Review Article

Regenerative Medicine and Perioperative Hypoxic Organ Damage: Targeting Hypoxia-Inducible Factors

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Abstract

Regenerative medicine is defined by utilizing the body's repair mechanisms to restore the normal function of tissues. An important perioperative issue for anesthesiologists is organ damage that is caused by hypo-perfusion mostly due to hypoxia. Our body's response to low oxygen concentration promotes a genomic pathway to increase the level of hypoxia-inducible factors (HIFs). Regenerative medicine can help to heal damaged tissue in the perioperative period. This review introduces HIFs and their protective effect in various organs, especially during surgery, as a pioneering role of regenerative medicine to prevent perioperative complications.

Keywords: Anesthesia, Hypoxia-Inducible Factor 1, Perioperative medicine, Regenerative medicine

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Please cite this article as: Tabashi S, Tajbakhsh A, Dahi M, Dabir S, Vosoughian M, Moshari M. Regenerative Medicine and Perioperative Hypoxic Organ Damage: Targeting Hypoxia-Inducible Factors. J Cell Mol Anesth. 2022;7(1):58-65. DOI: https://doi.org/10.22037/jcma.v6i4.34958

Introduction

Regenerative medicine is the "process of replacing, engineering or regenerating human or animal cells, tissues or organs to restore or establish normal function". This process should be derived from the body's repair mechanisms although this could happen in in-vivo or in-vitro environments (1). Therefore, two distinct views are considered for healing damaged tissue by regenerative medicine, first of all, we should understand the cellular mechanism of tissue repair and the second one is using these factors to regenerate damaged tissues that cannot regenerate on their own. Since regenerative medicine was known several decades ago, some therapies have been created such as orthopedic applications, wound healing bandages, and sophisticated grafts that all have Food and Drug Administration approval (2). In parallel with these, stem cell fields and genetic science are advancing rapidly, and this idea forms that organ transplantation could be replaced by regenerative medicine in the future. It would be worth it due to the increasing population ages and organ failures (3).

Despite most advances in anesthesia safety, perioperative mortality remains the unacceptable cause of death worldwide and must get as low as possible in non-critical patients. Perioperative hypoxic organ failure is a major risk factor of morbidity and mortality. There are no specific pharmacologic methods to decrease perioperative organ damage until now. Therefore deployment of regenerative medicine to achieve this goal could be beneficial (4).

In this review, we will explain pathophysiologic and molecular pathways of hypoxic injuries in various solid organs and the role of HIFs to use this

information in regenerative medicine in the future to save organs from hypoxic injury during the perioperative period.

Hypoxia-Inducible Factors: One of the most important mechanisms for organ injury in the perioperative period is hypoxia. It is defined as a reduction of oxygen available to cells. The rate of perioperative hypoxia is noteworthy in all types of surgery at any position, it is also associated with host conditions and could increase a patient's hospital stay and mortality rate. Hypo-perfusion to the heart, lungs, brain, kidneys, gut, and liver are the leading cause of morbidity and mortality among patients undergoing surgery (5).

The effect of hypoxia on stem cells was evaluated in various studies, and they could explain a genomic pathway for that. Expression of genes Oct4, Nanog, Sall4, and Klf4 was increased due to hypoxia in stem cells and the level of growth factors elevated, and finally, studies show more proliferation in hypoxic stem cells (6). On the other hand, there are pieces of evidence that hypoxia can prevent organ injury by hypoxia-inducible factors (HIFs) that again have a genomic pathway for its effect. HIFs can induce genes that facilitate adaptation to a low oxygen level (7) and are the main modulator of oxygen homeostasis in metazoan (8). Gregg L. Semenza and Guang Wang discovered HIFs in 1995. It contains alpha and beta subunits (9) and as an interesting idea in regenerative medicine in 2019, Wai, I et al found that cell exposure to HIFs in normoxic conditions can activate pro-survival pathways (10). Here we will review pieces of evidence that studied HIF's effects on different solid organs to understand the mechanism of HIFs in hypoxia in different solid organs.

