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REVIEW

Impact of Altitude on Cardiovascular Physiology: Literature Review and Update

Impacto de la Altitud en la Fisiología Cardiovascular: Revisión de la literatura y actualización

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ABSTRACT

Introduction: more than 140 million people in the world live at high altitudes, above 2500 meters (m) above sea level. Oxygen is vital for cellular metabolism; therefore, hypoxic conditions found at high altitude affect all physiological functions.
Method: a search for information was carried out in the SciELO, Scopus, PubMed/MedLine databases, the Google Scholar search engine, as well as in the ClinicalKeys services. Advanced search strategies were used to retrieve the information, by structuring search formulas using the terms "Cardiovascular Physiology", "Cardiovascular Physiology at Altitude", as well as their translations into Spanish " Fisiología Cardiovascular " and " Fisiología Cardiovascular en la altitud ".
Results and discussion: the heart is composed of three main types of cardiac muscle: atrial muscle, ventricular muscle, and specialized excitatory and conductive muscle fibers. The efficiency and work of the heart as a pump is often measured in terms of cardiac output, or the amount of blood the heart pumps per minute. Cardiac output is the product of stroke volume and heart rate Cardiovascular Changes at Altitude It is possible to think of the goal of acclimatization as maintaining oxygen delivery to the tissues as close to normal as possible. The cardiovascular system is central to this. Acute exposure to high altitude produces an increase in heart rate and cardiac output both at rest and for a given amount of work compared with sea level. In general, the normal heart tolerates even severe hypoxia very well. The heart, as a hemodynamic pump, has two mechanisms at its disposal to enhance its performance: heart rate and stroke volume, which together constitute cardiac output. The altitude electrocardiogram shows a variably increased amplitude of the P wave, deviation of the QRS axis to the right, and signs of right ventricular overload and hypertrophy.
Conclusions: advances in high-altitude research have shown that the cardiovascular system deploys some efficient mechanisms of acclimatization to oxygen deprivation, and the healthy heart adapts to hypoxia, even when severe, with preservation of systolic function and only minor impairment of LV and RV diastolic function. With acclimatization, desensitization of the adrenergic system, together with increased parasympathetic

influence, leads to a decrease in maximum heart rate and protection of the myocardium against potentially damaging energy imbalances. Acute exposure to high altitude stimulates the adrenergic system, increasing heart rate and cardiac output; although arterial pressure remains stable, pulmonary artery pressure increases due to hypoxic pulmonary vasoconstriction. Our improved understanding of the effect of altitude hypoxia on the cardiovascular system will allow better-informed, evidence-based advice for patients with pre-existing cardiovascular disease.

Keywords: Altitude; Cardiovascular System; Chronic Mountain Sickness; Pulmonary Hypertension.

