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Special article

The cardiovascular system and high-altitude exposure: from adaptation to disease. Part I

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ABSTRACT

Exposure to high altitude constitutes a complex physiological challenge, driven primarily by hypobaric hypoxia and, in some settings, by extreme environmental conditions such as severe cold and increased ultraviolet radiation. At the cardiovascular level, this exposure elicits a range of acute and chronic adaptations, including activation of the sympathetic nervous system, pulmonary vasoconstriction, and vascular and ventricular remodelling. In the Andean region, millions of people live at elevations above 2,500 metres above sea level, rendering them particularly susceptible to these physiological adaptations and the associated cardiovascular alterations. This manuscript represents the first part of a narrative review and aims to synthesise the available scientific evidence on mechanisms of adaptation to high altitude, as well as the characteristics of pulmonary hypertension, heart failure, and congenital heart disease observed in both native high-altitude populations and individuals originating from low-altitude areas. In addition, it seeks to identify existing gaps in current knowledge of these conditions in order to promote the development of specific diagnostic, preventive, and therapeutic strategies aimed at improving cardiovascular health among populations residing at or temporarily exposed to high altitude.

Keywords: Hypoxia; Altitude; Physiological Adaptation; Cardiovascular Diseases; Pulmonary Hypertension (Source: MeSH-NLM).

RESUMEN

El sistema cardiovascular y la exposición a gran altitud: desde la adaptación a la enfermedad. Parte I

La exposición a gran altitud constituye un desafío fisiológico complejo, determinado principalmente por la hipoxia hipobárica y, en algunos casos, por condiciones ambientales extremas como el frío intenso y la elevada radiación ultravioleta. A nivel cardiovascular, esta exposición induce una serie de adaptaciones agudas y crónicas que incluyen la activación del sistema nervioso simpático, la vasoconstricción pulmonar, así como el remodelamiento vascular y ventricular. En la región andina, millones de personas residen por encima de los 2500 metros sobre el nivel del mar, lo que las hace particularmente susceptibles a estas modificaciones fisiológicas y a las alteraciones cardiovasculares asociadas. El presente manuscrito constituye la primera parte de una revisión narrativa y tiene como objetivo sintetizar la evidencia científica disponible sobre los mecanismos de adaptación a la gran altitud y las características de la hipertensión pulmonar, de la insuficiencia cardiaca y de las cardiopatías congénitas observadas tanto en poblaciones nativas como en individuos provenientes de zonas de baja altitud. Asimismo, busca identificar los vacíos existentes en el conocimiento actual de estas entidades con el propósito de promover el desarrollo de estrategias específicas de diagnóstico, prevención y tratamiento dirigidas a mejorar la salud cardiovascular de las poblaciones que habitan o se exponen temporalmente a grandes alturas.

Palabras clave: Hipoxia; Altitud; Adaptación Fisiológica; Enfermedades Cardiovasculares; Hipertensión Pulmonar (Fuente: DeCS-BIREME).

Introduction

Millions of people worldwide are born, grow, and live in high-altitude regions, while a similar number visit these areas for tourism. Intermediate altitude is defined as 1,500-2,500 metres above sea level (m.a.s.l.), high altitude as 2,500-3,500 m.a.s.l., very high altitude as 3500-5500 m.a.s.l., and extreme altitude as above 5,500 m.a.s.l. From 2500 m.a.s.l. onwards, physiological responses begin to emerge that represent a significant challenge to the human body [1,2].

In Asia, between 2% and 45% of the population resides at high altitude; in China alone, approximately 80 million people live above 2500 m.a.s.l. In the South American Andes, this figure reaches around 35 million inhabitants [3]. In Peru, more than 5.5 million people live above 2500 m.a.s.l., representing 24% of the national population, mainly concentrated in the Andean region [4]. Although the fraction of inspired oxygen (FiO_2) remains constant at any altitude, the partial pressure of inspired oxygen (PiO_2) decreases due to the reduction in atmospheric pressure at higher elevations **(Figure 1)**.

