cardiac as well as pancreatic receptors with high affinity[42,43]. Glimepiride has affinity for pancreatic and cardiac SUR comparable to glibenclamide, thereby, does not differentiate between B cells, cardiac muscle, or smooth muscle KATP channels[43,44]. In contrast, preliminary studies reported that glimepiride had less cardiovascular activity than glibenclamide had[45-48]. Several reasons seem to correlate with this finding and, among them, highlight the difference in selectivity for SUR between *in vitro* and *in vivo* studies, and different effects of doses utilized in most studies and in treatment of patients with type 2 diabetes mellitus. In addition, gliclazide, a second generation sulfonylurea, is distinguished by having a higher selectivity for pancreatic SUR receptors[43,49].

Numerous studies using animal models support the hypothesis that IPC is impaired by glibenclamide[23,47,50,51]. Studies using human hearts analyzed IPC in isolated human atrial muscle trabeculae, obtained from type 2 diabetic patients treated with sulfonylureas before coronary artery surgery, and noted that IPC was abolished in patients receiving sulfonylureas[52]. Tomai *et al*[53] evaluated IPC in 20 patients pretreated with either glibenclamide or placebo. They recorded ST-segment changes on ECGs during 2 subsequent episodes of intracoronary balloon inflation. They concluded that human IPC during brief repeated coronary occlusions was completely abolished by pretreatment with glibenclamide. Similar results were shown when the effects of glibenclamide and glimepiride were compared during balloon inflation in percutaneous transluminal coronary angioplasty[45,54].

Tomai *et al*[55] investigated the effects of glibenclamide on the "warm up phenomenon", which is a clinical model of IPC. It refers to an increased tolerance to myocardial ischemia during the second of 2 consecutive exercise tests. In this study, glibenclamide abolished the improvement in ischemic threshold during the second exercise test, compared with placebo[55]. Ovünç[56], in a similar study reported concordant results and suggested that glibenclamide should be used with caution in patients with coronary heart disease and diabetes mellitus, because this agent leads to a decrease in ischemic threshold and exercise capacity. Ferreira *et al*[57], in a study in which IPC was evaluated by 2 consecutive exercise tests, also investigated the effects of chronic treatment with glibenclamide. Forty patients with angina pectoris were allocated into 3 groups: 20 nondiabetic patients, 10 diabetic patients receiving treatment with glibenclamide for at least 6 mo, and 10 diabetic patients receiving other treatments. All patients underwent 2 consecutive exercise tests. The results suggested that IPC protection was blocked in diabetic patients exposed to long-term treatment with glibenclamide. In a recent study, Bilinska *et al*[58] evaluated 64 men, 17 nondiabetic and 47 diabetic, aged 54 ± 5 years. Diabetic patients were allocated into 3 groups: one treated with glibenclamide, one with gliclazide, and the other with diet. All patients performed 2 consecutive exercise tests, with 30 min between them. The authors compared the improvement in ischemic parameters among these groups of patients and concluded that the warm-up effect was preserved in diabetic patients treated with diet, partially preserved in patients treated with gliclazide, and abolished in patients treated with glibenclamide. In contrast, other studies reported no effect of treatment with glibenclamide on the electrocardiographic shifts of the ST-segment during consecutive exercise tests[59,60].

In summary, most studies with glibenclamide (glyburide) reported deleterious effects on IPC, suggesting caution with the use of this agent in patients at high risk for myocardial ischemia.

In animal studies, glimepiride treatment facilitated the cardioprotective effect elicited by IPC[47,48,61-63]. Indeed, data from clinical studies is of great interest. Experimental findings on IPC cannot be directly extrapolated to humans, because in humans its mechanisms are different from those in other animal species. Thus, Klepzig *et al*[45] compared the effects of glibenclamide, glimepiride, and placebo administration on ST-segment shifts during balloon inflation in percutaneous transluminal coronary angioplasty. They concluded that IPC was maintained after glimepiride administration and prevented after glibenclamide. Lee *et al*[46], studied the impact of glibenclamide or glimepiride administration on cardioprotective effects in patients with and without diabetes undergoing coronary angioplasty. The results demonstrated that the

changes in the ST-segment and metabolic parameters were more severe after pretreatment with glibenclamide than with glimepiride, in patients with and without type 2 diabetes.

Only a few studies[45,46] have used IPC protocols in humans to evaluate the effect of glimepiride. To date, these trials have revealed beneficial effects on cardioprotective mechanisms.

In isolated Langendorff perfused rat hearts, the infarct sizes were smaller in the group treated with gliclazide compared with the group treated with glibenclamide. However, the glimepiride group had a smaller infarct size than the gliclazide group[48]. In an *in-vivo* rat study, Maddock *et al*[51] compared the effects of glibenclamide and gliclazide on IPC and nicorandil-induced protection. The IPC protocol consisted of 2 cycles of 5 min of regional ischemia/reperfusion preceding prolonged ischemia. Gliclazide had no adverse effects on IPC or on nicorandil-induced protection. Loubani *et al*[64] assessed the dose-response effect of gliclazide and glibenclamide on IPC. Different doses of glibenclamide and gliclazide were added for 10 min prior to implementation of the IPC protocol. The cardioprotection was abolished by gliclazide only at supratherapeutic concentrations, while glibenclamide prevented IPC at all concentrations.