RESUMEN

Introducción: más de 140 millones de personas en el mundo viven en grandes altitudes, por encima de los 2500 metros (m) sobre el nivel del mar. El oxígeno es vital para el metabolismo celular; por lo tanto, las condiciones hipóxicas encontradas en grandes altitudes afectan todas las funciones fisiológicas.
Método: se realizó una búsqueda de información en las bases de datos SciELO, Scopus, PubMed/MedLine, el buscador Google Scholar, así como en los servicios ClinicalKeys. Se utilizaron estrategias de búsqueda avanzada para recuperar la información, mediante la estructuración de fórmulas de búsqueda utilizando los términos "Cardiovascular Physiology", "Cardiovascular Physiology at Altitude", así como sus traducciones al español "Fisiología Cardiovascular" y "Fisiología Cardiovascular en la altitud".
Discusión y resultados: el corazón está compuesto por tres tipos principales de músculo cardíaco: músculo auricular, músculo ventricular y fibras musculares especializadas excitatorias y conductoras. La eficiencia y el trabajo del corazón como bomba a menudo se mide en términos de gasto cardíaco, o la cantidad de sangre que el corazón bombea por minuto. El gasto cardíaco es el producto del volumen sistólico y la frecuencia cardíaca Cambios cardiovasculares en la altitud Es posible pensar en el objetivo de la aclimatación como el de mantener el aporte de oxígeno a los tejidos lo más cercano posible a lo normal. El sistema cardiovascular es central para esto. La exposición aguda a grandes altitudes produce un aumento de la frecuencia cardíaca y del gasto cardíaco tanto en reposo como para una cantidad dada de trabajo en comparación con el nivel del mar. En general, el corazón normal tolera muy bien incluso la hipoxia severa. El corazón, como bomba hemodinámica, tiene dos mecanismos a su disposición para mejorar su rendimiento: la frecuencia cardíaca y el volumen sistólico, que juntos constituyen el gasto cardíaco. El electrocardiograma de altitud muestra una amplitud variablemente aumentada de la onda P, desviación del eje QRS a la derecha y signos de sobrecarga e hipertrofia del ventrículo derecho.
Conclusiones: los avances en la investigación en grandes altitudes han demostrado que el sistema cardiovascular despliega algunos mecanismos eficientes de aclimatación a la privación de oxígeno, y el corazón sano se adapta a la hipoxia, incluso cuando es severa, con preservación de la función sistólica y solo un deterioro menor de la función diastólica del VI y el VD. Con la aclimatación, la desensibilización del sistema adrenérgico, junto con el aumento de la influencia parasimpática, conduce a una disminución de la frecuencia cardíaca máxima y a la protección del miocardio contra desequilibrios energéticos potencialmente dañinos. La exposición aguda a grandes altitudes estimula el sistema adrenérgico, aumentando la frecuencia cardíaca y el gasto cardíaco; aunque la presión arterial permanece estable, la presión de la arteria pulmonar aumenta debido a la vasoconstricción pulmonar hipóxica. Nuestra mejor comprensión del efecto de la hipoxia de la altitud sobre el sistema cardiovascular permitirá un asesoramiento mejor informado y basado en la evidencia para los pacientes con enfermedades cardiovasculares preexistentes.

Palabras clave: Altitud; Sistema Cardiovascular; Mal de Montaña Crónico; Hipertensión Pulmonar.

INTRODUCTION

More than 140 million people in the world live at high altitudes, living above 2500 meters (m) above sea level. The Andean region has the highest population density above 3500 m above sea level. On the other hand, the number of people living at sea level who travel to medium, high or extreme altitudes for work or scientific reasons, for tourism or for sport, such as hikers, mountaineers and skiers, is increasing. Therefore, it is of interest to know the effects of altitude on physiological and structural aspects of the human organism.[1,2,3,4]

Human difficulties with the thin air at high altitude have been recognized since ancient times. Writings attributable to Aristotle (384-322 BC) describe journeys to Mount Olympus in Macedonia, and because the thin air there did not fill them with breath, they could not survive there unless they applied moist sponges to their noses. Reinhold Messner's description of the first ascent of Mount Everest without supplemental oxygen, Everest: Expedition to the Ultimate, is compelling. A study ascent was a major event in the history of high-

altitude physiology and forever ended the debate over whether an "oxygen-free" ascent of the world's highest peak was possible.[5,6,7,8,9] What made this climb so extraordinary is that, through a remarkable coincidence, the summit of Mount Everest is very close to the limit of human tolerance for hypoxia. If the summit were only a few meters higher, the basal oxygen requirements would exceed the maximum oxygen consumption and it would be impossible to reach it without the help of supplemental oxygen. Another expedition led by West, the American Medical Research Expedition to Everest (AMREE), which reached the summit of Everest in 1981 without oxygen, marked a before and after in this physiological challenge.[10,11,12,13] This expedition included important respiratory physiologists and great mountaineers such as Hackett and Milledge. These studies have served to improve the understanding of the physiology and illness of altitude, and also opened paths to help and understand how hypoxia affects critical patients and all those in whom hypoxemia and cellular hypoxia are present.[14,15,16,17] Oxygen is vital for cellular metabolism; therefore, hypoxic conditions found at high altitude affect all physiological functions. Importantly, the human body has both short- and long-term adaptations to altitude that allow it to partially compensate for the reduced amount of oxygen in the atmosphere. In this chapter, we present cardiovascular physiological changes at altitude.[18,19,20,21] In the pediatric age group, newborns present arterial hypertension at high altitudes and a thick middle layer of smooth muscle cells in the small pulmonary arteries and arterioles, findings similar to those described at sea level.[22,23,24,25,26] However, in newborns at sea level, rapid vascular remodeling occurs, thinning of the muscular layer with enlargement of the lumen, which determines a rapid decrease in pulmonary vascular resistance and pulmonary arterial pressure. While in newborns at high altitudes, vascular remodeling occurs slowly throughout life, so arterial hypertension and right ventricular hypertrophy persist into adulthood. Highlighting the importance of the human body facing a series of adaptations to altitude from birth, both short and long term, that allow it to partially compensate for the reduced amount of oxygen in the atmosphere.[27,28,29,30]

