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Special article

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

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ABSTRACT

In this second part of the narrative review on cardiovascular pathology at high altitude, the clinical and pathophysiological characteristics of acute and chronic coronary artery disease, cardiac arrhythmias, and arterial hypertension under conditions of hypobaric hypoxia are addressed. Finally, the main gaps in current knowledge and the opportunities for the development of research aimed at achieving a better understanding of these conditions in populations permanently residing at high altitude are highlighted.

Keywords: Hypoxia; Altitude; Cardiovascular Diseases; Arterial Hypertension; Arrhythmias (Source: MeSH-NLM).

RESUMEN

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

En esta segunda parte de la revisión narrativa sobre la patología cardiovascular en gran altitud, se abordan las características clínicas y fisiopatológicas de la enfermedad coronaria aguda y crónica, las arritmias cardíacas y la hipertensión arterial en condiciones de hipoxia hipobárica. Finalmente, se destacan los principales vacíos en el conocimiento actual y las oportunidades para el desarrollo de investigaciones orientadas a comprender mejor estas enfermedades en las poblaciones que habitan permanentemente a gran altitud.

Palabras clave: Hipoxia; Altitud; Enfermedades Cardiovasculares; Hipertensión Arterial; Arritmias (Fuente: DeCS-BIREME).

Acute and chronic coronary syndromes at high altitude

It is estimated that 19.8 million people died from cardiovascular disease (CVD) in 2022 (32% of all global deaths), of which 85% were due to myocardial infarction (MI) and stroke [1].

In Europe, the incidence of MI is 293 per 100,000 inhabitants [2], whereas in Peru, the overall rate reported in 2023 is 25.6 per 100,000 individuals [3]. Lower rates have been described at high altitude; for example, a study conducted in Bolivia at 4000 m.a.s.l. reported a prevalence of 2.9 per 100,000 inhabitants [4]. In Peru, lower rates are also observed in high-altitude regions: Pasco (4330 m.a.s.l.) 7.02 per 100,000; Junín (4107 m.a.s.l.) 8.49 per 100,000; Puno (3827 m.a.s.l.) 5.87 per 100,000; and Cusco (3400 m.a.s.l.) 11.43 per 100,000, compared with Lima and Callao at sea level, with rates of 32.89 and 48.64 per 100,000, respectively [3]. Additionally, lower coronary mortality has been reported; in a Swiss national cohort of individuals living between 259 and 1960 m, mortality decreased by 22% for every 1000 m increase in altitude [5].

Regarding traditional risk factors for CVD at altitude, male sex, overweight, hypertension (HTN), and type 2 diabetes mellitus (T2DM) are the most prevalent [6]. A study in the Middle East comparing high- and low-altitude populations found no differences in clinical presentation, although heart rate and blood pressure were higher at altitude. Hyperlipidaemia and a history of coronary artery disease were significantly more common at higher altitudes, whereas T2DM, smoking, and HTN were similar across altitudes [7]. High-altitude exposure has also been associated with increased coagulability. In a study comparing patients with acute coronary events at moderate altitude versus sea level, those living at high altitude had significantly higher mean platelet volume, suggesting increased platelet aggregability [8].

Acute exposure to high altitude triggers an increase in heart rate and pulmonary ventilation due to sympathetic activation, with responses proportional to the duration and intensity of hypoxia. This leads to increased coronary blood flow through coronary vasodilation [9]. In healthy individuals, myocardial blood flow (MBF) increases both at rest and during exercise when acutely exposed to 4500 m.a.s.l. In contrast, in patients with coronary artery disease exposed to 2500 m.a.s.l., MBF increases at rest but not during exercise. Regarding coronary flow reserve (CFR), in healthy individuals exposed to 4500 m.a.s.l., exercise-induced CFR is preserved, whereas in patients with coronary artery disease it decreases by approximately 18% at 2500 m.a.s.l. [10]. Therefore, in patients with coronary artery disease, altitude increases the risk of myocardial ischaemia, mainly because atherosclerosis may precipitate paradoxical coronary vasoconstriction in response to exercise and hypoxia [11].

