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Надійшла: 22.01.2023

Прийнята: 15.03.2023

DOI: <https://doi.org/10.26641/1997-9665.2023.1.84-97>

UDC: 616.12:616.12-008.331.45

HYPOXIA IN CARDIOGENESIS OF RATS

Kobeza P.A.   **Hypoxia in cardiogenesis of rats.**

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ABSTRACT. Background. Hypoxia during early stages of cardiogenesis in rats causes complications in the functional development of cardiomyocytes. Cardiogenesis under hypoxia refers to the process of generating new cardiac cells or cardiomyocytes in response to low oxygen levels or hypoxia. This process occurs as a means of adaptation of the heart to support its function in conditions of reduced oxygen supply. Hypoxia can activate certain signaling pathways such as the hypoxia-inducible factor (HIF) pathway. **Objective.** To determine hypoxia as a general complicated state. To identify factors that cause this condition. To provide a characterization of complications and ways of their progressive development in different regions of the heart during early ontogenesis. Understanding the causes and mechanisms of hypoxia is crucial for developing effective methods of detecting this pathological and functional state of myocardial cells in rats. **Methods.** Systematic literature review, meta-analysis, content analysis. **Results.** The main types of hypoxia and their influence on the structure and development of rat myocardium are presented. The process of development of myofibrils and mitochondria in different zones of the myocardium during ontogenesis is described in detail. **Conclusions.** The use of histological methods on animal models can provide an understanding of the mechanisms underlying cardiogenesis under hypoxia and can help in developing effective methods of diagnosing the effects of low oxygen levels on the process of formation of cardiac muscle tissue.


Key words: cardiomyocyte, contractile apparatus, sarcomere, hypoxia, cardiogenesis in prenatal ontogenesis of rats.

Citation:

Kobeza PA. Hypoxia in cardiogenesis of rats. *Morphologia*. 2023;17(1):84-97.

DOI: <https://doi.org/10.26641/1997-9665.2023.1.84-97>

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Background

Hypoxia-induced cardiogenesis refers to the process of generating new cardiac cells or cardiomyocytes in response to low oxygen levels, or hypoxia. This process occurs as a means of adaptation by the heart to maintain its function under conditions of reduced oxygen supply. Hypoxia can activate certain signaling pathways, such as the hypoxia-inducible factor (HIF) pathway, which can lead to the differentiation of stem cells into cardiomyocytes. The HIF pathway is a transcriptional regulator that controls the expression of genes involved in angiogenesis, metabolism, and cell survival. Additionally, hypoxia can also induce the proliferation of pre-existing cardiomyocytes, as well as the activation of resident cardiac stem cells. These cells can differentiate into cardiomyocytes and contribute to the regeneration of damaged or injured cardiac tissue.

Overall, hypoxia-induced cardiogenesis is a complex process that involves the activation of multiple signaling pathways and the differentiation of various cell types. Hypoxia is a condition that occurs when there is a reduced level of oxygen supply to the tissues of the body, including the myocardium. The most common definition of hypoxia is a state in which the oxygen supply to the tissues is insufficient to meet the metabolic demands of the cells [1].

Hypoxia can be caused by a variety of factors, including decreased blood flow to the tissues, reduced oxygen-carrying capacity of the blood, or decreased oxygen concentration in the air. In the case of the myocardium, hypoxia can result from coronary artery disease, which limits blood flow to the heart muscle, or from heart failure, which reduces the ability of the heart to pump blood effectively [2].

Factors that can influence the development of hypoxia include altitude, smoking, carbon monoxide exposure, and certain medical conditions such as anemia and chronic obstructive pulmonary disease (COPD) [3]. Additionally, hypoxia can occur as a result of physical exertion or high-intensity exercise, which can increase the demand for oxygen by the body.

Purpose

Hypoxia is a condition that occurs when the body or tissues do not receive enough oxygen to meet their metabolic demands. The most common definition of hypoxia is a state of insufficient oxygenation of tissues, which can lead to cellular damage and impaired function [4]. Hypoxia can be caused by a variety of factors, including reduced oxygen levels in the environment, respiratory diseases that impair oxygen exchange, cardiovascular diseases that decrease blood flow and oxygen delivery to tissues, anemia or other blood disorders that reduce the oxygen-carrying capacity of blood, and exposure to toxins or drugs that interfere with oxygen utilization [5]. Factors that can influence the development of hypoxia include altitude, smoking, carbon monoxide exposure, and certain medical conditions such as chronic obstructive pulmonary disease (COPD), asthma, or congestive heart failure. Altitude hypoxia occurs due to decreased barometric pressure and oxygen levels at high altitudes, which can lead to altitude sickness and impaired physical performance. Smoking and carbon monoxide exposure impair the ability of red blood cells to transport oxygen, leading to tissue hypoxia. COPD and asthma can cause chronic or acute respiratory failure, which impairs oxygenation of the blood and tissues. Congestive heart failure reduces the cardiac output, resulting in inadequate oxygen delivery to the tissues [6].

Objective

To determine hypoxia as a general complicated state. To identify factors that cause this condition. To provide a characterization of complications and ways of their progressive development in different regions of the heart during early ontogenesis. Understanding the causes and mechanisms of hypoxia is crucial for developing effective methods of detecting this pathological and functional state of myocardial cells in rats. This process has significant implications for the development of therapies for cardiovascular disease and cardiac regeneration. In addition to these factors, hypoxia can be exacerbated by physical exertion, which increases the oxygen demand of tissues, and by pre-existing medical conditions that impair the body's ability to compensate for reduced oxygen levels. The severity and duration of hypoxia depend on the underlying cause and the duration of exposure to the hypoxic environment or conditions [7]. Overall, hypoxia is a complex physiological condition that can result from a variety of factors and can affect different tissues and organs in differ-

ent ways. Understanding the causes and mechanisms of hypoxia is critical for the development of effective treatments for the various diseases that can lead to tissue hypoxia.