HIFs are heterodimeric proteins that contain two α and β subunits. They have a common part that contains a helix-loop-helix and a Per-ARNT-Sim (PAS) domain. The function of these parts in both subunits are similar and cause heterodimerization and DNA binding of HIFs proteins. In addition to the common part, the α subunit has an oxygen-dependent degradation domain (ODD) and two transactivation domains (TAD). TAD is responsible for the regulation of HIF target genes. α-subunit can have a variety of structures (HIF1-α, HIF2-α, and HIF3-α), but the β protein is expressed just as HIF1-β. To activate the transcription, the α subunit binds to the β part and the heterodimer bind to the target part of DNA as the

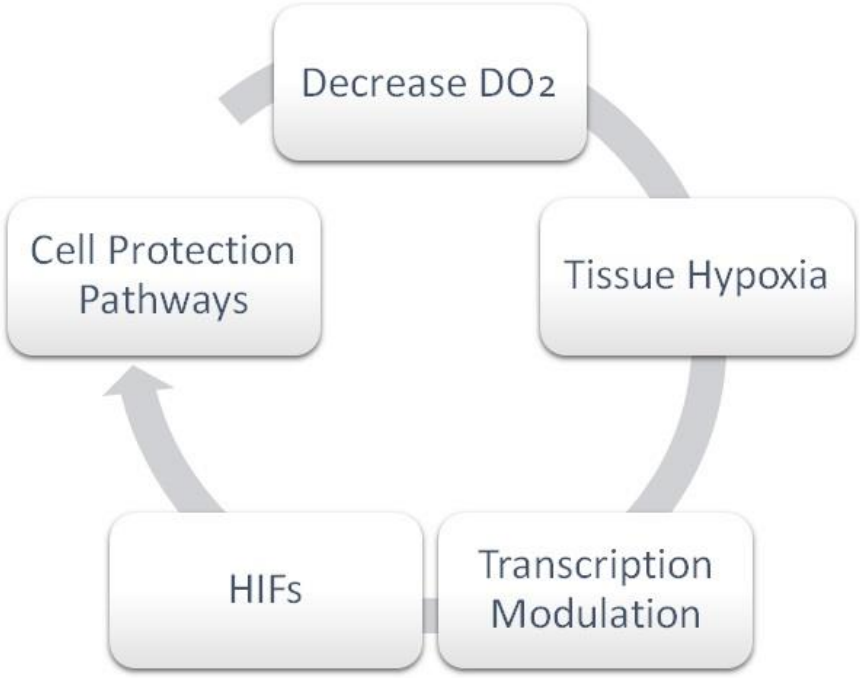

Figure 1. Effect of hypoxia.

Table 1: Summary of HIFs effects.

Organs	Effects	Pathway
Heart	cardioprotection in ischemia and reperfusion injury	Increase NO[1] Decrease endothelin 1 Increase ERBB1
Lung	dampening acute lung injury	Decrease inflammatory response Change VEGF[2] level
	prevent progression of emphysema	Change VEGF level
Kidney	Protection of AKI[3]	Ischemic preconditioning effect Increase glucose metabolism Increase erythropoiesis Increase angiogenesis Increase ALKs[4]
	Protect drug-induced injury	Decrease caspase-3 activity Decrease macrophage infiltration
Liver	Protection after ischemic-reperfusion injury	Change VEGF level
Brain	Protects apoptosis Protect cognitive dysfunction	Increase VEGF Increase EPO[5] Increase GLUT-1[6]

1. NO: Nitric Oxide
2. VEGF: vascular endothelial growth factor
3. AKI: Acute Kidney Injury
4. ALKs: Activin receptors Like Kinase
5. EPO: Erythropoietin
6. GLUT-1: Glucose Transporter-1

hypoxia-responsive elements (HERs). In all metazoan species, hypoxia-inducible factor-1α is expressed. It seems HIF-1α is more important in the hypoxic reaction of the body. HIF-2α expression is temporally and remains largely unknown. It is predominantly transcribed in endothelial cells, bone marrow macrophage, and neural crest derivatives while developing. HIF3-α is much less known (11, 12, 13). (Figure 1).