Life at high altitude not only exposes individuals to environmental stressors such as hypobaric hypoxia, cold and dry climates, and increased ultraviolet radiation, but in rural communities it also exacerbates socioeconomic vulnerability by limiting access to food, water, and basic services, thereby reducing quality of life [4,5]. These factors, together with genetic components, influence cardiovascular health, contributing to the development of altitude-related diseases and affecting life expectancy in these populations.

Conversely, individuals living at sea level may experience acute cardiovascular alterations when exposed to high altitude, particularly those with pre-existing heart disease. However, controlled or gradual exposure to hypoxia may induce hypoxic conditioning, with potential cardiovascular benefits [6].

The aim of this manuscript is to synthesise the available scientific evidence on the main cardiovascular diseases associated with high-altitude exposure, highlighting their relevance from both clinical and public health perspectives in the Andean region. From a clinical standpoint, hypobaric hypoxia may destabilise pre-existing conditions such as heart failure, pulmonary hypertension, congenital heart disease, ischaemic heart disease, and arrhythmias, while also giving rise to altitude-specific conditions such as high-altitude pulmonary hypertension (HAPH) or cor pulmonale, as well as acute syndromes such as high-altitude pulmonary oedema.

From a public health perspective, understanding these conditions is essential, as despite the existence of international consensus [2], there are no specific local guidelines for cardiovascular risk assessment and management at altitude, nor surveillance or prevention programmes adapted to the geographic context. Furthermore, the increasing number of travellers and migrants to high-altitude regions underscores the need to recognise acute cardiovascular changes induced by hypoxic exposure and their clinical implications.

	Locality	Altitude in meters above sea level	Partial pressure of inspired oxygen (mmHg)
Extreme altitude (>5000 m a.s.l.)	Huascarán La Rinconada	6760 5100	< 78
Very high altitude (3500–5000 m a.s.l.)	Cerro de Pasco Puno	4330 3820	78-90
High altitude (2500–3500 m a.s.l.)	Cusco Huancayo Cajamarca	3300 3260 2750	96-103
Moderate altitude (1500–2500 m a.s.l.)	Arequipa Huánuco	2330 1880	109 -124
Low altitude (500–1500 m a.s.l.)	Chosica	861	124-140
Sea level	Lima	0-150	>150

m.a.s.l.: metres above sea level. mmHg: millimetres of mercury.

Figure 1. Different Peruvian locations and the partial pressure of inspired oxygen according to altitude.

Physiology and cardiovascular adaptations to high altitude

Acute exposure to hypobaric hypoxia at high altitude activates the sympathetic nervous system, leading to tachycardia and an initial increase in cardiac output (CO). Simultaneously, hypoxic pulmonary vasoconstriction increases pulmonary artery pressure (PAP), a phenomenon that can be observed as early as five minutes after ascent [7]. After several days of exposure to reduced oxygen concentrations, autonomic adaptation occurs, attenuating tachycardia and reducing myocardial oxygen consumption, thereby protecting the heart from excessive metabolic demand [8].

The initial increase in CO tends to progressively normalise due to a reduction in plasma volume and systolic volume, resulting from diuresis and dehydration typical of high-altitude environments [6,9]. During acclimatisation, heart rate (HR) remains elevated, systolic volume decreases, PAP increases, and CO returns to baseline values [6,10]. Acute hypoxia may also induce transient right ventricular (RV) dilation, potentially impairing its function due to reduced ventricular filling pressure [7].

In the early phases of altitude exposure, systemic vasodilation mediated by endothelial and neurohumoral factors leads to a transient decrease in systemic blood pressure (BP). However, this effect is later replaced by a generalised hypertensive response with systemic vasoconstriction driven by carotid chemoreceptor activation, resulting in increased BP and attenuation of the normal nocturnal dip [9].

Global systolic function of both ventricles is generally preserved during acute hypoxia [7,11]. However, echocardiographic studies have demonstrated right ventricular diastolic dysfunction in healthy individuals exposed to hypoxia [12], along with increases in biventricular longitudinal strain, left ventricular (LV) torsion, circumferential strain, and systolic myocardial tissue velocity, reflecting compensatory sympathetic activation [7] **(Table 1)**.

During exercise under hypoxic conditions, greater increases in HR and BP are observed at any level of exertion compared with sea level. This is due to hypoxia-induced sympathetic activation and reduced partial pressure of inspired oxygen, which limits muscle oxygen availability and reduces maximal exercise capacity in proportion to altitude [13].

