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REVIEW | *Novel Mechanisms of Myocardial Ischemia, Ischemia-Reperfusion, and Protection by Myocardial Conditioning*

Cardioprotection by intermittent hypoxia conditioning: evidence, mechanisms, and therapeutic potential

Robert T. Mallet,[1] Eugenia B. Manukhina,[1,2,3] Steven Shea Ruelas,[1] James L. Caffrey,[1] and H. Fred Downey[1,3]

[1]*Department of Integrative Physiology and Anatomy, University of North Texas Health Science Center, Fort Worth, Texas;* [2]*Institute of General Pathology and Pathophysiology, Russian Academy of Medical Sciences, Moscow, Russian Federation; and* [3]*School of Medical Biology South Ural State University, Chelyabinsk, Russian Federation*

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Mallet RT, Manukhina EB, Ruelas SS, Caffrey JL, Downey HF. Cardioprotection by intermittent hypoxia conditioning: evidence, mechanisms, and therapeutic potential. *Am J Physiol Heart Circ Physiol* 315: H216–H232, 2018. First published April 13, 2018; doi:10.1152/ajpheart.00060.2018.—The calibrated application of limited-duration, cyclic, moderately intense hypoxia-reoxygenation increases cardiac resistance to ischemia-reperfusion stress. These intermittent hypoxic conditioning (IHC) programs consistently produce striking reductions in myocardial infarction and ventricular tachyarrhythmias after coronary artery occlusion and reperfusion and, in many cases, improve contractile function and coronary blood flow. These IHC protocols are fundamentally different from those used to simulate sleep apnea, a recognized cardiovascular risk factor. In clinical studies, IHC improved exercise capacity and decreased arrhythmias in patients with coronary artery or pulmonary disease and produced robust, persistent, antihypertensive effects in patients with essential hypertension. The protection afforded by IHC develops gradually and depends on β-adrenergic, δ-opioidergic, and reactive oxygen-nitrogen signaling pathways that use protein kinases and adaptive transcription factors. In summary, adaptation to intermittent hypoxia offers a practical, largely unrecognized means of protecting myocardium from impending ischemia. The myocardial and perhaps broader systemic protection provided by IHC clearly merits further evaluation as a discrete intervention and as a potential complement to conventional pharmaceutical and surgical interventions.

enkephalin; glycolysis; mitochondrial permeability transition; myocardial ischemia; nitric oxide; protein kinase; reactive oxygen species; sarcoplasmic reticulum

INTRODUCTION

Western medicine associates "intermittent hypoxia" with the repeated, often severe, arterial desaturation observed in obstructive sleep apnea (OSA). Since OSA is an accepted risk factor for cardiac disease (9, 183), the notion that other forms of intermittent hypoxia are cardioprotective may seem counterintuitive. The original observation that prior ischemia could protect the myocardium during subsequent ischemia may have once seemed equally surprising (133). Now, ischemic preconditioning is an accepted concept, although its practical applications thus far have been limited.

Even before ischemic preconditioning was discovered, Meerson and colleagues (122, 124) demonstrated that weeks of moderate intermittent hypoxic conditioning (IHC) mobilized mechanisms that defended myocardium from acute or prolonged ischemia and prevented life-threatening arrhythmias. Experimental animals similarly exposed to 3 wk of IHC were almost completely protected from infarct during a subsequent coronary occlusion-reperfusion protocol (107, 229). Despite these remarkable observations, the cardioprotective benefits of IHC have generated far less attention than the less practical ischemic preconditioning. IHC has safely been used clinically to protect subjects with developing coronary disease or those awaiting cardiac procedures (27, 46, 58, 178). Moreover, the fact that IHC impacts the entire body may offer important advantages over treatments targeting a single organ. Understanding how IHC achieves these remarkable results should generate new therapeutic approaches and perhaps a broader application, for instance, to reduce postsurgical hospital stays

Address for reprint requests and other correspondence: R. T. Mallet, Dept. of Integrative Physiology and Anatomy, Univ. of North Texas Health Science Center, 3500 Camp Bowie Blvd., Fort Worth, TX 76107 (e-mail: Robert.mallet@unthsc.edu).

and/or the cognitive impairment associated with cardiac bypass surgery.

This article reviews the literature documenting the direct cardioprotective benefits of IHC on myocardial infarction, cardiac function, arrhythmias, and coronary flow. In addition, evidence of indirect cardioprotective benefits of IHC on hypertension, exercise tolerance, particularly in patients with cardiac or respiratory diseases, and glucose homeostasis in patients with diabetes are considered. After addressing potential mechanisms of IHC-mediated cardioprotection, we conclude with a discussion of apparent impediments to widespread applications of IHC and suggestions for future IHC research. Studies investigating IHC use a variety of related conditioning programs. This article does not address details of individual programs unless these aspects impact the outcomes.

DIRECT CARDIOPROTECTIVE EFFECTS OF IHC

Hypoxia Conditioning Programs

Myriad hypoxia programs have been found to elicit cardioprotection (163). Ascent to altitude, or lowering the pressure in a chamber, produces hypobaric hypoxia, in which P_{O_2} is decreased, whereas the fraction of inspired O_2 (FI_{O_2}) approximates 21%. In normobaric hypoxia, FI_{O_2} is lowered at constant barometric pressure. The daily hypoxia sessions may consist of several hours of continuous exposure to normobaric or hypobaric hypoxia or multiple cycles of several minutes of normobaric hypoxia and reoxygenation. Table 1 categorizes these programs and shows reports exemplifying the cardioprotective capabilities of each.

IHC Reduces Infarct Size

In 1973, Meerson et al. reported in the *American Journal of Cardiology* (122) a seminal observation that, 2 days after coronary artery ligation, rats adapted to hypobaric hypoxia had 35% less ischemic necrosis and 85% fewer deaths than nonadapted rats. Despite the growing interest in protecting the heart, three decades elapsed before the next reports of IHC-mediated reduction of infarct size (29, 141). Infarcts were decreased from 67% to 50% of the ischemic myocardium, and arrhythmias were attenuated to a similar extent in hypoxia-conditioned versus control rats subjected to coronary artery occlusion-reperfusion (141). Isolated hearts from acutely conditioned mice were subjected to global ischemia-reperfusion (I/R) beginning 30 min or 24 h after IHC (29). Infarct size was ~40% in both unconditioned controls and 30 min after IHC. However, infarcts in animals challenged 24 h afterward were reduced by half, demonstrating that the protective adaptations associated with IHC require time to develop.

In dogs conditioned by a 20-day IHC program, the infarcts resulting from coronary artery occlusion-reperfusion 24 h later were reduced more than 95% (49, 107, 229). When the conditioning program was shortened, no protection was observed after 1 day, but after 10 days infarct sizes were intermediate, approximately one-third those in unconditioned dogs (107). Protection also failed to develop if the reoxygenation intervals were omitted. If β_1-adrenergic or δ-opioid receptor antagonists or antioxidants were administered daily before each conditioning session, the protection was abrogated (49, 107). These last outcomes exemplify the consistent observation that IHC uses a spectrum of interdependent signaling pathways.