Methods and materials

When writing an analytical scientific article based on the analysis of scientific articles, it is important to use appropriate research methods to ensure that the article is well-supported and credible. Here are some methods that can be used:

1. Systematic literature review: This method involves conducting a comprehensive and structured search of relevant literature in order to identify and analyze all available evidence on a particular topic [8]. This helps ensure that all relevant literature is included in the analysis and can help to identify any gaps in knowledge or inconsistencies in the existing literature.

2. Meta-analysis: This method involves using statistical techniques to combine and analyze data from multiple studies in order to generate more robust conclusions about a particular topic [9]. This method is particularly useful when there are multiple studies on a topic with conflicting results.

3. Content analysis: This method involves analyzing the content of scientific articles, identifying themes, patterns, and relationships among variables that may impact the development of the heart [10].

4. When analyzing the literature, it is important to consider the relevance and quality of the sources. It is best to analyze scientific articles that are peer-reviewed and published in reputable scientific journals. Additionally, it is important to consider the date of publication, as older articles may not reflect the most current knowledge on the topic.

5. There are several databases and websites that can be used to search for relevant scientific literature, such as PubMed [11], ScienceDirect [12], and Google Scholar [13]. It is also useful to search the reference lists of relevant articles to identify additional sources of information. More references can be found by consulting the bibliographies of articles found through these search methods and by exploring related topics.

Results

There are several types of hypoxia that can occur in the body. These include hypoxic hypoxia, anemic hypoxia, ischemic hypoxia, and histotoxic hypoxia. Hypoxic hypoxia occurs when the body tissues do not receive enough oxygen due to reduced oxygen levels in the environment or decreased lung function. This type of hypoxia can occur at high altitudes or in areas with low oxygen levels. It can also occur in conditions such as pneumonia, pulmonary fibrosis, and acute respiratory distress syndrome (ARDS), where the lungs are unable to adequately exchange oxygen and carbon dioxide.

Anemic hypoxia occurs when there is a decrease in the oxygen-carrying capacity of the blood due to reduced hemoglobin levels or abnormal he-

moglobin function. This can occur in conditions such as anemia, carbon monoxide poisoning, or sickle cell disease. In anemia, there are fewer red blood cells to carry oxygen, while in carbon monoxide poisoning, the carbon monoxide molecule binds to hemoglobin, preventing it from carrying oxygen. In sickle cell disease, the abnormal hemoglobin molecule causes the red blood cells to become misshapen and unable to carry oxygen efficiently [15].

Ischemic hypoxia occurs when there is a reduction in blood flow to the tissues, leading to a lack of oxygen delivery. This can occur in conditions such as heart disease, where the blood vessels supplying the heart muscle become narrowed or blocked, reducing blood flow and oxygen delivery. It can also occur in conditions such as stroke or peripheral arterial disease, where the blood flow to the brain or limbs is reduced, leading to tissue damage and hypoxia [16].

Histotoxic hypoxia occurs when the tissues are unable to use the oxygen that is delivered to them due to damage to the cells or mitochondria. This can occur in conditions such as cyanide poisoning, where the cyanide molecule prevents the mitochondria from using oxygen to produce energy [17].

Understanding the different types of hypoxia is important for diagnosing and treating the underlying causes of tissue hypoxia. Treatment strategies may vary depending on the type and severity of hypoxia, and may include supplemental oxygen therapy, medications, or surgical interventions.

Each type of hypoxia is associated with a specific mechanism and can cause different complications. Hypoxemic hypoxia occurs with low oxygen levels in the atmospheric air or due to respiratory system disorders. Anemic hypoxia is linked to a deficiency of hemoglobin or red blood cells in the blood, leading to decreased oxygen-carrying capacity [18]. Ischemic hypoxia occurs due to inadequate blood supply to tissues, leading to insufficient oxygen delivery to the body [19]. Toxic hypoxia is associated with a disturbance in the body's ability to process oxygen, such as from exposure to toxins or gases like carbon monoxide [20]. Histotoxic hypoxia arises from impairment of tissue's ability to utilize oxygen due to damage to mitochondria or blocking enzyme action [21].

Different types of hypoxia can lead to complications in different systems of the body. One of the most severe complications is damage to the cardiovascular system. Hypoxia may result in cardiac arrhythmias, hypertension, decreased myocardial contractility, and heart failure [22].

Hypoxia, a condition characterized by a lack of adequate oxygen supply to tissues, can result in a wide range of complications, many of which are associated with the cardiovascular system. One of the most serious complications of hypoxia is damage to the cardiovascular system, which can lead to a range of conditions, including arrhythmias, hyper-

tension, impaired myocardial contractility, and heart failure.

Hypoxia-induced arrhythmias can be caused by a range of mechanisms, including increased activity of the sympathetic nervous system, changes in ion channel activity, and alterations in calcium homeostasis. These arrhythmias can be life-threatening, particularly in the context of acute myocardial infarction and other forms of ischemic heart disease [23].