Chronic exposure to hypoxia promotes pulmonary vascular remodelling, characterised by smooth muscle hypertrophy and hyperplasia, endothelial proliferation, and extracellular matrix deposition, with arteriolar muscularisation leading to sustained pulmonary hypertension (PH) and adaptive RV hypertrophy [11,14]. Hypoxic pulmonary vasoconstriction, whose severity increases with altitude, contributes to elevated pulmonary artery pressure, reduced left ventricular LV filling, and impaired ventricular interdependence, resulting in a mild reduction in biventricular function [7,11,12]. This process is more pronounced in older men, who exhibit greater pulmonary vascular reactivity [6].

Studies in Han migrants, lowland inhabitants who relocated to high altitude in China, have shown an initial impairment in RV systolic function, which improves with prolonged residence, whereas structural alterations of the LV may persist after five years, without compromising systolic or diastolic function [15]. In contrast, high-altitude natives such as Sherpas exhibit unique genetic and physiological adaptations, including smaller LV volumes and higher total blood volume compared with acclimatised lowland individuals [7].

Prolonged acclimatisation is associated with a progressive increase in haemoglobin (Hb) concentration, initially due to haemoconcentration secondary to reduced plasma volume and subsequently driven by hypoxia-induced erythropoiesis [6,7,16]. Andean populations exhibit higher Hb levels than Sherpas, who maintain values similar to those observed in acclimatised lowland populations [7].

In high-altitude natives, elevated pulmonary pressures do not immediately reverse with oxygen administration due

Table 1. Physiology and cardiovascular adaptations to acute and chronic altitude exposure.

Physiological variable	Acute exposure	Chronic exposure
Heart rate	Increased	Normal
Systolic volume	Normal or increased	Decreased
Cardiac output	Increased	Normal
Systemic blood pressure	Initially decreased, then increased	Increased
Pulmonary arterial pressure	Transient increase	Sustained increase
Pulmonary vasoconstriction	Severe	Moderate to mild
Pulmonary vascular remodelling	No, only accentuated pulmonary vasoconstriction	Yes, vascular hypertrophy and thickening
Right ventricular hypertrophy	No	Yes
Right ventricular systolic function	Normal or increased	Mildly decreased
Right ventricular diastolic function	Greater impairment	Less impairment
Variations in left ventricular filling	Increased	Normal or decreased

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to structural remodelling of the pulmonary arteries. However, with prolonged descent to sea level and removal of the hypoxic stimulus, gradual regression of RV hypertrophy and normalisation of pulmonary pressures may occur over a period of up to two years [7,17].

The oldest populations living above 2500 m.a.s.l. include Tibetans and Sherpas in Asia and Ethiopians in Africa (over 25,000 years), whereas in the Americas, Aymara and Quechua populations have inhabited high altitudes for more than 11,000 years. These groups exhibit distinct clinical characteristics, particularly between Tibetan and Andean populations. Tibetans display genotypic adaptation driven by natural selection over millennia, whereas Andean populations are considered to be undergoing phenotypic adaptation [18]. Consequently, Tibetan and Andean populations respond differently to similar environmental stimuli [19]. For example, pulmonary arterial hypertension is more prevalent in Andean populations, whereas increases in systemic blood pressure are less marked compared with Tibetan populations, likely related to genetic factors involving dysregulation of hypoxia-inducible factor-1α (HIF-1α) [6].

The possibility of evolutionary genetic adaptation is plausible, given that these ethnic groups may have resided at high altitude longer than any other populations, making it a critical determinant of cardiovascular phenotypic variation at altitude [19,20]. Prolonged hypoxia induces adaptive changes regulated at the cellular level by the HIF family; among these, dysregulation of HIF-1α has been associated with several pathological processes [21].