IHC protocols generally improve outcomes after I/R in rodents but to a degree that can differ among protocols. No reduction in infarct size was observed after 6 wk of IHC hypobaric conditioning at 5,000 m for 6 h/day, but infarcts were reduced when the intensity and daily duration were increased to 7,000 m for 8 h/day (83). Interestingly, a shorter (4 wk), less-intense (5,000 m, 4 h/day) hypobaric program

Table 1. *Representative intermittent hypoxia conditioning programs and outcomes*

Program	Acute Challenge	Outcomes	Reference(s)
Hypobaric hypoxia: one daily bout			
Rat	Occlusion-reperfusion	↓ Infarct, ↓ arrhythmias	81, 121, 140
Rat	Isolated heart: occlusion-reperfusion	↓ Ventricular arrhythmias	3, 4
Rat	Isolated heart: I/R	↑ Left ventricular function	23, 141, 193
Rat	Isolated heart: I/R	↓ Infarct	194
Rat	Isolated mitochondria: anoxia-reoxygenation	↑ Bcl-2/Bax, ↓ mitochondrial permeability transition pore	105
Rat	Isolated heart: I/R	↓ DNA fragmentation	44
Rat	Isolated heart: Ca^{2+} paradox	↑ Left ventricular contractile function	187, 205
Normobaric hypoxia: one daily bout			
Rat	Isolated heart: I/R	↓ Infarct, ↓ enzyme release	214
Normobaric hypoxia: multiple daily cycles			
Mouse	Occlusion-reperfusion	↓ Infarct, ↑ Left ventricular function	127
Rat	Occlusion-reperfusion	↓ Infarct, ↓ arrhythmias, ↑ endothelial function	110
Rat	Occlusion-reperfusion	↓ Infarct, ↓ contracture	13
Dog	Occlusion-reperfusion	↓ Infarct, ↓ arrhythmias	49, 107, 229
Human (chronic obstructive pulmonary disease)	Exercise	↑ Exercise capacity	12, 26, 156
Human (coronary artery disease)	Exercise	↓ Arrhythmias, ↑ exercise tolerance	27, 46, 58, 101, 178
Human (hypertension)	24-h Blood pressure monitoring	↓ Systolic and diastolic arterial pressure	100
Human (prediabetic)	Glucose tolerance test; hypoxia	↑ Glycemic control, ↑ hypoxia tolerance	56, 160

Representative reports for each intermittent hypoxia program category are shown. Hearts were studied in situ unless otherwise specified. Occlusion-reperfusion, coronary artery occlusion and reperfusion; I/R, global ischemia-reperfusion of isolated, perfused hearts; ↑, increase in the outcome variable; ↓, decrease in the outcome variable.

applied to juvenile rats reduced the damage by half (194). This protection was confirmed and extended (192) in adult rats conditioned for programs as short as 1 day. IHC programs consisting of multiple daily hypoxia-reoxygenation cycles, each hypoxia exposure lasting only 2–10 min, also decreased infarcts by ~50% after myocardial I/R in rats (110, 127). The remarkable reduction of infarct size observed in canine hearts (49, 107, 229) exceeded that found in similar studies in small animals. Given the numerous species differences, these observations may indicate that coronary occlusion and reperfusion is a more serious insult for the hypermetabolic rodent heart.

IHC may reduce damage even when applied after the ischemic challenge. Rats were subjected to permanent coronary artery occlusion 1 wk before starting 14- or 28-day IHC. Echocardiography provided evidence for sustained improvements at 14 and 28 days of IHC including reduced left ventricular (LV) dilation, increased LV pressure development including faster contractions and relaxations, decreased cardiomyocyte apoptosis, and increased coronary blood flow (208). Scar volume and fibrosis were reduced 30% and 40%, respectively, at 14 and 28 days of IHC, whereas LV capillary density was increased by ~60% versus non-IHC controls. When IHC was initiated 2 wk after I/R, no benefit was observed (125), suggesting a critical window of opportunity in the postinjury remodeling process. The practical prospect of improving the functional recovery of postinfarct patients would seem to merit immediate attention.

IHC Improves Postischemic Cardiac Mechanical Function

In addition to reducing myocardial damage, IHC consistently improves cardiac function (87, 122, 125). IHC appears to preserve contractile function even in isolated cells. When cardiomyocytes from IHC-programmed rats were ischemically challenged in vitro, they shortened more rapidly and to a greater extent than those from unconditioned rats (31, 226). The preservation or recovery of function was also observed in isolated LV papillary muscles from hypoxia-conditioned rats (191, 220). When P_{O_2} was reduced, the contractile function of muscles from rats conditioned for 28 and 42 days was significantly better preserved than that of the controls or of rats conditioned for 14 days (220). The better contractile function was associated with an extended action potential, suggesting that IHC moderates Ca^{2+} transport.

Much like isolated cardiac cells and muscle, isolated perfused hearts from IHC mice recovered almost twice the developed pressure during reperfusion as their nonconditioned counterparts (29). Similar results were obtained in hearts from IHC rats (220, 225). After 30 min of zero-flow ischemia, LV dP/dt_{max} and the heart rate $\times$ LV developed pressure product in IHC hearts were again nearly double those of control hearts. IHC hearts also exhibited improved diastolic function evident in a greater LV dP/dt_{min} and lower LV end-diastolic pressure. While most studies of IHC have been conducted in adult animals, IHC initiated in neonatal rodents demonstrated a similar degree of protection (23, 102, 219). The developing heart was, however, less hypoxia tolerant since the protection observed at 3,000 m was absent at 5,000 m.

IHC Reduces Cardiac Arrhythmias and Fibrillation

Ischemia reduces the fibrillation threshold in rats, yet IHC prevents this shift without altering the resting electrocardiogram (120, 125) and restores the fibrillation threshold when applied after myocardial infarction (182). IHC stabilizes the electrical activity (182) and reduces arrhythmias during acute ischemia as well as during reperfusion (121, 124). These initial electrocardiac findings have been expanded to encompass a spectrum of model systems including human subjects. Patients with arrhythmias sensitive to emotional distress were treated with normobaric IHC for 10 or 20 days (101). Heart rhythm disorders improved progressively in all 23 participants between 10- and 20-day IHC. Premature ventricular complexes ceased in 11 patients, decreased by 75% in 6 patients, and decreased by 50% in the final 6 patients.

Cardiac myocytes isolated from IHC rats display a complex of antiarrhythmic changes (187). IHC at both 5,000 and 7,000 m produced progressive antiarrhythmic effects in intact open-chest animals during ischemia (3). When the same protocols were applied to isolated hearts, a biphasic response was observed analogous to the neonatal studies described earlier; thus, an appreciable antiarrhythmic effect was observed in the 5,000-m group but a proarrhythmic effect in the 7,000-m group. Comparison of the in situ and isolated heart results suggests a beneficial neural or humoral adaptation in situ (4).

A significant antiarrhythmic effect was reported during 15-min ischemia in in situ rat hearts after 21 and 28 days of hypobaric IHC. The arrhythmias were likewise reduced during the subsequent 120-min reperfusion. Perhaps most impressively, the protection persisted for 2 wk (220, 223). The antiarrhythmic effect was potentiated by estrogen, suggesting that sex and sexual maturity should also be considered moderating factors (221).

A marked reduction in cardiac arrhythmias was observed in in situ canine hearts after 20 days of normobaric IHC (107, 229). Although premature ventricular complexes (PVCs) were observed in all nonconditioned and two-thirds of IHC dogs, ventricular tachycardia and fibrillation were observed only in non-IHC dogs. The 80% reduction in reperfusion arrhythmia scores was abolished by daily pretreatment with metoprolol, naltrindole, or *N*-acetylcysteine before each IHC session (49, 107), suggesting mediation by adrenergic, opioid, and free radical signals. The electrocardiac protection was absent if the hypoxia lacked the intermittent reoxygenations.

