STM JOURNALS

Research & Reviews: Journal of
Veterinary Science and Technology

ISSN: 2319-3441(Online)
ISSN: 2349-3690 (Print)
Volume 15, Issue 1, 2026
January–April
DOI (Journal): 10.37591/RRJOVST

https://journals.stmjournals.com/rrjovst

Research RRJOVST

Impact of Hypoxia on Cardiopulmonary Adaptation in Canines: A Comprehensive Review

Sagar M

Abstract

Hypoxia triggers a series of cardiopulmonary responses that play an important role in oxygen delivery and the continuation of physiological activity in mammals. Canines are also a useful translational model of study to examine these adaptive responses because of their anatomical, physiological, and cardiopulmonary differences with humans. This review summarizes the experimental data of acute, subacute and chronic hypoxia in dogs with particular focus on the variations in cardiac functioning, pulmonary vascular remodelling, respiratory drive, haematological adaptation and molecular pathways. In hypoxic stress, dog species show compensatory tachycardia, cardiac output changes, increased sympathetic response, and myocardial oxygen consumption. Long-term effects of prolonged exposure in pulmonary responses are hypoxic pulmonary vasoconstriction, vascular smooth muscle hypertrophy and progressive pulmonary hypertension. The respiratory adjustments are in form of enhanced ventilation, changes in blood-gas parameters and sensitization of chemoreceptors. Haematologically, hypoxia initiates erythropoiesis, increases haemoglobin level, and red cell mass alteration to achieve the maximum oxygen delivery. The pathways of hypoxia-inducible factor (HIF) are involved in the regulation of angiogenesis, energy metabolism, and gene expression that are essential to the survival in low oxygen environments at the molecular level. The review outlines the significant experimental models, methodological and translational inferences of veterinary critical care, altitude physiology, and cardiopulmonary therapeutic studies. Nevertheless, there are still gaps in the knowledge of the long-term effects of hypoxia on cardiac remodelling, breed-specific differences and molecular interplay between hypoxia and inflammatory mediators. To enhance clinical practices of hypoxia related disorders in canines, future research that incorporates genomics, high resolution imaging, and sophisticated cardiopulmonary monitoring should be undertaken to bolster the evidence.

Keywords: Hypoxia, Cardiopulmonary adaptation, Canine physiology, Acute hypoxia, Chronic hypoxia, Pulmonary hypertension

INTRODUCTION

Hypoxia is the lack of the necessary level of oxygen in the tissues, which is a basic physiological difficulty that causes complex mechanisms of adaptation in various organ systems. The cardiopulmonary system in mammals is the major monitor of the oxygen inadequacy or the coordination area of prompt and prolonged adaptations to maintain metabolic balance. Canines are the best in studying hypoxia-induced responses because of their anatomical proximity to human cardiopulmonary physiology and the well-known application as a model in research. The knowledge about such adaptations is essential to veterinary health as well as further the development of translational information about altitude physiology, respiratory medicine, and cardiovascular research [1].

***Author for Correspondence**
Sagar M
E-mail: msgr1234567@gmail.com

MVSC Veterinary physiology, Department of veterinary physiology, Karnataka Veterinary, Animal and Fisheries University, Bangalore.

Received Date: November 27, 2025
Accepted Date: December 01, 2025
Published Date: December 02, 2025

Citation: Sagar M. Impact of Hypoxia on Cardiopulmonary Adaptation in Canines: A Comprehensive Review. Research and Reviews: Journal of Veterinary Science and Technology. 2026; 15(1): 13–24p.

Hypoxia may occur in many environments, such as high altitudes, airway blockage, pulmonary disease, anaesthesia, trauma, and heart-related failure of the lungs. The acuity, chronicity, normobaric or hypobaric nature of hypoxia, has a great impact on the nature of physiological adaptation. In dogs, the effect of hypoxia is a sudden surge in the activity of the sympathetic nervous system that results in tachycardia, augmented cardiac output, and augmented ventilatory effort. The short-term actions are geared towards the maximization of oxygen to the important organs. Structural and functional remodelling of the heart and the pulmonary vasculature including right ventricular hypertrophy, vascular smooth muscle proliferation, and high pulmonary arterial pressures, may be seen with prolonged exposure [2].

Hypoxic pulmonary vasoconstriction (HPV) is a characteristic adaptive response mechanism at the pulmonary level which divert blood flow to areas of the lungs with good ventilation to maximize the gas exchange. Nevertheless, HPV chronicity may help to develop pulmonary hypertension, which is a condition that has significant clinical consequences. Oxygen homeostasis is also assisted by respiratory adaptations which include increased respiratory rate and depth, changes in blood gas composition, and an increase of the chemoreceptor sensitivity. Hematological reactions including accelerated erythropoiesis and elevated haemoglobin concentration augment the oxygen-carrying ability of the blood in the persistent hypoxia [3].

At the molecular level, the hypoxia-inducible factors (HIFs) play the role of overriding cellular adjustment. These transcription factors control angiogenesis, energy metabolism and erythropoiesis and vascular remodelling, which gives a mechanistic connection between environmental oxygen concentrations and the cellular performance. The study of HIF signalling in canines helps to study the general cascade of hypoxia and new opportunities of therapeutic interventions.

Even after enormous studies, there are still great gaps in defining breed-specific variability and changes in long-term structural cardiac alterations, interactions between hypoxia and inflammatory or metabolic pathways in dogs [4]. In addition, as high-altitude training in working dogs gains increasing attention and anaesthetic care in hypoxia is considered, as well as the appearance of respiratory illnesses, there is an urgent need to unite the understanding of how the canine cardiopulmonary systems adjust to different hypoxic conditions.

