Myocardial Preconditioning: Characteristics, Mechanisms, and Clinical Applications

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Perioperative myocardial ischemia and dysfunction remain prevalent after cardiac surgery despite the use of conventional measures to provide myocardial protection. Myocardial preconditioning is a powerful, endogenously regulated means of myocardial protection that may also have some clinical usage for patients undergoing cardiac surgical procedures. The paradoxical concept of using ischemia as a stimulus for myocardial protection has been studied extensively in animals and humans. The specific characteristics and constituents of preconditioning have been well identified. The mechanism remains to be completely elucidated due to differences among species and experimental models. Some pharmacologic agents are capable of mimicking the classic mechanism of ischemic preconditioning. Pharmacologic and ischemic preconditioning may have significant clinical use and therapeutic efficacy as a means of providing myocardial protection during cardiac surgery, especially in procedures that do not use cardioplegia and cardiopulmonary bypass, such as minimally invasive coronary artery bypass grafting. This article reviews the characteristics, mechanisms, potential clinical applications, and therapeutic efficacy of myocardial preconditioning.

Myocardial ischemia occurs as a result of a metabolic supply/demand imbalance at the cellular level, usually in association with an excessive sympathetic response, coronary endothelial dysfunction or more commonly, an unstable atherosclerotic lesion.[1] Although ischemia might be associated with reversible myocardial dysfunction, a single or repeated episode can eventually culminate in cumulative injury manifesting as hibernating myocardium,[2] myocardial stunning,[3] apoptosis,[4] or eventually cellular necrosis and myocardial infarction (MI) (Fig 1). Perioperative myocardial morbidity is particularly concerning for patients undergoing coronary artery bypass grafting (CABG) considering the high prevalence of perioperative myocardial ischemia (37%),[5] MI (1% to 10%),[6] and "low cardiac output syndrome" (10% to 75%),[7] despite the use of routine conventional measures to optimize myocardial protection.

Over the past several years, knowledge of the pathophysiology of ischemia and its effect on myocardial function has continued to develop. Endogenous mechanisms of protection against myocardial injury are now known to exist that can ironically be induced directly, by brief episodes of ischemia. This paradoxical phenomenon known as "ischemic preconditioning" (IPC), has been suggested to have a therapeutic role as a means of providing myocardial protection in cardiac surgical procedures when cardioplegia delivery may be suboptimal or in minimally invasive "beating heart" procedures in which cardioplegic arrest and cardiopulmonary bypass (CPB) are intentionally avoided. Although much progress has been made in understanding how IPC can optimize myocardial resistance to subsequent injury, the actual mechanisms remain to be elucidated. This review focuses on the characteristics, known cellular and molecular mechanisms, and potential therapeutic applications of myocardial preconditioning.

Characteristics of Ischemic Preconditioning

In 1986, Reimer et al showed that four brief (10 minute) periods of coronary artery occlusion, followed by reperfusion decreased canine myocardial infarct size by almost 75% after a subsequent, sustained (40 minute) ischemic insult.[8] This paradoxical correlation of brief ischemic episodes and reperfusion associated with resistance to further myocardial injury, was subsequently termed "ischemic preconditioning" by

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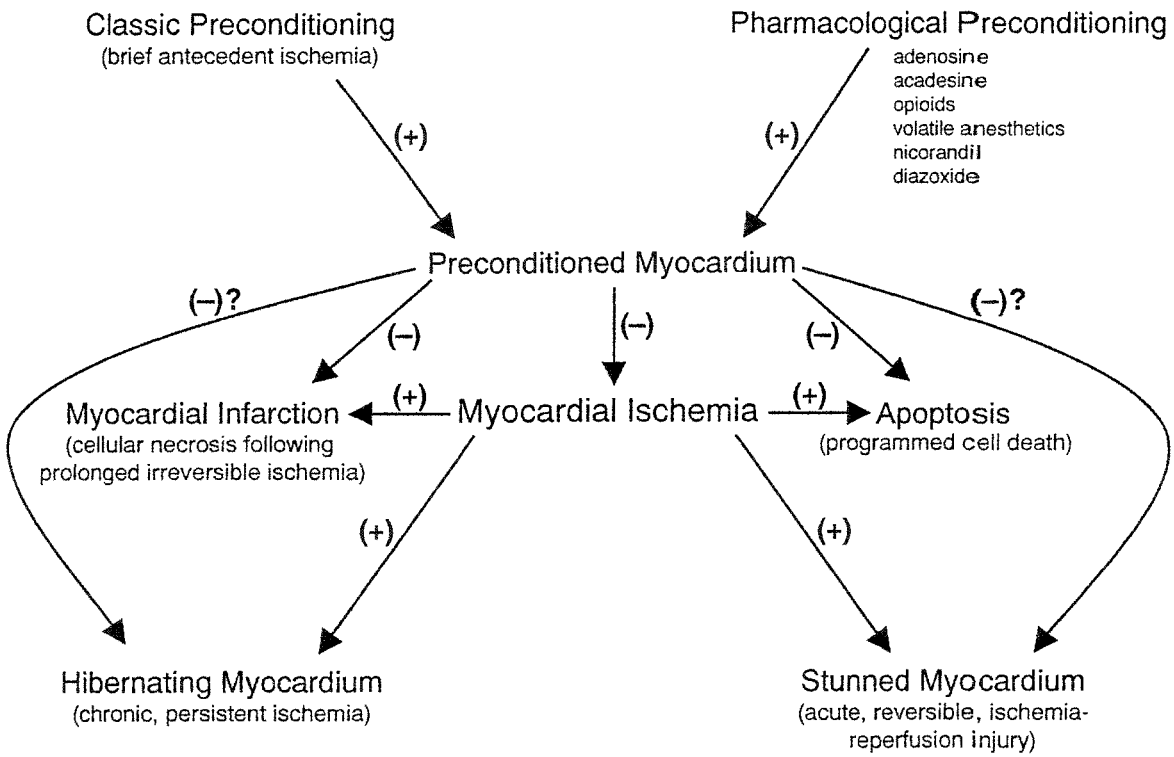