IHC Improves Coronary Blood Flow

Mild hypobaric IHC improved LV perfusion in rats (11). However, cardiac output was elevated in these IHC rat hearts as well, making it difficult to distinguish the effects of IHC per se from the functional hyperemic response to increased myocardial metabolic demand. Coronary blood flow was higher in isolated perfused hearts from conditioned rats before and after ischemia, but, as observed above, the higher flow was associated with greater function, making the assignment of cause and effect difficult (42). Coronary blood flow followed a similar pattern in neonatal animals, with higher flow consistently observed after 3,000-m conditioning. However, as observed with other measures of protection in this model, coronary flow declined when hypoxia was increased to 5,000 m (23, 102,

219). Thus, it appears that the developing heart is less adaptable than its adult counterparts.

As described earlier, IHC initiated 7 days postinfarction reduced infarct volume at 21 and 35 days (208). This effect was also accompanied by a sustained increase in coronary flow, but, again, the greater flow correlated with improved function. Closer inspection of the myocardium surrounding the infarcted area identified a 57% increase in capillary density in IHC hearts, providing the first clear structural basis of IHC-mediated enhancement of coronary flow, which may have contributed to the less-extensive fibrotic scars in those hearts.

Angina, a symptom of inadequate coronary blood flow was evaluated in 47 patients with ischemic heart disease (46). After 25 daily normobaric IHC sessions with 10% O_2, the frequency of angina declined by half, both in mild disease and in severe disease that had required continued medication. Exercise perfusion imaging is a noninvasive method for assessing myocardial perfusion in human subjects. Six patients were conditioned in a hypobaric chamber at 4,200 m in 14 weekly sessions during the 6 mo after coronary bypass surgery (37). Regional coronary perfusion was improved in all subjects after 6 mo, and, importantly, none of the subjects experienced serious symptomatic distress, including angina, during hypoxia.

In summary, multiple reports have demonstrated that IHC reduces infarct size, improves contractile recovery, and reduces arrhythmias in small and large animal models of I/R. The improved function is associated with increased blood flow and limited evidence of compensatory vascular remodeling. The tissue salvaged varies from ~50% in rodents to near 100% in dogs. The duration of the postischemic improvements is unclear as well as how long the post-IHC protections persist and whether they can be boosted at intervals. One encouraging study demonstrated a lasting reduction in damage when IHC was administered 1 wk after myocardial infarction (208). The animal studies are compelling, and since IHC appears safe, even for patients with coronary disease (27), detailed clinical studies are clearly warranted.

INDIRECT CARDIOPROTECTIVE EFFECTS OF IHC

Antihypertensive Actions of IHC

IHC is therapeutic, whereas OSA is a major risk factor for cardiovascular disease and hypertension (143). Cardiovascular responses to intermittent hypoxia depend on the degree of hypoxia, the duration of individual episodes, their frequency, and the length of sessions whether natural or programmed (51, 52). Each bout of OSA imposes brief, intense hypoxia stress; accordingly, studies of the mechanisms of OSA typically use cyclic intermittent hypoxia-reoxygenation protocols approximating the frequency and intensity of OSA (137, 161). Hypoxia periods modeling OSA are typically brief (e.g., 30–60 s), sufficiently intense ($FI_{O_2} < 0.08$) to produce appreciable arterial O_2 desaturation during the brief hypoxia exposures, and numerous, i.e., 30–120 exposures/h for 8–12 h/day (161). In contrast, cardioprotective IHC programs use either one daily prolonged (e.g., 4–8 h) bout or a limited number (e.g., 5–10/day) of shorter (e.g. 4–10 min) bouts of moderately intense (e.g. FI_{O_2}: 0.10–0.12) hypoxia.

These programs produce strikingly disparate blood pressure responses (161). Both IHC and OSA increase sympathetic activity (107, 115), but that associated with OSA persists during wakefulness and results in hypertension (35, 36, 94, 131, 161, 199). While intermittent hypoxia modeling OSA typically increases systemic arterial pressure (136, 201), cardioprotective IHC reduces blood pressure in rodents (146) and patients with hypertension (78, 100, 132, 186). Clinically hypertensive patients exposed to a 20-day normobaric IHC program had their arterial pressure restored to near normal, with the majority remaining normotensive 3 mo later without the assistance of antihypertensive medication (100). IHC does not raise arterial pressure during hypoxic intervals in healthy human subjects (97). Similarly, the arterial blood pressure in patients with mild chronic obstructive pulmonary disease was unaffected during the hypoxic intervals of a 3-wk IHC program (51). The hypoxia associated with IHC did produce a modest 4–6 beat/min increase in heart rate.

IHC Improves Exercise Tolerance in Patients with Cardiac or Respiratory Disease

IHC improved exercise tolerance and increased exercise threshold power by 25% in patients with ischemic heart disease and stable angina after myocardial infarction (46). The frequency of angina and spontaneous arrhythmias were both reduced. A similar increase in exercise tolerance was reported in patients with chronic obstructive pulmonary disease (26). These subjects had more hemoglobin, reached the anaerobic threshold later, and produced less lactate, suggesting improved O_2 delivery or O_2 utilization efficiency.

After a program of alternating IHC and hyperoxia, patients with stable coronary disease had lower blood pressure, increased ejection fraction, less angina, better glycemic control, and better exercise tolerance. The protocol was well tolerated, and patients related a better quality of life with less anxiety and depression (58, 178). Many of the benefits remained in force 1 mo later. Other studies in elderly subjects again found the protocol well tolerated with improved exercise performance and better cognition (12, 156). When IHC was administered before coronary artery bypass surgery, the combined IHC-hyperoxia protocol reduced circulating troponin and lactate concentrations, common measures of myocardial distress (181).

IHC Produces a Spectrum of Benefits in Patients With Diabetes

IHC preserved islet cell function and insulin secretion in chemically induced diabetes (85). The common diabetic sequelae of oxidative stress, declining nitric oxide (NO), endothelial dysfunction, and myocardial and vascular damage were also moderated (64, 149). In the insulin-resistant type 2 model of diabetes, IHC improved glucose tolerance, insulin signaling, and glucose trapping while moderating the gluconeogenesis pathway (179, 180). IHC also exerted an antihypertensive effect in type 2 diabetic rats (50).

IHC improves glycemic control in patients with type 2 diabetes, reducing blood glucose and postprandial glucose tolerance after one session (45). These findings were confirmed with longer IHC protocols in glucose-intolerant subjects (56, 160). Importantly, the improvements in glycemic control persisted and were still apparent 1 mo later. The increases in hypoxia-inducible factor (HIF)-1α paralleled glycemic control. Leone and Lalande (93) suggested that IHC might serve as a

therapeutic substitute for exercise in sedentary patients with diabetes and noted the IHC-associated increases in hemoglobin, blood volume, stroke volume, and O_2 consumption. In this regard, some (26, 27) but not all (166) human studies have reported increases in hemoglobin after IHC.

IHC Protects the Brain and Kidney

IHC impacts the entire body and can protect other organs in addition to the heart. There is extensive evidence of IHC-induced protection of the brain from ischemic stroke (6, 71, 173) and ethanol intoxication-withdrawal (75, 153) and improved motoneuron function in the hemisected spinal cord (6, 98, 138). IHC also protects the kidneys. In a rat model of type 2 diabetes mellitus, a 4-wk program of daily 6-h hypobaric (5,000 m) exposures decreased albuminuria, glomerular hyperplasia, and renal corpuscle fibrosis and preserved activity of the antioxidant enzyme superoxide dismutase (SOD) (180). A 7-day program of 15 h/day hypobaric hypoxia suppressed renal I/R-induced apoptosis, autophagy, leukocyte infiltration, and superoxide formation of the renal parenchyma while preventing the increased blood urea nitrogen and serum creatinine indicative of renal failure (212). Systemic disorders including heart failure, diabetes mellitus, hypertension, and metabolic syndrome threaten multiple organs. IHC may offer a simple, noninvasive intervention to simultaneously treat multiorgan dysfunction and damage.

