The complexity of metazoan life is sustained by energy generated through the oxidative metabolism of glucose and fatty acids in the mitochondria, which results in the production of reducing equivalents that are used to maintain an electrochemical gradient that drives ATP synthesis. This highly efficient mechanism for producing ATP is dependent on the utilization of O₂ as the terminal electron acceptor at complex IV of the respiratory chain. When electrons react with O₂, reactive oxygen species (ROS) are generated. Tonic, low-level ROS production results in a signal that mitochondrial function is intact, whereas increased ROS production, resulting from reduced or fluctuating O₂ availability, is a danger signal that the cell is at risk of oxidative damage and, if uncorrected, death. Our understanding of the mechanisms by which cells and organisms sense hypoxia has dramatically advanced over the last two decades, principally through the discovery of hypoxia-inducible factor 1 (HIF-1) and the delineation of its role as a master regulator of oxygen homeostasis. This paper will provide an update on advances that have occurred in the field of oxygen biology since it was last reviewed in the inaugural issue of Physiology (70).

Oxygen Sensing and Signal Transduction

Increased or decreased O₂ availability results in hypoxia or hypoxia, respectively. Hypoxia occurs physiologically as a result of excessive (“overshoot”) anogenuesis (80) and clinically when O₂ is delivered to patients at inappropriately high concentrations. Hypoxia is a fundamental physiological stimulus that occurs in response to tissue growth during normal development (11, 38, 80, 91, 92) and in disease states, such as anemia, hemorrhage, and pneumonia, that have afflicted humans and their ancestors throughout time and therefore have exerted selective pressure for the evolution of adaptive responses. In addition, modern man is afflicted by novel scourges associated with living long and/or unwisely, such as tobacco-related lung disease, atherosclerotic cardiovascular disease, and cancer, that have not exerted selective pressure due to their late onset, both with respect to reproduction of the individual and evolution of the species. Hypoxia can occur continuously or intermittently and be either acute or chronic in duration. Whereas chronic continuous hypoxia may occur either in a physiological or pathological context, chronic intermittent hypoxia only occurs in a pathological context. The distinction between physiological and pathological responses to hypoxia is important and will be delineated in greater detail below.

Continuous hypoxia

HIF-1 is a heterodimeric protein that is composed of a constitutively expressed HIF-1α subunit and an O₂-regulated HIF-1α subunit (88). Under normoxic conditions, the HIF-1α subunit is synthesized and subjected to hydroxylation on proline residue 402 and/or 564 by prolyl hydroxylase domain (PHD) proteins (principally PHD2) that use O₂ and/or α-ketoglutarate as substrates (Figure 1A) to catalyze a dioxygenase reaction in which one oxygen atom is inserted into the proline residue and the other oxygen atom is inserted into α-ketoglutarate to form succinate and CO₂ (12, 30). The protein OS-9 binds to both PHD2 and HIF-1α, thereby facilitating hydroxylation (4). Prolyl hydroxylation is required for the binding of the von Hippel-Lindau protein (VHL), which interacts with Elongin C and thereby recruits a ubiquitin ligase complex (30, 31). The protein SSAT2, which interacts with HIF-1α, VHL, and Elongin C, stabilizes the interaction of VHL with Elongin C, thereby facilitating ubiquitination of HIF-1α (2). Ubiquitination marks...
Intermittent hypoxia

Brief episodes of hypoxia and reoxygenation (intermittent hypoxia) are known to occur during swimming as a consequence of apneas triggered by the naso--pharyngeal reflex (60). Of greater concern is the chronic intermittent hypoxia that occurs as a result of obstructive sleep apnea and causes cardiovascular disease (34), as will be discussed below. Despite the fact that intermittent hypoxia involves short (15–30 s) episodes of hypoxia followed by longer (e.g., 5 min) periods of reoxygenation, HIF-1 activity is induced, albeit by mechanisms that are distinct from those regulating its activity under conditions of chronic hypoxia (96).