Conversely, experimental studies in mice have shown that gradual exposure to severe systemic hypoxaemia leads to inhibition of oxidative metabolism, reduced production of reactive oxygen species (ROS), decreased oxidative DNA damage, and reactivation of cardiomyocyte mitosis. Notably, hypoxaemic exposure one week after the induction of myocardial infarction (MI) triggered a robust regenerative response, characterised by reduced myocardial fibrosis, increased coronary collateral formation, and improved left ventricular systolic function. These findings suggest that the endogenous regenerative capacity of the adult mammalian heart can be reactivated through gradual systemic hypoxaemia, highlighting the potential therapeutic role of hypoxia in regenerative medicine [12].

Similarly, a small study found that intermittent exposure to hypobaric hypoxia (HH) may improve myocardial perfusion in patients with chronic coronary syndrome who were progressively exposed to simulated altitude, starting at 2400 m.a.s.l. and reaching 4200 m.a.s.l. This suggests a potential alternative strategy for the management of coronary artery disease [13,14]. Although these findings support a possible therapeutic role of HH in cardiac recovery after MI, further studies are required to better understand the mechanisms underlying improved cardiac function.

However, concerns remain regarding the safety of intermittent HH, particularly in post-MI patients. Intermittent HH may induce unfavourable biochemical changes, including reduced antioxidant capacity and increased lipid peroxidation, which may impair vascular endothelial function and deteriorate vascular haemodynamics. Additionally, intermittent HH can generate oxidative stress that reduces nitric oxide (NO) bioavailability, an endothelium-derived vasodilator, and may contribute to a hypertensive response [15].

Chronic exposure to hypoxia has been associated with cardiomyocyte synthesis of proteins such as hypoxia-inducible factor (HIF), which regulates the expression of multiple genes with cardioprotective properties. These include stimulation of NO synthesis, increased erythropoietin production, promotion of angiogenesis, enhanced mitochondrial energy production, and antioxidant effects [16]. Indeed, individuals living at high altitude have been shown to develop more coronary collateral vessels, as hypoxia stimulates the production of NO and vascular endothelial growth factor, leading to coronary vasodilation and angiogenesis [14,17]. Furthermore, certain nitric oxide-derived products have been linked to the development of coronary ectasia through activation of matrix metalloproteinases, enzymes responsible for degrading the extracellular matrix of the vascular wall [18]. However, a case-control study in patients with ST-segment elevation myocardial infarction found no association between chronic exposure to high altitude and the presence of coronary ectasia [19].

Regarding lipid metabolism under hypoxic conditions, cells adapt by reprogramming the expression of genes involved in energy metabolism through the HIF pathway. These genes encode proteins involved in fatty acid uptake, synthesis, storage, and utilisation, as well as lipoprotein endocytosis. This includes upregulation of low-density lipoprotein receptor-related protein, which mediates LDL internalisation in vascular smooth muscle cells, and increased expression of the VLDL

receptor in cardiomyocytes [20]. Accordingly, high-altitude populations have been reported to exhibit a high prevalence of hypertriglyceridaemia, hypercholesterolaemia, and low levels of high-density lipoprotein (HDL) cholesterol [21]. In a Peruvian study conducted at 4100 m.a.s.l., higher haemoglobin levels were directly associated with increased total cholesterol, LDL cholesterol, non-HDL cholesterol, and triglyceride concentrations [22].

In a cross-sectional analytical study in Peru, higher altitude was significantly and inversely associated with 10-year Framingham risk scores, mainly due to lower mean systolic blood pressure and a lower prevalence of diabetes; however, no differences were observed in total cholesterol or HDL levels [23].