Cardiovascular diseases and high altitude

High-altitude pulmonary hypertension

HAPH is defined as a clinical syndrome caused by chronic exposure to hypobaric hypoxia in regions located above 2500 m.a.s.l. It is characterised by a mean pulmonary artery pressure (mPAP) >30 mmHg or systolic pulmonary artery pressure (sPAP) >50 mmHg, measured by right heart catheterisation in the absence of excessive erythrocytosis [3]. It is classified within Group 3 of PH [22,23]. Its global prevalence ranges from 3% to 35%, while in Latin America it varies between 5% and 18%, being more frequent in men. It represents a major health problem in regions such as the Kyrgyz plateau in Ethiopia, the Andean region, and the Tibetan plateau in China [24].

The adaptive response to hypobaric hypoxia in high-altitude populations is hypoxic pulmonary vasoconstriction (HPV), which redistributes blood flow to match ventilation with perfusion and optimise gas exchange. With persistent exposure, pulmonary vascular smooth muscle remodelling occurs, leading to increased pulmonary vascular resistance (PVR) and elevated PAP [25]. Mechanisms involved in HAPH include endothelial dysfunction mediated by nitric oxide (NO) availability [26], oxidative stress through reactive oxygen species (ROS) [27], genetic inheritance involving multigenic variations within the NO pathway, the HIF pathway, and the renin-angiotensin system. Additionally, hypoxia-related signalling molecules, such as HIF-1α–3α, inhibition of voltage-gated potassium channels, and activation of AMP-activated protein kinase (AMPK), lead to membrane depolarisation, increased calcium influx, and pulmonary vasoconstriction [28,29] **(Figure 2)**.

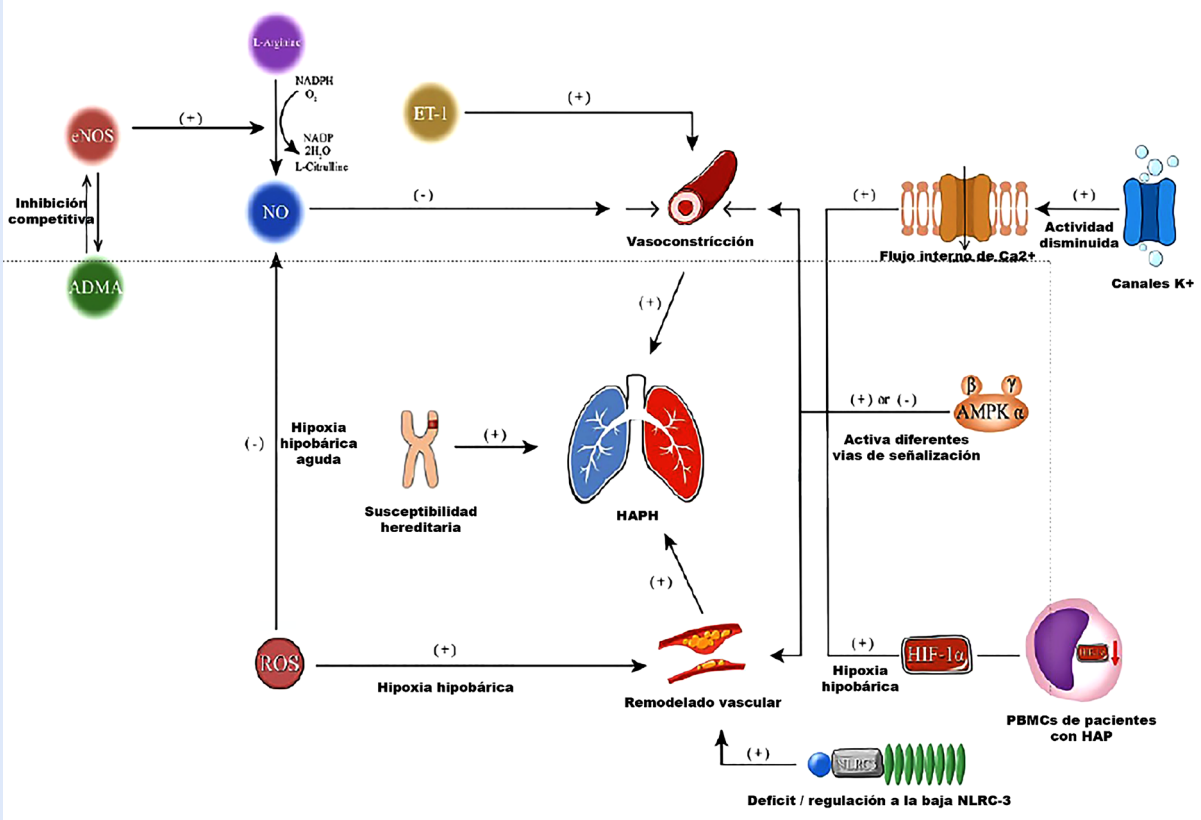
Clinical manifestations are non-specific and include fatigue, progressive dyspnoea, chest pain associated with headache, and cognitive impairment. In advanced stages, signs of right heart failure appear, such as jugular venous distension, hepatojugular reflux, peripheral oedema, hepatomegaly, and ascites [24]. Electrocardiography may show right axis deviation, complete right bundle branch block, and signs of RV overload. Echocardiography typically demonstrates right chamber dilation, tricuspid regurgitation, interventricular septal deviation, and RV dysfunction [30]. Cardiac magnetic resonance (CMR) is the preferred non-invasive modality for evaluating RV function, enabling early diagnosis and risk stratification [31]. The gold standard for diagnosis remains right heart catheterisation performed at altitude, with diagnostic criteria of mPAP >30 mmHg or sPAP >50 mmHg [3].

