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Hypoxia-induced cardioprotection: A review

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Abstract

Hypoxia, a state of reduced oxygen availability, exerts complex and often paradoxical effects on the heart. While chronic hypoxia is detrimental and leads to adverse cardiac remodeling and dysfunction, short-term or intermittent hypoxia can contribute towards protective adaptations that enhances the heart's ability to protect itself from ischemic injury. This protective adaptation, also known as hypoxic preconditioning, drives the activation of several essential signaling pathways, including the hypoxia-inducible factor (HIF) signaling, reactive oxygen species (ROS) signaling, nitric oxide (NO) regulation, and ATP-sensitive potassium channel (K_{ATP}) mediated regulation, leading to metabolic reprogramming, angiogenesis with vascular remodeling, and enhanced calcium handling, thereby increasing resistance to ischemic heart disease. We discuss strategies such as hypoxic conditioning and pharmacologically activated HIF signaling, along with targeted approaches to enhance glycolysis and K_{ATP} channel regulation and optimize sarcoplasmic reticulum calcium ATPase 2a (SERCA2a) mediated calcium handling in cardiomyocytes. In this review, we explore the mechanisms and therapeutic potential of short-term or intermittent hypoxia-mediated cardioprotection. Additionally, we highlight the importance of addressing challenges and limitations of using hypoxic preconditioning in clinical practice.

Key words: hypoxia, cardioprotection, hypoxic preconditioning, HIF, ischemic heart disease and heart failure

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Introduction

Hypoxia, a state of reduced oxygen availability, can occur due to various physiological or pathological conditions, such as high altitude, sleep apnea, or cardiovascular diseases (1, 2). It can be classified into several types based on its duration and pattern. The first type is acute hypoxia, which refers to a sudden decrease in oxygen availability, frequently triggered by events such as acute respiratory distress or high-altitude exposure. This abrupt change in oxygen levels can exhibit immediate and significant physiological reactions (3). The second type is chronic hypoxia, caused by prolonged periods of reduced oxygen availability due to conditions like chronic obstructive pulmonary disease or prolonged living at high altitude. This sustained exposure to low oxygen levels drives long-term physiological adaptations in the organism (4, 5). The third type is intermittent hypoxia, which refers to the periodic occurrence of low oxygen levels, as observed in patients with obstructive sleep apnea. The recurrent pattern of intermittent hypoxia can elicit distinct physiological adaptations within the organism (6). Each distinct state of hypoxia is characterized by unique underlying mechanisms and resulting physiological consequences (7, 8).

Studying the effects of hypoxia in cardiovascular diseases is critical, as many heart conditions involve ischemia and reduced oxygen supply to the myocardium (9). Ischemic heart disease, for example, is a leading cause of morbidity and mortality worldwide, and understanding the cellular and molecular responses to hypoxia is essential for developing effective interventions (10).

Interestingly, brief episodes of hypoxia, known as hypoxic preconditioning, can paradoxically induce protective mechanisms in the heart, potentially mitigating the damaging effects of prolonged ischemia (11). This cardioprotective response has been the subject of extensive research, as it offers a promising avenue for developing therapeutic strategies to manage ischemic heart disease and heart failure (12, 13).

This review will delve into the molecular mechanisms underlying the cardioprotective effects of hypoxia, exploring key pathways such as HIFs, ROS signaling, NO synthesis, K_{ATP} channels, metabolic adaptations, vascular remodeling and angiogenesis and calcium handling (14–16). Understanding these complex and interconnected mechanisms is crucial for designing more effective interventions to mitigate the devastating consequences of ischemic heart disease and heart failure.

Significance of Studying Hypoxia in Cardiovascular Pathologies

Hypoxia, or the state of reduced oxygen availability, is a potent regulator of cardiovascular function, influencing the cardiac and vascular systems at both molecular and systemic levels. Elucidating the role of hypoxia in cardiovascular diseases holds substantial significance for several reasons:

1. **Pathophysiological Insights**: Hypoxia plays a central role in the pathogenesis and progression of various cardiovascular diseases, including ischemic heart disease, heart failure, and pulmonary hypertension. It affects key processes such

as angiogenesis, erythropoiesis, and metabolic regulation, all of which are integral to cardiovascular health (17).

2. **Therapeutic Potential:** The controlled application of hypoxic stimuli, such as interval hypoxic training, has demonstrated promising results as a therapeutic approach. This method has the potential to enhance cardiovascular function and mitigate the risk of complications associated with hypoxia-related cardiovascular diseases (5).
3. **Epidemiological Significance:** The high incidence of cardiovascular conditions characterized by hypoxia, such as heart failure with reduced ejection fraction and ischemic heart disease, highlights the importance of investigating hypoxia. This research can inform the development of more effective prevention and treatment approaches for these prevalent cardiovascular pathologies (18).

Protective Effects of Hypoxia Preconditioning on the Heart

Hypoxia preconditioning refers to the process of exposing tissues to short, non-lethal episodes of hypoxia to build resistance against subsequent severe hypoxic or ischemic events. This phenomenon has shown potential protective effects on the heart, including:

- **Enhanced Cardiac Function**: Preconditioning can improve cardiac function by promoting angiogenesis, enhancing myocardial perfusion and reducing infarct size during ischemic events (19, 20).
- **Metabolic Adaptations**: Hypoxia preconditioning induces metabolic shifts that enhance the heart's ability to utilize glucose and other substrates more efficiently, thereby improving energy production under low oxygen conditions (21, 22).
- **Cellular Protection**: It activates various cellular pathways that enhance cell survival, reduce oxidative stress, and modulate inflammatory responses, contributing to overall cardioprotection (21, 23).

Molecular Mechanisms of Hypoxia-Induced Cardioprotection

The cardioprotective effects of hypoxia preconditioning are mediated through complex interconnected molecular pathways (24). Key mechanisms include:

Hypoxia-Inducible Factors (HIF)

HIFs are master transcriptional regulators that orchestrate the cellular response to low oxygen conditions (21, 25). They activate a multitude of genes involved in angiogenesis, metabolism, and cellular survival, thereby enhancing the heart's ability to adapt and survive under hypoxic stress (24). HIFs are heterodimeric transcription factors composed of an oxygen-regulated α subunit (HIF-1α, HIF-2α and HIF-3α) and a constitutively expressed β subunit (HIF-1β) (24, 26–28). Under normoxic conditions, the α subunits are hydroxylated by prolyl hydroxylase domain (PHD) enzymes, leading to their ubiquitination and proteasomal degradation (29–31). However, during hypoxia, the PHDs are inhibited, allowing the stabilization and nuclear translocation of HIFα subunits, where they dimerize