This literature review summarizes experimental data of the cardiopulmonary adaptations to hypoxia in canines, including cardiac, pulmonary, respiratory, haematological and molecular levels. It will assist in informing further research by reviewing the existing evidence and gaps in the field of knowledge to improve clinical decision making in the veterinary and comparative biomedical workers. A summary of the multisystem adjustments of hypoxia in canines are outlined in Figure 1 in which there is synchronization of cardiovascular, pulmonary, respiratory, haematological, metabolic and molecular adjustments, which all serve to ensure oxygen delivery and physiological homeostasis.

Hypoxia in Mammals Physiology

Hypoxia destabilizes the oxygen supply and demand imbalance of metabolic activities and triggers a cascade of synchronized cardiopulmonary and cellular reactions in mammals. The mechanisms of these processes in canines have universal mammalian patterns, as well as species-specific strengths, in particular cardiopulmonary resilience. The delivery of oxygen depends on efficient uptake of oxygen in the lungs, transportation in the cardiovascular system and cellular use. Low oxygen concentration causes the peripheral chemoreceptors especially, carotid bodies, to sense low PaO2 and promptly activate augmented ventilation. It causes hyperventilation that is rapid, and it raises the oxygen level in the alveoli, but can cause alkalosis of the respiration in the initial phase of exposure to hypoxia [5].

The cardiovascular responses are immediately after. Sympathetic activation in hypoxia-induced conditions elevates the heart rate, contractility and the heart output and redistribution of blood to vital organs. The pulmonary circulation is the sole response to systemic dilation by hypoxic pulmonary

vasoconstriction (HPV) that improves the ventilation-perfusion ratio only to initiate the development of pulmonary hypertension and right ventricular hypertrophy in the long-term [6].

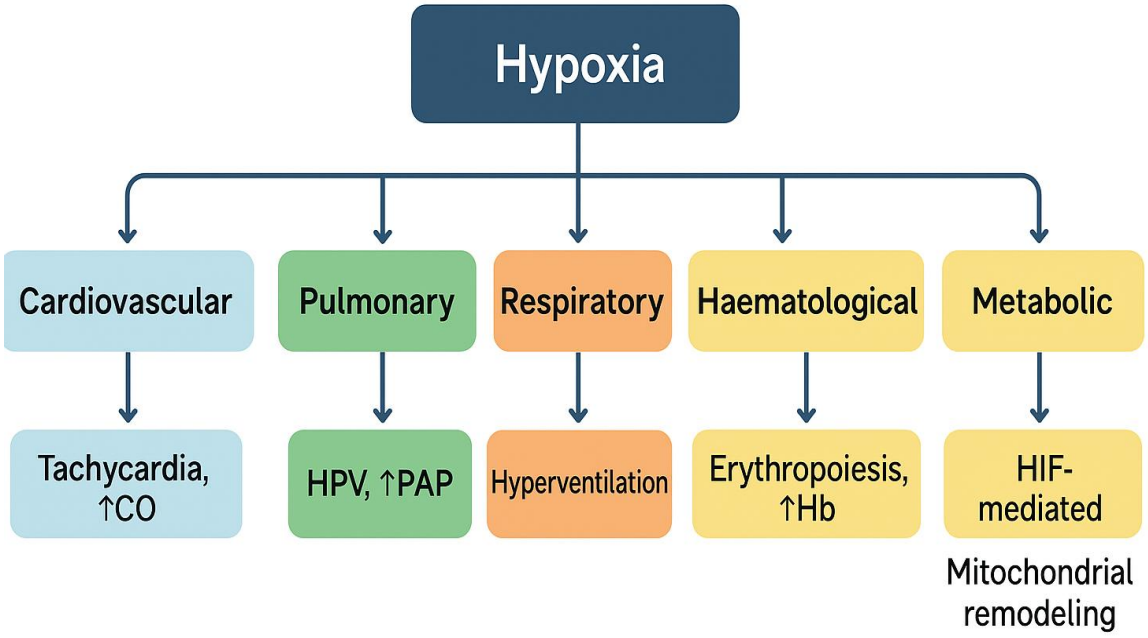

Figure 1. Overview of hypoxia-induced multisystem adaptations in canines.

When there is a reduction of oxygen at the cellular level, the body will no longer rely on oxidative phosphorylation, but rather on anaerobic glycolysis. This transition will be accompanied by an increase in lactate, as well as the activation of enzymes that are responsible for glycolysis. The hypoxia-inducible factors (HIF-1a and HIF-2a) are the key players in this whole process, as they control the expression of a variety of genes that are related to such processes as angiogenesis (e.g., VEGF), the formation of red blood cells, glucose metabolism, and the remodelling of mitochondria all these latter ones are slowly but surely helping the body acclimatize to low oxygen levels in the long run. Haematological responses also raise the oxygen transportation capacity. Renal oxygen deficiency triggers the production of erythropoietin, which results in an increase of red blood cells and haemoglobin concentration [7].

The extreme condition of erythrocytosis, though, besides its helpful aspect, can also result in increased blood viscosity and thus increased cardiac burden. Prolonged hypoxia is a cause of organ system alterations. The heart muscle will be intensively supplied by new capillaries and the existing ones enhanced by good mitochondrial performance, while in the lungs the arteries will get more smooth muscle cells and will be thicker vasculature. There might also be a following response in whole body tissues of stimulating the formation of new mitochondria, as well as changing the mode of metabolism towards one that uses less oxygen and is therefore more efficient. Another aspect of this is that the oxidative stress and the inflammatory signalling will also be influenced by hypoxia and ROS production, which is the case with cellular injury, but at the same time it might also be the case with adaptive preconditioning.