Figure 1. Spectrum of reversible to irreversible myocardial injury and the potential impact of ischemic and pharmacologic preconditioning.

Murray et al.[9] The absence of any changes in collateral blood flow supported the hypothesis that this protective effect of antecedent ischemia induced an inherent myocardial response.

Classic IPC refers to early myocardial protection associated with "a rapid adaptive response to a brief ischemic insult, which slows the rate of cell death during a subsequent, prolonged period of ischemia."[9] A typical model of IPC requires the presence of a preconditioning stimulus, followed by a period of reperfusion and a subsequent sustained ischemic insult. Over the past several years, IPC has been shown using several experimental methods in numerous animal species including humans, resulting in the realization that many variations of the classic theme might exist. For example, although a brief period of antecedent ischemia (coronary occlusion) is usually used, other reported preconditioning stimuli have included (1) the use of hypoxic perfusion or a reduction of coronary flow in buffer-perfused and blood-perfused heart preparations, (2) the combination of hypoxia, substrate-free perfusion and pacing stress in isolated cardiac muscle preparations, and (3) the combination of hypoxia with glucose-free substrate in isolated cardiomyocytes.[10] Some investigators have described "preconditioning at a distance" in which regional IPC created by left circumflex coronary artery occlusion was associated with remote myocardial protection after sustained left anterior descending coronary artery occlusion.[11] This example of remote preconditioning probably involves mechanisms that differ from classical IPC and perhaps implicate a role for neural or humoral factors. IPC typically requires a very brief period of ischemia to induce preconditioning, although the optimal number of episodes and duration of nonlethal IPC varies considerably among different species and experimental conditions.[10] In most animal models, the preconditioning stimulus must last for at least 1 minute, but not exceed 5 minutes to avoid irreversible injury.[12] There are similar species-dependent variations in the number of preconditioning episodes ranging from a single, 5 minute period in the rabbit[13] to 3 periods of 3 minutes in the rat.[14] There is no apparent cumulative effect associated with additional brief ischemic epi-

sodes[15] and in fact, protection may be attenuated after numerous, repeated periods of ischemia.[16]

The duration of early protection induced by IPC is relatively short-lived (30 minutes to 3 hours).[17-19] After early protection is lost, it can be reestablished in some species if a subsequent ischemic stimulus occurs several hours to days later.[20] Furthermore, IPC may induce delayed protection (ie, "second window of protection") from 12 hours to 72 hours after the initial stimulus.[17,21-23] The duration of lethal ischemia for which IPC is still protective is also limited. Periods of sustained ischemia greater than 30 to 90 minutes are associated with a significantly greater risk for irreversible myocardial injury, regardless of antecedent IPC.[10] Finally, the determinants of efficacy for IPC vary between experimental models, from the original gold standard of infarct size reduction to protection against arrythmias,[24] reduction of postischemic contractile dysfunction,[25] decreased energy demand during sustained ischemia,[26] reduction of myocardial apoptosis,[27] attenuation of platelet mediated coronary thrombosis,[28] and preservation of endothelium-dependent coronary vasodilation.[29-31]

Molecular and Cellular Mechanisms of Preconditioning

Several interdependent molecular and cellular events have been identified as essential components of IPC. The basic model for the mechanism of IPC includes the initial generation of one or more triggers followed by receptor stimulation, mediator regulation of secondary pathways, and the eventual involvement of an end-effector.