METHOD

A search for information was carried out in the SciELO, Scopus, PubMed/MedLine databases, the Google Scholar search engine, as well as in the ClinicalKeys services. Advanced search strategies were used to retrieve the information, by structuring search formulas using the terms "Cardiovascular Physiology", "Cardiovascular Physiology at Altitude", as well as their translations into Spanish " Fisiología Cardiovascular " and " Fisiología Cardiovascular en la altitud ". Boolean operators were used to combine the terms, with search formulas according to the syntax requested by each database. From the resulting documents, those written in the last 10 years, in Spanish or English, that provided updated information on this subject were selected.

RESULTS AND DISCUSSION

Physiology of Normal Cardiac Muscle. The heart is composed of three major types of cardiac muscle: atrial muscle, ventricular muscle, and specialized excitatory and conductive muscle fibers. Atrial and ventricular muscle types contract in the same manner as skeletal muscle, except that the duration of contraction is much longer.[31,32,33,34,35] However, the specialized excitatory and conductive fibers of the heart contract weakly because they contain few contractile fibrils; instead, they exhibit an automatic rhythmic electrical discharge in the form of action potentials or conduction of action potentials through the heart, providing an excitatory system that controls the rhythmic beating of the heart. The efficiency and work of the heart as a pump is often measured in terms of cardiac output or the amount of blood the heart pumps per minute. Cardiac output (CO) is the product of stroke volume (V) and heart rate (HR), and can be expressed by the equation $CO = V \times HR$.[36,37,38,39,40] Cardiac output varies according to body size and the metabolic needs of the tissues. It increases with physical activity and decreases during rest and sleep. The average resting CO in normal adults ranges from 4 to 6 bpm. The heart's ability to increase its output in accordance with the body's needs depends primarily on 4 factors: Preload or ventricular filling, Afterload or resistance to cardiac ejection of blood, Cardiac contractility and Heart rate.[41,42,43,44,45]

Functional organization of the circulatory system. The circulatory system consists of the heart, which pumps blood; the arterial system, which distributes oxygenated blood to the tissues; the venous system, which collects deoxygenated blood from the tissues and returns it to the heart; and the capillaries, where the exchange of gases, nutrients, and waste takes place. The circulatory system is a closed system divided into two parts: the low-pressure pulmonary circulation, which links the circulation with gas exchange in the lungs, and the high-pressure systemic circulation, which supplies oxygen and nutrients to the tissues.[46,47,48,49,50]

Cardiovascular changes at altitude. It is possible to think that the purpose of acclimatization is to maintain the oxygen supply to the tissues as close to normal as possible. The cardiovascular system is central to this. Acute exposure to high altitude results in an increase in heart rate and cardiac output both at rest and for a given amount of work compared to sea level. With acclimatization, heart rate and cardiac output return to their values at sea level at rest up to altitudes of approximately 4500 m. During exercise, for a given level of work, heart rate remains elevated compared to sea level, although cardiac output returns to sea level values.[51,52,53,54,55] Therefore, stroke volume must be reduced even though myocardial contractility is well preserved.

In general, the normal heart tolerates even severe hypoxia very well. Cardiac arrhythmias are rare at high altitude and even at extreme altitudes the ECG shows only the changes of pulmonary hypertension.[56,57,58,59,60] The increase in hemoglobin concentration that occurs as a result of plasma volume contraction and increased erythropoiesis has the effect of increasing the arterial oxygen content of the blood. Thus, a well-acclimatized individual at altitudes up to 5500 m will have a similar arterial oxygen content and therefore oxygen supply as at sea level.[61,62,63,64,65]

Heart and altitude. The consequences of acute hypoxia as a result of high altitude are an increase in heart rate (both at rest and during exercise), myocardial contractility, and cardiac output during the first few days. With acclimatization, cardiac output decreases at rest and during exercise in association with decreased left ventricular work but increased right ventricular work.[66,67,68,69,70]