with HIF-1β and bind to hypoxia response elements (HREs) in the promoters of target genes (24, 28, 32). HIF-1α is the most extensively studied isoform in the context of hypoxia-induced cardioprotection. Its activation triggers a multifaceted response involving metabolic reprogramming, angiogenesis, erythropoiesis, and cell survival pathways (25, 28, 32). HIF-1α induces the expression of glycolytic enzymes and glucose transporters, facilitating a shift from oxidative phosphorylation to glycolysis, which is more efficient in hypoxic conditions. This metabolic reprogramming reduces oxidative stress and preserves adenosine triphosphate (ATP) levels in cardiomyocytes (24, 28). HIF-1α upregulates the expression of vascular endothelial growth factor (VEGF) and other pro-angiogenic factors, promoting the formation of new blood vessels and improving oxygen delivery to the ischemic myocardium (24, 32). Additionally, HIF-1α activates the transcription of genes involved in cell survival pathways, such as the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) and Bcl-2 pathways, inhibiting apoptosis and promoting cardiomyocyte survival during ischemia and hypoxia-induced cell death (24, 32). While HIF-1α is primarily involved in acute cardioprotective responses, emerging evidence suggests that HIF-2α plays a crucial role in cardiac regeneration and long-term adaptation to hypoxia (33, 34). HIF-2α has been shown to induce the expression of cell cycle regulators, such as cyclin D1 and c-Myc, promoting cardiomyocyte proliferation and regeneration (32, 34). HIF-2α regulates the activation and differentiation of cardiac stem/progenitor cells, contributing to myocardial repair and regeneration in the context of ischemic heart disease and heart failure (35). HIF-2α modulates the expression of matrix metalloproteinases (MMPs) and their inhibitors, facilitating extracellular matrix remodeling and tissue repair (35). Recent studies have explored the therapeutic potential of HIF stabilizers, such as prolyl hydroxylase inhibitors (PHIs) and iron chelators, in preclinical models of myocardial infarction and ischemia-reperfusion injury (36–38). These interventions have demonstrated promising results in improving cardiac function, reducing infarct size, and enhancing angiogenesis. However, it is important to note that the HIF pathway is complex, and the specific roles of different HIF isoforms may vary depending on the context and duration of hypoxia exposure. Additionally, the crosstalk between HIFs and other signaling pathways, such as the wingless related integration site (WNT)/β-catenin and Notch pathways, contributes to the intricate regulation of hypoxia-induced cardioprotection and regeneration (32, 32, 34). Despite the promising role of HIF signaling in cardioprotection, several challenges remain. The specificity of HIF-1α as a therapeutic target for atherosclerosis, for instance, depends on the cell type in which it is expressed (39). A greater understanding of the timing and cellular distribution of HIF-1α in the plaque is needed to use it effectively for HIF-based therapies. Furthermore, as small molecules that modulate HIF signaling enter clinical trials, it will be important to determine what effects these treatments may have on patients with heart disease (36, 40). In summary, recent advances have highlighted the pivotal roles of HIFs, particularly HIF-1α and HIF-2α, in orchestrating cellular responses to hypoxia, including metabolic adaptation, angiogenesis, cell survival, and cardiac regeneration (Figure 1). Targeting the HIF pathway through pharmacological interventions holds promise for developing novel therapeutic strategies for ischemic heart diseases and heart failure (24, 25, 28, 32, 34).

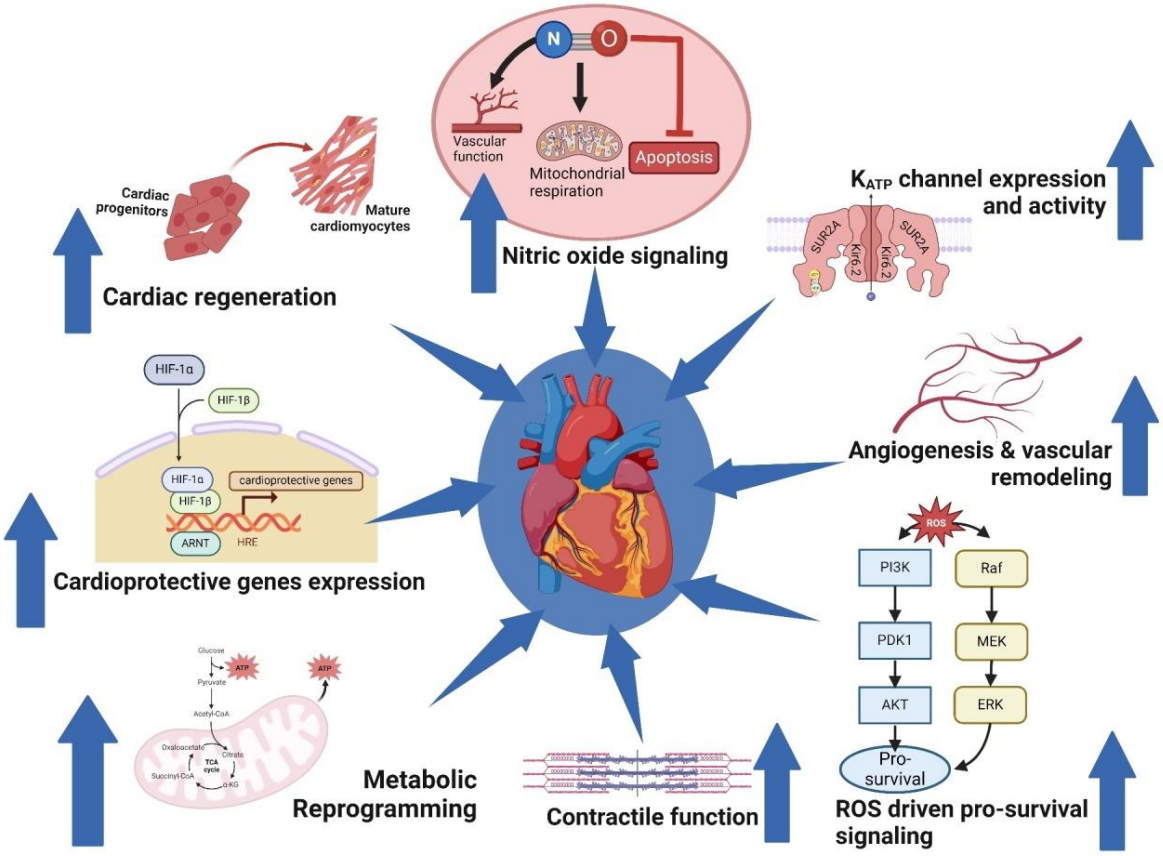

Figure 1. **Molecular and cellular mechanisms of hypoxia-induced cardioprotection. Short-term or intermittent hypoxia regulates several molecular and cellular adaptations in the heart which eventually drives pro-survival mechanisms that protect the heart from ischemic injury. The figure was created in www.Biorender.com.**

Slika 1. **Molekularni i ćelijski mehanizmi kardioprotekcije ostvarene pomoću hipoksije. Kratkoročna ili povremena hipoksija reguliše nekoliko molekularnih i ćelijskih adaptacija u srcu, što potom pokreće mehanizme za preživljavanje koji štite srce od ishemijskog oštećenja. Slika je kreirana pomoću www.Biorender.com.**

Reactive Oxygen Species Signaling

Reactive oxygen species (ROS) are chemically reactive molecules containing oxygen, which include free radicals such as superoxide ($O2^{\bullet-}$), hydroxyl radicals ($^{\bullet}OH$), and non-radical species such as hydrogen peroxide (H_2O_2) (41, 42). While they were traditionally viewed as harmful byproducts of aerobic metabolism, recent research has elucidated their dual role as both damaging and signaling molecules, particularly in the context of hypoxia-induced cardioprotection (43, 44). Hypoxia can induce the production of reactive oxygen species, which can paradoxically function as signaling molecules to

trigger protective mechanisms in a concentration-dependent manner. These include activating pro-survival pathways, modulating metabolic shifts, and regulating gene expression programs (25). However, excessive ROS production leads to oxidative stress, cellular damage, and apoptosis (45–47). Interestingly, ROS signaling is integral to the mechanisms of ischemic preconditioning and postconditioning, where brief periods of ischemia and reperfusion confer protection against subsequent prolonged ischemic insults. ROS act as triggers and mediators in the signaling pathways that underlie these protective phenomena, involving kinases such as Protein Kinase C (PKC), mitogen activated protein kinases (MAPKs), and Akt, as well as the opening of mitochondrial ATP-sensitive potassium channels (24, 48–50). These pathways culminate in the modulation of mitochondrial permeability and inhibition of apoptosis, contributing to cardioprotection (48). The recognition of ROS's role in hypoxia-induced cardioprotection has spurred interest in developing antioxidant therapies. However, clinical trials have yielded mixed results, underscoring the complexity of ROS signaling and the need for targeted approaches. Future therapies must consider the specific sources, timing, and cellular compartments of ROS production to effectively harness their protective potential without disrupting physiological signaling processes (48, 50–52). Overall, recent advances in our understanding of ROS signaling have elucidated its critical role in hypoxia-induced cardioprotection (Figure 1). ROS serve as double-edged swords, mediating cellular damage and signaling pathways that promote survival and adaptation to hypoxic stress. The intricate balance between these opposing effects is crucial for cardiovascular health (53, 54). Further research is needed to unravel the complex regulatory networks of ROS signaling and to develop targeted antioxidant therapies that can mitigate the detrimental effects of excessive ROS while preserving their beneficial signaling functions (54, 55).