Management includes non-pharmacological measures such as relocation to lower altitudes and oxygen therapy. Previous studies have shown a reduction in mPAP after two years of return to sea level, accompanied by gradual resolution of pulmonary hypertension symptoms [32]. Administration of oxygen for 30 minutes daily alleviates symptoms in patients with chronic mountain sickness, while long-term oxygen therapy (more than one year) not only corrects hypoxaemia but also improves quality of life [33].

Pharmacological treatment with phosphodiesterase-5 inhibitors and endothelin receptor antagonists has demonstrated reductions in mPAP in experimental studies; however, large-scale clinical trials are still lacking to support routine use. Prostacyclin analogues and carbonic anhydrase inhibitors have shown improvements in RV function and reductions in mPAP in animal models, but further studies in humans are required to confirm their effectiveness [34,35].

Heart failure and high altitude

Heart failure (HF) is currently a major public health problem not only in high-income countries but also in low- and middle-income settings. Epidemiological studies have shown that long-term mortality and the risk of recurrent hospitalisations are similar in HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF) [36]. However, in high-altitude populations, there are no large studies or registries describing the predominant HF phenotype. In Peru, a study conducted in 2006 by Calderón *et al.* [37] in a public hospital in Huancayo (3250 m.a.s.l.) found that among 139 patients with HF, 89.9% had HFpEF and only 10.1% had HFrEF.



ADMA: asymmetric dimethylarginine. AMPK: adenosine monophosphate-activated protein kinase. Ca2+: calcium ion. eNOS: endothelial nitric oxide synthase. ET-1: endothelin-1. HAPH: high-altitude pulmonary hypertension. HIF: hypoxia-inducible factor. HPH: hypoxic pulmonary hypertension. K+: potassium ion. NADPH: nicotinamide adenine dinucleotide phosphate. NLRC-3: NOD-like receptor family CARD domain-containing protein 3. NO: nitric oxide. PBMCs: peripheral blood mononuclear cells. ROS: reactive oxygen species.

Figure 2. Pathogenesis of high-altitude pulmonary hypertension [25].

Hypobaric hypoxia in high-altitude residents increases haemodynamic stressors, particularly due to elevated PAP and erythrocytosis, making right-sided HF clinically relevant as a consequence of HAPH and chronic mountain sickness (*cor pulmonale*) [38]. There is limited evidence regarding differences in prevalence or clinical manifestations of LV HF at altitude; however, hypobaric hypoxia may physiologically exacerbate symptoms in these patients.

Non-native individuals with HF who ascend to high altitude are at increased risk of decompensation due to enhanced beta-adrenergic activity, increased systemic BP and PAP, and reduced systolic volume, particularly in patients with HFrEF [39].

Individuals ascending to high altitude may develop acute mountain sickness (AMS), characterised by headache, nausea, vomiting, dizziness, and fatigue within 6-36 hours of exposure. Symptoms typically resolve within 2-4 days, although in some cases they may progress to high-altitude pulmonary oedema (HAPE) and high-altitude cerebral oedema, collectively referred to as acute high-altitude illnesses [1,6,40].