Why Dogs are the best test subjects of Hypoxia

The canines have been known to be very useful models in studying the cardiopulmonary physiology of hypoxia because they are anatomically, physiologically, and behavioural related to humans. Their cardiopulmonary design especially lung volume, airway branching pattern, alveolar structure, and cardiac chamber structure- is very similar to humans and thus any discovery made in canine study is very translatable to clinical and environmental physiology.

The strong cardiovascular system of the canine models can be seen as one of the main benefits of the canine models because it can be used to examine the effects of hypoxia on the cardiac performance in detail. In dogs, autonomic reactions are predictable to low oxygen conditions including sympathetic reactions, tachycardia, and elevated heart output. These reactions reflect the type of reactions in human subjects which means that canine information will be applicable in providing information in the effects of hypoxia on cardiac functions, myocardial metabolism and arrhythmogenic danger [8].

Canine pulmonary responses are similar to human beings as well. In dogs, hypoxic constriction of the pulmonary vasoconstriction (HPV) occurs with the effect of redistributing blood to more ventilated lung areas. These render them suitable in investigating pulmonary hypertension, vascular remodelling, and the dynamics of ventilation-perfusion when hypoxia occurs in an acute and chronic condition. These tools can also be incorporated in their lungs including pulmonary artery catheters, bronchoscopes, arterial blood gases monitoring and high-resolution imaging tools that might be impractical in smaller animal species.

Canines can endure hypoxic conditions which are controlled behaviourally. They are small and easy-tempered enough to be used in normobaric and hypobaric chamber research, one-dimensional treadmill-based exercise hypoxia research, and long-term acclimatization research [9]. German shepherds, labradors, and Huskies are working dog breeds, and all of them have a high aerobic capacity by nature, so they are ideal breeds to investigate exercise induced hypoxia and performance at high altitude.

Moreover, there is plenty of veterinary literature on dog respiratory and cardiovascular disorders, which offers a good starting point when interpreting the results of an experiment. Ethical regulations of the canine research are also there that provide humane research design that involves continuous observation and safeguarding of interventions, which leads to quality research with the provision of high ethics [10].

Together with other physiological similarities to humans, compatibility with complex instruments, predictability in behavioral response, and tolerance to a wide range of hypoxic regimes, canines are uniquely placed in the ideal position to study cardiopulmonary adaptation to hypoxia. Knowledge in the field of canines is used to help in the veterinary health of animals, particularly the high-altitude medicine as well as translational research in biomedics.

Canine Hypoxia types and experimental models.

Veterinary hypoxia incorporates a variety of types of oxygen deprivation that can be experimentally implicated to investigate cardiopulmonary acclimatization. Canines are good models as they possess clear physiological responses, resistance in terms of endurance and the translatability of human medicine. Investigations using experimental models usually focus on acute, chronic, normobaric, hypobaric, and exercise-induced hypoxia, which results in different stressors and adaptation mechanisms.

Acute hypoxia is associated with a sudden reduction in the inspired oxygen using low-FiO2 gas mixtures, simulated altitude or temporary airway obstruction. To maintain oxygen delivery, dogs react with acute response of chemoreceptor-induced hyperventilation, sympathetic arousal, tachycardia, and augmented cardiac output. Squeezing of the pulmonary vessels increases pulmonary artery pressures enhancing V/Q matching but could put stress on the right ventricle [11]. Acute hypoxia models mimic such clinical crises as desaturation caused by anaesthesia and acute airway obstruction.

Sustained exposure of days or weeks to low oxygen causes chronic hypoxia that causes long-term adaptation on the structural or molecular level. HIF-intermediate pathways boost erythropoiesis, boost hemoglobin concentration, stimulate pulmonary vascular remodelling, and stimulate right ventricular

hypertrophy. Metabolic reprogramming too elevates glycolytic reliance or efficiency of the mitochondrion. These are the models that are the focus of the investigation of altitude adaptability, chronic respiratory illness, and progressive cardiopulmonary conditions [12].

Normobaric and hypobaric hypoxia are different in their means of reducing oxygen. Normal pressure hypoxia under normobaric conditions reduces the oxygen concentration, and it is easier and reproducible in the laboratory. Hypobaric hypoxia is used to recreate the effects of an increase in altitude by decreasing the barometric pressure, introducing pressure-related physiological stress, including changes in fluid balance and higher ventilatory rates. Canine research indicates that cardiovascular and ventilatory reactions are enhanced by hypobaric atmospheres, and there is a need to identify the oxygen-specific and altitude-specific effects.

Exercise hypoxia is the condition that is triggered by the physical activity when the demand exceeds the supply of oxygen. In treadmill or endurance models, dogs particularly those that are athletic such as those of the Greyhound breed and the Huskies, show signs of hypoxia because of heightened metabolism, V/Q mismatch, and limitation of diffusion. These models can be applied to evaluate the performance physiology, cardiopulmonary thresholds, myocardial oxygen extraction, and early disease diagnosis. They also correspond to real-life situations associated with working and endurance dogs, which makes them useful in applied and translational studies [13]. Table 1 summarizes the major classifications of hypoxia used in canine experimental models, outlining the method of induction, key physiological responses, and primary research applications for each hypoxic condition.

Table 1. Classification of hypoxia and canine experimental models.