Nitric Oxide (NO) Synthesis and Regulation

Nitric oxide (NO) is a critical signaling molecule that mediates various cardioprotective effects, such as vasodilation, inhibition of platelet aggregation, and modulation of mitochondrial function. Hypoxia can stimulate nitric oxide synthesis by endothelial nitric oxide synthase (eNOS) and regulate its bioavailability, contributing to the protective phenotype (24, 56). Nitric oxide signaling can activate pro-survival pathways, such as the PI3K/Akt and MAPK cascades, and induce the expression of genes involved in angiogenesis, metabolic adaptation, and apoptosis inhibition (Figure 1) (57). NO also inhibits platelet aggregation and adhesion, which are common during ischemia reperfusion injury (58). By preventing platelet activation, NO reduces the risk of thrombosis, further enhancing blood flow to the ischemic myocardium. Additionally, NO modulates the inflammatory response, reducing the recruitment and activation of leukocytes that can exacerbate tissue damage (59, 60). At the mitochondrial level, NO has been shown to exert protective effects by inhibiting the opening of the mitochondrial permeability transition pore (mPTP). This action helps to maintain mitochondrial integrity and prevent cell death during ischemia-reperfusion events (59). Furthermore, NO interacts with components of the electron transport chain, such as cytochrome C

oxidase, modulating its activity to reduce oxidative stress and stabilize mitochondrial function (59). Recent studies have highlighted the role of nitric oxide in remote ischemic preconditioning (RIPC), where brief episodes of ischemia in a remote organ confer protection to the heart. NO signaling has been implicated in the transmission of protective signals from the remote organ to the heart, involving neural pathways and circulating factors (61, 62). Moreover, the development of NO-donating drugs and biomaterials that release NO in a controlled manner represents a significant advancement. These therapeutic strategies aim to harness the cardioprotective effects of NO without the adverse effects associated with systemic NO administration (62, 63). For instance, nitrate-functionalized patches that deliver NO directly to the myocardium have shown promise in enhancing cardiac repair and reducing infarct size in preclinical models (59). Overall, nitric oxide is a key player in the complex signaling networks that underlie hypoxia-induced cardioprotection. Its multifaceted actions on vascular function, inflammation, and mitochondrial regulation make it a crucial target for therapeutic interventions.

Regulation of ATP-Sensitive Potassium Channels

One of the key mechanisms by which hypoxia promotes cardioprotection is the modulation of ATP-sensitive potassium channels (K_{ATP}). K_{ATP} channels are present in the plasma membrane and the inner mitochondrial membrane of cardiac cells (64, 65). K_{ATP} channels play a crucial role in the heart's response to hypoxia by linking cellular metabolic status to membrane excitability (66). These channels are regulated by intracellular ATP levels; under normoxic conditions, high ATP concentrations inhibit K_{ATP} channels, keeping them closed (66, 67). However, during hypoxia, ATP levels decrease, and adenosine diphosphate (ADP) levels rise, leading to the opening of K_{ATP} channels. This opening helps to stabilize the membrane potential, reduce calcium overload, and prevent cellular depolarization, thereby protecting cardiomyocytes from hypoxic damage. The opening of K_{ATP} channels also induces mild depolarization of the inner mitochondrial membrane, which can inhibit the opening of the mitochondrial permeability transition pore (mPTP) and prevent the release of pro-apoptotic factors, and reduces mitochondrial-mediated cell death during ischemia-reperfusion injury (68, 69).

Hypoxia has been shown to activate K_{ATP} channels through various signaling pathways, including ROS signaling, nitric oxide, and the activation of protein kinase C (24). In fact, recent studies have shown sub hypoxia, mild hypoxia, mild to severe hypoxia and chronic hypoxia to regulate sulfonylurea receptor type 2A (SUR2A) subunit of the K_{ATP} channels in the heart through multiple signaling mechanisms, including extracellular signal-regulated kinase (ERK), PI3K/Akt, 5' adenosine monophosphate-activated protein kinase (AMPK), and intracellular ATP signaling pathways, respectively, to induce cardioprotection (70–73) (Figure 1). Interestingly, the cardioprotective effects of ischemic preconditioning and postconditioning are also mediated in part by the modulation of K_{ATP} channels (68, 74). The pharmacological activation of these K_{ATP} channels, using agents such as diazoxide or nicorandil, has been a focus of intensive research as a potential therapeutic strategy for cardioprotection (75–77). Recent studies have also shown that

regulating the levels of K_{ATP} channels by agents like nicotinamide and pyrazinamide can also confer cardioprotection (78–80). While the precise mechanisms by which K_{ATP} channel modulation confers cardioprotection are still being elucidated, these channels clearly play a central role in the adaptive responses of the heart to hypoxic stress.

Overall, the regulation of ATP-sensitive potassium channels represents a crucial mechanism by which hypoxia induces cardioprotective effects. K_{ATP} channels act as metabolic sensors, coupling cellular energy status to membrane potential and mitochondrial function. By promoting the opening of these channels, hypoxia can enhance the heart's resistance to ischemia-reperfusion injury, making it an attractive target for the development of new cardioprotective therapies.

Cellular and Functional Adaptations to Hypoxia

At the cellular level, hypoxia induces significant changes in gene expression, primarily mediated by HIFs. HIFs are stabilized under low oxygen conditions and regulate the transcription of numerous genes involved in critical processes such as metabolic reprograming, angiogenesis, and vascular remodeling, remodeling of contractility leading to cell survival (81). These transcriptional changes help cells adapt by enhancing oxygen delivery and optimizing energy production under hypoxic conditions. Additionally, hypoxia leads to the suppression of ATP-consuming processes and modulates protein synthesis, mitochondrial respiration, and nutrient acquisition to conserve energy and maintain cellular function (17, 82).

Metabolic Reprogramming

One of the hallmarks of the hypoxic response is a shift in cardiac metabolism, characterized by increased glycolysis and decreased oxidative phosphorylation. This metabolic adaptation enhances the heart's ability to generate ATP more efficiently under low oxygen conditions, thereby promoting cell survival (21, 24). HIFs play a central role in orchestrating these metabolic changes. HIF-1α, for example, upregulates the expression of glycolytic enzymes, such as hexokinase, pyruvate dehydrogenase kinase, and lactate dehydrogenase, while down-regulating the expression of mitochondrial enzymes involved in oxidative phosphorylation (40). This metabolic shift reduces oxygen consumption, as glycolysis is more oxygen-efficient than oxidative phosphorylation. Moreover, HIF-1α induces the expression of genes involved in angiogenesis, such as vascular endothelial growth factor, which enhances oxygen delivery to the myocardium (35) (Figure 1).

Interestingly, the metabolic reprogramming observed during hypoxia-induced cardioprotection shares similarities with the Warburg effect, a metabolic phenotype commonly observed in cancer cells (83). Like cancer cells, the hypoxic heart prioritizes glycolysis over oxidative phosphorylation, even in the presence of adequate oxygen (34). This metabolic shift is thought to provide multiple benefits, including the generation of reducing equivalents for antioxidant defense, the production of biosynthetic precursors for cellular repair and proliferation, and the maintenance of ATP levels under conditions of limited oxygen availability (34).

Recent studies have also highlighted the role of mitochondrial dynamics in the metabolic adaptation to hypoxia. Hypoxia can induce changes in mitochondrial morphology, such as increased fission and reduced fusion, which alter mitochondrial function and bioenergetics. These mitochondrial remodeling processes are regulated by HIF-1α and other signaling pathways, and they contribute to the overall metabolic reprogramming that occurs in the hypoxic heart (28).

Overall, the metabolic shift towards glycolysis and the associated changes in mitochondrial dynamics are crucial adaptive responses that help the heart maintain energy production and cellular viability under hypoxic conditions.

Angiogenesis and Vascular Remodeling

Hypoxia is a potent stimulus that can trigger angiogenesis, forming new blood vessels from existing ones. This adaptive response is essentially driven by the HIFs, which direct the transcriptional regulation of various pro-angiogenic genes, including vascular endothelial growth factor, angiopoietin-2 (ANGPT2), and stromal cell-derived factor-1α (SDF-1α) (35, 84). The increase in expression of these angiogenic factors promotes the proliferation, migration, and differentiation of endothelial cells, and contributes towards the formation of new capillaries and the remodeling of existing vasculature (85, 86). This adaptive response improves oxygen and nutrient delivery to the hypoxic myocardium, thereby optimizing metabolic and contractile function within the tissue (40) (Figure 1). This is particularly crucial in ischemic heart disease, where the restoration of blood flow to oxygen-deprived myocardial tissues can significantly improve cardiac function and reduce infarct size (87–89).