CARDIOPROTECTIVE MECHANISMS OF INTERMITTENT HYPOXIA

Research conducted over the last two decades has delineated a complex array of cardioprotective mechanisms mobilized by IHC. The complexity reflects the global nature of the stimulus and the wide selection of protocols, model systems, and target end points for studying and evaluating IHC (Table 1). This section attempts to summarize the potential mechanisms with the most experimental support. Figure 1 shows the relationships between these mechanisms. Figure 2 shows the numerous mediators and effectors of IHC while emphasizing the integrated character of the mechanisms due to the extensive crosstalk between their signaling cascades. Some, but not all, of these mechanisms are in common with those of the extensively studied ischemic preconditioning. Interestingly, nonischemic myocardial hypoxia achieved by regional coronary perfusion with deoxygenated blood (168) or crystalloid (126) was equally cardioprotective as preconditioning ischemia.

Enhancement of Intermediary Metabolism and ATP Production

Myocardial ischemia interrupts the ATP synthesis required to sustain contractile function and cardiomyocyte survival (38). However, hypoxic exposures trigger adaptations, including augmented carbohydrate metabolism and mitochondrial respi-

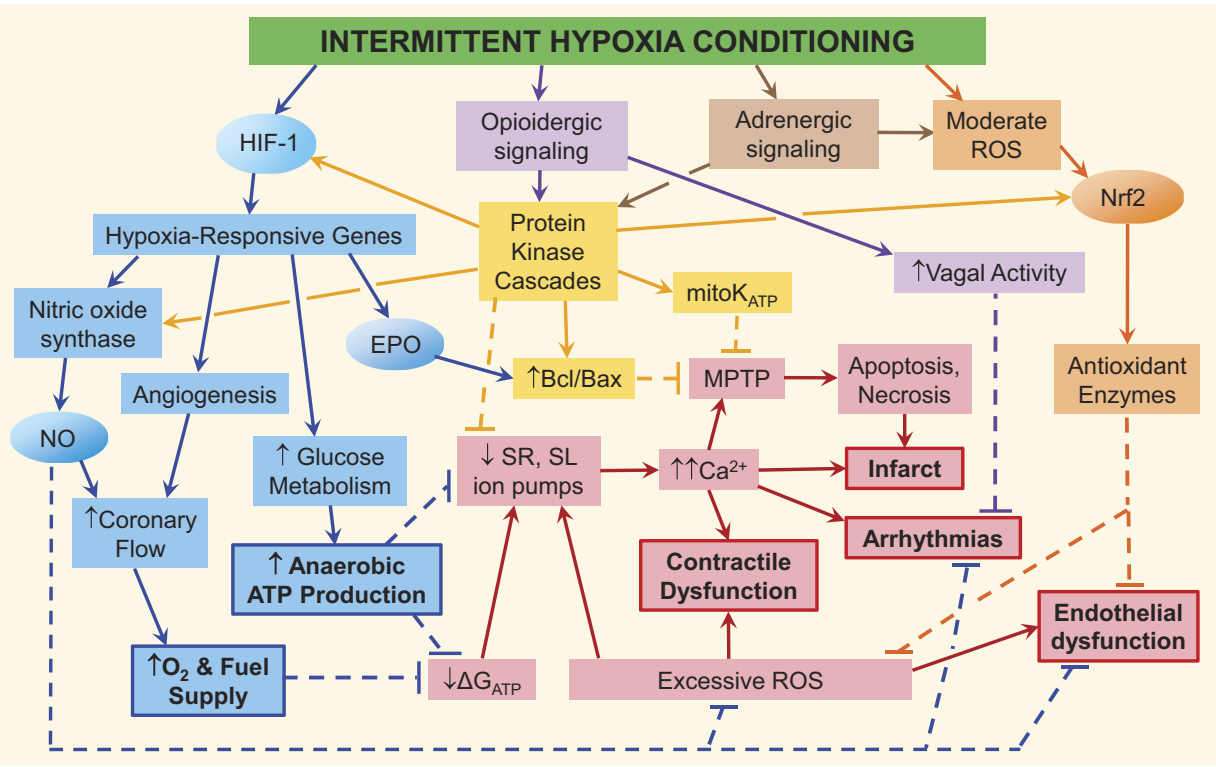

Fig. 1. Cardioprotective signaling cascades mobilized by intermittent hypoxia conditioning (IHC). Intermittent hypoxia-induced cardioprotective mechanisms include the hypoxia-inducible factor (HIF)-1-activated gene program (blue), adrenergically induced cardioprotective signaling (brown), ROS induction of the program of genes of nuclear factor erythroid-2 related factor 2 (Nrf2) encoding antioxidant enzymes (orange) and nitric oxide (NO) synthase (NOS; blue), enkephalinergic signaling cascade (purple), and protein kinase activation of mitoprotection, NOS, and cardioprotective genes (yellow). The ischemia-reperfusion (I/R)-triggered injury cascade is shown in red; dashed lines represent the suppression of this cascade by IHC-induced mechanisms. The bold font and borders indicate the principal manifestations of I/R injury and the favorable adaptations produced by the gene program of HIF-1. Ovals represent IHC-inducible transcription factors and cytoprotective molecules. EPO, erythropoietin; ΔG_{ATP}, Gibbs free energy of ATP hydrolysis; MPTP, mitochondrial permeability transition pore; mitoK$_{ATP}$, mitochondrial ATP-sensitive K^+ channel; SR, sarcoplasmic reticulum; SL, sarcolemma.

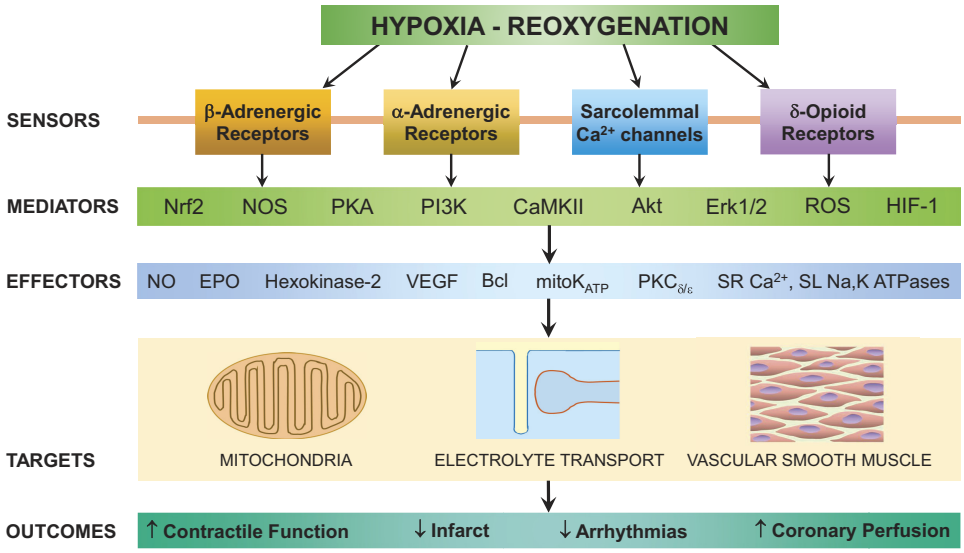

Fig. 2. Integrated cardioprotection by intermittent hypoxia conditioning-activated mechanisms. Sarcolemmal receptors and Ca^{2+} channels respond to neurohumoral signals by mobilizing signaling cascades mediated by protein kinases, transcription factors, nitric oxide (NO) synthase (NOS), and ROS. These cascades mobilize various effectors that suppress ischemia-reperfusion (I/R)-induced injury mechanisms targeting mitochondria, membrane Ca^{2+}, Na^+ transport, and coronary artery vasoactivity. Protection of these I/R-vulnerable components culminates in preservation of myocardial and coronary function and the prevention of cardiac rhythm disturbances and irreversible tissue damage. Nrf2, nuclear factor erythroid-2 related factor 2; PI3K, phosphatidylinositol 3-kinase, CaMKII, Ca^{2+}/calmodulin-dependent kinase II; HIF-1, hypoxia-inducible factor 1; EPO, erythropoietin; $mitoK_{ATP}$, mitochondrial ATP-sensitive K^+ channel; SR, sarcoplasmic reticulum; SL, sarcolemma.