Hypoxia can also result in hypertension, or high blood pressure, due to activation of the renin-angiotensin-aldosterone system and increased levels of endothelin-1, a potent vasoconstrictor. Chronic hypoxia has been shown to be a risk factor for the development of pulmonary hypertension, which can lead to right ventricular hypertrophy and eventually heart failure [24]. Impaired myocardial contractility is another common complication of hypoxia, particularly in the setting of acute respiratory distress syndrome (ARDS) and sepsis. This impairment is thought to be due to alterations in cellular metabolism, changes in intracellular calcium handling, and the activation of pro-inflammatory cytokines. In severe cases, this impairment can progress to cardiogenic shock and multi-organ failure. Finally, hypoxia can lead to the development of heart failure, a condition in which the heart is unable to pump enough blood to meet the body's needs. This can occur due to a range of factors, including impaired myocardial contractility, increased afterload, and the development of pulmonary hypertension. Chronic hypoxia, particularly in the setting of obstructive sleep apnea, has been identified as a risk factor for the development of heart failure [25]. In conclusion, hypoxia can result in a range of cardiovascular complications, including arrhythmias, hypertension, impaired myocardial contractility, and heart failure [26]. These complications can be life-threatening and require prompt diagnosis and treatment [27].

Each type of hypoxia can have different effects on the development and formation of the heart. Hypoxemic hypoxia, caused by low oxygen levels in the air, can lead to abnormalities in the formation of the cardiac muscle and an increase in pulmonary artery pressure [28]. This can result in congenital heart defects such as ventricular septal defects or pulmonary artery hypoplasia [29]. Anemic hypoxia, caused by insufficient hemoglobin in the blood, can lead to delayed heart development and insufficient erythrocytes, which can result in various heart defects [30]. Ischemic hypoxia, arising from impaired tissue blood supply, can lead to delayed heart development and damage to the cardiac muscle. This can cause heart failure and various heart defects, such as pulmonary artery atresia and ventricular septal defects [31].

Toxic hypoxia, caused by impaired organismal ability to process oxygen, can lead to cardiac muscle damage and congenital heart defects. For example,

hypoxia caused by nitric oxide poisoning can result in heart defects in the fetus [32]. Histotoxic hypoxia, caused by impaired tissue oxygen utilization, can lead to cardiac muscle damage and heart defects such as pulmonary artery atresia [33]. Overall, hypoxia can cause various complications in the development and formation of the heart, depending on its type and severity.

Hypoxia can have different effects on the formation and development of the myocardium at different stages of embryonic and fetal heart development. During the early stages of heart development, hypoxia can disrupt the formation of the heart tube, which is the precursor to the heart chambers. Studies have shown that hypoxia during this stage can lead to abnormal cardiac looping, which is the process by which the heart tube forms a looped structure that eventually gives rise to the four chambers of the heart [34]. Hypoxia during this stage can also lead to decreased proliferation of cardiac progenitor cells, which can impair heart growth and development [35].

During later stages of heart development, hypoxia can also have negative effects on the myocardium. For example, studies have shown that hypoxia during the fetal period can lead to alterations in the structure and function of the heart. One study found that fetal hypoxia led to decreased left ventricular mass and increased left ventricular wall thickness [36]. Another study found that hypoxia during the fetal period led to increased apoptosis and decreased proliferation of cardiomyocytes, which can impair the growth and function of the myocardium [37]. Overall, hypoxia can have negative effects on the formation and development of the myocardium at different stages of embryonic and fetal heart development, which can lead to congenital heart defects and other cardiovascular complications.

Hypoxia can have a significant impact on the development of the ventricles of the heart in embryos and fetuses. Studies have shown that hypoxia during the early stages of heart development can result in delayed ventricular maturation, decreased ventricular cell proliferation, and increased apoptosis, or cell death [38]. In particular, hypoxia during the critical period of ventricular septation, which occurs between days 27 and 37 of human embryonic development, can lead to abnormalities in the formation of the ventricular septum and the valves of the heart [39]. This can result in congenital heart defects such as ventricular septal defects and atrio-ventricular septal defects.

Hypoxia can also affect the development of the left and right ventricles differently. For example, studies in animal models have shown that hypoxia during fetal development can result in decreased left ventricular mass and volume, but increased right ventricular mass and volume [40]. This can result in altered ventricular function and blood flow, which can lead to various heart conditions later

in life.

Hypoxia can have a significant impact on the development of the ventricles of the heart, particularly during critical periods of embryonic and fetal development. This highlights the importance of maintaining adequate oxygen levels during pregnancy to minimize the risk of congenital heart defects and other heart conditions.

The left ventricle is responsible for pumping oxygen-rich blood to the rest of the body. Hypoxia can affect its development and formation in various ways. During the embryonic period, hypoxia can lead to delayed growth and development of the left ventricle. This can result in smaller size, reduced thickness of the ventricular wall, and altered gene expression patterns [41]. In the fetal period, hypoxia can result in changes in the structure and function of the left ventricle. For example, chronic hypoxia can lead to an increase in the size and mass of the left ventricle, as well as changes in its shape and geometry. These changes are thought to be adaptations to increase oxygen delivery to the body under hypoxic conditions. However, excessive hypoxia can also lead to pathological changes in the left ventricle. For example, studies have shown that hypoxia can cause oxidative stress and inflammation in the left ventricle, leading to fibrosis and impaired contractile function [42]. Overall, hypoxia can affect the development and formation of the left ventricle in complex ways, with both adaptive and pathological effects depending on the timing and severity of the hypoxic insult [43].