Heart rate. The increased heart rate at high altitude is related to increased sympathetic activity and vagal retraction.[71,72,73,74,75,76] For a given level of exercise, heart rate is higher at altitude, although the heart rate achievable with maximal exercise is reduced compared with the heart rate achievable with maximal exercise at sea level and in parallel with maximal oxygen consumption.[77,78,79,80,81,82] At 5260 m, vagal blockade by glycopyrrolate completely restored maximal heart rate to sea level values, while cardiac output did not increase. Acute increase in inspiratory PO2 to sea level values increased work performance and restored cardiac output. These data indicate that increased parasympathetic neuronal activity accounts for the decrease in heart rate during exercise, whereas the reduction in cardiac output in hypoxia may be related to decreased maximal work capacity, i.e. decreased skeletal muscle signals.[83,84,85,86]

Heart rate in the study of cardiac adaptation to altitude has to be considered as well, whether the subject is at rest or exercising. At rest after acute exposure to altitude, some subjects maintain a heart rate similar to that at sea level up to 6000 m. However, others show an increase in heart rate which means that there are other factors of an individual nature. During exercise, the maximum heart rate is lower with increasing altitude. At the summit of Everest (extreme altitude) for example, it is 135 beats per minute.[87,88] The most likely explanation is that heart rate follows maximum oxygen consumption which is also decreased at altitude and there is still controversy among authors. The "mirror" pattern of variation in heart rate at rest and arterial oxygen saturation (SaO_2) illustrates the close relationship between hypoxemia and adrenergic activation in acute and prolonged hypoxia. Although moderate exercise heart rate is initially increased at altitude, maximal exercise heart rate is slightly reduced in acute hypoxia and significantly decreased with prolonged exposure (>24 hrs) to high altitude.[89,90] Decreased heart rate during maximal exercise has been observed in many studies performed in the field and under simulated conditions. Both the sympathetic and parasympathetic systems have been explored to find a physiological explanation for this decrease in maximal heart rate. The most compelling evidence is that ß-adrenergic receptors are downregulated. This mechanism is well known in pharmacology: when an agonist is constantly elevated, the corresponding receptor is downregulated, leading to desensitization of the entire pathway as an adaptive phenomenon against excessive stimulation.[91,92,93,94]

Heart as a pump. The heart, as a hemodynamic pump, has two mechanisms to improve its performance: heart rate and stroke volume, which together constitute cardiac output. It is not surprising, therefore, that when faced with a decrease in inspired oxygen pressure, such as at altitude, cardiac output increases until other mechanisms take charge of compensating for this deficiency.[95,96,97,98] Some authors have observed that cardiac output is increased upon reaching altitude and that this value would reach a maximum value 5 days later. However, after 12 days cardiac output would return to normal levels at sea level. This return to normal values is attributed to the increase in hemoglobin. At extreme altitudes, it has been observed that heart rate increased and stroke volume decreased for a given level of work.

Cardiovascular system and its effects of high altitude exposure. The major effects of acute hypoxia on the heart and lungs are shown in (figure 1.) Hypoxia directly affects vascular tone of pulmonary and systemic resistance vessels and increases ventilation and sympathetic activity by stimulation of peripheral chemoreceptors. Interactions occur between the direct effects of hypoxia on blood vessels and chemoreceptor-mediated responses in the systemic and pulmonary circulation. As shown in figure 1, there is an antagonism between the direct effects of hypoxia on resistance vessels and those mediated by chemoreceptors in both the systemic and pulmonary circulations. During the first few hours of exposure, hypoxic vasodilation tends to override sympathetic vasoconstriction in the systemic circulation, resulting in unchanged or slightly decreased systemic blood pressure. Blood pressure and systemic vascular resistance then increase for at least three to four weeks due to increased sympathetic activity and reduced tissue hypoxia associated with acclimatization.[99]

The increase in blood pressure is not completely reversed by administration of oxygen, alpha-blockers, or beta-blockers suggesting that additional mechanisms may be involved. The interindividual variation in blood pressure response to hypoxia may be explained in part by the finding that individuals with an acute, brisk hypoxic ventilatory response also have a high blood pressure response to hypoxia.