Vascular remodeling is defined by structural and functional changes that occur in blood vessels following alterations in hemodynamics, metabolic demands, physiological and pathological stimulations (90). This process involves alterations in the architecture of the vascular wall, including changes in endothelial cell function, smooth muscle cell proliferation, extracellular matrix composition, and vessel diameter (91). Hypoxia is a potent driver of vascular remodeling, triggering the activation of a variety of signaling cascades that ultimately lead to maladaptive changes in the vasculature. For instance, hypoxia can stimulate the production of matrix metalloproteinases, which degrade the extracellular matrix and facilitate the migration and proliferation of vascular smooth muscle cells (92, 93). This can result in the expansion and remodeling of the vascular network, which enhances blood flow and oxygen delivery to the myocardium (33, 94). These processes are mediated by various signaling pathways, including those involving HIFs, VEGF, and nitric oxide, which collectively promote endothelial cell proliferation, smooth muscle cell relaxation, and extracellular matrix remodeling (93). However, pathological vascular remodeling can be detrimental to the heart. Excessive or uncontrolled remodeling leads to vascular stiffness, reduced compliance, and impaired blood flow (95, 96).

In conclusion, the hypoxia-induced angiogenic and vascular remodeling responses represent crucial adaptive mechanisms that improve oxygen delivery to the myocardium and enhance cardiac function under low oxygen conditions. By understanding the

molecular processes that drive hypoxic adaptations, we can identify potential therapeutic targets to treat ischemic heart disease and other cardiovascular pathologies.

Contractile Function and Remodeling

Hypoxia can have complex and sometimes paradoxical effects on cardiac contractile function and remodeling that is essentially dependent on duration and severity of the hypoxic exposure (97). In the short term, acute hypoxia can impair contractility due to the reduced ATP utilization and decreased ATP production, as well as the accumulation of metabolic byproducts like lactate (98).

However, intermittent or preconditioning exposure to hypoxia can lead to the activation of signaling pathways that ultimately improve carbohydrate metabolism and mitochondrial respiratory capacity, ATP production, calcium handling, and contractile function, and protect the heart from ischemic injury (28, 89). The mechanisms underlying the improved contractile function after hypoxic preconditioning are usually complex and diverse and involve various adaptations, including metabolic reprogramming, enhanced calcium handling, and the activation of pro-survival signaling pathways (89) (Figure 1). For instance, the upregulation of glycolytic enzymes such as hexokinase, phosphofructokinase, and lactate dehydrogenase helps regulate the glycolytic pathway efficiently, enabling a shift towards more oxygen-efficient ATP production, which can aid in maintaining contractile function, thereby affording cardioprotective effects (99). Moreover, HIF-1α has been shown to regulate the expression of key calcium-handling proteins, such as the sarcoplasmic reticulum calcium ATPase 2a (SERCA2a), which can enhance calcium cycling from cytoplasm into sarcoplasmic reticulum and improve excitation-contraction coupling during stress (100, 101).

In contrast, chronic hypoxia can lead to adverse remodeling of the heart, which is defined by the development of cardiac hypertrophy, fibrosis, and impaired diastolic function (102–104). These detrimental effects are often mediated by the activation of pathways involving oxidative stress, inflammation, and neurohormonal activation (102, 105, 106).

Overall, hypoxic preconditioning has been an effective strategy with cardioprotective effects. However, the impacts of hypoxia on cardiac contractility and remodeling are intricate and diverse, involving the interplay of varied signaling pathways and metabolic adaptations. Understanding these mechanisms is pivotal for developing targeted interventions to enhance cardiac function.

Therapeutic Implications and Future Directions

Our understanding from the study of hypoxia-induced cardioprotection has important therapeutic implications. Identifying some of the key molecular pathways and underlying mechanisms involved in physiological adaptation of the heart to hypoxia has uncovered potential new targets with therapeutic implications for the treatment of various diseases, including ischemic heart disease and heart failure (24, 89, 107).

Developing safe and effective methods of intermittent hypoxic training for patients with high-risk cardiac ischemic disease and the use of pharmacological agents that can

provide the benefits of intermittent hypoxia through targeting HIF-1α or its downstream signaling under normoxic conditions could have the potential for providing cardioprotection (25, 108). Exposure to mild intermittent hypoxia has shown beneficial cardiovascular outcomes, with a decrease in blood pressure in participants with obstructive sleep apnea and hypertension (109). Using remote ischemic preconditioning in patients undergoing coronary artery bypass graft surgery showed significantly lower levels of troponin-T release following surgery, indicating that it could effectively reduce myocardial injury (110). In patients with ST-segment elevation myocardial infarction, remote ischemic conditioning prior to primary percutaneous coronary intervention decreased infarct size, myocardial salvage and myocardial edema (111). Moreover, other therapeutic approaches such as modulation of mitochondrial function, enhancing angiogenesis, targeting metabolic pathways, like enhancing glycolysis and oxidative phosphorylation so as to maintain ATP production to meet the energy demands, regulating contractile function through optimizing calcium handling in cardiomyocytes, essentially by modulating SERCA2a activity, has the potential for cardioprotection under ischemic heart disease (89, 112). Recent studies have shown the benefits of using intracoronary adenosine readily binding to adenosine receptor during reperfusion, which can limit the infarct size and also reduce the coronary no-reflow (113, 114). Using beta blockers such as Metoprolol during early administration before reperfusion has also been shown to be cardioprotective (115). Roxadustat, a HIF prolyl-hydroxylase inhibitor pretreatment, significantly reduced infarct size following ischemia reperfusion injury (116).

However, translation of preclinical findings to the clinical setting has significant challenges. The complexity of the hypoxic response, the potential for off-target effects, and lack of innovative delivery systems for delivering hypoxic therapies to the region of injury in the heart have contributed to the limited success of clinical trials to date (117–119).

Future research should focus on understanding the context-dependent and cell-specific roles of HIF-1α and HIF-2α in the heart, as well as identifying novel downstream effectors and signaling involved in hypoxic preconditioning (24, 40). Additionally, the development of more sophisticated and targeted therapeutic strategies, such as gene therapy and tissue engineering approaches, may hold promise for the effective clinical translation of hypoxia-induced cardioprotection (35, 49). Identifying reliable biomarkers from patients responding to hypoxic preconditioning therapies and monitoring their status of efficacy, along with developing personalized hypoxic preconditioning treatments based on patient's age, comorbidities and genetic makeup, could also facilitate clinical trials (120–122).

Conclusion

In conclusion, hypoxia drives cardioprotection through complex and diverse adaptative responses that protect the heart from ischemic heart diseases. Some of the key mechanisms that drive these protective responses include activation of HIF signaling pathway, reactive oxygen species signaling, regulation of nitric oxide synthesis, and regulation of K_{ATP} channels. At the cellular level, hypoxia drives metabolic

reprogramming that enhances glycolysis, regulating mitochondrial dynamics, increased angiogenesis and vascular remodeling, and modulation of contractile function (Figure 2).