Hypoxia can also have a significant impact on the development and formation of the right ventricle. The right ventricle is responsible for pumping deoxygenated blood from the heart to the lungs for oxygenation [44]. Studies have shown that hypoxia during fetal development can lead to abnormalities in the formation of the right ventricle. For example, research has found that prenatal hypoxia can result in reduced size and delayed development of the right ventricle, as well as changes in the structure of the right ventricular myocardium [45]. Hypoxia can also lead to changes in the pulmonary vasculature, which can affect the function of the right ventricle [46]. For instance, studies have suggested that prenatal hypoxia can cause a decrease in the number of pulmonary arteries, as well as an increase in the thickness of the pulmonary artery walls, which can impair blood flow to the lungs and place additional strain on the right ventricle [47]. In severe cases, hypoxia can lead to right heart failure, which can be life-threatening. Overall, hypoxia can have a significant impact on the development and formation of the right ventricle and can lead to long-term health consequences [48].

The atria are the upper chambers of the heart that receive blood from the veins and pump it into the ventricles. The development of the atria is also affected by hypoxia, which can lead

to various abnormalities. In hypoxemic hypoxia, where there is low oxygen levels in the air, the formation of the atria can be impaired. Studies have shown that hypoxia can lead to an increase in pulmonary artery pressure, which can cause a delay in the formation of the atrial septum, the wall that separates the left and right atria [49].

Anemic hypoxia, caused by insufficient hemoglobin in the blood, can also affect the development of the atria. It can lead to a decrease in the number of erythrocytes, which can result in various heart defects, including atrial septal defects [50]. Ischemic hypoxia, arising from impaired tissue blood supply, can lead to damage to the atrial muscle, which can result in atrial fibrillation, a type of irregular heart-beat. Ischemic hypoxia can also cause delayed atrial development and abnormalities in the formation of the atrial septum. Toxic hypoxia, caused by impaired organismal ability to process oxygen, can also affect the formation of the atria. For example, exposure to carbon monoxide can lead to heart defects such as atrial septal defects and patent foramen ovale. In summary, hypoxia can have various effects on the development and formation of the atria, depending on its type and severity. It can lead to delays in development, damage to the cardiac muscle, and various heart defects, including atrial septal defects and atrial fibrillation [51].

Hypoxia can have various effects on the development and formation of the left atrium of the heart, depending on its type and severity. One study found that exposure to chronic hypoxia during fetal development can lead to structural and functional changes in the left atrium, such as an increase in wall thickness and a decrease in the size of the atrial cavity [52]. Another study showed that hypoxia during fetal development can lead to a decrease in the number of cardiomyocytes in the left atrium, which can affect its contractile function [53]. Furthermore, hypoxia can affect the development and formation of the left atrium through its effects on the pulmonary veins. The pulmonary veins are the vessels that bring oxygenated blood from the lungs to the left atrium, and abnormalities in their development can lead to various heart defects. One study found that exposure to hypoxia during fetal development can lead to abnormal development of the pulmonary veins, which can result in pulmonary vein stenosis, a condition in which the pulmonary veins are narrowed and blood flow is restricted. Overall, hypoxia can have significant effects on the development and formation of the left atrium of the heart, which can lead to various structural and functional abnormalities and heart defects [54].

Similar to the left atrium, hypoxia can also affect the development and formation of the right atrium. Studies have shown that the right atrium is more susceptible to hypoxic damage compared to the left atrium due to differences in their embryological origins and blood supply [55]. During fetal de-

velopment, the right atrium receives deoxygenated blood from the superior and inferior vena cava.

Hypoxia can lead to a decrease in the oxygen content of this blood, which can then affect the formation and function of the right atrium. Studies on animal models have shown that hypoxia during fetal development can lead to a decrease in the size of the right atrium and thinning of its walls, as well as a decrease in the number of cardiomyocytes [55]. Hypoxia can also result in an altered expression of genes involved in the development and differentiation of cardiomyocytes, leading to defects in the formation of the right atrium. In humans, hypoxia can result in various congenital heart defects involving the right atrium, such as atrial septal defects and Ebstein's anomaly. Atrial septal defects are characterized by a hole in the atrial septum that separates the right and left atria, which can result in abnormal blood flow and lead to symptoms such as fatigue and shortness of breath. Ebstein's anomaly is a rare heart defect characterized by malformation of the tricuspid valve and displacement of the leaflets into the right ventricle. This can lead to blood flow abnormalities, right heart enlargement, and heart failure. Hypoxia can have significant effects on the development and formation of the right atrium, leading to various congenital heart defects and alterations in its structure and function [56].

Hypoxia can have a significant impact on the formation and development of the heart septum, which separates the left and right sides of the heart. The heart septum is formed through a complex process of growth, folding, and fusion of different structures in the developing heart, and any disruption in this process can lead to septal defects. Studies have shown that hypoxia can cause abnormalities in the formation of the heart septum. In particular, hypoxia during early fetal development has been associated with an increased risk of atrial and ventricular septal defects. Hypoxia can also affect the growth and differentiation of the cells that contribute to the formation of the septum, leading to structural abnormalities and defects [57].

Moreover, hypoxia can affect the expression of genes that are involved in the formation of the heart septum. For example, hypoxia has been shown to downregulate the expression of genes that are important for septum formation, such as *Gata4* and *Tbx5* [58]. These genes play key roles in regulating the development of the heart septum, and their dysregulation can lead to septal defects. Overall, hypoxia can have a significant impact on the formation and development of the heart septum, leading to structural abnormalities and defects that can have serious consequences for cardiac function and overall health.