Heart: Myocardial ischemia can happen during surgery due to hemorrhagic shock or hemodynamic fluctuations in response to anesthetic drugs or surgical simulations. In these situations, the level of HIF1-α in the peri-infarct area is increased, and they are evidence that HIFs have a cardioprotective role in ischemia and reperfusion injury. Lee et al. show in their study that the risk of ischemia and reperfusion injury is more in mice with myocyte-specific HIF2-α deletion (14).

The exact mechanism of decreasing injury is unknown, but there is evidence that HIFs factors are an important component of ischemic preconditioning (IPC) and ischemic postconditioning (IPostC) effect in few but important organs. IPC and IpostC happen before and after long exposure to ischemia for attenuating ischemic injury to an organ and have a vital role during anesthesia. They are short repetitive ischemic-reperfusion cycles that happen exactly before

and after major ischemia. It could help solid organs adapt after prolonged hypoxia exposure, and HIFs are beneficial in IPC and IPostC in heart ischemia (15). Mandel et al. in 2020 performed a randomized control trial on 32 rabbits and found that in ischemic heart disease during hypoxic-hyperoxic preconditioning, the elevation of NO synthase level and attenuation of proinflammatory cytokine production such as endothelin-1 can enforce organ protection (16). The other mechanism that can explain the protective effect of HIFs in heart ischemia and reperfusion injury is that HIF2-α can increase the level of Epidermal Growth Factor Receptor-1 (ERBB1) protein in a post-transcriptional way and it also enhances transcriptional induction of amphiregulin. ERBB1or Epidermal Growth Factor Receptor-1 is highly expressed in myocytes more than the other part of the heart, and it is one of the four subtypes of ErbB receptor tyrosine kinases. The main cardioprotection effect of ERBB1 happens in ligation with amphiregulin (14).

Lung: Acute lung injury (ALI) in perioperative time is not rare and can increase the rate of mortality. The main risk factors for postoperative ALI are intraoperative excessive crystalloid administration, intraoperative transfusion, underlying ischemic heart disease, and interstitial lung disease (17). These conditions cause pulmonary edema and infiltration of protein-rich fluid to the alveolar space, leading to regional alveolar cell hypoxia and generalized hypoxemia due to diminution of gas exchange (15).

During ALI, HIF1-α are activated in alveolar cells type 2 and help dampen inflammation and maintain endothelial integrity. It seems that HIFs in acute lung injury have two basic roles. One of them is acting as a barrier to disruption. It occurs with increasing vascular epithelial growth factor (VEGF) level. Upregulation of HIF1-α leads to a high level of VEGF, which attenuates hypoxia-induced pulmonary vascular leak. The second one acts as protection against cytokine storm that suggests an increased level of HIF1-α due to inflammatory levels of NO can suppress wound healing. It can cause an appropriate healing response to hypoxia after epithelial injury (15, 18). Therefore, HIFs can be a new expectance in the treatment of ALI. On the other hand, HIF1-α can also cause pathologic events like pulmonary hypertension and increase the probability of tumor growth (19).

The effect of HIF2-α is more limited. It can prevent the progression of emphysema in at-risk patients. It is expressed in pulmonary endothelial cells and can protect the lungs by decreasing Vascular Endothelial Growth Factor (VEGF) antagonism (20). Emphysema is a pathologic condition that destroys alveolar structures and makes air space in the lung parenchyma. During anesthesia it usually happens in patients with a history of chronic obstructive pulmonary disease (COPD); especially after positive pressure ventilation or moderate to severe airflow obstruction (21).