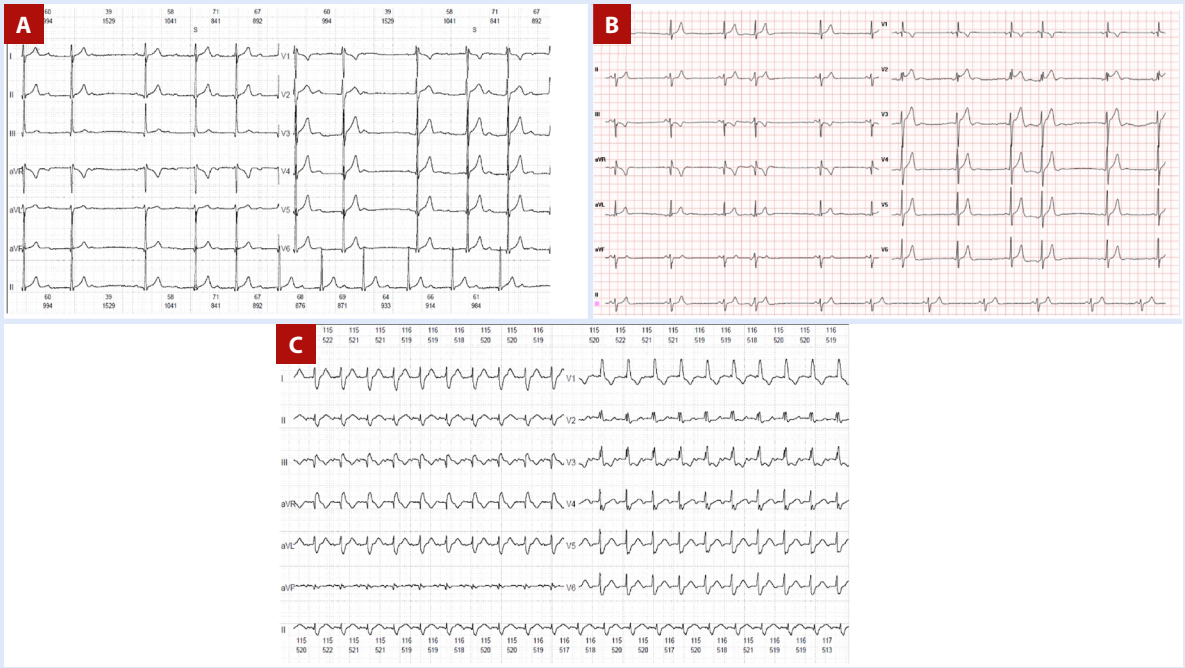
Although current evidence remains limited, the following recommendations can be considered for patients with coronary artery disease travelling to high altitude [11-38]:

- Patients should be advised to maintain adequate hydration, avoid exercise on the first day at altitude, and plan gradual increases in physical activity.
- A pre-travel cardiac evaluation is recommended (including echocardiography and exercise testing), and ongoing medications should be continued.
- Patients should wait at least 6 months after an uncomplicated acute coronary syndrome or revascularisation before travelling to high altitude.
- According to the Canadian Cardiovascular Society (CCS) functional classification:

    - Low-risk patients (CCS 0-1) may safely ascend up to 4200 m.a.s.l. and perform light to moderate physical activity.
    - Moderate-risk patients (CCS 2-3) may ascend cautiously up to 2500 m.a.s.l., but more intense physical activity is contraindicated.
    - High-risk patients (CCS IV) should avoid high-altitude exposure.

Cardiac arrhythmias and high altitude

The Altitude Non-differentiated ECG Study (ANDES) systematically reviewed the available literature on electrocardiographic (ECG) changes in healthy high-altitude native populations. The main ECG characteristics described included rightward QRS axis deviation, signs of right ventricular hypertrophy, a higher prevalence of T-wave inversion in right precordial leads, and a longer corrected QT interval (QTc)



BIRDHH: incomplete right bundle branch block. BCRDHH: complete right bundle branch block.

Figure 1. Electrocardiograms of patients living above 2500 m.a.s.l. with arrhythmic conditions sharing a baseline right bundle branch block (RBBB) pattern. **A)** ECG of a 55-year-old man: second-degree atrioventricular block (Mobitz I) with incomplete right bundle branch block (IRBBB). **B)** ECG of a 37-year-old woman: sinus bradycardia with IRBBB and an isolated atrial extrasystole. **C)** ECG of a 61-year-old man: atrial flutter with 2:1 conduction and complete RBBB (Courtesy of Dr Cynthia Vargas).

compared with sea-level residents, although still within normal limits. Although increases in P-wave amplitude or duration, variations in the PR interval, and a higher prevalence of complete right bundle branch block (RBBB) were reported, these findings were not conclusive [24].