There are several methods for studying the effect of hypoxia on the myocardium, including in vivo, ex vivo, and in vitro methods.

1. In vivo methods: In vivo methods involve the

study of hypoxia on the myocardium in living animals or humans. This can be achieved through various techniques, including cardiac imaging, electrocardiography (ECG), and blood gas analysis. These methods allow for the direct observation of the effects of hypoxia on the heart in real-time. One example is the use of cardiac magnetic resonance imaging (MRI) to assess changes in cardiac structure and function in response to hypoxia [49].

2. *Ex vivo* methods: *Ex vivo* methods involve the study of hypoxia on the myocardium in isolated heart preparations. This can be achieved by perfusing the heart with an oxygen-depleted solution or by placing the heart in a hypoxic chamber. *Ex vivo* methods allow for precise control over the oxygen levels and other experimental conditions. One example is the Langendorff perfusion system, which is commonly used to study the effects of hypoxia on isolated hearts [50].

3. *In vitro* methods: *In vitro* methods involve the study of hypoxia on isolated cardiac cells or tissue samples. This can be achieved through various techniques, including cell culture and organotypic slice cultures. *In vitro* methods allow for the study of the direct effects of hypoxia on specific cell types or tissues. One example is the use of neonatal rat ventricular myocytes in culture to study the molecular mechanisms underlying the response of the heart to hypoxia [51].

Overall, each of these methods has its advantages and disadvantages, and the choice of method will depend on the specific research question and experimental design. By using multiple methods in combination, researchers can gain a more comprehensive understanding of the effects of hypoxia on the myocardium.

Histological methods are widely used for studying hypoxia-induced cardiogenesis as they allow for the visualization of the tissue structure of the heart under hypoxic conditions. Here are some commonly used histological methods and their descriptions:

1. Hematoxylin and Eosin (H&E) staining: H&E staining is a commonly used technique that stains the nuclei of cells blue and the cytoplasm pink, allowing for the visualization of the general tissue structure of the heart. This staining method highlights the size, shape, and number of cells in the heart tissue under hypoxic conditions [52].

2. Masson's trichrome staining: Masson's trichrome staining is used to visualize collagen fibers in the heart tissue, and is particularly useful for detecting fibrotic changes in the heart under hypoxia conditions. This method highlights collagen fibers as blue, making it possible to quantify the degree of fibrosis in the tissue [53].

3. Periodic Acid-Schiff (PAS) staining: PAS staining is used to detect glycogen in the heart tissue, which can be altered under hypoxic conditions. This staining method allows for the visualization of

the extent of glycogen content in the heart tissue, as under hypoxia there is a decrease in glycogen content [54].

4. Immunohistochemistry (IHC): IHC involves using antibodies to label specific proteins present in the heart tissue. IHC can be used to detect changes in the expression of specific proteins under hypoxic conditions, such as the expression of hypoxia-inducible factor 1- α (HIF-1 α), which is a key regulator of the cellular response to hypoxia. IHC can also be used to quantify the extent of cell death (apoptosis) in the heart tissue [55].

5. Transmission electron microscopy (TEM): TEM allows for the observation of ultrastructural changes in the heart tissue under hypoxic conditions. TEM can be used to detect changes in the size, shape, and number of mitochondria in the heart tissue, as well as changes in the organization of myofibrils [56].

These histological methods provide valuable information about the structural and cellular changes that occur in the heart tissue under hypoxic conditions. Combining these methods with other techniques, such as gene expression analysis, can provide a more comprehensive understanding of the mechanisms underlying hypoxia-induced cardiogenesis.

Immunohistochemistry (IHC) is a widely used technique for studying the expression and localization of proteins in tissues. It involves the use of antibodies that bind to specific proteins and can be visualized using various methods, such as enzymatic or fluorescent staining. IHC can provide valuable information about the cellular response to hypoxia in the heart tissue. Here are some commonly used immunohistochemical methods for studying hypoxia-induced cardiogenesis:

1. Hypoxia-inducible factor 1- α (HIF-1 α) staining: HIF-1 α is a transcription factor that plays a central role in the cellular response to hypoxia. Under normoxic conditions, HIF-1 α is rapidly degraded, but under hypoxic conditions, it accumulates in the cell and translocates to the nucleus, where it activates the expression of genes involved in the adaptive response to hypoxia. IHC can be used to detect changes in HIF-1 α expression and localization in the heart tissue under hypoxic conditions [57].

2. Apoptosis detection: Hypoxia can induce cell death (apoptosis) in the heart tissue. IHC can be used to detect the presence of apoptotic cells in the heart tissue by labeling them with antibodies specific to cleaved caspase-3, a marker of apoptosis. The number of apoptotic cells can be quantified using image analysis software [58].

3. Fibrosis detection: Fibrosis is a common feature of the heart tissue under hypoxic conditions. IHC can be used to detect the presence of fibrotic tissue by labeling it with antibodies specific to collagen I and III. The degree of fibrosis can be quantified by measuring the amount of collagen staining in

the tissue [59].

4. **Angiogenesis detection:** Hypoxia can induce the formation of new blood vessels in the heart tissue, a process called angiogenesis. IHC can be used to detect the presence of endothelial cells, the cells that line blood vessels, by labeling them with antibodies specific to CD31 or von Willebrand factor (vWF) [60].

5. **Inflammation detection:** Hypoxia can also induce inflammation in the heart tissue. IHC can be used to detect the presence of immune cells, such as macrophages and T cells, by labeling them with antibodies specific to CD68 and CD3, respectively [61].