Triggers and Receptors of Classic IPC

There is some consistency among animal and experimental models in confirming the individual, additive, or synergistic roles for a number of neuroendocrine and paracrine triggers of IPC.[32] Numerous studies have implicated endogenous adenosine, generated from adenosine triphosphate (ATP) hydrolysis and released by myocytes and vascular endothelium during brief periods of ischemia, as an important trigger.[33] Pretreatment with adenosine or adenosine analogs before lethal coronary occlusion has been shown to reduce infarct size.[34,35] In addition, blockade of adenosine receptors during IPC abolishes both classic and delayed myocardial protection[36] suggesting a role for the activation of both A_1 and A_3 receptors.[33,36] Differences among various animal species[37] and inconsistencies in human clinical trials[38-40] have contributed to the controversy implicating a universal role for adenosine. A number of other receptor-specific triggers have also been identified as important components of the IPC, including acetylcholine (muscarinic),[41] catecholamines (α_1 receptors),[42] angiotensin II,[43] bradykinin (B_2 receptors),[44] nitric oxide (NO),[45,46] endothelin,[47] and opioids (δ_1 receptors).[48-50] Reactive oxygen species (eg, superoxide, H_2O_2, hydroxyl radicals) generated by brief ischemia and reperfusion have also been recognized as possible triggers in the initiation of classic IPC.[51]

Mediators and Signaling Pathways of Classic IPC

The mechanism of IPC has been further delineated by a number of investigators and most likely involves the interaction of several mediators and signaling pathways. Downey et al[52] have proposed that after trigger generation, the stimulation of adenosine, bradykinin or opiod receptors coupled to G protein-coupled receptors (A_1/A_3-adenosine; B_2-bradykinin; δ_1-opiods) activate phospholipase C (and/or D), increasing diacylglycerol production which subsequently activates the protein kinase C (PKC) signaling cascade (Fig 2). Finally, activated PKC phosphorylates an end-effector (ie, ATP-sensitive K^+ channel).

The PKC hypothesis is based mainly on the observation that direct activation of PKC with either phorbol ester or 1-oleyl-2-acetyl glycerol mimics the infarct limiting effect of IPC in some animals.[52] In addition, nonspecific PKC antagonists (staurosporine, chelerythrine, polymixin)[52] block myocardial protection by IPC. Although the PKC model has also been shown in human cardiomyocytes,[53] canine and porcine models have not consistently supported a role for PKC in classic IPC suggesting that species-dependent variables and specific PKC isoenzymes should also be taken into consideration.[54,55] Additional kinase systems have been identified that may have interdependent roles in IPC. Tyrosine kinase (TK) is involved in preconditioning rabbit hearts.[56] In the pig, however, preconditioning