Acute exposure to hypobaric hypoxia at high altitude affects the autonomic nervous system, leading to changes in heart rate (HR), which increases at rest and during submaximal exercise during the first week of exposure, and subsequently decreases due to increased vagal tone [25]. Other findings, such as right axis deviation, RBBB, and changes in P-wave and T-wave amplitudes, are commonly observed during ascent and typically resolve after return to lower altitude [25,26]. Dante Peñaloza and Echevarría demonstrated that rightward and posterior axis deviation in lowland individuals exposed to 4500 m.a.s.l. developed progressively and slowly, explained by changes in cardiac position and early right ventricular hypertrophy. Additionally, T-wave inversion in right precordial leads appeared during the first months of exposure and gradually decreased over one year, suggesting a functional adaptation to hypoxaemia and right ventricular overload. They also found that one year of residence at high altitude was insufficient to produce QRS changes comparable to those observed in native high-altitude populations [27]. **Figure 1** illustrates ECG tracings of high-altitude individuals showing the characteristic RBBB pattern.

Arrhythmias and acute exposure to high altitude

Exposure to high altitude may favour the development of cardiac arrhythmias due to hypoxaemia, electrolyte imbalances, and periodic breathing, although the available evidence remains limited. The autonomic nervous system plays a key role in the generation of bradyarrhythmias through antagonistic activation of sympathetic and parasympathetic pathways. Periodic breathing, similar to sleep apnoea, further exacerbates this imbalance. In addition, hyperventilation during acute high-altitude exposure leads to respiratory alkalosis with hypokalaemia and hypocalcaemia, alterations that prolong the QT interval and increase the risk of ventricular arrhythmias, particularly in the setting of dehydration, electrolyte disturbances, and vulnerable populations [28].

These findings were corroborated in the SUMMIT study, where more than one in three healthy individuals developed bradyarrhythmias (38%) or ventricular tachyarrhythmias (5.9%) while climbing Mount Everest (above 5300 m.a.s.l.). Most rhythm disturbances were recorded below 7300 m.a.s.l., where climbers generally did not use supplemental oxygen, whereas fewer arrhythmias were observed with supplemental oxygen despite greater altitude exposure [29]. Similarly, a study using implantable Holter monitoring in 16 healthy British military personnel exposed to the summit of Mount Dhaulagiri (8167 m.a.s.l.) found rhythm disturbances in 56.3% of cases, occurring only above 4100 m.a.s.l. Notably, 53.3% of participants experienced significant pauses (>3 seconds) with increasing altitude and duration of exposure, most of which were sinus pauses, with high-grade conduction block observed in only two cases [30].

Sudden death (SD) is one of the leading causes of mortality among tourists ascending to high altitude, particularly in men, older individuals, and those with a history of myocardial infarction. The risk of fatal arrhythmias and SD is low in individuals with stable coronary artery disease or heart failure travelling to altitudes below 2500 m.a.s.l. When left ventricular ejection fraction is normal and no arrhythmias are detected during exercise testing at sea level, the risk of SD remains low even at altitudes up to 3500 m.a.s.l. However, gradual acclimatisation is recommended, along with avoidance of intense physical exertion, maintenance of adequate hydration and nutrition, and continuation of usual pharmacological treatment. In patients with pacemakers or implantable cardioverter-defibrillators, device function should be verified prior to high-altitude exposure [31-33].

Arrhythmias in high-altitude residents

Prolonged exposure to high altitude leads to a reduction in HR through desensitisation of the adrenergic pathway, as a protective and adaptive mechanism to low oxygen availability. This may contribute to a lower prevalence of arrhythmias in high-altitude natives compared with individuals acutely exposed to altitude.

There is limited evidence regarding whether high-altitude natives have a higher or lower risk of arrhythmias compared with sea-level populations. A study conducted in La Paz [34], aimed at identifying the most frequent arrhythmias in patients with right ventricular dysfunction due to left-sided heart disease or congenital heart disease, found that the most common arrhythmias were atrial fibrillation (AF) (77%), atrial flutter (11%), atrial tachycardia (10%), and ventricular and supraventricular extrasystoles (2%). No cases of ventricular tachycardia were identified. In multivariable analysis, erythrocytosis and moderate-to-severe right atrial dilation were associated with the development of supraventricular arrhythmias, particularly AF.