Bilinska *et al*[58] evaluated the effects of diet, glibenclamide, or gliclazide on the warm-up phenomenon in type 2 diabetic patients with stable angina. They concluded that the warm-up effect was partially preserved in the gliclazide-treated and abolished in the glibenclamide-treated group.

The analysis of the reported data described above suggests that gliclazide does not induce potentially harmful IPC effects.

EFFECT OF GLINIDES ON IPC

The drugs from the glinide class are characterized as insulinotropic agents with a rapid onset and short duration of action. Although glinides do not have a sulfonylurea structure, their role as an insulin secretagogue occurs by binding to the Kir6.2/SUR1 complex, which leads to the closure of KATP channels.

Glinides non-selectively inhibit the pancreatic, myocardial, and non-vascular smooth muscle KATP channels[65]. For these reasons, the selectivity of glinides for the pancreatic compared with the cardiovascular KATP channels has relevance for IPC. Unfortunately, little is known about the ability of the clinically used glinides to interfere with IPC. An original study conducted in our service[66], evaluated the effect of repaglinide on the warm-up phenomenon. Forty-two patients with type 2 diabetes mellitus and coronary artery disease underwent 2 consecutive treadmill exercise tests. After 7 d of receiving repaglinide, 83% of patients no longer had myocardial IPC.

Due to the great difference of *in vitro* selectivity ratios of repaglinide and other drugs in the glinide class (mitiglinide and nateglinide)[43,65], clinical studies assessing the effect of glinides on type 2 diabetic patients with coronary artery disease would be of great interest for both therapeutic and scientific reasons.

EFFECT OF INCRETINS ON IPC

Incretins are gut-derived peptides secreted in response to meals, specifically in the presence and absorption of nutrients in the intestinal lumen. The major incretins are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide. Incretin is mainly represented by GLP-1. The half-life of GLP-1(7-36) in circulation is very brief (1 to 2 min), as it is rapidly degraded by the enzyme dipeptidyl peptidase-IV (DPP-IV) to the metabolite GLP-1(9-36), which does not act on the GLP-1 receptor. GLP-1 receptors are expressed in pancreatic islet cells and in the kidney, lung, brain, gastrointestinal tract, and heart[67]. The incretin modulator class includes the GLP-1 analogues or mimetics, which are functional agonists of the GLP-1 receptor. In addition, oral inhibitors of DPP-IV, in essence, increase the plasma concentrations of the biologically active form of endogenously secreted incretins[68]. Bose *et al*[69] observed in an isolated rat heart model that GLP-1(7-36) is protective against myocardial ischemia-reperfusion injury when given either as a preconditioning mimetic or at reperfusion. Although several investigators have reported the cardioprotective effect of GLP-1, there is a lack of studies about its effects on IPC. Our research group compared the actions of the DPP-IV inhibitor (vildagliptin) and repaglinide using an IPC protocol. The results showed that vildagliptin preserved IPC in 72% of 54 patients, while repaglinide maintained the cardioprotective response in only 17% of 42 patients[70]. Our group demonstrated 2 effects of hypoglycemic drugs on IPC. These findings support the importance of identifying underlying mechanisms of endogenous myocardial protection to improve the protective effect of pharmacological therapy (Table 1).

EFFECTS OF GLITAZONES ON IPC

The glitazones or thiazolidinediones offer the first therapeutic option specifically directed at reversing the basic problem of type 2 diabetes, which is resistance to insulin. These drugs act on tissues such as liver and skeletal muscle, sensitizing them to insulin action, and thereby increasing glucose uptake and decreasing its hepatic output. The oldest and best-studied glitazone is troglitazone, which was withdrawn from the market by the United States Food and Drug Administration (FDA) because of concerns about its safety. Muriglitazar, which stimulates both PPARγ and alpha receptors, increased adverse cardiovascular events and was also withdrawn by its manufacturer after rejection by the FDA. Roziglitazone and pioglitazone are also drugs in the PPARγ agonist family. Nissen *et al*[71] reported in a meta-analysis a significant increase in the risk of myocardial infarction with rosiglitazone and a trend towards increased risk of death from cardiovascular causes. This information has been includ-