The signal transduction pathways by which intermittent hypoxia activates HIF-1 have been delineated in the PC12 rat pheochromocytoma cell line, in which hypoxia was previously (13) shown to induce membrane depolarization and increased intracellular Ca2+ ([Ca2+]i). When these cells were exposed to 60 cycles of intermittent hypoxia, the hydroxylation reactions are inhibited as a result of substrate (O2) deprivation and/or increased mitochondrial production of ROS, which may inactivate the hydroxylases by oxidizing a ferrous ion in the catalytic site (24, 30). The loss of hydroxylase activity increases HIF-1 stability and transactivation function, leading to its dimerization with HIF-1β, binding of HIF-1 to its recognition sequence 5’-(A/G)CGTG-3’ (71) in target genes, and increased transcription of target gene sequences into mRNA.
1.5% O₂ for 30 s followed by 20% O₂ for 5 min, HIF-1α protein and HIF-1 transcriptional activity were induced and increased further after 120 cycles (95). In these cells, intermittent hypoxia triggered NADPH oxidase-dependent ROS production, which induced phospholipase C activity, leading to the generation of inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (FIGURE 1B). Binding of IP3 to its cognate receptor led to mobilization of intracellular Ca²⁺, which activated calcium-calmodulin kinase (CamK) and, together with diacylglycerol, induced protein kinase C (PKC) activity. PKC stimulated mTOR-dependent HIF-1α synthesis and inhibited PHD2-dependent degradation of HIF-1α (96). CamK phosphorylated the coactivator p300, thereby promoting its interaction with HIF-1α, leading to transcriptional activation (95). In contrast to continuous hypoxia, in which HIF-1α is rapidly degraded (t₁/₂ < 5 min) on reoxygenation (88), HIF-1α levels remain persistently elevated following intermittent hypoxia due to the persistent activation of mTOR (96), a finding that has significance in the context of obstructive sleep apnea, in which pathological cardiovascular and respiratory responses persist for hours after the termination of intermittent hypoxia (63).

Oxygen-Independent Mechanisms for Regulating HIF-1α

In addition to the O₂-dependent pathways described above, O₂-independent pathways regulating the synthesis and the degradation of HIF-1α have been delineated. These pathways appear to be particularly important in the context of cancer.

Regulation of HIF-1α degradation

Although the PHD2-VHL pathway is the critical mechanism regulating HIF-1α stability in response to changes in O₂ concentration (FIGURE 1A), recent studies have revealed that the RACK1 protein can bind to HIF-1α and interact with Elongin C, thereby recruiting an E3 ubiquitin-protein ligase complex (46). RACK1 can substitute for VHL to promote ubiquitination and degradation of HIF-1α (96).
degradation of HIF-1α (FIGURE 2A), with the critical distinction that RACK1-HIF-1α interaction is not O2-regulated. Although RACK1 was originally identified as a protein that stabilized interactions between PKC and its substrates, PKC activity is not required for RACK1-mediated ubiquitination and degradation of HIF-1α (46).

RACK1-mediated HIF-1α degradation has been demonstrated in two contexts. First, heat shock protein 90 (HSP90) is known to bind to HIF-1α, and HSP90 inhibitors have been shown to inhibit tumor growth and to induce proapoptotic degradation of HIF-1α even in cells lacking VHL (26). RACK1 was shown to compete with HSP90 for binding to the PAS-A subdomain of HIF-1α (46). Treatment with an HSP90 inhibitor such as 17-allylamino-17-demethoxygeldanamycin results in upregulated RACK1 binding leading to increased ubiquitination and degradation of HIF-1α. The ability of HSP90 inhibitors to induce HIF-1α degradation is dependent on RACK1 expression (46). These studies have delineated a novel mechanism of action contributing to the anti-cancer effect of HSP90 inhibitors.

RACK1 also appears to contribute to the mechanism of action of another important drug, cyclosporine A, which is an immunosuppressant that prevents tissue rejection following transplantation by inhibiting calcineurin, a Ca2+/calmodulin-dependent serine/threonine protein phosphatase (44). Calcineurin A has been shown to inhibit hypoxia-induced HIF-1α expression (14, 37). RACK1 consists of seven copies of the tryptophan-aspartate-rich WD40 repeat domain on separate RACK1 monomers such that dimerization is required for RACK1 to recruit Elongin C to HIF-1α (47). Phosphorylation of RACK1 promotes its dimerization, and the catalytic subunit of calcineurin binds to RACK1 and mediates its dephosphorylation, thereby inhibiting dimerization and RACK1-dependent HIF-1α degradation (FIGURE 2A). Ionomycin, a calcium ionophore, was shown to increase HIF-1α levels even in RCC4 cells, which lack functional VHL (47). Thus, calcineurin activation represents another mechanism, in addition to those identified in the response to intermittent hypoxia (FIGURE 1B), by which calcium signaling can increase HIF-1α activity (FIGURE 2A).