ratory capacity, that increase ATP production and lower ATP demand during subsequent ischemic threats (47). These adjustments pave the way for rapid restoration of myocardial ATP and phosphocreatine after acute anoxia (87) or I/R (193).

Any increase in O_2-independent glycolytic capacity should extend the critical window of cellular survival during sustained ischemia. Hypoxia-conditioned cardiomyocytes increase their glycogen stores, which enables them to later delay lethal rigor during ATP-depleting hypoxia (169). In rats, extended daily hypoxia augmented hexokinase and preserved mitochondrial integrity, positioning the animal to function better in low-O_2 environments (80, 195). Glycolysis serves as the preferred energy source for intracellular Ca^{2+} management (20, 207); thus, increased glycolytic enzymes and glycogen may sustain cytosolic Ca^{2+} transients and sarcoplasmic reticulum (SR) Ca^{2+} sequestration in hypoxia-conditioned cardiomyocytes (202). Glucose and glycogen are more O_2 efficient than other fuels, and the hypoxia-induced metabolic remodeling may increase mechanical efficiency in hypoxia-adapted hearts (123).

Electrolyte Transport and Ca^{2+} Management

Cardiac contractile function is orchestrated by SR Ca^{2+} release and extracellular influx during systole and the reuptake and extracellular extrusion during diastole. I/R threatens these systems either by depriving them of ATP or by generating reactive oxygen species (ROS) that disable the transporters and channels (Fig. 1) (67, 76, 228). In this regard, hypoxia conditioning in neonatal rat cardiomyocytes doubled calreticulin, a key SR Ca^{2+}-binding protein, and protected cells from apoptosis and necrosis during severe hypoxia (227). When subjected to an in vitro model of I/R, conditioned cardiomyocytes demonstrated larger systolic Ca^{2+} transients and more rapid and complete diastolic Ca^{2+} sequestration versus cardiomyocytes from nonconditioned rats. SR Ca^{2+} release and sarcolemmal Na^+/Ca^{2+} exchange both functioned better in cardiomyocytes from IHC rats (214). Hypoxia conditioning of intact rats also doubled SR calreticulin and preserved SR Ca^{2+} uptake during a later left anterior descending coronary artery (LAD) occlusion. This adaptation was abrogated by inhibition of p38 MAPK (202). Preceding hypobaric IHC reduced ischemic contracture and increased LV recovery in parallel with better preserved SR Ca^{2+}-ATPase activity and phospholamban function (205, 215). Also in rats, hypobaric IHC limited Ca^{2+} overload during myocardial ischemia and hastened the postischemic disposal of excess cytosolic Ca^{2+} (105, 227). These Ca^{2+} management adjustments were associated with reduced infarct size after LAD occlusion and reperfusion (214). An IHC program in guinea pigs increased the sarcolemmal Na^+-K^+-ATPase current density by 52% and its protein content by 76%. Cardiomyocytes from these animals resisted inactivation of the pump current during anoxia-reoxygenation, and the associated improvements in contractile recovery were sensitive to the Na^+-K^+ pump inhibitor ouabain (62).

In summary, IHC augments SR and sarcolemmal Ca^{2+} and Na^+ transport mechanisms and SR Ca^{2+} storage capacity. Reinforcing cation homeostasis before I/R presumably limits the subsequent impairment and may serve to minimize intracellular Ca^{2+} overload and maintain diastolic membrane potential. These adjustments may explain the smaller infarcts, fewer arrhythmias, and improved contractile function observed in the IHC-programmed, postischemic myocardium (Fig. 2).

Mitochondrial Mechanisms of Cardioprotection

Mitochondrial ATP-sensitive K^+ ($mitoK_{ATP}$) channels, key mediators of ischemic preconditioning (213), have also been implicated in IHC cardioprotection (Figs. 1 and 2). In dogs subjected to coronary artery occlusion-reperfusion, intracoronary perfusion with hypoxic buffer strikingly decreased the subsequent tissue injury (126), whereas blockade of sarcolemmal K_{ATP} and $mitoK_{ATP}$ channels blunted the protection. Hearts from IHC rats had significantly fewer arrhythmic PVCs during ischemia than controls, and, again, K_{ATP} channel blockade increased arrhythmias in both groups. Pharmacologically opening these same channels decreased arrhythmias only in the control group, suggesting the channels were already open in the IHC group (4). In support of this thesis, the $mitoK_{ATP}$ channel antagonist 5-hydroxydecanoate abolished the IHC cardioprotection without expanding infarcts in control rats, whereas two different channel openers decreased infarcts only in controls

(141). MCC-134 {1-[4-(H-imidazol-1-yl)benzoyl]-*N*-methylcyclobutane-carbothioamide}, which inhibits mitoK_{ATP} channels but also opens sarcolemmal K_{ATP} channels, abolished the antiarrhythmic and anti-infarct protection in IHC rats (82, 83), suggesting differing final pathways for metabolic and electrical protection. In another study, IHC and control hearts were injured by Ca^{2+}-free perfusion and Ca^{2+} reintroduction. The resulting depression in LV contractile function and subsequent hypercontracture was observed only in control rat hearts. However, the robust preservation of contractile performance by IHC and cardiomyocyte morphology were again abrogated by pharmacological blockade of the mitoK_{ATP} channel (204), suggesting a pivotal mitochondrial role in the cardioprotection afforded by IHC against infarct and arrhythmias.

Another mitochondrial channel, the large-conductance Ca^{2+}-activated K^+ (BK_{Ca}) channel, has been implicated in ischemic preconditioning, where cardioprotection was abrogated by the BK_{Ca} inhibitor paxilline (30) and by transgenic ablation of BK_{Ca} expression (171). Borchert et al. (21) examined the role of BK_{Ca} in cardioprotection afforded by continuous exposure of rats to 10% O_2 for 3 wk. Ventricular cardiomyocytes isolated from these rats showed increased tolerance to metabolic inhibition by sodium cyanide, the BK_{Ca} antagonist paxilline blocked the hypoxia-induced cytoprotection, and the BK_{Ca} activator NS-1619 increased ischemic resistance of cardiomyocytes from nonhypoxic rats. The role of BK_{Ca} channels in IHC cardioprotection is not known but merits investigation.