Table 1 Effects of hypoglycemic drugs on ischemic preconditioning

Study	Model	Diabetic drug	Effect
Animal studies			
Gross *et al*[23], 1992	Dogs	Glibenclamide (glyburide)	Abolished
Toombs *et al*[50], 1993	Rabbits	Glibenclamide	Abolished
Mocanu *et al*[47], 2001	Rats	Glimepiride	Preserved
Maddock *et al*[51], 2004	Rats	Glibenclamide	Abolished
		Glimepiride	Preserved
Hausenloy *et al*[61], 2013	Rats	Glimepiride	Preserved
Ye *et al*[62], 2008	Rats	Pioglitazone	Preserved
		Glibenclamide (glyburide)	Abolished
		Glimepiride	Preserved
Horimoto *et al*[63], 2002	Rabbits	Glibenclamide	Abolished
		Glimepiride	Preserved
Bose *et al*[69], 2005	Rats	Native sequenced human GLP-1	Preserved
Zhu *et al*[73], 2011	Rats	Pioglitazone	IPC mimic
Sasaki *et al*[74], 2007	Rats	Pioglitazone	IPC mimic
Ahmed *et al*[75], 2011	Rats	Pioglitazone	IPC mimic
Li *et al*[76], 2008	Rats	Pioglitazone	Preserved
Wynne *et al*[77], 2005	Rats	Pioglitazone	IPC mimic
Sarraf *et al*[78], 2012	Porcine	Pioglitazone	Abolished
		Rosiglitazone	Abolished
Human studies			
Cleveland *et al*[52], 1997	Atrial muscle trabeculae	Glibenclamide (glyburide)	Abolished
Tomai *et al*[53], 1994	Human	Glibenclamide	Abolished
Klepzig *et al*[45], 1999	Human	Glibenclamide	Abolished
		Glimepiride	Preserved
Lee *et al*[54], 2002	Human	Glibenclamide	Abolished
Tomai *et al*[55], 1999	Human	Glibenclamide	Abolished
Ovünç[56], 2000	Human	Glibenclamide	Abolished
Ferreira *et al*[57], 2005	Human	Glibenclamide	Abolished
Bilinska *et al*[58], 2007	Human	Glibenclamide	Abolished
		Gliclazide	Partially preserved
Bogaty *et al*[59], 1998	Human	Glibenclamide	Preserved
Correa *et al*[60], 1997	Human	Glibenclamide	Preserved
Loubani *et al*[64], 2005	Right atrial appendages	Glibenclamide	Abolished
		Gliclazide	Preserved (but abolished in supratherapeutic concentrations)
Hueb *et al*[66], 2007	Human	Repaglinide	Abolished
Rahmi *et al*[70], 2013	Human	Repaglinide	Abolished
		Vildagliptin	Preserved

GLP-1: Glucagon-like peptide-1; IPC: Ischemic preconditioning.

ed in the prescribing information for all rosiglitazone-containing products. However, the glitazones have been shown to improve many of the traditional as well as the emerging risk factors associated with CVD[72]. The effect of the glitazones, rosiglitazone, and pioglitazone on IPC is still a matter of debate in the literature, as experimental studies demonstrate contradictory results. Methodological differences are one of the reasons for that. In studies using rat models, pioglitazone was associated with beneficial effects on cardiomyocyte injury, limiting infarct size, and ventricular arrhythmias[73-75]. These beneficial effects may be related to the opening of mitochondrial (ATP)-sensitive potassium channels[76] and by other kinases like phosphatidylinositol 3 kinase and P42/44 MAPK by pioglitazone[77]. On the other hand, in a porcine model, pioglitazone and rosiglitazone had the opposite results[78]. Finally, in the clinical setting, the possible actions of the glitazones on IPC are still uncertain.

EFFECTS OF METFORMIN ON IPC

The cardiovascular benefits observed in diabetic patients with chronic coronary artery disease with the use of metformin[79] have also been observed in experimental studies, which have shown positive results of metformin in the cardiovascular system, and that includes its effect in IPC. It is still not completely understood how metformin protects IPC in the heart, but it is postulated that it activates some kinases involved in IPC, such as (AMP)-activated protein kinase[80], which increases adenosine, activating cardioprotective mechanisms. Recent studies have also demonstrated that metformin increases hexokinase Ⅱ, another important kinase found in mitochondria, which seems to be one of the end-effectors of IPC, and that ultimately protects many cell types, including cardiomyocytes, against apoptosis and ischemic cell death[81]. Ischemia inhibits the loss of hexokinase Ⅱ from mitochondria, consequently preventing the opening of the mitochondrial permeability transition pore. This pore is responsible for the stabilization of the mitochondrial membrane potential, the prevention of cytochrome C release and also the reduction in reactive oxygen species production, which all finally lead to mitochondrial protection against ischemic injury[82,83]. These actions

associated with metabolic alterations, such as the prevention of acidosis through enhanced coupling of glycolysis and glucose oxidation and inhibition of fatty acid oxidation[81], are the responsible pathways by which metformin protects the myocardium from ischemia, in addition to its well-known effects in glucose control.

CLINICAL IMPLICATIONS

Ischemic preconditioning is a complex, dynamic phenomenon that can be the target of drug activities affecting the heart's ability to adapt to ischemic stress. In the clinical setting, however, the literature contains conflicting results regarding whether the use of conventional oral hypoglycemic agents affect cardiovascular mortality[84-90]. The findings from studies about the effects of hypoglycemic drugs on IPC have implications for diabetic patients, especially for those with a high risk of myocardial ischemic events, because the results infer that the myocardium may or may not benefit from a cardioprotective response when under the influence of such drugs. The most important consideration in this matter is that therapeutic options for diabetes treatment go beyond glucose-lowering efficacy in populations with increased risk of coronary ischemic events, and further large clinical trials will be necessary to determine whether the interference with myocardial preconditioning translates into clinical evidence.

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