Type of Hypoxia	Method of Induction in Canines	Key Physiological Features	Primary Experimental Use
Acute Hypoxia	Low-FiO2 gas mixtures (10-15 percent), high-rate ascent simulation, acute airway blockage.	Rapid hyperventilation, tachycardia, sympathetic response, hypoxemia, respiratory alkalosis.	Physiology of emergencies, models of anaesthesia desaturation, acute stresses of the lungs.
Chronic Hypoxia	Prolonged hypoxia chambers, intermittent low-FiO2 exposures, simulated high altitude exposure.	Erythropoiesis by EPO, hypertrophy of RV, remodelling of the pulmonary vascular, metabolic reprogramming.	Physiology of altitude, chronic respiratory disease path models, pulmonary hypertension studies.
Normobaric Hypoxia	Less oxygen in ambient conditions at normal barometric pressure in closed chambers.	Hypoxia in the form of oxygen-specific stress without the effects of pressure.	Controlled hypoxia experiments, metabolic and ventilator studies.
Hypobaric Hypoxia	Altitude simulating chambers of low barometric pressure.	High ventilatory drive, Fluid changes, extreme cardiovascular stress.	Adaptation to altitude, pulmonary pressures research, high-altitude medicine.
Exercise-Induced Hypoxia	Treadmill running, interval workloads endurance trials,	Higher demand on metabolism, V/Q mismatch, diffusion impairment, high cardiac output.	Physiology of performance, physiology of working dogs, early warning of cardiopulmonary disease.

Adaptations of the heart to Hypoxia

Hypoxia-dependent cardiac phenotypes in canines are related to a complex of acute and more chronic reactions that maintain myocardial oxygen supply, contractile force, and pump operation in the conditions of reduced oxygen supply. Such physiological adaptations including sympathetic stimulation and metabolic adaptation, structural reorganization and electrophysiological stabilization demonstrate the great cardiopulmonary adaptability of the dog and provide important insights into cardiology, altitude medicine, and critical-care studies in humans.

Sympathetic stimulation is the main cause of acute hypoxic reactions leading to tachycardia, enhanced contractility and heightened cardiac output to sustain oxygen delivery to the body despite

falling PaO2. The redistribution of coronary blood flow to important myocardial areas and the accelerated transition of the heart to glycolytic production of ATP under the catalysis of early HIF-1a occur. Despite the fact that these mechanisms can maintain short-term functionality, they make the body more vulnerable to ischemia in case of constant hypoxia [14].

Chronic hypoxia initiates structural remodelling, the most dramatic of which is right ventricular hypertrophy due to persistent hypertension of the pulmonary and augmentation of afterload. Angiogenesis, increased capillary density, and myocardial extraction is facilitated by angiogenesis, microvascular growth promoted by HIF-VEGF, and oxygen diffusion. Mitochondrial efficiency increases, oxygen use reduces, and the autonomic balance is altered to be more para-sympathetic to reduce the metabolic stress. Table 2 is a comparison of cardiopulmonary response to acute and chronic hypoxia in canines and the differences in the onset, ventilatory drive, cardiac output, myocardial metabolism, and pulmonary vascular adaptation. Figure 2 shows the cascade of adaptations to chronic hypoxia in dogs that is integrated to constitute progressive right ventricular hypertrophy, pulmonary vascular remodelling, and the HIF-mediated molecular pathways.

Table 2. Acute versus chronic hypoxia: comparative cardiopulmonary effects.

Parameter	Acute Hypoxia	Chronic Hypoxia	Mechanistic Basis
Onset & Duration	Minutes to hours	Days to weeks	Difference in exposure time activating rapid vs. genomic pathways
Ventilatory Response	Rapid hyperventilation; respiratory alkalosis	Stabilized ventilation via central acclimatization; increased chemoreceptor sensitivity	Carotid body activation vs. long-term neural adaptation
Cardiac Output	Increases sharply due to sympathetic activation	Moderately elevated or normalized after adaptation	SNS drive vs. autonomic rebalancing
Heart Rate	Tachycardia	Near-normal or slightly elevated	Acute vs. chronic chemoreflex Acute chemoreflex vs. chronic autonomic adjustment.
Myocardial Oxygen Use	Alteration towards glycolysis; low reserves of oxygen.	Improved mitochondrial efficiency; better oxygen extraction	HIF-1 metabolic conversion; mitochondrial remodelling.
Pulmonary Vascular Response	Strong hypoxic pulmonary vasoconstriction (HPV)	Persistent HPV; vascular remodelling, pulmonary hypertension	ROS signaling; smooth muscle proliferation

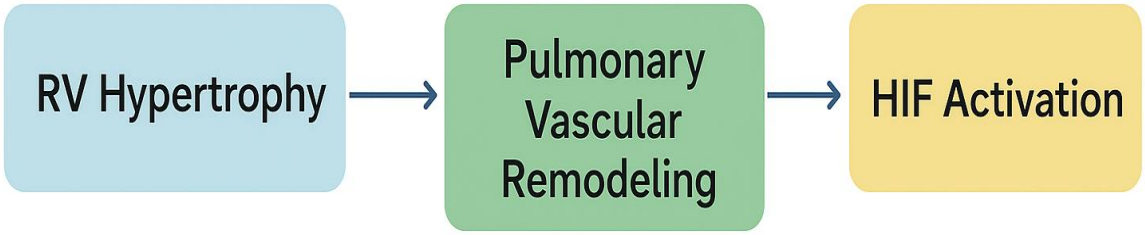

Figure 2. Chronic hypoxia adaptation map: rv hypertrophy, pulmonary vascular remodelling & hif activation.

Some of the electrophysiological changes are initial arrhythmogenic vulnerability (because of the changes in ion channel activity) and subsequently more stable action potential dynamics with long-term exposure. Contractile functioning is restored gradually as mechanisms of calcium handling are adjusted.