Preventing Mitochondrial Permeability Transition and Apoptosis

ROS and excess Ca^{2+} open large pores spanning the mitochondrial membranes. The resultant uncontrolled influx of material through these mitochondrial permeability transition pores (MPTP) threatens the cardiomyocyte (Fig. 1) by collapsing the mitochondrial membrane potential ($\Delta\psi_{mito}$), thereby compromising ATP synthesis. The concurrent release of cytochrome *c* and added ROS may perpetuate the process, culminating in cell death (7). In rats, IHC delayed MPTP opening, cytochrome *c* release, and the onset of contracture induced by I/R (226), excess Ca^{2+} (105), and chemical ROS generation (226). From the opposite perspective, opening the MPTP abolished the IHC-mediated protection from ischemic Ca^{2+} overload (226). In isolated hearts from neonatal rats, IHC protected mitochondria during I/R by preserving K_{ATP} channel function and preventing MPTP opening. Drugs that reversed these specific actions blunted the mitochondrial protection (23).

IHC shifts the balance of apoptosis mediators in favor of survival. Hexokinase activity reduces the incorporation of proapoptotic Bax into the outer mitochondrial membrane, restricting MPTP opening and the resultant apoptosis (5, 145). IHC increases the mitochondria-associated hexokinase-2 isoform in parallel with MPTP suppression (195). An intense IHC protocol ameliorated ischemically initiated cardiomyocyte apoptosis (192). Antiapoptotic Bcl-2 content rose fourfold, whereas markers of cellular damage, DNA fragmentation, and lipid peroxidation declined. Similar IHC protocols in mice reduced infarct size in combination with an increase in the survival protein heme oxygenase-1 and a decline in the apoptotic mediator C/EBP homologous protein (CHOP) (127). Hearts isolated from male IHC rats had an elevated prosurvival Bcl-2-to-Bax ratio and, as a result, less postischemic DNA damage (44). Newer studies have suggested that the favorable antiapoptotic Bcl-2-to-Bax ratio is a consistent finding in IHC-programmed hearts (80, 105). Potential hypoxia-induced mediators include decreased proapoptotic caspase-9 and increases in the pro-Bcl transcription factor GATA4 (105, 144).

ROS as Cardioprotectants

Excessive ROS production during I/R is cytotoxic (Fig. 1), but lower concentrations trigger a spectrum of adaptive responses, including redox-sensitive protein kinases and transcription factors that increase myocardial resistance to subsequent, more severe stress (54, 89). Conversely, antioxidant supplementation during IHC interrupts this low-level signaling and can blunt cardioprotection (49, 81).

To interrogate the cardioprotective role of IHC-induced ROS, rats were treated with the antioxidant *N*-acetylcysteine (81). A decrease in myocardial glutathione/glutathione disulfide during IHC suggested moderately intense ROS formation. IHC alone decreased infarct size by half, but when combined with the ROS scavenger, the infarct increased again. *N*-acetylcysteine treatment decreased infarct size in the nonhypoxic group such that the infarcts in the two antioxidant-treated groups were now equal. Pretreatment of dogs daily with *N*-acetylcysteine likewise prevented both anti-infarct and antiarrhythmia cardioprotection afforded by the IHC program (49). In another report (194), another ROS scavenger, mercaptopropionylglycine, administered during reperfusion abolished the cardioprotection. Combined, these observations suggest that ROS signaling is needed for both development and execution of the cardioprotective mechanisms.

When hypoxia in dogs was continuous, lacking periodic reoxygenations, cardioprotection failed to develop, suggesting that the continuous hypoxia eliminated multiple opportunities for low-level ROS signaling (49). Similar studies in rats found that cyclic hypoxia-reoxygenation was protective but that continuous hypoxia was not (14). IHC decreased the duration of ventricular arrhythmias after I/R, whereas continuous hypoxia actually increased arrhythmias (119, 121, 124). Furthermore, 6 h/day of IHC increased postischemic LV contractile recovery versus controls, whereas nearly continuous 23.5 h/day hypoxia worsened LV recovery (216). Cellular DNA damage increased 10-fold, and caspase activity doubled during I/R in hearts from rats conditioned to continuous hypoxia. Simply reoxygenating rats for 60 min each day attenuated the damage, blunted apoptotic caspase activity, improved contractile performance, and reduced infarcts compared with continuous hypoxia (128, 129). In striking opposition, two other rat studies have reported that continuous hypoxia reduced ischemia-induced infarct size and arrhythmias and that 60 min daily of reoxygenation abrogated the protection (77, 139). The reasons for these contradictory effects of once-daily reoxygenation are unclear and merit investigation.

Adrenergic and Opioidergic Signaling

Although protracted hyperadrenergic activity is cytotoxic and a central factor in chronic cardiovascular disease, transi-

tory adrenergic activation by IHC may elicit cardioprotective adaptations (Figs. 1 and 2). Adrenergic receptor function was evaluated in electrically stimulated papillary muscles from IHC-conditioned rats (191). The α_1-adrenoceptor agonist phenylephrine produced greater increases in developed tension in muscles from conditioned animals. Contractile force was also better preserved in IHC muscles during simulated ischemia, an effect blunted by the α-adrenoceptor blocker prazosin. In a later study in rats (57), IHC-enhanced recovery of postischemic LV function and reductions in infarct size were mimicked by phenylephrine and abolished by prazosin, by a more selective α_{1B}-adrenoceptor antagonist and by a PKC-ε inhibitor (57). Although IHC strikingly reduced ischemic tissue damage and reperfusion arrhythmias in dogs, the development of this protection was abrogated by daily β_1-adrenoceptor blockade with metoprolol (107).

Endogenous opioids have been implicated in a variety of cardioprotective strategies, including aerobic exercise (40, 130), ischemic preconditioning (157, 158) and postconditioning (218), and IHC. Rats conditioned with continuous hypoxia had elevated amounts of a variety of opioid peptides in both the circulation and myocardium (117). In these rats, the final expression of the hypoxia-induced anti-infarct cardioprotection was blocked by acute preischemic injection of several different μ- and δ-selective antagonists, whereas the δ_1-antagonist and, less surprisingly, the κ-antagonist were conspicuously ineffective. In dogs, daily δ-opioid receptor blockade before each IHC session prevented the development of myocardial resistance to ischemic infarct and arrhythmias (49). Opioidergic blockade also blunted IHC-mediated increases in parasympathetic transmission and local parasympathetic innervation, suggesting that opioid-mediated cardioprotection may use cholinergic mechanisms (48). Also, IHC increased the content of the neurotrophic monosialoganglioside GM-1, which favors vagotonic δ_1-receptors over vagolytic δ_2-receptors (91), in cholinergic neurites (48). These conflicting reports indicate the potentially critical differences in the mechanisms responsible for the development of cardioprotection versus those involved in the acute delivery of that protection.

Intermittent Hypoxia Activation of Cardioprotective Gene Expression

Cyclic hypoxia-reoxygenation activates two powerful transcription factors, HIF-1 and nuclear factor erythroid-2 related factor 2 (Nrf2), which promote expression of a spectrum of cytoprotective proteins (Fig. 1). HIF-1 triggers the expression of glycogen-synthesizing and glycolytic enzymes, which foster hypoxemic tolerance, VEGF, which promotes angiogenesis and tissue perfusion, and erythropoietin, which exerts anti-infarct and antiapoptotic effects (24, 63, 147, 164). Recent studies have demonstrated IHC induction of myocardial VEGF (148, 166) and erythropoietin synthesis (18).