Hypertension and high altitude

Hypertension (HTN) is a major public health problem associated with substantial morbidity and mortality worldwide. High-altitude populations are also affected and share similar pathophysiological mechanisms and complications with individuals living at lower altitudes. Current therapeutic approaches do not differ according to existing guidelines; however, certain subgroups of hypertensive patients at high altitude present specific characteristics that warrant consideration.

According to the Peruvian Tornasol I and Tornasol II studies, the prevalence of HTN at high altitude is approximately 27% [35]. More recently, the "May Measurement Month" (MMM) initiative, led globally by the International Society of Hypertension and the World Hypertension League, with support from the The Lancet Commission on Hypertension, conducted a study in the Puno region of Peru (3860-4600 m.a.s.l.) in 2025, reporting a prevalence of HTN of 34.27%. Notably, 38% of men and 66%

Table 1. Proposed classification of patients with hypertension at high altitude.

Groups	Classification of hypertensive patients at high altitude
I	High-altitude hypertensive patients similar to those at low altitude
II	Diastolic hypertensive patients associated with hyperviscosity due to excessive erythrocytosis at altitude
III	Native high-altitude hypertensive patients relocating to lower altitudes
IV	Low-altitude hypertensive patients ascending to high-altitude regions

of women were unaware of their hypertensive status. Among those previously diagnosed, 62% of men and 38% of women had uncontrolled blood pressure levels (>140/90 mmHg) despite receiving treatment (unpublished data).

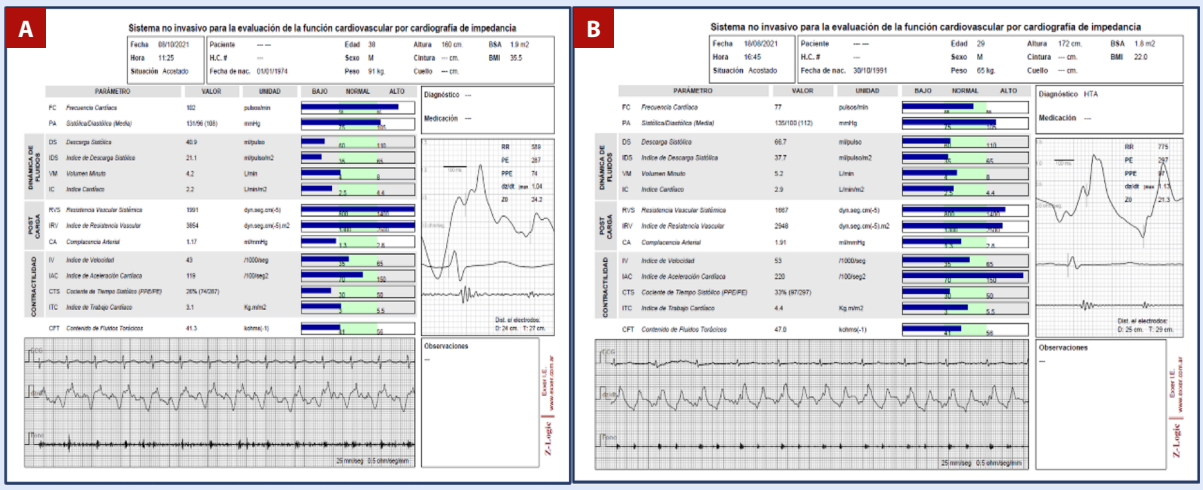
It is important to highlight that a study conducted in residents chronically exposed to altitude in Cerro de Pasco reported an HTN prevalence of 7% using conventional measurements, which increased to 20% when assessed with 24-hour ambulatory blood pressure monitoring (ABPM). These findings suggest that HTN prevalence may be underestimated when conventional measurement methods are used [36]. Additionally, a greater increase in nocturnal blood pressure has been observed, associated with reduced oxygen saturation during sleep and the occurrence of central sleep apnoea, often accompanied by periodic breathing patterns [37].

We propose an approach to patients with HTN at high altitude by classifying them into four groups **(Table 1)**, based on findings from our high-altitude laboratory.

Group I does not differ from hypertensive patients at low altitude; they share the same pathophysiology, disease course, and associated complications.