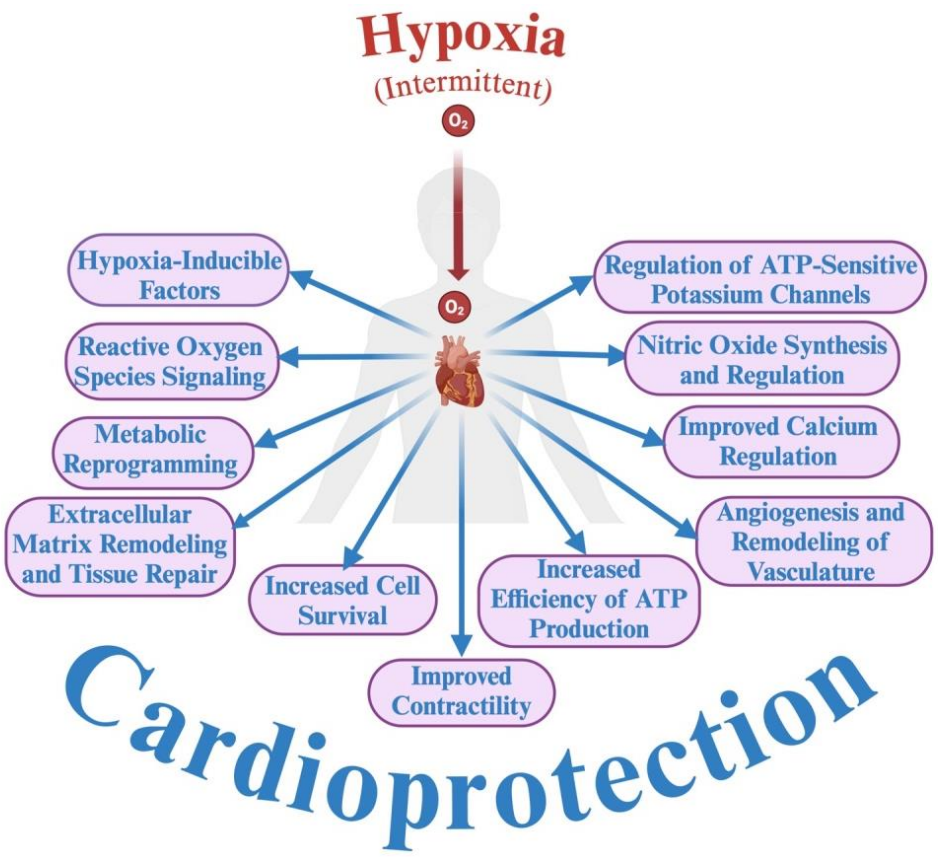

Figure 2. **Mechanisms of hypoxia-induced cardioprotection. Short-term or intermittent hypoxia protects the heart by activating various pathways including hypoxia-inducible factor signaling, reactive oxygen species signaling, nitric oxide production and regulation, and regulation of ATP-sensitive potassium channels. These pathways drive increased ATP production efficiency and utilization, tissue regeneration, cell survival, remodeling of cardiac contractility, calcium regulation, and angiogenesis, which ultimately leading to cardioprotection against ischemic injury. The figure was created in www.Biorender.com.**

Slika 2. **Mehanizmi kardioprotekcije ostvarene pomoću hipoksije. Kratkoročna ili povremena hipoksija štiti srce aktivacijom različitih puteva, uključujući signalizaciju faktora indukovanog hipoksijom, signalizaciju reaktivnih kiseoničnih vrsta, proizvodnju i regulaciju azot-monoksida, kao i regulaciju ATP-senzitivnih kalijumskih kanala. Ovi putevi dovode do povećane efikasnosti proizvodnje i korišćenja ATP, regeneracije tkiva, preživljavanja ćelija, preoblikovanja kontraktilnosti srca, regulacije kalcijuma i angiogeneze, što na kraju dovodi do kardioprotekcije koja štiti od ishemijskih oštećenja. Slika je kreirana pomoću www.Biorender.com.**

Conflict of Interest

None.

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None.

References

1. Semenza GL. Hypoxia-inducible factors in physiology and medicine. Cell. 2012 Feb 3;148(3):399–408.
2. Ziello JE, Jovin IS, Huang Y. Hypoxia-Inducible Factor (HIF)-1 regulatory pathway and its potential for therapeutic intervention in malignancy and ischemia. Yale J Biol Med. 2007 Jun;80(2):51–60.
3. Grocott M, Montgomery H, Vercueil A. High-altitude physiology and pathophysiology: implications and relevance for intensive care medicine. Crit Care. 2007;11(1):203.
4. Das KK, Majid DSA, Prabhakar NR. Editorial: vascular pathophysiology in hypoxia. Front Physiol. 2023;14:1235383.
5. Kumar H, Choi DK. Hypoxia inducible factor pathway and physiological adaptation: a cell survival pathway? Mediators Inflamm. 2015;2015:584758.
6. Viscor G, Torrella JR, Corral L, Ricart A, Javierre C, Pages T, et al. Physiological and biological responses to short-term intermittent hypobaric hypoxia exposure: from sports and mountain medicine to new biomedical applications. Front Physiol. 2018;9:814.
7. Bagali S, Hadimani GA, Biradar MS, Das KK. Introductory chapter: primary concept of hypoxia and anoxia. In: Das KK, Biradar MS, editors. Hypoxia and Anoxia. Rijeka: IntechOpen; 2018. p. Ch. 1.
8. Gupta N, Zahid Ashraf M. Hypoxia signaling in cardiovascular diseases. In: K. Das K, Shivanagouda Biradar M, editors. Hypoxia and Anoxia [Internet]. IntechOpen; 2018 [cited 2024 Aug 11]. Available from: https://www.intechopen.com/books/hypoxia-and-anoxia/hypoxia-signaling-in-cardiovascular-diseases.
9. Hausenloy DJ, Yellon DM. Myocardial ischemia-reperfusion injury: a neglected therapeutic target. J Clin Invest. 2013 Jan;123(1):92–100.
10. Yellon DM, Hausenloy DJ. Myocardial reperfusion injury. N Engl J Med. 2007 Sep 13;357(11):1121–35.
11. Hausenloy DJ, Yellon DM. Ischaemic conditioning and reperfusion injury. Nat Rev Cardiol. 2016 Apr;13(4):193–209.
12. Korge P, Ping P, Weiss JN. Reactive oxygen species production in energized cardiac mitochondria during hypoxia/reoxygenation. Circ Res. 2008 Oct 10;103(8):873–80.
13. Ping P, Murphy E. Role of p38 mitogen-activated protein kinases in preconditioning: a detrimental factor or a protective kinase? Circ Res. 2000 May 12;86(9):921–2.

14. Semenza GL. Oxygen sensing, hypoxia-inducible factors, and disease pathophysiology. Annu Rev Pathol. 2014;9:47–71.
15. Prabhakar NR, Semenza GL. Adaptive and maladaptive cardiorespiratory responses to continuous and intermittent hypoxia mediated by hypoxia-inducible factors 1 and 2. Physiol Rev. 2012 Jul;92(3):967–1003.
16. Doenst T, Nguyen TD, Abel ED. Cardiac metabolism in heart failure: implications beyond ATP production. Circ Res. 2013 Aug 30;113(6):709–24.
17. Lee P, Chandel NS, Simon MC. Cellular adaptation to hypoxia through hypoxia inducible factors and beyond. Nat Rev Mol Cell Biol. 2020 May;21(5):268–83.
18. Gassmann M. The impact of hypoxia on our body: from integrative physiology to human disease. Cell Mol Life Sci. 2009 Nov;66(22):3537–8.
19. Zhang L, Ma J, Liu H. Protective effect of ischemic postconditioning against ischemia reperfusion-induced myocardium oxidative injury in IR rats. Molecules. 2012 Mar 27;17(4):3805–17.
20. Rosenberg JH, Werner JH, Moulton MJ, Agrawal DK. Current modalities and mechanisms underlying cardioprotection by ischemic conditioning. J Cardiovasc Transl Res. 2018 Aug;11(4):292–307.
21. Loor G, Schumacker PT. Role of hypoxia-inducible factor in cell survival during myocardial ischemia-reperfusion. Cell Death Differ. 2008 Apr;15(4):686–90.
22. Otani H. Ischemic preconditioning: from molecular mechanisms to therapeutic opportunities. Antioxid Redox Signal. 2008 Feb;10(2):207–47.
23. Calmettes G, Ribalet B, John S, Korge P, Ping P, Weiss JN. Hexokinases and cardioprotection. J Mol Cell Cardiol. 2015 Jan;78:107–15.
24. Ong SG, Hausenloy DJ. Hypoxia-inducible factor as a therapeutic target for cardioprotection. Pharmacol Ther. 2012 Oct;136(1):69–81.
25. Eckle T, Köhler D, Lehmann R, El Kasmi KC, Eltzschig HK. Hypoxia-inducible factor-1 is central to cardioprotection. Circulation. 2008;118(2):166–75.
26. Zimna A, Kurpisz M. Hypoxia-inducible factor-1 in physiological and pathophysiological angiogenesis: applications and therapies. Biomed Res Int. 2015;2015:549412.
27. Sarkar K, Cai Z, Gupta R, Parajuli N, Fox-Talbot K, Darshan MS, et al. Hypoxia-inducible factor 1 transcriptional activity in endothelial cells is required for acute phase cardioprotection induced by ischemic preconditioning. Proc Natl Acad Sci U S A. 2012 Jun 26;109(26):10504–9.
28. Heck-Swain KL, Koeppen M. The intriguing role of hypoxia-inducible factor in myocardial ischemia and reperfusion: a comprehensive review. J Cardiovasc Dev Dis. 2023 May 14;10(5).
29. Hashimoto T, Shibasaki F. Hypoxia-inducible factor as an angiogenic master switch. Front Pediatr. 2015 Apr;3:33.
30. Kietzmann T, Mennerich D, Dimova EY. Hypoxia-inducible factors (HIFs) and phosphorylation: impact on stability, localization, and transactivity. Front Cell Dev Biol. 2016;4:11.
31. Ke Q, Costa M. Hypoxia-inducible factor-1 (HIF-1). Mol Pharmacol. 2006 Nov;70(5):1469–80.
32. Lucero García Rojas EY, Villanueva C, Bond RA. Hypoxia inducible factors as central players in the pathogenesis and pathophysiology of cardiovascular diseases. Front Cardiovasc Med. 2021;8:709509.