HAPE is defined as acute respiratory failure caused by environmental hypoxia following recent ascent to altitude in previously healthy individuals without pre-existing cardiopulmonary disease [41]. Although most individuals tolerate and adapt adequately to hypobaric hypoxia, some are susceptible and fail to develop appropriate physiological or acclimatisation responses, increasing their risk of altitude-related illness [40].

HAPE occurs in two clinical settings: in non-residents ascending to altitudes above 3000 m.a.s.l. (type 1 or ascent-related HAPE), and in acclimatised residents or high-altitude natives who return to altitude after a temporary stay at low altitude (type 2 or re-ascent HAPE) [42]. Management includes oxygen therapy and descent to lower altitude; if descent is not feasible, calcium channel blockers (e.g., nifedipine), corticosteroids, or portable hyperbaric chambers may be used [43].

Patients with HFrEF should be clinically stable before travelling to high altitude. Haemoglobin levels should be assessed, and iron supplementation considered if anaemia is present [44]. Although it remains unclear whether treatment thresholds for iron deficiency differ between sea-level and high-altitude populations, achieving haemoglobin levels appropriate for altitude is recommended. The use of ACE inhibitors or angiotensin receptor blockers appears unaffected by altitude;

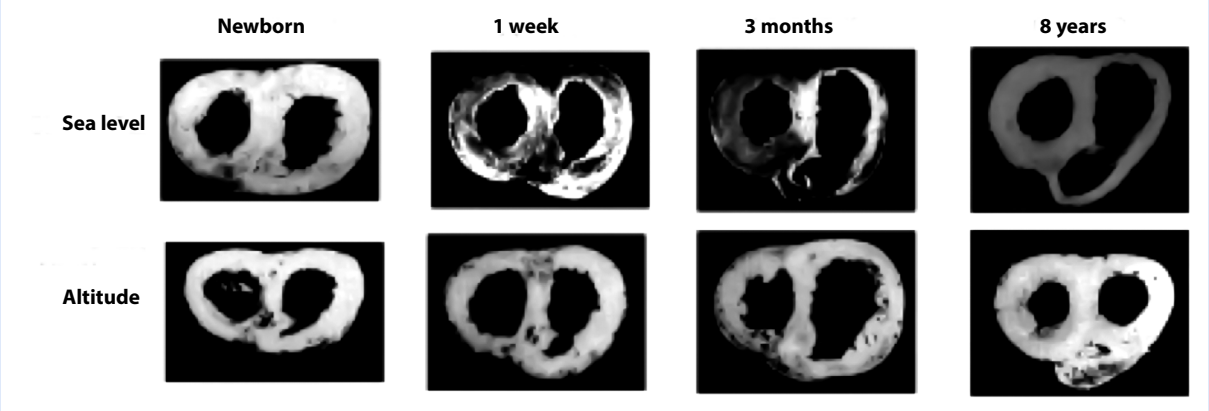


Figure 3. Anatomical specimens of hearts from high-altitude natives and sea-level individuals [55].

however, non-cardioselective beta-blockers such as carvedilol may reduce the hyperventilatory response at altitude, thereby decreasing functional capacity compared with cardioselective agents [45]. Diuretics may increase volume depletion at altitude and should therefore be carefully monitored. Acetazolamide, used in some patients with HFrEF, may reduce pulmonary congestion and the risk of AMS [44]. In patients with HFpEF, optimisation of hypertension and atrial fibrillation management is essential, as both are common in this population. In all patients with HF, gradual ascent is recommended (approximately 300 m/day above 2500 m.a.s.l.) [44].

Congenital heart disease and high altitude

Congenital heart diseases (CHD) are the most common congenital anomalies. According to the Pan American Health Organization, approximately 8 million babies worldwide are born each year with a major congenital anomaly, and one in three deaths attributable to these conditions is due to CHD. These are defined as any structural abnormality of the heart or great vessels resulting from disturbances in embryogenesis between the third and tenth week of gestation [46,47]. Their aetiology is typically related to genetic and environmental factors; among the latter, high-altitude exposure, particularly above 2500 m.a.s.l., has been proposed as a potential contributor [46-48].