Group II, according to preliminary studies of hypertensive patients with excessive erythrocytosis at altitude, shows a haemodynamic pattern assessed by impedance cardiography characterised by a normal cardiac index, increased peripheral resistance, and normal or reduced thoracic fluid content **(Figure 2)**. These patients typically present with normal systolic blood pressure and elevated diastolic blood pressure and are usually younger **(Figure 3)**.

Group III includes high-altitude native hypertensive individuals who relocate to lower altitudes and exhibit a distinct blood pressure behaviour; with the same medication, their blood pressure decreases, requiring adjustment of antihypertensive doses. Suppression of the renin-angiotensin-aldosterone system, reduced blood viscosity, and elimination of hypoxic vasoconstriction likely contribute to blood pressure reduction after descent **(Figure 4)**.



CI: impedance cardiography. PAD: diastolic blood pressure.

Figure 2. A) Impedance cardiography (IC) of a 38-year-old man, born in La Rinconada, Puno (5100 m.a.s.l.), with elevated diastolic blood pressure and haemoglobin level of 24.8 g/dL. **B)** IC of a 29-year-old man, born in Ananea, Puno (4550 m.a.s.l.), with hypertension diagnosed 3 months prior, untreated, and haemoglobin level of 25.1 g/dL.

Group IV comprises patients originally from and diagnosed at low altitude who are exposed to high altitude. These individuals experience increases in blood pressure due to generalised sympathetic hypertonia and consequent vasoconstriction. Arterial hypoxaemia is sensed by peripheral carotid chemoreceptors, and the signal transmitted to the midbrain triggers this response. The result is a consistent and persistent rise in blood pressure within hours of exposure, proportional to the altitude reached [36].

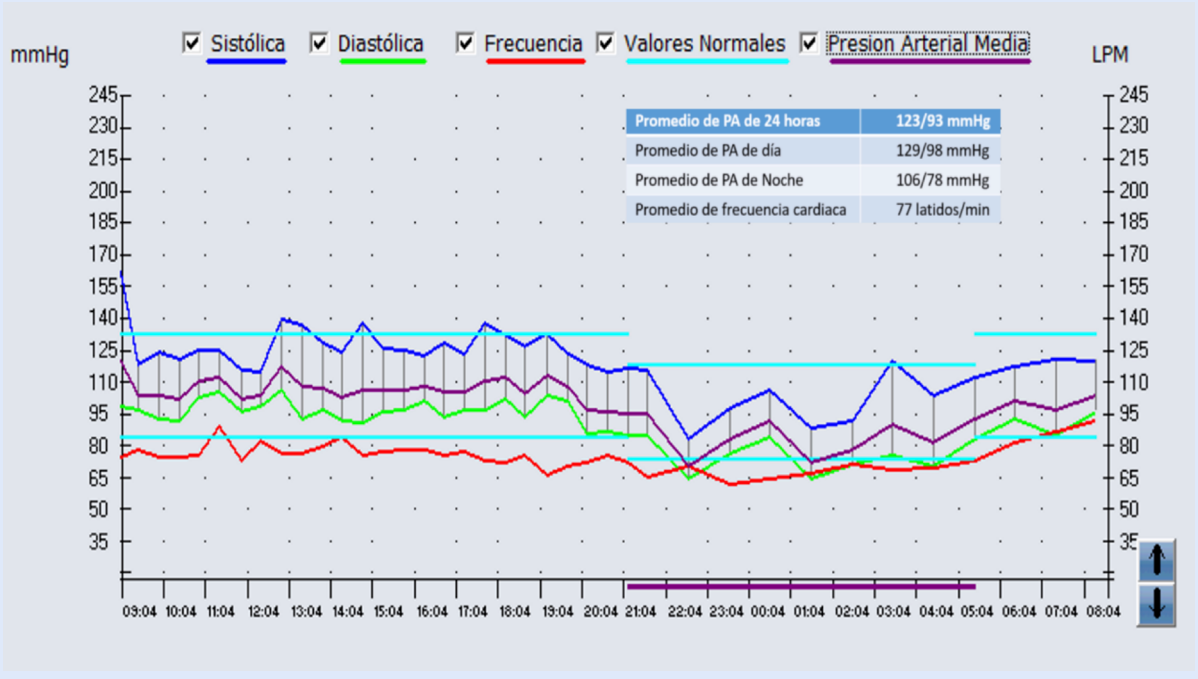
Regarding clinical management, Group I should follow current guideline-based recommendations. In Group II, based on their characteristic haemodynamic profile, a combination of drugs targeting the renin-angiotensin-aldosterone system and calcium channel blockers is suggested. Reducing blood hyperviscosity is also essential, achieved through phlebotomy in combination with carbonic anhydrase inhibitors and statins, which have been shown to significantly reduce haemoglobin levels and, consequently, blood viscosity in these patients. Group III requires clinical reassessment at lower altitudes to adjust medication doses as needed. Patients in Group IV should undergo individualised evaluation by their physicians prior to ascending to high altitude [38].