Kidney: Organ ischemia in surgery is not rare. Various events such as inadequate hemostasis, improper surgical technique, transplantation, patients underlying conditions can result in an imbalance of oxygen supply and demand. One of the endangered solid organs to ischemia is the kidney. The primary etiology of Acute kidney injury (AKI) is prerenal, renal, and post-renal. During anesthesia prerenal AKI often happens following renal hypoperfusion, renal AKI by nephrotoxic drugs, and post-renal AKI due to genitourinary system obstruction (22).

The ischemic preconditioning effect can modify prerenal AKI. Animal studies show that preconditional activation of HIFs has an important role in protecting the ischemic injury. In fact, during hypoxia HIFs affect kidneys in three main pathways to reduce hypoxemia and kidney protection. They are anaerobic glucose metabolism, erythropoiesis, and angiogenesis. HIF1-α mostly regulates the first mechanism and the last two ones are regulated dominantly by HIF2-α. Increasing erythropoietin can enhance blood's oxygen capacity and protect kidneys by reducing apoptosis and inflammation in tubular cells. On the other hand, maintaining appropriate angiogenesis by VEGF can preserve glomerular function (23).

The other mechanism of effect HIFs is related to a specific group of receptors for Tumor Growth Factors (TGFs) called Activin receptors Like Kinase (ALKs). It is considered a biomarker that is elevated in early acute kidney injury. It is supposed to have a protective role because its deletion in tubular epithelial cells can lead to epithelial damage and fibrosis (24). Studies show aryl hydrocarbon receptor nuclear translocator

Table 2: Summary of anesthetic drugs on HIFs.

Drug	Changes in HIFs	Final effects
Isoflurane	Increase	Increase Erk1/2[1] Enhance the growth of cancer cells
Xenon	Increase	Renal protection
Sevoflurane	Increase	Increase growth of cancer cells
Halothane	Decrease	
Propofol	Decrease	Decrease apoptosis in ischemic/reperfusion injury of liver Decrease inflammation Decrease growth of cancer cells
Ketamine	Increase	Cognitive dysfunction Memory impairment

Erk1/2: Extracellular signal-related kinases

(ARNT), which is one of the common parts of α and β subunits of HIFs, can inhibit the progression of chronic kidney disease by transcriptional induction of Activin receptor Like Kinase (ALK3) (25).

HIFs also have protective effects in nephrotoxic kidney cells. When there is gentamycin-induced acute kidney injury (AKI). HIF-1α reduces caspase-3 activity and macrophage infiltration to protect against ischemic injury (26).

Liver: As mentioned earlier. the hypoxic environment can be created in anesthesia due to hemodynamic instability, in patients with cor pulmonale disease, the effect of anesthetic drugs on the liver or other organ circulation, during clamp and declamping of the portal vein in liver transplantation surgery or any ischemic reperfusion injury (IRI) that could happen in all abdominal vascular surgery. As an oxygen-sensitive solid organ, the liver would be affected by HIFs differently from the other organs. In these situations, HIFs are produced inside or outside the liver and can affect the liver in IRI or any other conditions described below.

After IRI it seems HIF1-α has the main role in liver protection by inducing transcription of genes involved in cellular metabolism, cytoprotection, and angiogenesis. The prominent role of HIF1-α in IRI is mostly by ischemic postconditioning than ischemic preconditioning effect (15). But the effect of HIF2-α in Hepatic ischemia is more unknown. In general, there is evidence of the protective effect of HIF2-α after ischemia. Acute activation of HIF2-α leads to epithelial regeneration via the VEGF pathway and regulation of energy metabolism. Chronic activation also helps cellular remodeling and can cause liver fibrosis (27). But HIF2-α has various effects on liver cells when there are other pathologies. Studies show that HIF-2α which is dominantly produced by endothelial cells in hypoxia, exacerbates Non-Alcoholic Fatty Liver Disease (NAFLD) (28) and alongside with HIF-1α could augment acetaminophen-induced hepatotoxicity (29, 30). It can also increase inflammation in patients with inflammatory bowel disease (27).