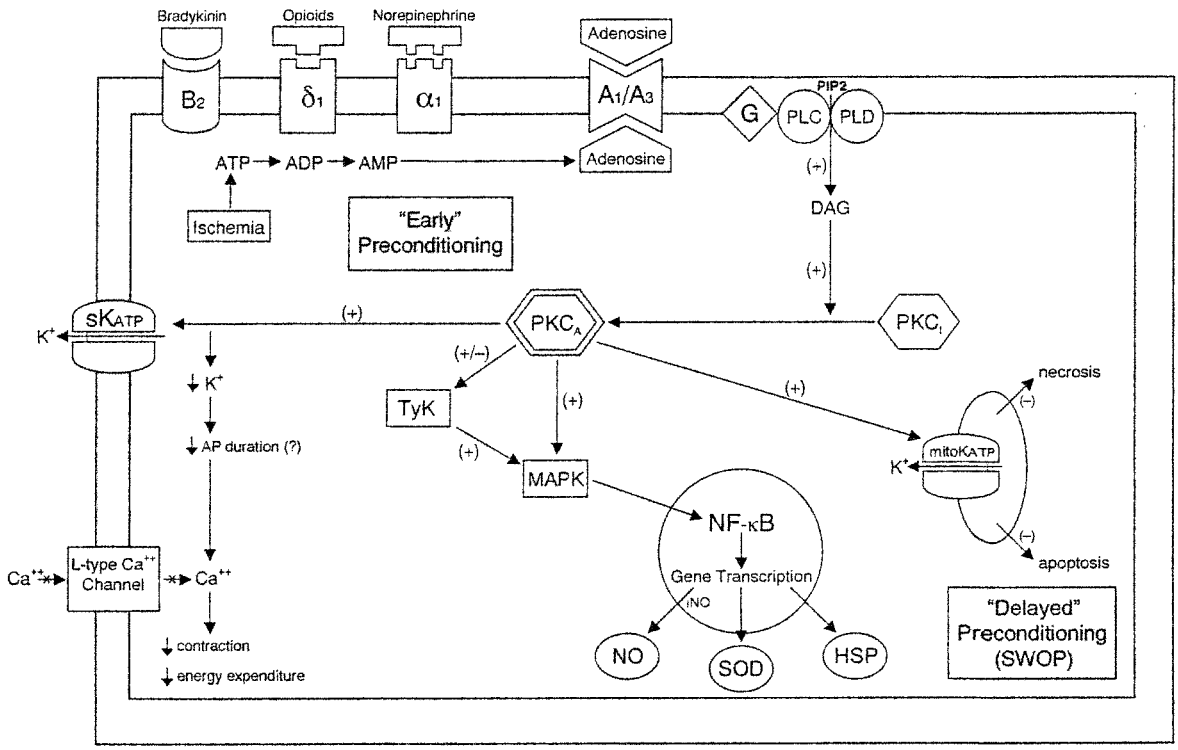

Figure 2. Summary of theoretical signaling mechanisms for classic "early" preconditioning and "delayed" preconditioning "second window of protection" (SWOP). Abbreviations: ATP, adenosine triphosphate; ADP, adenosine diphosphate; AMP, adenosine monophosphate; B_2, bradykinin receptor type 2; δ, opioid delta receptor; α_1, alpha adrenergic receptor type 1; A_1/A_3, adenosine receptor types 1 and 3; G, G regulatory protein; PLC/PLD, phospholipase C and D; PIP_2, phosphoinositolbiphosphate; DAG, diacylglycerol; PKC_I and PKC_A, protein kinase C inactive and active forms; sKATP, sarcolemmal adenosine triphosphate-dependent, potassium channel; TyK, tyrosine kinase; MAPK, mitogen activated protein kinase; NF-κB, nuclear factor kappa B; iNO, inducible nitric oxide synthase; NO, nitric oxide; SOD, superoxide dismutase; HSP, heat shock proteins; $mitoK_{ATP}$, mitochondrial adenosine triphosphate-dependent potassium channel.

was only blocked by simultaneous administration of a TK inhibitor (genistein), together with a PKC inhibitor (staurosporine), suggesting the presence of two parallel kinase systems for mediating IPC.[57] In rat hearts, a phospholipase D-coupled TK pathway is activated during preconditioning and subsequently activates the PKC and downstream mitogen-activated protein kinases (MAPKs).[58] Increased MAPK after transient ischemia[59] may be involved in the phosphorylation of factors that are directly responsible for the myocardial protective effects of IPC and apoptosis.[58] Finally, Przyklenk and Kloner[10] proposed that a brief, modest and nonlethal increase in intracellular calcium (Ca^{++}) during IPC and reperfusion may elicit favorable Ca^{++} regulation that is responsible for the anti-infarct effect of IPC.

End-Effector Mechanisms of Classic IPC

Large conductance ATP-sensitive K^+ channels exist in high density in sarcolemmal membranes of cardiac cells (sK_{ATP}) and appear to be promising candidates for the end-effectors of IPC. It is frequently cited that during IPC, stimulation of G protein-coupled receptors activates PKC which subsequently opens sK_{ATP} channels. Once the sK_{ATP} channel is opened, there is an efflux of K^+ from the cell and the action potential duration is shortened resulting in a decrease in L-type Ca^{++} channel activity and a subsequent reduction in Ca^{++} load during lethal ischemia and reperfusion[59] (Fig 2). A decrease in intracellular Ca^{++} is associated with diminished myocardial contraction and a reduction in the expenditure of high-energy phosphates that are required to

re-establish Ca^{++} concentrations.[50] Several lines of evidence support an effector role of sK_{ATP} channels in the mechanism of classical IPC, including the demonstration that sK_{ATP} channel agonists (nicorandil, pinacidil, bimakalin) mimic the effect of IPC in reducing infarct size.[60,61] Furthermore, sK_{ATP} channel antagonists (glibenclamide, sodium 5-hydroxydecanoate) abolish the infarct-limiting effects of IPC as well as the preconditioning effects of adenosine,[35] isoflurane,[62] morphine[49] and PKC.[63]

Recent studies have challenged the purported significance of the sK_{ATP} channels by showing that the cardioprotective effect of sK_{ATP} channel agonists is not associated with action potential shortening.[64] More importantly, K_{ATP} channels have been shown to exist in the inner membrane of mitochondria ($mitoK_{ATP}$) as well as the sarcolemmal membrane of cardiac muscle.[65] Mitochondria are known to play a pivotal role in controlling cell viability.[66] Because IPC has recently been shown to protect cardiomyocytes against necrosis[67] and apoptosis,[27] it is not surprising that $mitoK_{ATP}$ channels have become a primary area of interest in the mechanism of myocardial preconditioning (Fig 2). Selective agonists (diazoxide) of the $mitoK_{ATP}$ channel have been shown to mimic the cardioprotective effect of IPC, whereas specific inhibitors (5HD) attenuate cardioprotection by IPC and diazoxide.[68,69] Moreover, $mitoK_{ATP}$ channels can be regulated by PKC and their activation may be more relevant to IPC than the activation of the sarcolemmal K_{ATP} channels.[70] The enhanced expression of anti-apoptotic Bc12 proteins has been proposed as the mechanism of apoptosis prevention by a "second window of protection" (SWOP).[71] Understanding the relative contributions of sarcolemmal and mitochondrial K_{ATP} channels in mediating early and delayed cardioprotection by IPC will be essential for the future development of therapies that have clinical applications.[72] In addition, understanding of the role of mitochondria in regulating cell viability will help to further delineate any correlation between the mechanisms of IPC and both apoptosis and necrosis.