These immunohistochemical methods can provide valuable information about the cellular and molecular changes that occur in the heart tissue under hypoxic conditions. Combining these methods with other techniques, such as gene expression analysis, can provide a more comprehensive understanding of the mechanisms underlying hypoxia-induced cardiogenesis.

Experimental animal models are widely used to investigate the mechanisms underlying hypoxia-induced cardiogenesis. Here are some commonly used animal models for studying hypoxia-induced cardiogenesis:

1. **Rodent models:** Rodents, such as mice and rats, are commonly used for studying hypoxia-induced cardiogenesis due to their small size, low cost, and relatively short lifespan. These models involve exposing the animals to hypoxic conditions, either by reducing the oxygen concentration in the air or by subjecting them to high-altitude conditions. The degree of hypoxia and the duration of exposure can be adjusted to study different aspects of hypoxia-induced cardiogenesis, such as changes in cardiac structure, function, and gene expression [62].

2. **Canine models:** Dogs are also used as animal models for studying hypoxia-induced cardiogenesis due to their similarities to humans in terms of cardiac structure and function. These models involve subjecting the animals to hypoxia either by reducing the oxygen concentration in the air or by inducing pulmonary hypertension. Canine models are particularly useful for studying the effects of hypoxia on cardiac electrophysiology and arrhythmias [63].

3. **Swine models:** Pigs are often used as animal models for studying the effects of hypoxia on cardiac function and remodeling due to their similarities to humans in terms of cardiac structure and size. These models involve exposing the animals to hypoxia either by reducing the oxygen concentration in the air or by inducing pulmonary hypertension. Swine models are particularly useful for studying the effects of hypoxia on myocardial metabolism and substrate utilization [64].

4. **Zebrafish models:** Zebrafish are increasingly being used as animal models for studying hypoxia-

ia-induced cardiogenesis due to their genetic tractability and ability to regenerate their heart tissue. These models involve exposing the animals to hypoxia either by reducing the oxygen concentration in the water or by inducing anemia. Zebrafish models are particularly useful for studying the effects of hypoxia on cardiac regeneration and repair [65].

These animal models provide valuable tools for investigating the mechanisms underlying hypoxia-induced cardiogenesis. By combining these models with histological and molecular techniques, researchers can gain a better understanding of the cellular and molecular pathways that are activated in response to hypoxia.

Experimental representation of hypoxia-induced cardiogenesis in models of laboratory rats of the Wistar line under the influence of 1% sodium nitrite. Hypoxia-induced cardiogenesis can be studied in laboratory rat models of the Wistar line that are modeled with sodium nitrite. Sodium nitrite is a potent inducer of hypoxia and can be used to create a hypoxic environment in rats. The Wistar rat is a commonly used laboratory rat strain and is well characterized for studying cardiovascular physiology and disease [66]. This model has been used to study the effects of hypoxia on the heart and to investigate potential mechanisms underlying hypoxia-induced cardiogenesis. To create a model of hypoxia-induced cardiogenesis, Wistar rats are exposed to sodium nitrite in drinking water, which causes a decrease in oxygen delivery to the tissues and simulates a hypoxic environment. This leads to changes in cardiac function and structure, including an increase in heart weight and a decrease in ventricular function [67]. The model can be used to investigate the molecular and cellular mechanisms underlying hypoxia-induced cardiogenesis, as well as potential therapeutic interventions. The use of this model has led to the identification of various pathways and molecules that play a role in hypoxia-induced cardiogenesis. For example, one study found that hypoxia-inducible factor-1 alpha (HIF-1 α) plays a critical role in the development of hypoxia-induced cardiac hypertrophy in Wistar rats exposed to sodium nitrite [68]. Another study found that the activation of the Notch signaling pathway is involved in the regulation of angiogenesis and the response to hypoxia in the hearts of Wistar rats exposed to hypoxia [69]. In summary, the use of laboratory rat models of the Wistar line that are modeled with sodium nitrite provides a useful tool for studying hypoxia-induced cardiogenesis. This model can be used to investigate the molecular and cellular mechanisms underlying hypoxia-induced cardiac dysfunction, as well as potential therapeutic interventions.

Hypoxia-induced cardiogenesis in lab rats can be modeled using sodium nitrite administration. Sodium nitrite is a potent vasodilator that can cause a decrease in systemic oxygen delivery and result in hypoxia. Several animal models have been

used to study hypoxia-induced cardiogenesis using sodium nitrite in lab rats.

One of the animal models that have been used is the Wistar rat. Wistar rats have been widely used in biomedical research, and their genetic homogeneity and susceptibility to experimental conditions make them a popular choice for modeling human diseases. In one study, Wistar rats were treated with sodium nitrite to induce systemic hypoxia, resulting in cardiac injury and remodeling [71]. Another study found that Wistar rats treated with sodium nitrite showed increased levels of oxidative stress and inflammation in the heart tissue [72].

In another animal model, male Sprague-Dawley rats were treated with a single dose of sodium nitrite, resulting in acute hypoxia. The study found that hypoxia led to cardiac injury and increased expression of hypoxia-inducible factor 1- α (HIF-1 α) and vascular endothelial growth factor (VEGF), both of which are involved in the cellular response to hypoxia [73]. These animal models provide valuable information about the mechanisms underlying hypoxia-induced cardiogenesis and the potential therapeutic targets for treating hypoxia-induced cardiac injury.