Metabolic reprogramming prefers the use of glucose and lactate to fatty acids and enhances the yield of ATP per oxygen molecule as well as the overall energy efficiency. Enhanced resilience is further elevated by the increase of glycogen stores and mitochondrial biogenesis [15].

These canine hypoxia studies are clinically relevant to the management of pulmonary hypertension, right-heart adaptation, ischemic heart disease, and heart failure; diseases in which oxygen constraint is a leading pathophysiological event.

Adaptations of the lungs to Hypoxia

Hypoxia pulmonary adaptation in dogs entails closely coordinated ventilatory, vascular, alveolar and molecular responses which collaborate to maintain gas exchange in the face of a decrease in oxygen supply. Dogs are a good research animal in the study of hypoxia-induced pulmonary physiology because of the high lung capacity, and the effective alveolar architecture. Regardless of hypoxia being acute, chronic, normobaric, hypobaric and exercise-induced, the canine lung triggers activities that improve oxygen uptake, control vascular tone, and homeostasis.

Carotid body-initiated increases in respiratory rate and tidal volume initiate ventilatory responses, which quickly enhance alveolar oxygenation. Acute hyperventilation causes respiratory alkalosis, whereas chronic hypoxia causes central acclimatization stabilizing breathing patterns and sensitivity of chemoreceptors [16].

Pulmonary vascular changes focus on hypoxic pulmonary vasoconstriction (HPV), and it shifts the blood flow to the well-ventilated areas to maximize the match of V/Q. Though it helps in the short term, chronic HPV results in vascular remodelling, pulmonary artery high pressures and finally result in chronic hypoxic pulmonary hypertension associate the pulmonary changes with right heart work. The mechanisms of these effects are ROS signaling, inhibition of potassium channels, and growth of smooth muscles [17].

In response to hyposaline environment, alveolar changes comprise an augmentation in alveolar recruitment and surfactant generation and remodelling of type I and II pneumocytes, each of which raises the diffusion capacity. Prolonged hypoxia induces pulmonary angiogenesis, which increases capillary networks and supplies oxygen to the body and maintains oxygenation.

HIF-1a and HIF-2a prevail in the molecular processes, which govern angiogenesis via VEGF, EPO, metabolic reprogramming, alterations in NO and endothelin, pathways, which affect vascular tone [18].

Ventilatory and Respiratory Responses

The canine body responds to hypoxia at the fastest, dynamic transition, respiratory and ventilatory, which takes place within a few seconds after the level of oxygen in the surroundings is diminished. Carotid body chemoreceptors initiate these responses with falling PaO2, which induce instant changes in breathing to replenish sufficient oxygen supply.

The acute hypoxia causes a fast hyperventilation characterized by elevated respiratory rate and tidal volume. This increases the oxygen tension in the alveoli and increases diffusion across the alveolar-capillary membrane. This leads to respiratory alkalosis that temporarily enhances oxygen loading but may reduce central respiratory drive which needs continuous peripheral chemoreceptor stimulation. Bronchodilation also occurs as a result of acute hypoxia, which lowers airway resistance and enhances airflow [19].

Ventilatory acclimatization occurs because of chronic hypoxia. Eventually, the primary hyperventilation is restored to normalcy as the central chemoreceptors adjust to a new CO2 and pH environment. Peripheral chemoreceptors get sensitized, and they guarantee improved decreases to additional hypoxic periods. The structural changes such as better respiratory muscle endurance, high diaphragmatic oxidative capacity and higher thoracic compliance also facilitate efficient ventilation at sustained low-oxygen levels.

Hypoxia causes an increase in ventilatory requirements during exercise. Canines augment V/Q matching, improve chemoreflex sensitivity, and tend to breath rapidly and shallowly to satisfy high metabolic demands especially in athletic breeds having high V/Q reserves [20].

Haematological Adaptation and Metabolic Adaptation

The adaptation of the haematological and metabolic systems of canines to endure hypoxia is essential to delivery of oxygen and cellular homeostasis in response to extended hypoxia. Those alterations are controlled by hormonal cues and hypoxia-induced gene cascades to promote oxygenation and maximize energy generation in the instances of oxygen scarcity [21].

Haematological Adaptations

This occurs when HIF-2a is activated, and this leads to one of the first responses to long-term exposure to low oxygen: the secretion of erythropoietin (EPO) by the kidneys is increased. Such an increase in EPO subsequently prompts the bone marrow to proliferate more red blood cells, which increases the total red blood cell mass, raises haematocrit and haemoglobin levels, and finally elevates oxygen carrying capacity of blood.

There is also a change in oxygen affinity of haemoglobin as a result of chronic hypoxia.An elevation in the level of 2,3-DPG in the erythrocytes causes the right shift of the oxyhaemoglobin dissociation curve which facilitates the rapid release of oxygen in the tissues. Enhanced microvascular flow is also seen through enhanced RBC deformability [22].

Though an increase in haematocrit raises blood viscosity, vasodilation and a decrease in systemic vascular resistance ensure hemodynamic stability despite the increased blood viscosity.

Metabolic Adaptations

Chronic hypoxia causes a very interesting change in the way the tissues in the dog work making them switch their use of the conventional oxidative phosphorylation to more efficient routes of energy generation. The major role in this is played by HIF-1a, which increases the synthesis of glycolytic enzymes and glucose transporters, thereby increasing aerobic glycolysis and supporting ATP levels.

In response, the mitochondria become more efficient, decrease proton leak, and prefer glucose to fatty acids in maximizing the number of ATPs produced per oxygen molecule consumed. Additionally, the upregulation of monocarboxylate transporters (MCTs) allows for the conversion of lactate into a valuable metabolic substrate, especially in skeletal and cardiac muscle.