Hypoxia activates the HIF-1-driven gene program by dampening prolyl hydroxylation and degradation of the α-subunit of HIF-1 (15). Continuous hypoxia increases myocardial HIF-1α, and, importantly, both erythropoietin and VEGF (170). Hypoxia also promoted a number of Nrf2-responsive genes for key antioxidant enzymes and proteins (170). An IHC program that reduced ischemic infarct size and cellular DNA damage also increased mRNA for myocardial SOD, VEGF, and HIF-1α. HIF-1α and VEGF content were likewise increased along with the pro-survival Bcl-2 (192). Adrenergic activity and ROS may facilitate the HIF-1 gene program by phosphorylating HIF-1α, making it resistant to proteasomal degradation (25). The two signals may be synergistic, with PKA increasing HIF-1α phosphorylation and ROS suppressing its dephosphorylation (19).

The transcription factor Nrf2 activates a gene program encoding an extensive panel of antioxidant enzymes (70, 165, 209) and has been implicated in cardioprotection resulting from ischemic preconditioning (33, 43). Under normoxic conditions, Nrf2 is sequestered, bound to proteins that promote its ubiquitinylation and proteasomal degradation (43, 118). ROS oxidize this complex and release Nrf2, which is then free to promote its portfolio of antioxidant enzymes (10, 43). Like HIF-1α, Nrf2 also is stabilized by phosphorylation and may benefit from IHC-mediated moderation of a variety of protein kinases and phosphatases.

A single 10-min hypoxic challenge reduced cell death in cultured H9c2 rat cardiomyoblasts during simulated I/R the next day. The initial hypoxia triggered Nrf2 translocation to the nucleus, binding to the antioxidant response element and the expression of its antioxidant portfolio during the secondary anoxic challenge 24 h later (70, 209, 210). The protection just described was abrogated when siRNAs were used to interrupt the Nrf2-mediated expression of antioxidant proteins or the related Nrf2 stabilizer DJ-1 (32, 150, 209, 210). Whether DJ-1 responds to IHC or is simply an essential cofactor in the Nrf2 pathway is unclear. In a recent study in rats subjected to four cycles of alternating 4-day hypobaric hypoxia and 4-day recovery to model sojourns at altitude, MnSOD and glutathione peroxidase, antioxidant enzyme products of the gene program of Nrf2, were increased in the LV, in association with increased LV contractile performance (2).

Protein Kinase Signaling Activated by Intermittent Hypoxia

Several protein kinases have been implicated in IHC during both conditioning and the ischemic challenge (Figs. 1 and 2). In two models, cardioprotection was blunted by a Ca^{2+}-calmodulin dependent protein kinase II (CaMKII) inhibitor (204, 205). IHC-evoked improvements in many aspects of Ca^{2+} management discussed above were likewise abolished by inhibition of PKA, PKC, and/or CaMKII (205, 214, 215). The protection and coincident adjustments in Ca^{2+} management observed in conditioned neonatal cardiomyocytes were all attenuated by p38 MAPK inhibition delivered before conditioning (202, 227). These results support a mechanism in which IHC improves the capacity for Ca^{2+} sequestration as a defense against Ca^{2+} overload.

Protein kinase activation in conditioned hearts is a common theme, with their inhibition abolishing or attenuating protection (13). In some cases, kinase inhibition was effective when applied before IHC (p38 MAPK and ERK1/2) and other cases only when applied before I/R (PKC) (13). These results indicate again that the acquisition of protection and its ultimate execution are distinct processes with different participants and temporal relationships.

PKC is a key participant in Ca^{2+} homeostasis and hypoxia induces four isoforms, of which one, PKC-δ, initially appears pivotal in cardioprotective signaling (99, 140). IHC altered the intracellular distribution of PKC-δ and both nonselective and

PKC-δ-selective inhibitors, administered just before coronary occlusion, attenuated the subsequent infarct reduction. Hypoxia-conditioned rats consuming an *n*-3 fatty acid-enriched diet had smaller infarcts than unconditioned rats, whereas those consuming an *n*-6 diet had large infarcts similar to unconditioned rats. PKC-δ was elevated in *n*-3-treated hearts but not in *n*-6-treated hearts (66). IHC also facilitated PKC-δ activation and translocation. Attenuating these key adjustments with *N*-acetylcysteine abrogated the cardioprotection, suggesting again that ROS are involved and at least moderate ROS signaling is required (81). Despite the absence of effect in these studies, PKC-ε may also serve a critical role in IHC cardioprotection. Overexpression of constitutively active PKC-ε improved key aspects of mitochondrial respiration and membrane potential during 2 wk of uninterrupted hypoxic stress (117). Hearts had higher HIF-1α, which was colocalized with active PKC-ε.

The coupled protein kinases phosphatidylinositol-3-kinase (PI3K) and Akt have been implicated in cardioprotection induced by β-adrenergic agonists (155, 211). Activated PKA initiates sequential phosphorylation of PI3K and its Akt substrate. In mice, Akt activation accompanied the reduction in I/R-induced myocardial infarct afforded by 14-day IHC, and the Akt inhibitor wortmannin blunted the protection (127). Similarly, in intermittent hypoxia-conditioned rats, Akt activation was associated with improved postischemic contractile performance, again inhibited by wortmannin (194). Akt phosphorylates several targets, thereby activating endothelial NO synthase (eNOS), promoting PKC-ε translocation to the mitochondrial membrane, and inactivating the MPTP-promoting kinase glycogen synthase kinase (GSK)-3β. When kinase activity was evaluated in a protective IHC program, Akt, PKC-ε, and GSK-3β were all phosphorylated during ischemic challenge, and PKC-ε associated strongly with the membrane fraction (194). In that study, inhibition of PI3K or PKC-ε before the final ischemia abolished the cardioprotective effects of IHC, the phosphorylation of Akt, GSK-3β, and PKC-ε, and the translocation of PKC-ε. In confirmation, ischemia resistance in IHC hearts was abolished by PKC-ε inhibition (57). Cardiomyocytes from conditioned hearts expressed elevated PKC-ε, and the resulting ischemic resistance was attenuated by inhibition of PKC-ε (68). Although hypoxia moderates multiple protein kinases, their role in cardioprotection remains controversial, with the best support for PKC-δ and PKC-ε.

Role of NO in IHC-Mediated Cardioprotection

NO exerts a variety of salutary effects during myocardial I/R (16, 53). Stimulation of NO synthesis, inhalation of gaseous NO, or administration of NO donors reduces infarct size in mice (134), rats (142), rabbits (200), cats (198), and dogs (135). NOS inhibition (69, 200) or suppression of eNOS (73, 177) worsened I/R injury. NO reduces arrhythmogenesis in dogs (184), rats (17), and pigs (188). NO activates cGMP production to mobilize the cardioprotective signaling of PKG (88). As a potent coronary vasodilator, NO may reduce infarct size by increasing collateral inflow from the tissues adjacent to the area at risk (65, 79). NO also limits infiltration by neutrophils, reducing again the opportunity for both occlusive and oxidant damage during I/R (159). Aside from these major influences, NO also activates a variety of antistress (109), antioxidant (39, 56), and antiapoptotic adaptations (104, 197).

IHC increases HIF-1, which promotes expression of all three NOS isoforms, inducible NOS (iNOS) (152), neural NOS (95), and eNOS (34), increasing the capacity for cardiac NO synthesis. Hypoxia increases Ca^{2+} influx through L-type Ca^{2+} channels (103). The added Ca^{2+} activates eNOS (203) and stabilizes HIF-1α (217), thereby sustaining a beneficial feedback loop. IHC improves NO production in a variety of model systems, including cells, blood vessels, muscles, and isolated hearts (72, 90, 174–176). iNOS appears to be the primary source of cardioprotective NO (92) during IHC (41). IHC increased myocardial iNOS expression (61, 84), and inhibition of iNOS abolished the associated cardioprotection (15, 41, 172). Some reports have suggested that eNOS expression is similarly elevated in IHC-exposed animals (8, 90, 167). The direct reduction of nitrite to NO is also enhanced by hypoxia (106).