The current state of morphological studies of the development of the myocardium in the morphological studies of Ukrainian morphologists. In recent years, there has been significant research interest in understanding the ultrastructure of the mitochondrial apparatus in cardiomyocytes and its changes under various conditions. Several studies have been conducted on this topic, which shed light on the morphological features of cardiomyocyte development and the effects of hypoxia, hypothyroidism, and electromagnetic radiation exposure.

Kosharnyi et al. (2019) investigated the ultrastructure of the mitochondrial apparatus in left ventricular cardiomyocytes of rats exposed to different levels of electromagnetic radiation under conditions of hypothyroidism. Their findings contribute to our understanding of the impact of electromagnetic radiation on cardiomyocyte ultrastructure. [74]. Ivanchenko and Tverdokhlib (2013) explored the formation of the mitochondrial apparatus of contractile cardiomyocytes under normal conditions and hypoxic damage to cardiogenesis. They discussed how these conditions affect the cardiomyocyte ultrastructure and mitochondrial apparatus formation. [75, 80] Ivanchenko (2013) studied the ultrastructural rearrangements of mitochondria in contractile cardiomyocytes of rat ventricles under chronic prenatal hypoxia conditions. The findings of this study provide insight into how hypoxia can impact the development of cardiomyocyte mitochondria. [76, 81]

Kozlov et al. (2014) investigated the changes in the mitochondria of contractile cardiomyocytes in rats during postnatal ontogeny. This study provides valuable information on the changes in mitochondri-

al ultrastructure that occur during different stages of postnatal development. [77, 82]

Shevchenko (2019) examined the morphological features of atrial myocardium embryonic development and how it is affected by hypoxia [78] In another study (2016), Shevchenko investigated the development of the vascular component of rat atrial myocardium on the background of atrial surface-volume characteristics changes after the influence of acute prenatal hypoxia [79].

Perspectives of hypoxia research. Myocardial hypoxia, a state of inadequate oxygen supply to the heart, is a significant contributor to cardiovascular disease. Research in recent years has focused on elucidating the underlying mechanisms of hypoxia in the heart, particularly in rats, in order to develop new therapeutic interventions. This review aims to provide an overview of the latest studies in this area.

One study by Chen et al. [83] investigated the role of hypoxia-inducible factor-1 α (HIF-1 α) in myocardial hypoxia. The authors found that HIF-1 α expression increased in hypoxic rats, leading to an increase in glycolysis and angiogenesis. They concluded that targeting HIF-1 α could be a promising strategy for treating myocardial hypoxia.

Another study by Wu et al. [84] investigated the role of long noncoding RNA (lncRNA) in myocardial hypoxia. The authors found that lncRNA expression changed significantly in hypoxic rats, and that inhibiting lncRNA reduced oxidative stress and improved cardiac function. They suggested that targeting lncRNA could be a novel therapeutic strategy for treating myocardial hypoxia.

A study by Zhang et al. [85] investigated the role of microRNA (miRNA) in myocardial hypoxia. The authors found that miRNA expression changed significantly in hypoxic rats, and that targeting specific miRNAs improved cardiac function and reduced apoptosis. They suggested that targeting miRNAs could be a promising therapeutic approach for treating myocardial hypoxia.

Another study by Wang et al. [86] investigated the role of autophagy in myocardial hypoxia. The authors found that autophagy was upregulated in hypoxic rats, and that inhibiting autophagy reduced apoptosis and improved cardiac function. They suggested that targeting autophagy could be a potential therapeutic strategy for treating myocardial hypoxia.

Overall, recent studies have identified several potential therapeutic targets for treating myocardial hypoxia, including HIF-1 α , lncRNA, miRNA, and autophagy. Further research is needed to fully understand the mechanisms underlying myocardial hypoxia and to develop effective treatments.

Recent research has shed new light on the potential of histological methods for studying hypoxia. Several studies published within the past year have demonstrated the utility of various histological techniques in investigating the effects of hypoxia on different tissues, including the heart, brain, and liver

[87-89].

One promising approach is the use of immunohistochemical staining to detect and quantify specific markers of hypoxia, such as HIF-1 α and VEGF. A recent study by Zhang et al. found that HIF-1 α expression in the myocardium was significantly upregulated in response to hypoxia, and that this increase was accompanied by increased VEGF expression [87]. This suggests that immunohistochemistry may be a valuable tool for studying the mechanisms underlying hypoxic injury in the heart.

Another area of research involves the use of electron microscopy to investigate the ultrastructural changes that occur in response to hypoxia. For example, a recent study by Xu et al. used electron microscopy to examine the effects of hypoxia on the mitochondria of rat liver cells, and found that hypoxia induced mitochondrial fragmentation and autophagy [88]. This approach could potentially be applied to other tissues as well, providing insights into the cellular and subcellular changes that occur during hypoxia. Overall, these recent studies demonstrate the potential of histological methods for studying hypoxia, and suggest that these techniques could be valuable tools for investigating the mechanisms underlying hypoxic injury in various tissues.

Hypoxia during the process of cardiogenesis can lead to significant cardiac damage in rats and other animal models, resulting in structural and functional changes in the heart [89-93]. Rats exposed to sodium nitrite-induced hypoxia can develop myocardial pathology, including oxidative stress, inflammation, fibrosis, and apoptosis [93]. Histological techniques such as H&E staining, Masson's trichrome staining, PAS staining, immunohistochemistry, and TEM can provide valuable information about the structural and cellular changes that occur in the heart tissue under hypoxic conditions [94]. H&E staining can be used to detect changes in the size, shape, and number of cells in the heart tissue under hypoxia conditions [95, 96]. Masson's trichrome staining can be used to observe the degree of fibrosis that occurs in the heart tissue under hypoxic conditions [97-104]. Immunohistochemistry can be used to detect changes in the expression of specific proteins under hypoxic conditions, such as the expression of HIF-1 α and the extent of cell death (apoptosis) in the heart tissue [105, 106].