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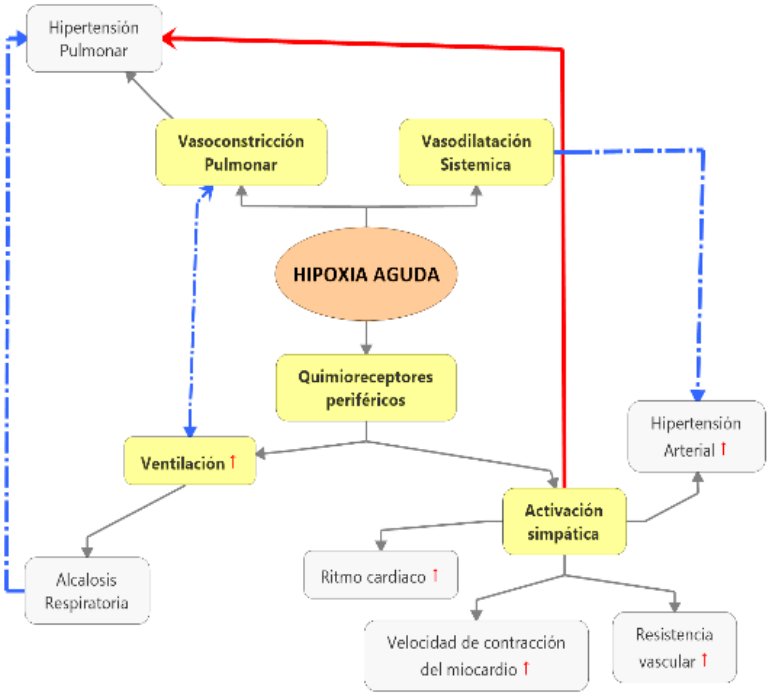

Figure 1. Effects of hypoxia on systemic and pulmonary circulation

Hypoxia and Altitude. As of April 2023, the search term "hypoxia" produced over 184 000 results in the PubMed database, the earliest of which dates back to 1945. However, interest in the effects of oxygen deprivation on living organisms began in the mid-19th century, when scientists working in high-altitude regions primarily used the terms anoxia or anoxemia. A clear clinical distinction between anoxia and hypoxia was first made by Carl Wiggers in 1941. Hypoxia is a decrease in oxygen and is variable with time and location in the body, whereas anoxia is the absence of oxygen. High-altitude environments are characterized by various physical constraints, including cold temperatures and an increased level of ultraviolet radiation. However, the most demanding condition is hypoxia due to the progressive decrease in barometric pressure. The pressure of oxygen in inspired air (PiO_2) is given by the following equation: $PiO_2 = FiO_2 \times$ (Pb –$PAGh_2$ O), where FiO_2 is the fraction of oxygen in inspired air, Pb is the barometric pressure, and Ph2 O is the air pressure. Thus, barometric pressure and inspired oxygen pressure decrease, resulting in alveolar hypoxia and hypoxemia, which leads to hypoxic pulmonary vasoconstriction (HPV), a moderate increase in pulmonary arterial pressure (PAP) and right ventricle (RV) pressure, compatible with a normal life at altitude. HPV allows a better balance between the pulmonary ventilation/perfusion (V/Q) ratio and increases pulmonary diffusion capacity; compared to sea level, translating into a lower alveolar-arterial oxygen gradient (A-a = 3 to 5 mmHg).

FiO_2 is not altitude-dependent and is currently equal to 0,2093 (20,93 %), but this value has fluctuated since the formation of the Earth. High-altitude environments are characterized by various physical constraints, including cold temperatures and increased levels of ultraviolet radiation. However, the most demanding condition is hypoxia due to progressively decreasing barometric pressure (figure 2).