Mechanism for Delayed Myocardial Protection After IPC

The mechanism for delayed myocardial protection associated with IPC shares many of the elements of classic early preconditioning including some triggers and activation of similar signaling cascades[52] (Fig 2). In contrast to early IPC, gene activation and subsequent de novo synthesis of regulatory proteins are also important for the late reappearance of this (SWOP). Heat shock proteins (HSPs), have been implicated as ideal regulators due to their involvement in the correct folding of many proteins, protein translocation, and the process of repairing or degrading damaged proteins as a defense strategy to ensure survival.[73] Marber et al[23] first reported in rabbits that the expression of the inducible 70-kd HSP (HSP 70) by brief ischemia or heat stress conferred resistance to myocardial infarction. Increased levels of HSP 70 have also been implicated in the late cardioprotection against stunning after preconditioning in pig hearts.[74] Although other investigators have been unable to show a correlation between the expression of HSP 70 and preconditioning,[75] two low-molecular-weight HSPs ($\alpha\beta$-crystallin, HSP 25/27) have been shown to protect rat cardiomyocytes against ischemic injury.[76] The direct relationship between HSPs and either early ischemic tolerance or delayed myocardial protection remains to be determined.

Activation of superoxide dismutase and induction of inducible nitric oxide synthase (iNOS) have also been suggested to play important roles as protein effectors of delayed preconditioning. In a series of experiments, Bolli et al proposed that a brief period of ischemic stress increased NO production (presumably by endothelial, constitutive nitric oxide synthase) and O_2^- production[77] (Fig 3). NO and O_2^- (superoxide anion) could then react and activate PKC either directly or through the production of peroxynitrite or hydroxyl radical. Activation of PKC initiates a complex signal transduction cascade which involves tyrosine kinases, MAPKs, the transcription of nuclear factor NF-κB and other gene promoters, leading to upregulation of iNOS production and increased generation of NO during the second ischemic challenge. According to this paradigm, NO plays two different roles in delayed protection against stunning, initially by triggering the development of the cardioprotective mechanism and subsequently by protecting against myocardial stunning through the upregulation of iNOS. There is significant overlap, however, between the proposed NO pathway of

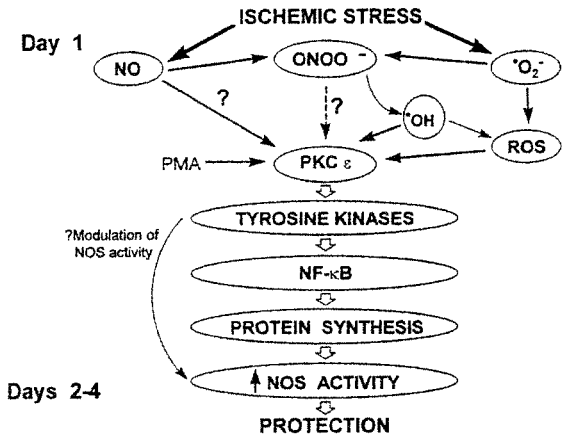

Figure 3. Molecular mechanism for the NO hypothesis of delayed preconditioning. Abbreviations: NO, nitric oxide; $ONOO^-$, peroxynitrite; O_2^-, superoxide anion; OH, hydroxyl radical; PKCε, protein kinase C-epsilon isoform; NF-κB, nuclear factor kappa B; NOS, nitric oxide synthase. (Reprinted with permission from Bolli R, Dawn B, Tang X, et al: The nitric oxide hypothesis of late preconditioning. Basic Res Cardiol 93: 325-338, 1998.[77])

preconditioning and the role of NO in the cellular signaling mechanism leading to cell apoptosis and necrosis.[66] How the cardiomyocyte delicately initiates the protective mechanism for ischemic preconditioning and simultaneously avoids destruction by activating a similar apoptotic signalling pathway, remains to be elucidated.