SSAT1, which shares 46% amino acid identity with SSAT2, also binds to HIF-1α and promotes its ubiquitination and degradation (21). However, in contrast to SSAT2, which stabilizes the interaction of VHL and Elongin C (FIGURE 1A) and thereby promotes O2-dependent ubiquitination (21), SSAT1 acts by stabilizing the interaction of HIF-1α with RACK1 (FIGURE 2A). Thus the paralogs SSAT1 and SSAT2 play complementary roles in promoting O2-independent and O2-dependent degradation of HIF-1α, respectively.

**Regulation of HIF-1α synthesis**

The principal mechanism for transducing extracellular signals to the nucleus is by the binding of growth factors, cytokines, and other ligands to cognate receptors that recruit kinases and G-protein-coupled receptors on the cell surface, leading to the activation of the phosphatidylinositol-3-kinase (PI3K) and MAP kinase pathways (FIGURE 2B). Signal transduction through these pathways stimulates cell survival, growth, and proliferation. An inevitable consequence of cell growth and proliferation is increased O2 consumption, and it is perhaps not surprising that these same signal transduction pathways induce what can be considered pre-emptive HIF-1 activity because it occurs in an O2-independent manner (19, 42, 85, 98).

Treatment of MCF-7 human breast cancer cells with heregulin, which binds to heterodimers composed of the human epidermal growth factor receptor family members HER2 and HER3, activates PI3K, which phosphorylates the serine-threonine kinase Akt (protein kinase B). Activated Akt phosphorylates and activates the mammalian target of rapamycin (mTOR). Phosphorylation of RACK1 promotes its interaction with and inhibits Akt (44, 46), a critical regulator of cap-dependent mRNA translation (FIGURE 2A), and these actions of mTOR increase the rate of translation of a subset of cellular mRNAs (25, 28). Heregulin treatment increases the synthesis of HIF-1α protein in MCF-7 cells, and this effect is blocked by rapamycin, which is a specific inhibitor of mTOR activity (42). As in the case of HSP90 inhibitors (FIGURE 2A), rapamycin and its derivatives are a class of drugs currently in clinical trials as anti-cancer agents, and their anti-cancer effects are strongly associated with their inhibition of HIF-1α (50, 83).

**HIF-1α-Mediated Adaptive Responses to Hypoxia**

HIF-1α mediates cell autonomous, tissue-restricted, and systemic homeostatic responses to hypoxia. An illustrative example of each of these is described below.

**Erythropoiesis**

HIF-1α regulates erythropoiesis by increasing the production of red blood cells. In hypoxic conditions, the level of HIF-1α increases, and this increase in HIF-1α leads to the upregulation of genes involved in erythropoiesis. These genes include those encoding glycoprotein hormone α-subunit, β-subunit, and polypeptide hormone-subunit, which are essential for the production of erythropoietin (EPO), a hormone that stimulates the production of red blood cells.

EPO is produced in the kidneys in response to low oxygen levels and is crucial for the production of red blood cells. EPO binds to its receptor on the surface of erythroid progenitor cells, leading to the activation of the PI3K-AKT-mTOR signaling pathway, which stimulates cell proliferation and differentiation. This process is essential for the production of red blood cells, which are responsible for the transport of oxygen throughout the body.

**Angiogenesis**

HIF-1α also plays a critical role in angiogenesis, the formation of new blood vessels. In hypoxic conditions, HIF-1α upregulates the expression of angiogenic factors such as VEGF and SDF-1, which stimulate the recruitment and proliferation of endothelial cells, leading to the formation of new blood vessels.

**Transcriptional Regulation**

Subsequently, HIF-1α interacts with the hypoxia-responsive elements (HREs) located in the promoter regions of target genes, leading to the induction of gene expression and the initiation of cellular responses to hypoxia. This process is critical for the maintenance of tissue oxygen homeostasis and the survival of cells in hypoxic environments.
transcription led to the discovery of HIF-1 (72).