High altitude regions above 2500 m are found in South America (Andean countries), North America (Rocky Mountains and Alaska), Europe (Alps and Pyrenees), Africa (Atlas and East African plateaus) and Asia (Himalayas and Tibetan plateau). Physiological effects of hypoxia. Oxygen is vital for all human cells and therefore hypoxic conditions affect all physiological functions. Each cell can be considered an oxygen sensor due to the presence of genetic sequences known as hypoxia-sensitive elements. In acute hypoxia (minutes to hours), activation of these elements triggers the expression of several factors, leading to the stabilization of hypoxia-inducible factors (HIF1, HIF2, and HIF3). In turn, HIFs induce the expression of messengers and hormones (such as erythropoietin, vascular endothelial growth factor, and glucose transporters) involved in the physiological response to hypoxia. Native people at altitude have lower ventilation/minute and lower response of peripheral chemoreceptors (carotid and aortic) to arterial oxygen pressure (PaO_2) and carbon dioxide ($PaCO_2$), observed in native people at sea level, which is related to the genesis of hypercapnia and secondarily to hypoxemia. The adaptations of the rib cage at altitude have allowed an increase of 1,8 cm in the anteroposterior diameter of the thorax and in lung volumes: forced vital capacity 384 ml and in residual volume of 13 %, with a decrease in functional residual capacity of 11 %.[100]

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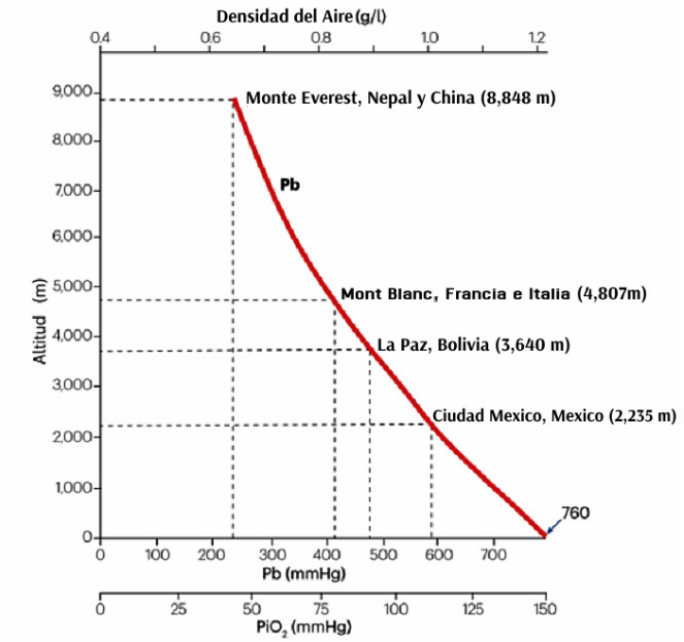

Figure 2. Altitude, barometric pressure, air density and inspired oxygen pressure

Cardiovascular response to hypoxia. The cardiovascular system has an important role in the integrated response to hypoxia, which involves two mechanisms: centrally mediated activation of the adrenergic system and a direct peripheral effect on the cells of the heart and blood vessels. Activation of medullary adrenergic centers is driven by input from carotid chemoreceptors that are sensitive to hypoxemia. The entire sympathetic nervous system is activated, as evidenced by an increase in plasma and urinary catecholamine concentrations. An increase in arterial plasma catecholamine levels has been consistently observed with prolonged hypoxia. Activation of the adrenergic system has also been demonstrated by increased activity in peroneal adrenergic nerves. Cardiac output and stroke volume have been studied under a variety of normobaric and hypobaric hypoxic conditions. Cardiac output increases at altitude, primarily due to increased heart rate. Stroke volume decreases slightly, as measured during Operation Everest II, when stroke volume decreased by 14 % at rest and after moderate exercise (60 W) at 7620 m. This change is not due to decreased venous return to the heart, as some investigators claim, because blood volume is maintained (the decrease in plasma volume is compensated for by an increase in red blood cell volume). The decrease in stroke volume is actually caused by a slight reduction in left ventricular end-diastolic volume as a consequence of increased right ventricular pressure related to elevated pulmonary artery pressure (PAP). This mechanical effect of high right ventricular (RV) pressure on the interventricular septum may slightly affect left ventricular (LV) filling. However, these mechanisms do not significantly alter cardiac function. Stroke volume reached a plateau earlier in hypoxia than in normoxia, suggesting a slight impairment of cardiac filling related to decreased LV diastolic function, or impaired RV function due to elevated pulmonary vascular resistance.[101]