Preconditioning Human Myocardium

In Vitro Evidence of IPC in Human Cardiomyocytes

Despite the preponderance of data suggesting the existence of endogenous mechanisms for myocardial protection in animals, it has been more difficult to show similar mechanisms of IPC in humans. The most supportive evidence indicating that human myocardium is amenable to preconditioning comes from in vitro studies of isolated human cardiomyocytes. Ikonomidas et al first reported that anoxic preconditioning confers resistance to sustained ischemia in cultured human ventricular cardiomyocytes.[78] Hypoxia and rapid pacing have been used to show that adenosine is involved in protecting isolated human atrial trabeculae from ischemia-induced contractile dysfunction.[79] Evidence from other models of early preconditioning have also confirmed a role for adenosine, bradykinin and α1-adrenergic receptors, as well as PKC and K_{ATP} channels suggesting that the mechanism of IPC in humans and animals may be similar.[80,81] In addition, SWOP has recently been shown in cultured human ventricular myocytes.[82]

Clinical Evidence of Myocardial IPC in Humans

Several studies have shown that patients with angina (within 24 to 48 hours before MI) have smaller infarct size and decreased short-term morbidity and mortality independent of collateral circulation and the use of anti-anginal medications.[83] The recent Thrombolysis in Myocardial Infarction 9B Trial showed a temporal correlation between onset of angina and subsequent MI. In this trial, patients who experienced angina within 24 hours before infarction had a lower peak CPK level and a lower incidence of cardiac related morbidity at 30 days postinfarction compared with the "no angina group" or those whose angina began more than 24 hours preinfarction.[84] Furthermore, in patients with prodromal angina within 24 hours before anterior MI, Ishihara et al showed an increased incidence of infarct-associated graft patency, improved reperfusion after thrombolytic therapy, and lower in-hospital mortality which was sustained throughout a 5-year follow-up period.[85] Antecedent angina before MI may also protect against reperfusion arrhythmias.[86] Despite these optimistic results, the evidence from other investigations of preinfarct angina has been less consistent, suggesting the existence of several confounding variables (extent of coronary artery disease, age, duration of angina, etc). Some investigators have been unable to show any benefit associated with preinfarct angina especially in elderly patients (≥65 years old),[87] whereas other studies have even implicated that preinfarct angina may be detrimental.[88]

Additional clinical correlates of myocardial tolerance induced by angina include the concepts of "walk through" or "warm-up" angina. Warm-up angina describes the phenomenon in which patients are able to continue exerting themselves after a brief rest period after an initial episode of angina. The warm-up phenomenon has been shown by comparing the performance on two consecutive exercise tests separated by a

short resting period. The severity of angina, ST segment depression on electrocardiogram recordings, myocardial oxygen consumption,[89] ischemic duration, recovery time needed,[90] and wall motion dysfunction on echocardiography[91] are significantly less during the second exercise test. Walk through or "second wind in angina" refers to the scenario in which patients suffer through anginal pain without resting and can continue exerting themselves with fewer or no symptoms.[92] These observations that brief episodes of angina confer resistance to further exertion-induced angina resemble the cardioprotection afforded by IPC and are thought to be associated with reduced myocardial oxygen consumption rather than increased collateral circulation.

Patients undergoing percutaneous transluminal coronary artery angioplasty (PTCA) provide a unique opportunity to study myocardial adaptation to ischemia and reperfusion. Several studies of patients undergoing single-vessel PTCA have shown less ST segment deviation on surface or intracoronary electrocardiogram, decreased lactate production and less angina during subsequent, occlusive balloon inflations in comparison with the first inflation.[93] In addition, a higher ejection fraction and smaller increases in left ventricular filling pressure have also been observed following later balloon inflations.[94] No beneficial effects of sequential episodes of myocardial ischemia can be appreciated after a balloon inflation of less than 60 seconds.[95] The beneficial effects of repetitive balloon angioplasty can be mimicked by intracoronary infusion of adenosine or dipyridamole[39,96] and abolished by the K_{ATP} channel blocker, glibenclamide[97] or α_1-adenosine receptor antagonist, bamiphylline.[38] Although these observations are consistent with the experimental findings of IPC, some investigators have been unable to show a benefit following repeated coronary artery occlusion[98] and others have suggested that the acute recruitment of collaterals may be responsible for the protection.[94]

IPC During Conventional CABG Surgery

Once the feasibility of preconditioning the human heart can be determined and the specific mechanism defined, clinicians can take advantage of prophylactic preconditioning as a primary or supplemental means of providing myocardial protection. In 1993, Yellon et al used two 3-minute periods of aortic cross-clamping interspersed with 2 minutes of reperfusion as an IPC stimulus during CPB in patients undergoing CABG surgery. A single[99,100] 10-minute period of aortic cross-clamping and electrical ventricular fibrillation followed the second period of IPC. In comparison with the control group which was not preconditioned, ATP depletion was significantly decreased in biopsies from the IPC hearts after the ischemic insult.[99,100] This same group of investigators subsequently showed that the serum troponin T level was lower at 72 hours post-CPB in the preconditioned patients compared with those in the control group.[101] Other investigators have shown that IPC provides myocardial protection in addition to the concomitant use of cardioplegia.[102,103] Despite these encouraging results, IPC induced by aortic cross-clamping during CABG may not provide any additional myocardial protection from that afforded by CPB[104] or cardioplegic arrest (normothermic or hypothermic) alone.[105,106] Perrault et al even reported that IPC during CABG did not enhance cardioplegic protection and that it might be deleterious because CPK release was significantly greater compared with controls.[107]