Subsequently, HIF-1 has been shown to orchestrate erythropoiesis by coordinately regulating the expression of multiple genes encoding proteins responsible for the intestinal uptake, tissue recycling, and delivery of iron to the bone marrow for its use in the synthesis of hemoglobin (FIGURE 3A), including transferrin (66), transferrin receptor (48, 81), ceruloplasmin (53), and hepcidin (59). In addition, HIF-1 also activates transcription of the EPO receptor (51).

Erythropoiesis is impaired in Hif1a–/– (homozygous HIF-1α-null) embryos and the erythropoietic defects in HIF-1α-deficient erythroid colonies could not be corrected by cytokines, such as vascular endothelial growth factor (VEGF) or EPO, but were ameliorated by administration of Fe-salicylaldehyde isonicotinoylhydrazone, a compound that can deliver iron into cells independently of iron transport proteins, which was consistent with reduced levels of transferrin receptor in HIF-1α-deficient embryos and yolk sacs (93). In contrast, deficiency of HIF-2α (which, like HIF-1α, is O2 regulated, dimerizes with HIF-1β and activates target gene expression) has a major effect on EPO production in adult mice (23).

Angiogenesis

Erythropoiesis represents an adaptive response to systemic hypoxia. In contrast, angiogenesis represents a local tissue response to decreased oxygenation. As cells grow and proliferate, their consumption of O2 increases and HIF-1 activity is induced, either as a result of pre-emptive growth factor-mediated induction (FIGURE 2B) or as a result of tissue hypoxia (FIGURE 1A). HIF-1 then coordinately activates the transcription of multiple genes encoding angiogenic growth factors and cytokines (FIGURE 3B), including vascular endothelial growth factor (VEGF), stromal-derived factor 1 (SDF-1), placental growth factor (PLGF), angiopoietin 1 and 2, and platelet-derived growth factor B (5, 8, 18, 32, 76), which bind to cognate receptors on vascular endothelial and smooth muscle cells as well as on endothelial progenitor cells, mesenchymal stem cells, and other bone marrow-derived angiogenic cells (FIGURE 3B). In addition, HIF-1 regulates the expression of CXCR4 (77), which is the receptor for SDF-1, and VEGFR1 (22, 101).
55), which binds VEGF and PLGF. Thus, as described above for erythropoiesis, HIF-1 functions as a master regulator to control angiogenesis at multiple levels and vasorelaxation fails in Hif1a−/− (homozygous HIF-1α-null) embryos (27, 67), whereas Hif1a+/− (heterozygous HIF-1α-null) adult mice have impaired vasorelaxation following arterial occlusion (5).

Whereas the hypoxia-induced expression of HIF-1 provides a mechanism to ensure that every cell receives adequate perfusion in young and healthy animals, age and diabetes impair angiogenesis, apoptosis, and wound healing (45). Remarkably, the budding yeast 

Saccharomyces cerevisiae 

also switches COX subunits in response to hypoxic conditions (40) but does so by a completely different molecular mechanism since yeast do not have a HIF-1 homolog. The similar regulation of Glucose and energy metabolism

Figure 3C

Individual cells must adapt to O2 deprivation by reprogramming their metabolism. The metabolic alterations that are induced by hypoxia are profound (Figure 3C). Perhaps the most striking adaptation identified thus far is a subunit switch that occurs in cytochrome c oxidase (COX; complex IV), in which the COX4-1 regulatory subunit is replaced by the COX4-2 isoform as a result of HIF-1-mediated transcriptional activation of genes encoding COX4-2 and LON, a mitochondrial protease that is required for the hypoxia-induced degradation of COX4-1 (20). This subunit switch serves to optimize the efficiency with which COX transfers electrons to O2 under hypoxic conditions. Remarkably, the budding yeast Saccharomyces cerevisiae also switches COX subunits in response to hypoxia (40) but does so by a completely different molecular mechanism since yeast do not have a HIF-1 homolog. The similar regulation of COX activity in yeast and human cells indicates that the selection for O2-dependent homeostatic regulation of mitochondrial respiration is ancient and likely to be shared by all eukaryotic organisms (20).