IHC reduces coronary endothelial dysfunction during I/R (110). That dysfunction arises primarily from oxidative stress (28), which NO may moderate by promoting antioxidant systems (39, 55). Itself a highly soluble antioxidant, NO may scavenge free radicals directly (151), a concept supported by reciprocal changes in NO and ROS in the hypoxic rat heart (170). IHC-mediated NO may also reduce myocardial Ca^{2+} overload by improving Ca^{2+} reuptake (108) and by protecting membrane transporters from oxidative stress (206).

Although NO is clearly cardioprotective, its overproduction is detrimental; thus, under select circumstances, both NOS inhibitors and NO donors have proven cardioprotective (111, 196). Excess NO condenses with superoxide to form toxic peroxynitrite, a powerful oxidant and nitrating agent (74). During I/R, excess NO has been attributed to both leukocyte iNOS (190) and to myocardial eNOS activated by excess Ca^{2+} (222). Modest increases in plasma nitrite and nitrate suggest an equally modest IHC-mediated increase in NO synthesis (111, 114). IHC effectively prevents NO overproduction during I/R (59, 154) and after acute myocardial infarction without reperfusion (114). Moderation of NO synthesis during I/R in conditioned animals is supported by lower myocardial iNOS and eNOS expression (60, 154), lower myocardial peroxynitrite contents during reperfusion (59), enhanced postischemic coronary endothelial function (110), and increased resistance to acute hypotension after myocardial infarction (114).

Despite increasing NO synthesis, IHC can limit NO overproduction by restricting available NOS substrate arginine (224), by chelating Fe^{2+}, a NOS cofactor (1), and by increasing capacitive storage for NO by sequestration. IHC facilitates nontoxic storage by binding NO in *S*-nitrosothiols and dinitrosyl iron complexes (112, 114) and by increasing NO storage capacity (112, 113, 185). Concordant with this mechanism, administration of NO complexes was cardioprotective during myocardial infarction and cardioplegic arrest (86, 148).

In summary, IHC increases cardiac NO production, which is cardioprotective during myocardial ischemia, primarily by improving coronary endothelial function, coronary perfusion, and perhaps collateral inflow to the area at risk (Figs. 1 and 2). At the same time, IHC increases the capacity to absorb the toxic overflow of NO, e.g., from activated neutrophils converging on the injury during reperfusion.

POTENTIAL CLINICAL APPLICATIONS OF IHC AND IMPEDIMENTS TO THEIR IMPLEMENTATION

As reviewed here, IHC has proved consistently beneficial in a wide variety of preclinical models and has been safely implemented in at-risk patients with hypertension, coronary artery disease, resistant arrhythmias, and lung disease. In Eastern Europe, successful cardioprotective applications of IHC have been recently reported (58, 178). It also should be noted that airline flight and cabin crews experience an occupational form of intermittent hypoxia as frequently as several times daily, ascending to and returning from a barometric equivalent of 2,500 m with each flight. One study reported: ". . . flying personnel have low all-cause mortality. . . mostly due to a reduced cardiovascular mortality reflecting a low (acute myocardial infarction) incidence during the working life as well as after retirement" (96). Despite this favorable evidence, there are no reports adopting IHC in Western clinical practice. The factors limiting the clinical use of IHC merit discussion.

For clinical conditions potentially treatable with IHC, pharmacological therapy is currently available. To what extent IHC could complement or reduce the need for medications must be determined. There are also many practical gaps. Can IHC be made more economical and convenient? What is the optimal IHC regimen? How frequently should IHC be administered, how long do its effects persist, and can it be boosted periodically? Do these parameters differ depending on the condition being treated? Importantly, would funding be available for the rather mundane but critical research required to answer these questions, and to what extent would preclinical findings translate to the clinical setting?

To our knowledge, sex-specific responses to IHC have not been reported. Estrogens have been proposed to afford protection against oxidative stress associated with OSA in premenopausal women (22). Whether women and men would respond differently to IHC, and whether those differences might disappear after menopause, merits investigation. Another topic for future study is the impact of maternal IHC during gestation on fetal development and the long-term consequences for the offspring's cardiovascular health.

Perhaps the most vital clinical benefit of IHC would be for patients with or at risk of ischemic heart disease. Experimental findings suggest that a prophylactic program might delay the onset of myocardial infarction by the antiarrhythmic action of IHC and by its ability to improve coronary circulatory function. Even in the event of acute myocardial infarction, the antiarrhythmic benefits of prior IHC could be lifesaving. Furthermore, upon coronary reperfusion, prior IHC should lessen dangerous arrhythmias and improve cardiac function. It might even be possible that IHC would limit deleterious postinfarction ventricular remodeling. However, impediments to implementing a prophylactic program of IHC are daunting, including the above-mentioned paucity of practical information necessary for implementing any clinical IHC program. Could patients be persuaded to continue a long-term program of IHC if the benefits had not been proven clinically? Could IHC be safely self-administered unsupervised? In this regard, there are already available a variety of devices for self-administration of IHC to enhance athletic performance (56, 163). Finally, the cost of such a long-term clinical trial would be significant.

Physicians might perceive that exposing heart patients to low O_2 is far too risky, yet these are precisely the patient populations who might benefit most. One might expect that supervised pretreatment before elective heart surgery would reduce risk and tissue damage, hasten recovery, shorten hospital stays, and perhaps lessen the postsurgical cognitive impairments. One consistent impediment to clinical applications of IHC is its mistaken link to OSA and associated cardiovascular disorders. In this review, we have attempted to demonstrate that IHC is not only distinct from OSA but that the resulting outcomes are diametrically opposite.

Few studies have examined the pro- versus anti-inflammatory character of moderate IHC. In sedentary men, an 8-wk regimen of daily 60-min exposures to moderate hypoxia (15% O_2) dampened intense exercise-induced leukocyte-platelet aggregation and circulating IL-1β but did not alter other pro- and anti-inflammatory cytokines (189). Exposure of healthy young adult men to four cycles of 5-min 10% O_2 and 5-min room air breathing decreased circulating TNF-α and IL-4 by over 90% (162). The comparative impact of moderate IHC versus OSA on systemic inflammation warrants further study.

The growing understanding of the mechanisms of IHC may foster the development of pharmacological interventions to mobilize these mechanisms, yet the complexity of the cardioprotective signaling cascade of IHC likely precludes monotherapy. Conversely, high dosages of antioxidants (49, 81) and antagonists of β-adrenergic (107) and opioid receptors (49, 116) have been shown to abrogate IHC cardioprotection. It is not yet known whether IHC or IHC mimetics would afford cardioprotection in the presence of clinically calibrated dosages of β-blockers, opioid antagonists, and antioxidants.

IHC appears safe, is consistently beneficial, noninvasive, practical, and potentially inexpensive and thus may merit serious consideration as a therapeutic modality. The most powerful argument for applying IHC in clinical settings is the mounting evidence of the safety and efficacy of IHC in patients with chronic illnesses (27, 46, 56, 58, 100, 101, 160, 178). We hope this review will broaden the perspective of researchers, clinicians, and stakeholders to reconsider the clinical potential of IHC.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

R.T.M. prepared figures; R.T.M., E.B.M., S.S.R., J.L.C., and H.F.D. drafted manuscript; R.T.M., E.B.M., S.S.R., J.L.C., and H.F.D. edited and revised manuscript; R.T.M., E.B.M., S.S.R., J.L.C., and H.F.D. approved final version of manuscript.

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