Overall, the use of histological techniques in animal models can provide insights into the mechanisms underlying hypoxia-induced cardiogenesis and can help in the development of effective treatments to mitigate the harmful effects of hypoxia on cardiac function [114].

Congenital heart disease (CHD) is a common condition affecting individuals of all ages, with an estimated prevalence of 0.8-1% in the general population [114]. The etiology of CHD is multifactorial, with both genetic and environmental factors contributing to its development. Hypoxemia, or low levels

of oxygen in the blood, is a common complication associated with CHD, and can have profound effects on the developing heart [115].

Hypoxemia in CHD can result from a variety of factors, including abnormal pulmonary blood flow and ventilation-perfusion mismatch [117]. The severity and duration of hypoxemia can have significant impacts on the structure and function of the heart. For example, hypoxemia can lead to alterations in mitochondrial metabolism and energy production, which can contribute to heart failure and other cardiovascular complications [118]. Early intervention is crucial in managing hypoxemia in patients with CHD [116]. Factors that predict the need for early intervention include the type and severity of the CHD, as well as the degree and duration of hypoxemia [119]. Advances in imaging technologies, such as cardiac MRI and CT, have improved our ability to diagnose and monitor CHD, and to guide interventions aimed at improving oxygenation [120]. In conclusion, hypoxemia is a common and significant complication associated with CHD. Research focused on understanding the mechanisms underlying hypoxemia-induced cardiac injury and identifying novel interventions to improve oxygenation is critical for improving outcomes in patients with CHD. Advances in imaging technologies and other diagnostic tools will continue to play an important role in the diagnosis and management of CHD-associated hypoxemia [121].

Conclusion

Recent advancements in electron microscopy and histological techniques have enabled researchers to gain a better understanding of the cellular and molecular mechanisms involved in hypoxia. Here are seven conclusions regarding the importance of studying hypoxia using these cutting-edge methods:

1. Electron microscopy allows for high-resolution imaging of cellular structures and organelles, providing insight into the structural changes that occur in cells during hypoxia [1].

2. Histological techniques, such as immunohistochemistry and in situ hybridization, allow for the detection of specific molecules and proteins within tissues, aiding in the identification of key signaling pathways involved in hypoxia.

3. Studying hypoxia using electron microscopy and histology can help identify potential therapeutic targets for hypoxia-related diseases, such as cancer and ischemic injury.

4. The use of advanced imaging techniques can aid in the development of non-invasive diagnostic methods for hypoxia-related conditions, such as magnetic resonance imaging and positron emission tomography.

5. Studying hypoxia at the cellular and molecular level can provide a better understanding of how different tissues and organs respond to hypoxia, potentially leading to the development of personalized treatment options.

6. The use of electron microscopy and histological techniques can help elucidate the role of hypoxia in various physiological processes, such as embryonic development and wound healing.

7. Advances in electron microscopy and histology have led to the discovery of new mechanisms involved in hypoxia, such as hypoxia-induced autophagy, which may have important implications for the treatment of hypoxia-related diseases.

In conclusion, the study of hypoxia using ad-

vanced electron microscopy and histological techniques is of paramount importance, as it has the potential to shed light on the mechanisms underlying hypoxia-related diseases and lead to the development of new therapies and diagnostic tools.

Information on conflict of interest

There are no potential or apparent conflicts of interest related to this manuscript at the time of publication and are not anticipated.

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Кобеза П.А. Гіпоксія в кардіогенезі щурів.

РЕФЕРАТ. Актуальність. Гіпоксія на ранніх етапах кардіогенезу щурів викликає ускладнення функціонального розвитку кардіоміоцитів. Кардіогенез, в стані гіпоксії, відноситься до процесу генерації нових серцевих клітин або кардіоміоцитів у відповідь на низький рівень кисню або гіпоксію. Цей процес відбувається як засіб адаптації серця для підтримки своєї функції в умовах зниженого постачання киснем. Гіпоксія може активувати певні сигнальні шляхи, такі як шлях фактора, індукованого гіпоксією (HIF). **Мета.** Визначити гіпоксію, як загальний ускладнений стан. Виявити чинники, які зумовлюють цей стан. Надати характеристику ускладнення та шляхи їх прогресивного розвитку в різних ділянках серця в період раннього онтогенезу. Розуміння причин і механізмів гіпоксії має вирішальне значення для розробки ефективних методів виявлення цього патологічного та функціонального стану клітин міокарда щурів. **Методи.** Систематичний огляд літератури, мета-аналіз, контент-аналіз. Результати Наведено основні види гіпоксії та їх вплив на структуру та розвиток міокарда щурів. Детально описано процес розвитку міофібрил і мітохондрій у різних зонах міокарда в онтогенезі. **Підсумок.** Використання гістологічних методів на тваринних моделях може дати розуміння механізмів, що лежать в основі кардіогенезу в стані гіпоксії, і може допомогти в розробці ефективних методів діагностики впливу низького рівня кисню на процес формування серцево-м'язової тканини.

Ключові слова: кардіоміоцити, скоротний апарат, саркомер, гіпоксія, кардіогенез у пренатальному онтогенезі щурів.