A more drastic alteration is the shunting of pyruvate away from the mitochondria by the HIF-1-mediated activation of the PDH1 gene encoding pyruvate dehydrogenase (PDH) kinase 1 (35, 56), which phosphorylates the catalytic subunit of PDH, the enzyme that converts pyruvate into acetyl coenzyme A (AcCoA) for entry into the mitochondrial tricarboxylic acid cycle (Figure 3C), which generates reducing equivalents that are donated to the electron transport chain. The reduced delivery of substrate to the mitochondria for oxidative phosphorylation results in reduced ATP synthesis, which must be compensated for by increased glucose uptake via glucose transporters and increased conversion of glucose to lactate by the activity of glycolytic enzymes and lactate dehydrogenase A (Figure 3C), which are all encoded by HIF-1 target genes (27, 67, 69, 71).

Induction of PDH1 expression will inhibit the oxidative metabolism of AcCoA derived from glucose but will not affect the oxidative metabolism of AcCoA derived from fatty acids. The most dramatic response to persistent hypoxia is the active destruction of mitochondria by selective mitochondrial autophagy that is required for the inhibition of HIF-1α hydroxylase activity (24). Exposure of wild-type (WT) MEFs to hypoxia for 48 h results in reduced ROS levels, in contrast to Hif1a−/− MEFs in which ROS levels are markedly increased (35, 97).

The following conclusions can be drawn regarding the metabolic adaptation to hypoxia. The increase in glycolysis and decrease in respiration that occur in response to hypoxia do not represent a passive effect of substrate (O2) deprivation but instead represent an active response of the cell to counteract the reduced efficiency of respiration under hypoxic conditions, which in the absence of adaptation results in the accumulation of toxic levels of ROS. These studies indicate that a major role of HIF-1α is to establish, at any O2 concentration, the optimal balance between glycolytic and oxidative metabolism that maximizes ATP production without increasing ROS levels. Finally, analysis of lung tissue from non-hypoxic Hif1α−/− mice, which are heterozygous for a HIF-1α-null allele and thus partially HIF-1α deficient, revealed an ~50% decrease in mitochondrial mass compared with WT littermates (97). This remarkable finding indicates that HIF-1 regulates mitochondrial metabolism even in the tissue exposed to the highest Po2.

“...This remarkable finding indicates that HIF-1 regulates mitochondrial metabolism even in the tissue exposed to the highest Po2...”

Continuous pulmonary hypertension

The only organ system in which the right ventricle responds is the pulmonary circulation. The only organ system in which the right ventricle responds is the pulmonary circulation.
HIF-1-Mediated Pathological Responses to Hypoxia

Continuous hypoxia and pulmonary hypertension

The only organ to receive 100% of cardiac output is the lungs, which receive the blood that is pumped from the right ventricle. The pulmonary arterial circulation functions to load erythrocytes with O₂. Blood is then returned to the left heart from which it is pumped through the systemic circulation to all tissues of the body. Chronic pulmonary vascular dilatation in response to hypoxia, which is an autoregulatory response to hypoxia to shunt blood away from lung tissue that is not oxygenated. Whereas this is an adaptive response in the setting of pneumonia, it is maladaptive in the setting of chronic lung disease, in which alveolar hypoxia is widespread. The right ventricle is forced to pump against greater resistance (pulmonary hypertension), resulting in ventricular hypertrophy and ultimately heart failure. HIF-1 plays a key role in this maladaptive response as determined in a mouse model in which animals are maintained in an ambient O₂ concentration of 10% for 3 wk (94).

HIF-1 mediates multiple pathogenic responses of pulmonary artery smooth muscle cells (PASMCs) to hypoxia. HIF-1 inhibits the expression of the voltage-gated potassium channels Kᵥ2.1 and Kᵥ1.5 (90) and activates expression of the TRPC1 and TRPC6 store-operated calcium channels (89). Increased [K⁺], and [Ca²⁺], trigger depolarization of PASMCs (74) and vessel constriction (FIGURE 4A). In addition, HIF-1 promotes the expression of endothelin-1, both in PASMCs and endothelial cells, leading to activation of endothelin receptors on PASMCs, which promotes further Kᵥ channel downregulation and vasoconstriction (89). HIF-1 also induces expression of the sodium-hydrogen exchanger NHE1, which increases intracellular pH (73). Increased [H⁺], and [Ca²⁺], in PASMCs promote cell proliferation. Finally, HIF-1 induces PASMC hypertrophy through mechanisms that have yet to be delineated (74). The combination of PASMC hypertrophy, constriction, and proliferation causes the reduction in the luminal diameter of pulmonary arterioles that underlies pulmonary hypertension (FIGURE 4A).