Brain: HIFs play a controversial role in the central nervous system (CNS). It protects against apoptosis and cognitive dysfunction by expressing vascular endothelial growth factor (VEGF), erythropoietin (EPO), and glucose transporter-1 (GLUT-1), especially after subarachnoid hemorrhage. It has also been shown to initiate neurogenesis after hypoxic-ischemia in rats. On the other hand, HIFs may potentiate neural apoptosis in rats after repetitive exposures. This may lead to cognitive deficits and neurotoxicity. HIFs may act both as a pro- or anti-survival mechanism. This depends on the type, duration, and location of the pathology. In CNS it may initiate apoptosis by inducing pro-apoptosis proteins like BNI P3, also it can express IAP2 to attenuate expression protein Bax and down-regulate apoptosis (31, 32) (Table1).

Anesthetics and HIFs: Numerous studies have been

conducted to find correlations between anesthetic drugs and HIFs. Research into organ protection properties from anesthetics showed information from their effect on cell signaling specially HIFs. Here, we would like to summarize known proven facts regarding this topic.

Volatile anesthetics, including Isoflurane, Desflurane, and Xenon, affect upregulating HIFs. This cytoprotective effect, also known as preconditioning, originates from controlling proliferation, angiogenesis, and metabolism. Isoflurane upregulate HIF-1α protein expression by activating extracellular signal-related kinases (Erk1/2) (33). The noble gas Xenon has renal protective properties in Ischemic-Reperfusion via the expression of HIF-1α (34).

Sevoflurane is shown to promote the expansion of human glioma stem cells by activation of HIF-1α (35). Also, HIFs gene up-regulation has been shown in rats exposed to sevoflurane in a CNS ischemic model (36). On the other hand, it has been shown that sevoflurane may prevent an increase in HIFs levels during intra-conditioning settings in in-vitro cellular line models (37).

Halothane, on the other hand, which has no longer been used in modern anesthesia, acts differently from other volatile anesthetics. Halothane reversibly inhibits HIF-1α activation by inhibiting its transactivation domain function at clinical doses (38).

Propofol, a common intravenous (IV) anesthetic, suppresses HIF-1α protein synthesis by reducing translation of its mRNA. In a non-clinical hypoxic environment (1-20%), Propofol inhibits the increasing level of HIFs and will reduce the level of HIFs in a well-known manner (33, 39). It has been shown that this inhibition of HIF-1α may attenuate apoptosis in ischemic/reperfusion injury of the liver (40). Also, this suppression in macrophages may explain the inhibitory effect of Propofol on the inflammatory system (39).

Sodium Thiopental, a common IV anesthetic, inhibits the translation of mRNA related to HIF-1α. In oppose to propofol, Thiopental will not reduce levels of HIFs. This suggests a different mechanism of action between IV anesthetics (33).

Ketamine, whose neurodegenerative properties are well studied, may induce apoptosis by increasing HIF-1α levels in brain tissue. As stated above HIFs have dual functions: pro- and anti- survival. By administrating ketamine in neonatal rats, the level of HIF-1α is increased, which may induce apoptosis and result in cognitive dysfunction and memory impairment (31, 41).

Local anesthetics such as Lidocaine or Bupivacaine have not been shown to affect HIFs or their gene responses (33).

Also, anesthesia-induced HIFs may act as a double-edged sword due to their protective effect on cancer cells as a player in tumorigenesis and metastasis. Therefore, high levels of HIFs are associated with poor prognosis in different types of cancers (33, 35). In summary, data suggest that volatile anesthetics like isoflurane or sevoflurane may enhance the growth of cancer cells, in contrast to propofol which may have a beneficial effect by attenuating proliferation, mitigation, or invasion of cancer cells (35) (Table 2).

Conclusion

Regenerative medicine is gaining a dominant role in the future of medicine. Although its role in the perioperative period is not well studied, multiple mechanisms could be the pioneer. This review introduces HIFs as a starting point to promote the perioperative period and reduce following complications. Although other mechanisms and procedures in regenerative medicine could be introduced in the following years, we supposed that HIFs could inaugurate regenerative medicine in the perioperative period.

Acknowledgment

None.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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