IPC During Minimally Invasive CABG Surgery

Ischemic myocardial preconditioning may be more useful during CABG surgery when cardioplegia delivery is suboptimal or impractical (severe coronary artery disease, ventricular hypertrophy, severely calcified aorta) as well as in "beating heart" procedures when CPB and cardioplegic arrest are intentionally avoided. During minimally invasive direct coronary artery bypass grafting (MIDCAB) and "off-pump" CABG (OPCAB), a period of obligatory myocardial ischemia occurs while the coronary anastomosis is being performed and the corresponding coronary artery is occluded. Potential benefits of preconditioning during minimally invasive CABG surgery include less myocardial dysfunction and improved hemodynamic stability during native coronary occlusion as well as a smaller MI size should occlusion, thrombosis or spasm occur perioperatively.[108] Jacobsohn et al described the impact of IPC on myocardial protection during a MIDCAB procedure.[109] Preconditioning was performed by occluding the left anterior descending coronary artery (LAD) for 3 minutes (isch-

emia), followed by 3 minutes of reperfusion, and then 5 additional minutes of ischemia, followed by 5 minutes of reperfusion. There was a total of 15 minutes of ischemic time while the left internal mammary artery (LIMA) to LAD anastomosis was being performed. During the preconditioning periods, there were no ST segment nor T wave changes and no new regional wall motion abnormalities (RWMAs) as assessed by transesophageal echocardiography. The initial preconditioning stimulus depressed contractility more than the subsequent stimulus, suggesting a protective effect, and contractility improved significantly after revascularization (Fig 4). The period of preconditioning was well tolerated, however the beneficial effects could not be determined definitively in the absence of a control.

Malkowski et al investigated the effects of IPC (5 minutes of LAD occlusion, 5 minutes of reperfusion) in 17 patients undergoing MIDCAB procedures involving a single LAD-LIMA anastomosis (10 to 12 minutes of LAD occlusion).[108] New left ventricular RWMAs and increased pulmonary arterial pressures were observed during IPC which normalized to baseline during reperfusion; IPC however, did not prevent a similar increase in regional left ventricular dysfunction and elevated pulmonary pressures during subsequent LAD occlusion (Fig 5).

Discrepancies between in vitro and in vivo studies, and among various clinical trials may be related to inadequate IPC stimuli, different measures of outcome (myocardial dysfunction *v* infarction) or the presence of collaterals which may limit any benefit of regional IPC. Because IPC may inherently induce myocardial dysfunction, further randomized trials should be conducted to determine its definitive benefits, before this technique is routinely used during minimally invasive CABG procedures.

Pharmacologic Preconditioning During CABG Surgery

Several studies have identified a number of pharmacologic agents that may mimic IPC without having to manipulate coronary blood flow. Endogenous adenosine has been implicated as an important mediator of IPC in humans.[110] In addition, exogenous adenosine has been shown to precondition myocardium in a human model of ischemia reperfusion.[110] The results from