Hypoxia also enhances the stability of glycogen in major tissues giving them a ready anaerobic energy supply. Increased antioxidant defense including high levels of superoxide dismutase and catalase limit the oxidative stress of low-oxygen metabolism [23].

Integrated Significance

All these studies taken together allow canines to maintain oxygenation, energy generation and body durability at low oxygen levels. These synchronized responses can be vital to veterinary management of hypoxic responses as well as to use canine models of comparative cardiopulmonary and metabolic studies.

Molecular Processes (HIF Pathways, Gene Regulation)

The pathways of hypoxia-inducible factor (HIF) are implicated in the molecular reactions to hypoxia in dogs and are the principal ones that activate the genes whose expression depends on oxygen. They allow the affected tissues to detect a reduction in oxygen supply and initiate the adaptive transcription programs that guarantee survival and balance the body's physiological processes [24].

The Hypoxia-Inducible Factor (HIF) Signalling Pathway is signalled by hypoxia, including human hypoxic stress, and is regulated by multiple signaling pathways like Myocardial Ischemia/Ischemic Stroke, p304/Hif-alpha, and p164/Hif-2.

At normal oxygenation, HIF-1a and HIF-2a are quickly hydrolysed by enzymes of prolyl hydroxylase domain (PHD) that identifies them as surface targets of the proteasome. The PHD activity is suppressed during hypoxia and allows the stabilization and accumulation of subunits of HIF. These stabilized proteins are transported to the nucleus, dimerize with HIF-b and bind hypoxia response elements (HREs) of target genes [25].

HIF-1a in a dog is primarily involved in the acute response to hypoxia that includes the expression of glycolytic enzymes, glucose transporters and synthesis of angiogenic factors including vascular endothelial growth factor (VEGF). HIF-2a, on the other hand, is more connected to the state of the long term oxygen deficiency that leads to the growth of the erythropoietin (EPO) and the gradual alterations in the vascular and metabolic functions.

Regulation of Genes

Hypoxia affects hundreds of genes in the haematological, metabolic and cardiopulmonary systems.

Key Gene Targets Include

- The Erythropoietin (EPO) that causes the red blood cells to be produced more.
- The angiopoietins and VEGF that stimulate microvascular growth and angiogenesis.
- The synthesis of anaerobic ATP is increased by glycolytic enzymes and GLUT1. Pulmonary vasoconstriction is controlled by Endothelin-1 (ET-1).

Isoforms NOS of nitric oxide synthase change oxidative balance and vascular tone.

Hypoxia as well as canine lung tissue augments the expressions of genes associated with smooth muscle proliferation and this will bring about hypoxic pulmonary vasoconstriction and pulmonary hypertension. The main genes under hypoxia-inducible factor (HIF-1α and HIF-2α) in the heart cells increase the resistance to oxidative stress with the canines and similarly makes the mitochondria to perform optimally [26]. Table 3 lists the key genes regulated by hypoxia-inducible factors (HIF-1α and HIF-2alpha) in canines, and the physiological role and contribution of the genes to the erythropoietic, angiogenic, metabolic, and vascular adaptations in

Table 3. Key hypoxia-inducible factor (HIF)–regulated genes.

Gene / Protein	Regulated By (HIF-1α / HIF-2α)	Physiological Role	Impact on Hypoxic Adaptation in Canines
Erythropoietin (EPO)	HIF-2α	Stimulates production of the RBC	Increases the mass of RBCs, hemoglobin and oxygen transportation capacity.
Vascular Endothelial Growth Factor (VEGF)	HIF-1α	Stimulates angiogenesis and vascular remodelling.	Enlarges capillary plexuses; enhances myocardial and pulmonary oxygenation.
Glucose Transporter-1 (GLUT-1)	HIF-1α	Promotes glucose intake	Stimulates cellular glycolysis via low oxygen; promotes cellular ATP.
Lactate Dehydrogenase-A (LDH-A)	HIF-1α	Converts pyruvate to lactate	Supports anaerobic metabolism during hypoxia
Pyruvate Dehydrogenase Kinase-1 (PDK-1)	HIF-1α	Inhibits mitochondrial pyruvate entry	Reduces oxidative phosphorylation; shifts metabolism toward glycolysis
Endothelin-1 (ET-1)	HIF-1α	Vasoconstrictor regulating vascular tone	Contributes to pulmonary vasoconstriction and pulmonary hypertension
Nitric Oxide Synthase (NOS) Isoforms	HIF-1α	Produces nitric oxide for vascular regulation	Balances vasoconstriction; modulates pulmonary pressures
Transferrin & Transferrin Receptor	HIF-1α / HIF-2α	Iron transport for erythropoiesis	Supports hemoglobin synthesis during chronic hypoxia
Heme Oxygenase-1 (HO-1)	HIF-1α	Antioxidant and cytoprotective enzyme	Reduces oxidative stress; enhances cellular survival

Monocarboxylate Transporters (MCTs)	HIF-1α	Lactate transport across membranes	Supports lactate utilization as an energy substrate

HIF-mediated pathways collectively form a multicellular network of coordinated molecules which help to sustain oxygen delivery, vascular remodelling, metabolic plasticity and cardiopulmonary adjustments. These processes highlight the importance of canines in translational research of hypoxia disorder-related conditions in veterinary medicine and human medicine [27].