The electrocardiogram at altitude shows variably increased amplitude of P wave, right QRS axis deviation, and signs of RV overload and hypertrophy. Sometimes, an electrocardiogram may remain unchanged up to extreme altitudes. Systemic blood pressure. Changes in blood pressure may depend on individual conditions, absolute altitude of exposure, and duration of stay at altitude. A recent study has reported that after acute exposure to 3700 m, diastolic blood pressure and mean arterial pressure gradually and continuously increased in healthy young male adults. More detailed analyses showed that higher blood pressure was accompanied by poor sleep quality and an increased incidence of acute mountain sickness. Furthermore, systolic blood pressure also increased significantly after exercise at high altitude. Other studies have also reported a significant increase in systolic and diastolic blood pressure in the initial phase of altitude exposure. Centrally mediated activation of the adrenergic system has a vasoconstrictive effect on peripheral α-adrenergic receptors, which may lead to increases in peripheral vascular resistance and blood pressure. Furthermore, an increase in heart rate and cardiac output may contribute to an increase in blood pressure independently of vascular resistance. In contrast, hypoxia has a direct relaxing effect on vascular smooth muscle cells, leading to vasodilation and decreased vascular resistance. The overall effect depends on the time of exposure and the intensity of the hypoxic stimulus. The effect of acute hypoxia on blood pressure illustrates these dichotomous responses between central and peripheral mechanisms. Hypoxia-induced activation of the autonomic nervous system is a potent activator of central sympathetic activity, triggered by increased oxygen-related activity of carotid

chemoreceptors that in turn induces a peripheral vasoconstrictor response through sympathetic-dependent contraction of vascular smooth muscle cells.

Cardiovascular adaptation to short-term high altitude hypoxia. With ascent to high altitude, there is a non-linear decrease in barometric pressure and a reduction in ambient partial pressure of oxygen (PO_2) and subsequently a decrease in PO_2 at each point along the oxygen transport cascade from inspired air to the alveolar space, arterial blood, tissues, and venous blood. The higher the elevation reached, the greater the fall in PO_2 in the human body. These decreases in oxygen tensions trigger a variety of physiological responses in the cardiovascular system over a period of minutes to weeks after initial exposure to altitude hypoxia that allow the individual to adapt to or compensate for the hypoxic environment. At high altitude, in the short term, the low PO_2 of inspired air will normally concomitantly reduce SaO_2, so compensatory adjustment may immediately take place to meet the large and constant O_2 demand of aerobic tissue and cell metabolism. The carotid bodies sense the initial lack of oxygen, leading to an increase in respiratory rate. Cardiovascular functions then change in response to short-term high-altitude hypoxia.

The main cardiac response to short-term high-altitude hypoxia is adjustment of cardiac function, including changes in heart rate (HR) and cardiac output, left ventricular ejection fraction (LVEF), ventricular systolic and diastolic function, and arterial blood pressure (ABP). At high altitude, an initial response is for the heart to beat faster. Cardiac contractility and submaximal cardiac output also increase acutely during the first few days at altitude. This acute increase in cardiac output can largely be explained by the increase in heart rate and may be offset by the reduction in stroke volume. There are several possible mechanisms involved in short-term high-altitude hypoxia-mediated cardiac dysfunction. One of the important mechanisms is changes in the autonomic nervous system, including the parasympathetic nervous system (SNS) and the sympathetic nervous system (SNS).

Peripheral chemoreceptors mainly include the carotid bodies and aortic chemoreceptors, which act as hypoxia sensors in arterial walls. The carotid bodies act as sensitive monitors of arterial O_2 tension (PaO^2), whereas aortic chemoreceptors mainly monitor arterial O_2 content (CaO_2). Thus, the carotid bodies evoke stronger respiratory responses than aortic chemoreceptors. A study in humans exposed to hypoxia demonstrated that the carotid bodies are primarily responsible for the ventilatory and vascular response, whereas aortic chemoreceptors mainly mediated the tachycardic response. Another study indicated that hyperventilation induced by hypoxic stimulation of the carotid bodies decreased vagal traffic to the heart through the Hering-Breuer reflex, which plays an important indirect role in the tachycardic response to hypoxia. Meanwhile, hypoxic stimulation of carotid bodies also directly activated SNS to accelerate heart rate by increasing circulating catecholamines. Furthermore, hypoxic activation of peripheral chemoreceptors was targeted to restore baroreflex control of HR and sympathetic nervous system (SNS) activity to higher levels, so that HR and sympathetic vasoconstriction increased, which were independent of respiratory rate and tidal volume. Hypertrophy of the right ventricle, classic in the high-altitude inhabitant, is due to pulmonary arterial hypertension only and not to the increase in blood viscosity, since the left ventricle is not hypertrophied and, on the contrary, in chronic adaptation with polyglobulia there is a tendency towards systemic hypotension. In chronic adaptation, polyglobulia decreases cardiac output (which was increased during acute adaptation) allowing energy savings by decreasing the work of the heart at rest. Polyglobulia also decreases the work of the respiratory muscles, to save energy.