33. Cerychova R, Pavlinkova G. HIF-1, metabolism, and diabetes in the embryonic and adult heart. Front Endocrinol (Lausanne). 2018;9:460.
34. Zhao Y, Xiong W, Li C, Zhao R, Lu H, Song S, et al. Hypoxia-induced signaling in the cardiovascular system: pathogenesis and therapeutic targets. Signal Transduct Target Ther. 2023 Nov 20;8(1):431.
35. Shohet RV, Garcia JA. Keeping the engine primed: HIF factors as key regulators of cardiac metabolism and angiogenesis during ischemia. J Mol Med (Berl). 2007 Dec;85(12):1309–15.
36. Xu R, Wang F, Yang H, Wang Z. Action sites and clinical application of HIF-1α inhibitors. Molecules. 2022 May 26;27(11).
37. Hirota K. HIF-α prolyl hydroxylase inhibitors and their implications for biomedicine: a comprehensive review. Biomedicines. 2021 Apr 24;9(5).
38. Behrouzi B, Weyers JJ, Qi X, Barry J, Rabadia V, Manca D, et al. Action of iron chelator on intramyocardial hemorrhage and cardiac remodeling following acute myocardial infarction. Basic Res Cardiol. 2020 Mar 5;115(3):24.
39. Aarup A, Pedersen TX, Junker N, Christoffersen C, Bartels ED, Madsen M, et al. Hypoxia-Inducible Factor-1α Expression in Macrophages Promotes Development of Atherosclerosis. Arteriosclerosis, Thrombosis, and Vascular Biology. 2016 Sep 1;36(9):1782–90.
40. Knutson AK, Williams AL, Boisvert WA, Shohet RV. HIF in the heart: development, metabolism, ischemia, and atherosclerosis. J Clin Invest. 2021 Sep 1;131(17).
41. Rababa'h AM, Guillory AN, Mustafa R, Hijjawi T. Oxidative stress and cardiac remodeling: an updated edge. Curr Cardiol Rev. 2018 Mar 14;14(1):53–9.
42. Panth N, Paudel KR, Parajuli K. Reactive oxygen species: a key hallmark of cardiovascular disease. Adv Med. 2016;2016:9152732.
43. Buonocore G, Perrone S, Tataranno ML. Oxygen toxicity: chemistry and biology of reactive oxygen species. Semin Fetal Neonatal Med. 2010 Aug;15(4):186–90.
44. Ray PD, Huang BW, Tsuji Y. Reactive oxygen species (ROS) homeostasis and redox regulation in cellular signaling. Cell Signal. 2012 May;24(5):981–90.
45. Hong Y, Boiti A, Vallone D, Foulkes NS. Reactive oxygen species signaling and oxidative stress: transcriptional regulation and evolution. Antioxidants (Basel). 2024 Mar 1;13(3):312.
46. Li X, Zhang Q, Nasser MI, Xu L, Zhang X, Zhu P, et al. Oxygen homeostasis and cardiovascular disease: a role for HIF? Biomed Pharmacother. 2020 Aug;128:110338.
47. Kibel A, Lukinac AM, Dambic V, Juric I, Selthofer-Relatic K. Oxidative Stress in Ischemic Heart Disease. Oxid Med Cell Longev. 2020 Dec 29;2020:6627144.
48. Becker LB. New concepts in reactive oxygen species and cardiovascular reperfusion physiology. Cardiovasc Res. 2004;61(3):461–70.
49. Liu M, Galli G, Wang Y, Fan Q, Wang Z, Wang X, et al. Novel therapeutic targets for hypoxia-related cardiovascular diseases: the role of HIF-1. Front Physiol. 2020;11:774.
50. Harvey AP, Grieve DJ. Reactive oxygen species (ROS) signaling in cardiac remodeling and failure. In: Laher I, editor. Systems Biology of Free Radicals and Antioxidants. Berlin, Heidelberg: Springer Berlin Heidelberg; 2014. p. 951–92.

51. Rodrigo R, González-Montero J, Sotomayor CG. Novel combined antioxidant strategy against hypertension, acute myocardial infarction and postoperative atrial fibrillation. Biomedicines. 2021 May 30;9(6):620.
52. Rodrigo R, Prieto JC, Aguayo R, Ramos C, Puentes Á, Gajardo A, et al. Joint cardioprotective effect of vitamin C and other antioxidants against reperfusion injury in patients with acute myocardial infarction undergoing percutaneous coronary intervention. Molecules. 2021 Sep 21;26(18):5702.
53. Cadenas S. ROS and redox signaling in myocardial ischemia-reperfusion injury and cardioprotection. Free Radic Biol Med. 2018 Mar;117:76–89.
54. Russell EG, Cotter TG. New insight into the role of reactive oxygen sapecies (ROS) in cellular signal-transduction processes. Int Rev Cell Mol Biol. 2015;319:221–54.
55. Zhang Y, Du Y, Le W, Wang K, Kieffer N, Zhang J. Redox control of the survival of healthy and diseased cells. Antioxid Redox Signal. 2011 Dec 1;15(11):2867–908.
56. Hannemann J, Böger R. Dysregulation of the nitric oxide/dimethylarginine pathway in hypoxic pulmonary vasoconstriction-molecular mechanisms and clinical significance. Front Med (Lausanne). 2022;9:835481.
57. Gao F, Gao E, Yue TL, Ohlstein EH, Lopez BL, Christopher TA, et al. Nitric oxide mediates the antiapoptotic effect of insulin in myocardial ischemia-reperfusion. Circulation. 2002;105(12):1497–502.
58. Lee HM, Choi JW, Choi MS. Role of nitric oxide and protein S-nitrosylation in ischemia-reperfusion injury. Antioxidants (Basel). 2021 Dec 27;11(1):57.
59. Zhu D, Hou J, Qian M, Jin D, Hao T, Pan Y, et al. Nitrate-functionalized patch confers cardioprotection and improves heart repair after myocardial infarction via local nitric oxide delivery. Nat Commun. 2021 Jul 23;12(1):4501.
60. Banez MJ, Geluz MI, Chandra A, Hamdan T, Biswas OS, Bryan NS, et al. A systemic review on the antioxidant and anti-inflammatory effects of resveratrol, curcumin, and dietary nitric oxide supplementation on human cardiovascular health. Nutr Res. 2020 Jun;78:11–26.
61. Russo I, Barale C, Melchionda E, Penna C, Pagliaro P. Platelets and cardioprotection: the role of nitric oxide and carbon oxide. Int J Mol Sci. 2023 Mar 24;24(7).
62. Bolli R. Cardioprotective function of inducible nitric oxide synthase and role of nitric oxide in myocardial ischemia and preconditioning: an overview of a decade of research. J Mol Cell Cardiol. 2001 Nov;33(11):1897–918.
63. Liang H, Nacharaju P, Friedman A, Friedman JM. Nitric Oxide Generating/Releasing Materials. Future Sci OA. 2015 Aug;1(1):FSO54.
64. Zhu Z, Sierra A, Burnett CML, Chen B, Subbotina E, Koganti SRK, et al. Sarcolemmal ATP-sensitive potassium channels modulate skeletal muscle function under low-intensity workloads. J Gen Physiol. 2014 Jan 1;143(1):119–34.
65. Paggio A, Checchetto V, Campo A, Menabò R, Di Marco G, Di Lisa F, et al. Identification of an ATP-sensitive potassium channel in mitochondria. Nature. 2019 Aug 29;572(7771):609–13.
66. Foster MN, Coetzee WA. KATP Channels in the Cardiovascular System. Physiol Rev. 2016 Jan;96(1):177–252.
67. Zingman LV, Alekseev AE, Hodgson-Zingman DM, Terzic A. ATP-sensitive potassium channels: metabolic sensing and cardioprotection. J Appl Physiol (1985). 2007 Nov;103(5):1888–93.