Implications in the Clinic and on a Translational Level

Clinical and translational importance of the investigation of hypoxia-impaired cardiopulmonary adaptations in dogs is of considerable clinical and translational importance to veterinary and human medicine. Since the dogs have close physiological, cardiopulmonary and metabolic similarities to human, the findings of the canine hypoxia studies should be used as a leading guide to understanding the illnesses that are typified by the dysfunction of oxygen delivery in the body such as chronic obstructive pulmonary disease (COPD), pulmonary hypertension, congestive heart failure, and altitude illnesses[28].

The identification of hypoxia-related adaptations plays a role in veterinary practice in diagnosing and treating respiratory illnesses, improving anaesthetic practice, and in the explanation of exercise intolerability in working and athletic dogs. Dogs are also used to establish safe exposure limits during a journey by air, altitude field trips and stamina exercises. Further, comprehension of trends in ventilatory drive, erythropoiesis and cardiac remodeling can improve predictive capability of progressive events in chronic cardiopulmonary diseases [29].

Canine hypoxia translationally advances information of the human medicine that has vital insights. Canines are very similar to human reactions to hypoxic pulmonary vasoconstriction, right ventricular adaptation, metabolic reprogramming, and HIF-mediated regulation of the expressions. The fact that dogs resemble humans means that the animals are ideal in assessing the efficacy of pharmacological interventions against pulmonary hypertension, myocardial ischemia, angiogenesis, and metabolic flexibility during hypoxic stress. New treatments, including cardioprotective agents, vasodilators and HIF stabilizers, are also developed based on experimental findings [30].

Furthermore, canine research leads to the development of critical-care interventions, namely, oxygen administration, ventilatory care, and treatment of acute respiratory distress. The canine-based hypoxia research as a cross of veterinary physiology and the human translational research is still influencing our knowledge of oxygen deprivation and its effects on the body, and this research is relevant to species in terms of diagnostics, therapies, and prevention.

LITERATURE GAPS AND FUTURE RESEARCH

Although there have been great breakthroughs in the study of cardiopulmonary adaptations caused by hypoxia in dogs, there are still a number of research gaps. Isolated physiological responses are usually studied whereas there is a lack of integrated, multi-system analysis. The interplay of the cardiovascular, respiratory, metabolic and molecular processes at different levels of hypoxia has not been fully understood. Longitudinal studies of long-term effects of chronic hypoxia including the development of pulmonary hypertension, right ventricular failure, and metabolic dysregulation are also deficient [31].

The other significant limitation is that there is dearth of standardized canine-wild protocols on hypoxia. The differences in the term of hypoxic exposure (normobaric and hypobaric); resting and exercise-induced conditions block the comparability of results. Also, genetically and breed-specific differences in hypoxic tolerance particularly the brachycephalic, working and high altitude-adapted breeds have not been sufficiently investigated.

New technologies provide new opportunities to research in the future. More detailed information about real-time adaptations can be obtained with the use of high-resolution imaging, telemetric monitoring, metabolomics, and gene-expression profiling. By further investigating the molecular regulators other than the HIF pathways, including microRNAs, epigenetic changes and mitochondrial signaling, potential new targets of therapy may be found. Lastly, the translational human-canine models should be developed to improve the interface between veterinary research and human clinical practices to improve the treatment of hypoxia based cardiopulmonary diseases [32].

CONCLUSION

The dog indeed serves as a very informative model for understanding the detailed changes in cardiopulmonary, haematological, metabolic, and molecular aspects that occur during hypoxia exposure. Their similarities in physiology with humans and the fact that they can tolerate hypoxic conditions, help to get important insights about the responses to hypoxia in both short and long term. Throughout the cardiac remodeling, ventilatory responses, pulmonary vascular responses, and the HIF-mediated gene expression, canine studies show that there is a multi-system approach to ensuring that oxygen is delivered to tissues, and that metabolic conditions are maintained in stressful settings.

These results have major implications on veterinary medicine, physiology of high altitudes, as well as, human medicine in a translational manner. There are however still gaps in research that are of importance such as standardized experimental procedures, longitudinal studies and further investigation into breed-specific variability. The further progress in the molecular profiling, imaging, and integrative physiology will help to learn more about hypoxia and develop specific therapies of hypoxia-related disorders. Finally, research using dogs is a fundamental basis to further the cardiopulmonary science of other species.

REFERENCES

1. Ortiz-Prado E, Dunn JF, Vasconez J, Castillo D, Viscor G. Partial pressure of oxygen in the human body: a general review. Am J Blood Res. 2019;9(1):1.
2. Studley WR, Lamanna E, Nold-Petry CA, Qin CX, Bourke JE. Insights from precision-cut lung slices investigating mechanisms and therapeutics for pulmonary hypertension. Respir Res. 2025;26:220.
3. Archer SL, Snary KJ, Bentley RE, Alizadeh E, Weir EK. Hypoxic pulmonary vasoconstriction: an important component of the homeostatic oxygen sensing system. Physiol Res. 2024;73(Suppl 2):S493.
4. Li S, Kim H, Baek SJ. Genetic insights from long-lived mammals: lessons for companion animal aging and health. J Vet Sci. 2025;26(Suppl 1):S5.
5. Dempsey JA, Smith CA. Update on chemoreception: influence on cardiorespiratory regulation and pathophysiology. Clin Chest Med. 2019;40(2):269–83.
6. Dunham-Snary KJ, Wu D, Sykes EA, Thakrar A, Parlow LR, Mewburn JD, et al. Hypoxic pulmonary vasoconstriction: from molecular mechanisms to medicine. Chest. 2017;151(1):181–92.
7. Fu Q, Colgan SP, Shelley CS. Hypoxia: the force that drives chronic kidney disease. Clin Med Res. 2016;14(1):15–39.
8. Shoemaker JK, Gros R. A century of exercise physiology: key concepts in neural control of the circulation. Eur J Appl Physiol. 2024;124(5):1323–36.
9. Bachmann KF, Moller PW, Hunziker L, Maggiorini M, Berger D. Mechanisms maintaining right ventricular contractility-to-pulmonary arterial elastance ratio in VA ECMO: a retrospective animal data analysis of RV–PA coupling. J Intensive Care. 2024;12(1):19.
10. Menard J, Goggs R, Mitchell P, Yang Y, Robbins S, Franklin-Guild RJ, et al. Effect of antimicrobial administration on fecal microbiota of critically ill dogs: dynamics of antimicrobial resistance over time. Anim Microbiome. 2022;4(1):36.
11. Langer T, Santini A, Bottino N, Crotti S, Batchinsky AI, Pesenti A, et al. “Awake” extracorporeal membrane oxygenation (ECMO): pathophysiology, technical considerations, and clinical pioneering. Crit Care. 2016;20(1):150.