In Peru, approximately 1 in 100 live births presents with some form of CHD, yet only about 30% receive adequate medical care, significantly affecting life expectancy. This situation makes CHD a major public health concern [49]. In a Peruvian paediatric referral centre, children exposed to altitudes above 2260 m.a.s.l. during gestation had a 20% higher relative probability of CHD compared with those whose gestation occurred at ≤2260 m.a.s.l. [46].

The distribution of the most common CHDs appears to vary by altitude. At higher altitudes, patent ductus arteriosus (PDA) is the most frequent defect, followed by atrial septal defect (ASD), whereas at lower altitudes (<2500 m.a.s.l.), ventricular septal defect (VSD) predominates [50-53]. Proposed explanations include prenatal hypoxia and oxidative stress resulting from reduced oxygen availability [48], given the critical role of oxygen in ductus arteriosus closure. Additional contributing factors at altitude include prematurity and complicated deliveries, both of which are more common in high-altitude regions with limited access to healthcare and poorer socioeconomic conditions. These factors are associated with higher rates of prematurity and low birth weight. The higher frequency of ASD compared with VSD at altitude may be related to persistently elevated pulmonary vascular resistance, which could impair closure of the foramen ovale. Subsequent normal growth may lead to enlargement of the fossa ovalis, valve dysfunction, and the development of an atrial septal defect. A similar mechanism may explain the increased frequency of ASD in patients with tetralogy of Fallot born at high altitude [51,52]. Other altitude-associated defects include those causing obstruction of the LV outflow tract, such as aortic stenosis, coarctation of the aorta, and hypoplastic left heart syndrome [53].

The teratogenic mechanism involved is likely related to chronic hypobaric hypoxia during embryogenesis. Additionally, other factors beyond altitude may contribute to the development of these defects, including climate, temperature, and environmental exposures such as mining activity and air pollution [53,54]. The interaction of these factors, together with the genetic background of high-altitude populations, may influence the incidence of congenital heart disease at altitude.

Given that PDA and ASD are the most common CHDs, it is important to recall that these conditions produce pulmonary vascular overcirculation, which determines the severity of clinical manifestations. Pulmonary vascular resistance is high at birth; therefore, the pressure gradient between pulmonary and systemic circulation across the defect is minimal or absent. Consequently, murmurs and clinical manifestations appear only when pulmonary pressures decrease below

systemic levels, allowing left-to-right shunting and pulmonary overcirculation. It is well established that at high altitude, pulmonary pressures do not decrease as rapidly as at sea level. A pioneer in this field was Dante Peñaloza, who demonstrated that newborns at high altitude have a thick layer of vascular smooth muscle in small pulmonary arteries and arterioles. At sea level, rapid vascular remodelling leads to a prompt decrease in pulmonary vascular resistance. In contrast, in individuals born at high altitude, vascular remodelling occurs more slowly over time. This significantly influences the natural history of these conditions, resulting either in delayed onset of clinical manifestations (murmurs and heart failure) or, in some cases, rapid progression to irreversible PH, particularly in large defects with significant left-to-right shunting [55,56].

Specimens reported by Peñaloza also demonstrate persistent right ventricular hypertrophy in high-altitude residents, associated with sustained elevated pulmonary pressures and limited pulmonary vascular remodelling, which delays the reduction in pulmonary vascular resistance [55] **(Figure 3)**.

In Latin America, many CHDs are still diagnosed in the postnatal period, often based on clinical signs such as tachypnoea, cyanosis, abnormal pulses, and heart murmurs. However, murmurs may be absent even in severe CHDs, limiting their diagnostic utility. Therefore, prenatal diagnostic evaluation, such as fetal echocardiography, should be promoted as part of routine antenatal care, as it enables early diagnosis and appropriate management of complex CHDs. Additionally, it is important to validate at high altitude the use of pulse oximetry, a widely used tool at sea level for postnatal CHD screening [57].

Author contributions

MCD: conceptualisation, methodology, investigation, supervision, original draft writing, and review and editing. **MLS, ADL, OAT, AGL, CRB, FGV, SRC, JSP:** investigation, original draft writing, and review and editing.

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