Cardiovascular adaptation to long-term hypoxia. Acute short-term exposure to high altitude has been recognized as a type of cardiovascular stress and produces an immediate increase in heart rate, cardiac output, and a transient increase in blood pressure, but without significant changes in ejection fraction. However, prolonged exposure to high altitude or people residing at high altitude show compensatory changes in the cardiovascular system that have allowed them to adapt to chronic high altitude hypoxia. In prolonged high altitude hypoxia, the heart must preserve adequate contractile function despite decreased oxygen tension in the cardiac circulation. A study had performed studies in young men during acclimatization to simulated altitude in a chamber for 40 days and their results showed that indices of left ventricular systolic function, including ejection fraction, ratio of peak systolic pressure to end-systolic volume, and mean normalized systolic ejection rate at rest and exercise, were maintained in all subjects at high altitude despite reduced preload, pulmonary hypertension, and severe hypoxemia, meaning remarkably preserved contractility and excellent tolerance of normal myocardium to long-term high altitude hypoxia. Another study also demonstrated that cardiac contractility remained normal during exposure to altitude-induced hypoxia with preservation of LV ejection fraction and percentage of LV fractional shortening. Cardiac adaptation to long-term high altitude hypoxia is characterized by a variety of functional adjustments to maintain homeostasis with minimal energy expenditure. These adjustments may help protect the heart from the development of ischemic heart disease. An epidemiological study reported that men residing at high altitude were protected against death from ischemic heart disease. Epidemiological observations on the cardioprotective effect of high altitude were confirmed in several experimental models. The cardioprotective effect of adaptation to high altitude hypoxia is age-dependent. For example, a recent experiment with rats challenged at an altitude of 5 000 m from 7 weeks

of age to their entire life, showed that cardiac tolerance to acute hypoxia was significantly increased in rats up to 18 months of age, but was lost in senescent rats (25 months of age). Similarly, individuals living at high altitude in the Andes lost their adaptation and have a higher incidence of pulmonary hypertension in their old age. Cardiac functional adaptation, cardiac structural adaptation also occurs after prolonged exposure to high altitude hypoxia. One of the changes in response to sustained HAH is the development of right ventricular (RV) hypertrophy. Long-term altitude-induced RV hypertrophy is a beneficial adaptation that helps to counteract the increased afterload caused by persistent pulmonary hypertension and to maintain normal cardiac output. Hypertrophic RV is associated with significant changes in the cardiac protein profile. Experimental results in rats exposed to intermittent hypoxia at high altitude have shown that the concentration of collagenous and non-collagenous proteins was significantly increased in both the hypertrophic RV and the non-hypertrophic LV. Cardiac enlargement can result from both an increase in the number of individual cellular elements (hyperplasia) and an increase in their volume (hypertrophy).

CONCLUSIONS

Advances in high-altitude research have shown that the cardiovascular system deploys some efficient mechanisms of acclimatization to oxygen deprivation, and the healthy heart adapts to hypoxia, even when severe, with preservation of systolic function and only minor impairment of LV and RV diastolic function. With acclimatization, desensitization of the adrenergic system, together with increased parasympathetic influence, leads to a decrease in maximum heart rate and protection of the myocardium against potentially damaging energy imbalances. Acute exposure to high altitude stimulates the adrenergic system, increasing heart rate and cardiac output; although arterial pressure remains stable, pulmonary artery pressure increases due to hypoxic pulmonary vasoconstriction. Patients with cardiovascular disease may be at increased risk of adverse events at altitudes above 2,500 m, due to hypoxemia, high adrenergic activity, and pulmonary hypertension. Our improved understanding of the effect of altitude hypoxia on the cardiovascular system will enable better informed, evidence-based advice for patients with pre-existing cardiovascular disease.

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