12. Almodovar S, Swanson J, Giavedoni LD, Kanthaswamy S, Long CS, Voelkel NF, et al. Lung vascular remodeling, cardiac hypertrophy, and inflammatory cytokines in SHIV nef-infected macaques. Viral Immunol. 2018;31(3):206–22.
13. Taylor CT, Scholz CC. The effect of HIF on metabolism and immunity. Nat Rev Nephrol. 2022;18(9):573–87.
14. Karim S, Chahal A, Khanji MY, Petersen SE, Somers VK. Autonomic cardiovascular control in health and disease. Compr Physiol. 2023;13(2):4493–511.
15. Liu J, Zhou G, Wang X, Liu D. Metabolic reprogramming consequences of sepsis: adaptations and contradictions. Cell Mol Life Sci. 2022;79(8):456.
16. Perez CM, Hazari MS, Ledbetter AD, Haykal-Coates N, Carll AP, Cascio WE, et al. Acrolein inhalation alters arterial blood gases and triggers carotid body-mediated cardiovascular responses in hypertensive rats. Inhal Toxicol. 2015;27(1):54-63.
17. Signori D, Magliocca A, Hayashida K, Graw JA, Malhotra R, Bellani G, et al. Inhaled nitric oxide: Role in the pathophysiology of cardio-cerebrovascular and respiratory diseases. Intensive Care Med Exp. 2022;10(1):28.
18. Ramakrishnan S, Anand V, Roy S. Vascular endothelial growth factor signaling in hypoxia and inflammation. J Neuroimmune Pharmacol. 2014;9(2):142–60.
19. Mouradian GC, Lakshminrusimha S, Konduri GG. Perinatal hypoxemia and oxygen sensing. Compr Physiol. 2021;11(2):1653–77.
20. Pamenter ME, Powell FL. Time domains of the hypoxic ventilatory response and their molecular basis. Compr Physiol. 2016;6(3):1345–85.
21. Lee P, Chandel NS, Simon MC. Cellular adaptation to hypoxia through hypoxia inducible factors and beyond. Nat Rev Mol Cell Biol. 2020;21(5):268–83.
22. Woyke S, Oberacher H, Plunser D, Siebenmann C, Turner R, Regli IB, et al. A new approach to haemoglobin oxygen affinity research at high altitude: determination of haemoglobin oxygen dissociation curves and 2,3-bisphosphoglycerate in an experimental human crossover hypoxic chamber study. Eur J Appl Physiol. 2025:1–6.
23. Ferramosca A, Di Giacomo M, Zara V. Antioxidant dietary approach in treatment of fatty liver: new insights and updates. World J Gastroenterol. 2017;23(23):4146.
24. Bishop T, Ratcliffe PJ. Hypoxia-inducible factor 2α: at the interface between oxygen sensing systems in physiology and pathology. Physiology (Bethesda). 2025.
25. Ortmann BM, Burrows N, Lobb IT, Arnaiz E, Wit N, Bailey PS, et al. The HIF complex recruits the histone methyltransferase SET1B to activate specific hypoxia-inducible genes. Nat Genet. 2021;53(7):1022–35.
26. Alruwaili N, Kandhi S, Sun D, Wolin MS. Metabolism and redox in pulmonary vascular physiology and pathophysiology. Antioxid Redox Signal. 2019;31(10):752–69.
27. Lucas-Cava V, Sánchez-Margallo FM, Moreno-Lobato B, Dávila-Gómez L, Lima-Rodríguez JR, García-Martínez V, et al. Prostatic artery occlusion: initial findings on pathophysiological response in a canine prostate model. Transl Androl Urol. 2022;11(12):1655.
28. Ritter S, Zadik-Weiss L, Almogi-Hazan O, Or R. Cannabis, one health, and veterinary medicine: cannabinoids' role in public health, food safety, and translational medicine. Rambam Maimonides Med J. 2020;11(1):e0006.
29. Divers SJ. Clinical evaluation of reptiles. Vet Clin North Am Exot Anim Pract. 1999;2(2):291–331.
30. Della Rocca Y, Fonticoli L, Rajan TS, Trubiani O, Caputi S, Diomede F, et al. Hypoxia: molecular pathophysiological mechanisms in human diseases. J Physiol Biochem. 2022;78(4):739–52.
31. Thenappan T, Ormiston ML, Ryan JJ, Archer SL. Pulmonary arterial hypertension: pathogenesis and clinical management. BMJ. 2018;360.
32. Serocki M, Bartoszewska S, Janaszak-Jasiecka A, Ochocka RJ, Collawn JF, Bartoszewski R. miRNAs regulate the HIF switch during hypoxia: a novel therapeutic target. Angiogenesis. 2018;21(2):183–202.