Mice heterozygous for a knockout allele at the locus encoding HIF-1α (Hif1a+/–) mice (36, 94) or HIF-2α (Hif2a+/–) mice (97) are resistant to the systemic hypertension induced in response to chronic intermittent hypoxia. HIF-1 also induces expression of the sodium-hydrogen exchanger NHE1, which increases intracellular pH (73). Increased [H⁺], and [Ca²⁺], in PASMCs promote cell proliferation. Finally, HIF-1 induces PASMC hypertrophy through mechanisms that have yet to be delineated (74). The combination of PASMC hypertrophy, constriction, and proliferation causes the reduction in the luminal diameter of pulmonary arterioles that underlies pulmonary hypertension (FIGURE 4A).

Acute hypoxia (77). This phenotype is a striking complement to the impaired pulmonary vasoconstrictive and cardiorespiratory responses to chronic hypoxia that are observed in Hif1a+/– mice (36, 94).

Chronic intermittent hypoxia and systemic hypertension

Whereas chronic continuous hypoxia induces pulmonary hypertension, chronic intermittent hypoxia (CIH) induces systemic hypertension. CIH occurs in individuals with obstructive sleep apnea (OSA), in which airway occlusion results in cessation of breathing leading to hypoxemia, which then arouses the individual to breathe. OSA may be a contributing factor in 30% of patients with essential hypertension (43). The carotid body is a small chemosensory organ located at the bifurcation of the internal and external carotid arteries that senses arterial Pₐo₂. CIH induces signaling from the carotid body that activates the systemic response to hypoxia. This finding that CIH induces systemic hypertension in the setting of chronic intermittent hypoxia is widespread. The right ventricle is forced to pump against greater resistance (pulmonary hypertension), resulting in ventricular hypertrophy and ultimately heart failure. HIF-1 plays a key role in this maladaptive response as determined in a mouse model in which animals are maintained in an ambient O₂ concentration of 10% for 3 wk (94).

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pithetic nervous system, leading to increased catecholamine secretion, which increases arterial tone, leading to hypertension (43, 61). Exposure of HIF-1α mice and their WT littermates to CIH for 10 days results in marked increases in systolic and diastolic blood pressures and a significant elevation in plasma norepinephrine concentration in the WT mice, whereas their HIF-1α−/− littermates are unaffected (59). Remarkably, the carotid bodies of HIF-1α−/− mice, although structurally and histologically normal, do not respond to hypoxia, although they respond normally to CO2 and cyanide (36, 59).

CIH induces ROS production in rodents (62) and humans (16) and induces HIF-1α expression (58). Administration of the superoxide scavenger manganese tetrakis(1-methyl-4-pyridyl)porphyrin pentachloride to WT mice blocks CIH-induced ROS production (57), hypertension (39), and HIF-1α induction (58). Remarkably, in HIF-1α−/− mice, there is a complete loss of CIH-induced HIF-1α expression and ROS production (58). These results indicate that ROS production is required for HIF-1α induction and that HIF-1α induction is required for ROS production, suggesting a feed-forward mechanism in which ROS induces HIF-1α, which induces more ROS, leading to higher HIF-1α expression (FIGURE 4B). In contrast to the physiological response to continuous hypoxia observed in MEFs described above, in which HIF-1α activity ameliorates increases in ROS levels, the pathological response to CIH is characterized by hypoxic pulmonary hypertension, a nonphysiological complication of obesity, has not been subject to evolutionary selection because it occurs in response to an environment that is not hypertensive. Although structurally and histologically normal, obese mice and their WT littermates to CIH for 10 days leading to hypertension (43, 61). Exposure of WT mice to CIH for 10 days increases the norepinephrine concentration in the WT mice, where-


The matching in metabolic and molecular physiological processes explains why these tissues have not been tested in the comprehended delivery and necessary, be it a part of the model observed by August Krogh, collaborator, to report model half-life is the sole cell type surrounding the simple model. Over 30 years ago, oxygen transport, as described. Oxygen transport capacity response to inadequate tissue oxygenation. Hypoxia oxygen tension of Krogh's idea was a preconceptual one. Over 30 years ago, Krogh's idea of arteriolar tree, the capillary bed of the heart is a variable of the heart, and there is a microvessel C-G model. Although such a large project, such as Poggesi (26) leaving the academic sector.