68. Jin C, Wu J, Watanabe M, Okada T, Iesaki T. Mitochondrial K+ channels are involved in ischemic postconditioning in rat hearts. J Physiol Sci. 2012 Jul;62(4):325–32.
69. Behera R, Sharma V, Grewal AK, Kumar A, Arora B, Najda A, et al. Mechanistic correlation between mitochondrial permeability transition pores and mitochondrial ATP dependent potassium channels in ischemia reperfusion. Biomed Pharmacother. 2023 Jun;162:114599.
70. Mohammed Abdul KS, Jovanović S, Du Q, Sukhodub A, Jovanović A. A link between ATP and SUR2A: A novel mechanism explaining cardioprotection at high altitude. Int J Cardiol. 2015 Jun 15;189:73–6.
71. Mohammed Abdul KS, Jovanović S, Du Q, Sukhodub A, Jovanović A. Mild hypoxia in vivo regulates cardioprotective SUR2A: A role for Akt and LDH. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease. 2015 May;1852(5):709–19.
72. Mohammed Abdul KS, Jovanović S, Jovanović A. Exposure to 15% oxygen in vivo up-regulates cardioprotective SUR2A without affecting ERK1/2 and AKT: a crucial role for AMPK. J Cell Mol Med. 2017 Jul;21(7):1342–50.
73. Mohammed Abdul KS, Jovanović S, Sukhodub A, Du Q, Jovanović A. Upregulation of cardioprotective SUR2A by sub-hypoxic drop in oxygen. Biochim Biophys Acta. 2014 Nov;1843(11):2424–31.
74. Ardehali H. Signaling mechanisms in ischemic preconditioning. Circ Res. 2006;99(8):798–800.
75. Ichinose M, Yonemochi H, Sato T, Saikawa T. Diazoxide triggers cardioprotection against apoptosis induced by oxidative stress. Am J Physiol Heart Circ Physiol. 2003 Jun;284(6):H2235-41.
76. Suzuki M, Saito T, Sato T, Tamagawa M, Miki T, Seino S, et al. Cardioprotective effect of diazoxide is mediated by activation of sarcolemmal but not mitochondrial ATP-sensitive potassium channels in mice. Circulation. 2003 Feb 11;107(5):682–5.
77. Rim SJ, Hong GR, Im JW, Min PK, Mun JY, Seo HS, et al. The cardioprotective effect of intravenous nicorandil for ischemia/reperfusion injury. Korean Circ J. 2005;35:88–93.
78. Sukhodub A, Du Q, Jovanović S, Jovanović A. Nicotinamide-rich diet protects the heart against ischaemia-reperfusion in mice: a crucial role for cardiac SUR2A. Pharmacol Res. 2010 Jun;61(6):564–70.
79. Sukhodub A, Sudhir R, Du Q, Jovanović S, Reyes S, Jovanović A. Nicotinamide-rich diet improves physical endurance by up-regulating SUR2A in the heart. J Cell Mol Med. 2011 Aug;15(8):1703–12.
80. Sinha S, Du Q, Jovanović S, Sukhodub A, Jovanović A. Pyrazinamide may possess cardioprotective properties. J Antibiot (Tokyo). 2019 Sep;72(9):714–7.
81. Hu Y, Lu H, Li H, Ge J. Molecular basis and clinical implications of HIFs in cardiovascular diseases. Trends Mol Med. 2022 Nov;28(11):916–38.
82. Cox GK, Gillis TE. Surviving anoxia: the maintenance of energy production and tissue integrity during anoxia and reoxygenation. J Exp Biol. 2020 Jul 10;223(Pt 13).
83. Kuhn AR, van Bilsen M. Oncometabolism: a paradigm for the metabolic remodeling of the failing heart. Int J Mol Sci. 2022 Nov 11;23(22).
84. Yamakawa M, Liu LX, Date T, Belanger AJ, Vincent KA, Akita GY, et al. Hypoxia-inducible factor-1 mediates activation of cultured vascular endothelial cells by inducing multiple angiogenic factors. Circ Res. 2003 Oct 3;93(7):664–73.

85. Gogiraju R, Bochenek ML, Schäfer K. Angiogenic endothelial cell signaling in cardiac hypertrophy and heart failure. Front Cardiovasc Med. 2019;6:20.
86. Fong GH. Mechanisms of adaptive angiogenesis to tissue hypoxia. Angiogenesis. 2008 Jun;11(2):121–40.
87. Martín-Bórnez M, Falcón D, Morrugares R, Siegfried G, Khatib AM, Rosado JA, et al. New insights into the reparative angiogenesis after myocardial infarction. IJMS. 2023 Aug 1;24(15):12298.
88. Chang JC, Lien CF, Lee WS, Chang HR, Hsu YC, Luo YP, et al. Intermittent hypoxia prevents myocardial mitochondrial Ca2+ overload and cell death during ischemia/reperfusion: the role of reactive oxygen species. Cells. 2019 Jun 9;8(6):564.
89. 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. 2018 Aug 1;315(2):H216–32.
90. Jiang Q, Wang L, Si X, Tian JL, Zhang Y, Gui HL, et al. Current progress on the mechanisms of hyperhomocysteinemia-induced vascular injury and use of natural polyphenol compounds. Eur J Pharmacol. 2021 Aug;905:174168.
91. Huang X, Akgün EE, Mehmood K, Zhang H, Tang Z, Li Y. Mechanism of hypoxia-mediated smooth muscle cell proliferation leading to vascular remodeling. Pabelick C, editor. BioMed Res Int. 2022 Dec 24;2022:3959845.
92. Wang X, Khalil RA. Matrix metalloproteinases, vascular remodeling, and vascular disease. In: Advances in Pharmacology [Internet]. Elsevier; 2018 [cited 2024 Aug 8]. p. 241–330. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1054358917300571.
93. Monaci S, Coppola F, Filippi I, Falsini A, Carraro F, Naldini A. Targeting hypoxia signaling pathways in angiogenesis. Front Physiol. 2024 Apr 25;15:1408750.
94. Aghajanian A, Zhang H, Buckley BK, Wittchen ES, Ma WY, Faber JE. Decreased inspired oxygen stimulates de novo formation of coronary collaterals in adult heart. J Mol Cell Cardiol. 2021 Jan;150:1–11.
95. Renna NF, De Las Heras N, Miatello RM. Pathophysiology of vascular remodeling in hypertension. Int J Hypertens. 2013;2013:808353.
96. Risler NR, Cruzado MC, Miatello RM. Vascular remodeling in experimental hypertension. Scientific World Journal. 2005;5:959–71.
97. van Beek JHGM. Effects of hypoxia and hypercapnia on cardiac contractility and energetics. In: Dahan A, Teppema L, Van Beek JHGM, editors. Physiology And Pharmacology of Cardio-Respiratory Control. Dordrecht: Springer Netherlands; 1998; p. 19–24.
98. Wheaton WW, Chandel NS. Hypoxia. 2. Hypoxia regulates cellular metabolism. Am J Physiol Cell Physiol. 2011 Mar;300(3):C385–93.
99. Chen S, Zou Y, Song C, Cao K, Cai K, Wu Y, et al. The role of glycolytic metabolic pathways in cardiovascular disease and potential therapeutic approaches. Basic Res Cardiol. 2023 Nov 8;118(1):48.
100. Silter M, Kögler H, Zieseniss A, Wilting J, Schäfer K, Toischer K, et al. Impaired Ca(2+)-handling in HIF-1alpha(+/-) mice as a consequence of pressure overload. Pflugers Arch. 2010 Mar;459(4):569–77.