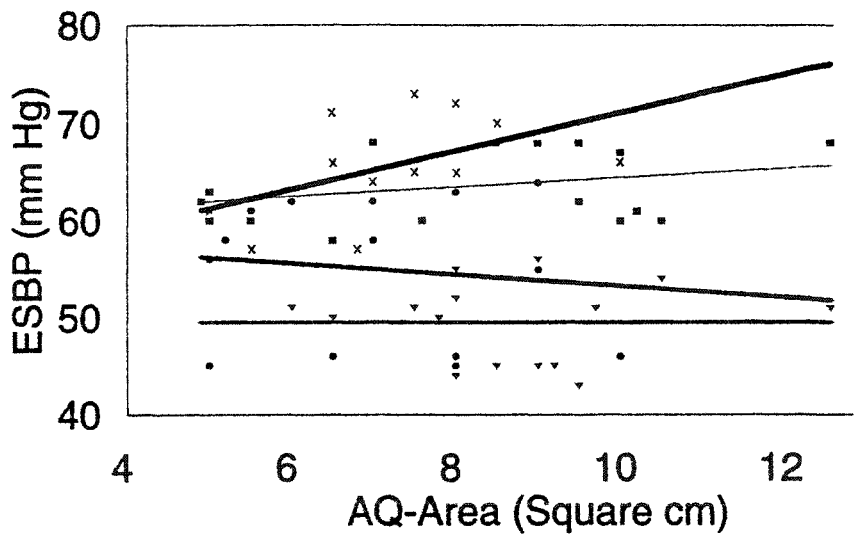

Figure 4. End-systolic points from the pressure area loops performed during a MIDCAB procedure at baseline, after an initial 3 minute period of ischemic preconditioning (first IP), after a subsequent 5 minute period (second IPC) and after left internal mammary artery—left anterior descending coronary artery revascularization (after MIDCAB). Contractility was expressed as the ratio of end-systolic blood pressure (ESBP) to left ventricular area (AQ area = end-systolic left ventricular area measured by transesophageal echocardiography using acoustic quantification). The initial IP stimulus depressed contractility more than the subsequent IP stimulus. Contractility improved after revascularization. ■, baseline; ▼, first IPC; ●, second IPC; X, after MIDCAB. (Reprinted with permission from Jacobsohn E, Young C, Aronson S, Ferdinand F: The role of ischemic preconditioning during minimally invasive coronary artery bypass surgery. J Cardiothorac Vasc Anesth 11:787-792, 1997.[109])

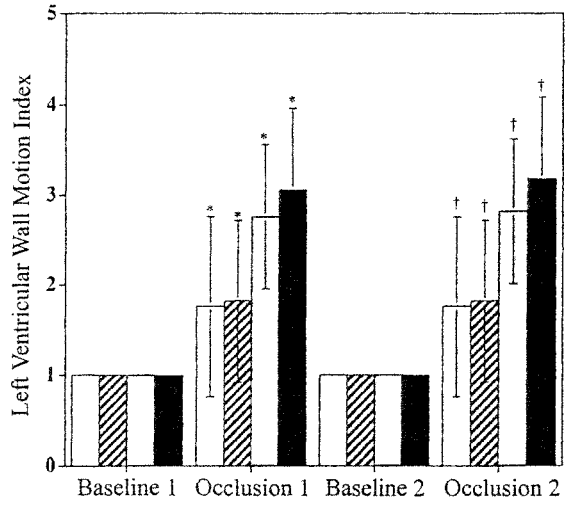

Figure 5. Left ventricular regional wall motion was assessed by intraoperative transesophageal echocardiography in 17 patients undergoing MIDCAB procedures. Measurements were made at baseline (baseline 1), during ischemic preconditioning (occlusion 1); after subsequent reperfusion (baseline 2) and during performance of the left internal mammary artery—left anterior descending coronary artery anastomosis (occlusion 2). Using a 16-segment model, LV regional wall motion was indexed (1 = normal; 2 = hypokinesia; 3 = akinesia; and 4 = dyskinesia) for the anteroapical (solid bars), apical-septal (gray bars), midanteroseptal (open bars) and midanterior (hatched bars). There were statistically significant differences ($p < .05$) between baseline 1 and occlusion 1 and between baseline 2 and occlusion 2. No significant change was observed between occlusions 1 and 2 in these regions. Postoperative LV function returned to normal in all 17 patients after revascularization. (Reprinted with permission from the American College of Cardiology [Journal of the American College of Cardiology, 1998, 31:1035-1039].[108])

clinical trials using adenosine as a pharmacologic preconditioning agent have been less consistent. Some investigators have shown that adenosine may be advantageous as a preconditioning agent when administered independently[111,112] or together with IPC.[113] In other studies however, the addition of adenosine to cardioplegia has not been consistently beneficial in reducing perioperative myocardial morbidity in patients undergoing elective CABG surgery.[40,114] Acadesine, a synthetic adenosine regulator, has been shown to increase the availability of adenosine in ischemic tissues undergoing ATP depletion,[115] and has therefore been implicated as a potential myocardial pharmacologic preconditioning agent.[116-118] Nicorandil, an agonist of K_{ATP} channels, also increases ischemic tolerance in humans during PTCA.[119] In addition, some opiods,[49] several volatile anesthetics,[120-122] and NO donors[77] have all been implicated as potential pharmacologic preconditioning agents.

Practical and ethical restrictions in performing clinical trials using ischemia as a preconditioning stimulus have presented significant challenges in trying to study the potential therapeutic efficacy of this technique. Further delineation of the molecular and cellular constituents of preconditioning will provide a basis for the further development of pharmacologic agents which may provide myocardial protection without having to induce ischemia by altering coronary blood flow.

Conclusion

IPC is an extremely important mechanism of endogenously mediated myocardial protection. Evidence from animal models and both in vitro and in vivo studies in humans has helped to understand and confirm the existence of the molecular and cellular components of IPC. Variation among species and experimental models however, has helped to identify the complexity of the mechanism and the characteristics of IPC. Several pharmacologic agents have also been identified that may mimic "classic IPC" and provide equivalent or even improved myocardial protection without having to induce ischemia by altering coronary blood flow. The clinical usage of myocardial preconditioning may be particularly useful in certain cardiac surgical populations such as those patients undergoing coronary revascularization procedures or even heart transplantation.[122,125] Ultimately, additional randomized, controlled clinical trials will have to be performed to further delineate the potential therapeutic efficacy of IPC and pharmacologic myocardial preconditioning.

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