101. Lipskaia L, Chemaly ER, Hadri L, Lompre AM, Hajjar RJ. Sarcoplasmic reticulum Ca(2+) ATPase as a therapeutic target for heart failure. Expert Opin Biol Ther. 2010 Jan;10(1):29–41.
102. Toldo S, Abbate A. Diastolic dysfunction in chronic hypoxia: IL-18 provides the elusive link. Acta Physiol. 2014 Oct 8;213(2):298–300.
103. Rajgarhia A, Ayasolla KR, Zaghloul N, Lopez Da Re JM, Miller EJ, Ahmed M. Extracellular superoxide dismutase (EC-SOD) regulates gene methylation and cardiac fibrosis during chronic hypoxic stress. Front Cardiovasc Med. 2021 May 31;8:669975.
104. Xie S, Deng Y, Pan Y ying, Ren J, Jin M, Wang Y, et al. Chronic intermittent hypoxia induces cardiac hypertrophy by impairing autophagy through the adenosine 5′-monophosphate-activated protein kinase pathway. Arch Biochem Biophys. 2016 Sep;606:41–52.
105. Chen L, Einbinder E, Zhang Q, Hasday J, Balke CW, Scharf SM. Oxidative stress and left ventricular function with chronic intermittent hypoxia in rats. Am J Respir Crit Care Med. 2005 Oct 1;172(7):915–20.
106. Hartupee J, Mann DL. Neurohormonal activation in heart failure with reduced ejection fraction. Nat Rev Cardiol. 2017 Jan;14(1):30–8.
107. Panza GS, Puri S, Lin HS, Badr MS, Mateika JH. Daily exposure to mild intermittent hypoxia reduces blood pressure in male patients with obstructive sleep apnea and hypertension. Am J Respir Crit Care Med. 2022 Apr 15;205(8):949–58.
108. Tekin D, Dursun AD, Xi L. Hypoxia inducible factor 1 (HIF-1) and cardioprotection. Acta Pharmacol Sin. 2010 Sep;31(9):1085–94.
109. Panza GS, Puri S, Lin HS, Badr MS, Mateika JH. Daily Exposure to Mild Intermittent Hypoxia Reduces Blood Pressure in Male Patients with Obstructive Sleep Apnea and Hypertension. Am J Respir Crit Care Med. 2022 Apr 15;205(8):949–58.
110. Hausenloy DJ, Candilio L, Laing C, Kunst G, Pepper J, Kolvekar S, et al. Effect of remote ischemic preconditioning on clinical outcomes in patients undergoing coronary artery bypass graft surgery (ERICCA): rationale and study design of a multi-centre randomized double-blinded controlled clinical trial. Clin Res Cardiol. 2012 May;101(5):339–48.
111. White SK, Frohlich GM, Sado DM, Maestrini V, Fontana M, Treibel TA, et al. Remote ischemic conditioning reduces myocardial infarct size and edema in patients with ST-segment elevation myocardial infarction. JACC Cardiovasc Interv. 2015 Jan;8(1 Pt B):178–88.
112. Zhang Q, Zhao W, Li S, Ding Y, Wang Y, Ji X. Intermittent hypoxia conditioning: a potential multi-organ protective therapeutic strategy. Int J Med Sci. 2023;20(12):1551–61.
113. Bulluck H, Sirker A, Loke YK, Garcia-Dorado D, Hausenloy DJ. Clinical benefit of adenosine as an adjunct to reperfusion in ST-elevation myocardial infarction patients: An updated meta-analysis of randomized controlled trials. Int J Cardiol. 2016 Jan 1;202:228–37.
114. Desmet W, Bogaert J, Dubois C, Sinnaeve P, Adriaenssens T, Pappas C, et al. High-dose intracoronary adenosine for myocardial salvage in patients with acute ST-segment elevation myocardial infarction. Eur Heart J. 2011 Apr;32(7):867–77.
115. Roolvink V, Ibáñez B, Ottervanger JP, Pizarro G, van Royen N, Mateos A, et al. Early Intravenous Beta-Blockers in Patients With ST-Segment Elevation Myocardial Infarction Before Primary Percutaneous Coronary Intervention. J Am Coll Cardiol. 2016 Jun 14;67(23):2705–15.

116. Deguchi H, Ikeda M, Ide T, Tadokoro T, Ikeda S, Okabe K, et al. Roxadustat Markedly Reduces Myocardial Ischemia Reperfusion Injury in Mice. Circ J. 2020 May 25;84(6):1028–33.
117. Navarrete-Opazo A, Mitchell GS. Therapeutic potential of intermittent hypoxia: a matter of dose. Am J Physiol Regul Integr Comp Physiol. 2014 Nov 15;307(10):R1181-1197.
118. Baranauskas MN, Fulton TJ, Fly AD, Martin BJ, Mickleborough TD, Chapman RF. High intraindividual variability in the response of serum erythropoietin to multiple simulated altitude exposures. High Alt Med Biol. 2022 Mar;23(1):85–9.
119. Timon R, Martinez-Guardado I, Brocherie F. Effects of intermittent normobaric hypoxia on health-related outcomes in healthy older adults: a systematic review. Sports Med Open. 2023 Feb 26;9(1):19.
120. Spiegelberg L, Houben R, Niemans R, De Ruysscher D, Yaromina A, Theys J, et al. Hypoxia-activated prodrugs and (lack of) clinical progress: the need for hypoxia-based biomarker patient selection in phase III clinical trials. Clin Transl Radiat Oncol. 2019 Feb;15:62–9.
121. Han YS, Lee JH, Lee SH. Regulation of hypoxia-induced cell death and application of hypoxic preconditioning to stem cell transplantation. J Transplant Stem Cel Biol. 2014;2(1):5.
122. Verges S, Chacaroun S, Godin-Ribuot D, Baillieul S. Hypoxic Conditioning as a New Therapeutic Modality. Front Pediatr. 2015 Jun 22;3:58.

Kardioprotekcija ostvarena pomoću hipoksije – pregled

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Kratak sadržaj

Hipoksija predstavlja stanje smanjene dostupnosti kiseonika koje ima složene i često paradoksalne efekte na srce. Premda je hronična hipoksija štetna i dovodi do nepovoljnog preoblikovanja srca i disfunkcije, kratkotrajna ili povremena hipoksija može doprineti zaštitnim adaptacijama koje povećavaju sposobnost srca da se zaštiti od ishemijskog oštećenja. Ova zaštitna adaptacija, poznata kao hipoksično prekondicioniranje, pokreće aktivaciju nekoliko ključnih signalnih puteva, uključujući signalizaciju faktora indukovanog hipoksijom (HIF), signalizaciju reaktivnih kiseoničnih vrsta (ROS), regulaciju azot-monoksida (NO) i regulaciju putem ATP-osetljivih kalijumskih kanala (K_{ATP}), što dovodi do metaboličkog reprogramiranja, angiogeneze sa vaskularnim preoblikovanjem i poboljšane regulacije kalcijuma, čime se povećava otpornost na ishemijsku bolest srca. U radu razmatramo strategije kao što su hipoksično kondicioniranje i farmakološka aktivacija HIF signalizacije, zajedno sa ciljanim pristupima za poboljšanje glikolize i regulacije K_{ATP} kanala, kao i optimizaciju upravljanja kalcijumom putem kalcijum-ATPaze 2a sarkoplazmatskog retikuluma (SERCA2a) u kardiomiocitima. U ovom pregledu istražuju se mehanizmi i terapijski potencijal kardioprotekcije ostvarene kratkoročnom ili povremenom hipoksijom. Takođe naglašavamo važnost pružanja odgovora na ograničenja i izazove koji se javljaju pri korišćenju hipoksičnog prekondicioniranja u kliničkoj praksi.

Ključne reči: hipoksija, kardioprotekcija, hipoksično prekondicioniranje, HIF (faktor indukovan hipoksijom), ishemijska bolest srca i srčana insuficijencija