Finally, HTN is not a contraindication to high-altitude exposure, except in patients with high cardiovascular risk, in whom pharmacological treatment should be optimised and education provided regarding potential risks and preventive measures **(Table 2)** [38]. Therefore, hypertensive patients should not be discouraged from travelling to high altitude.

Conclusion

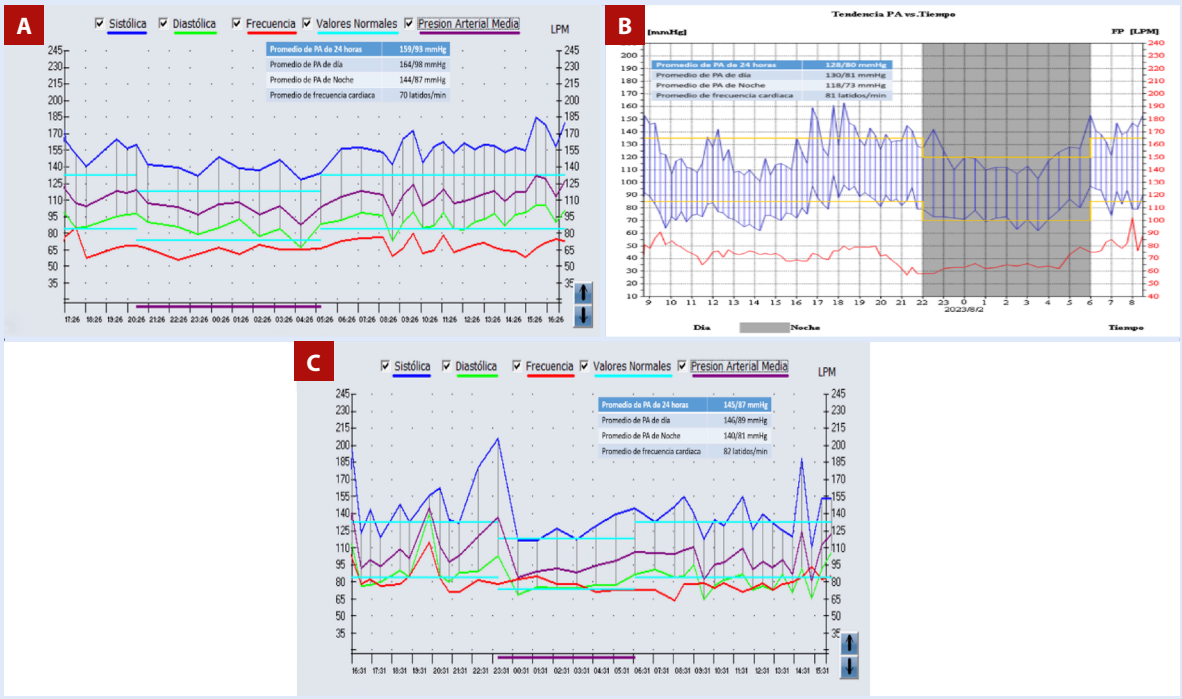
The mechanisms of cardiovascular adaptation and maladaptation in response to acute or chronic hypoxia remain an area of ongoing scientific debate. Cardiovascular diseases commonly observed at sea level exhibit distinct pathophysiological features at high altitude, underscoring the need to understand these differences to optimise prevention, diagnosis, and treatment in both native high-altitude populations and individuals acutely exposed to these environments. Important questions remain regarding the determinants of adaptive responses, as some individuals develop effective compensatory mechanisms while others experience cardiovascular dysfunction; these differences are likely influenced by genetic, epigenetic, environmental, and lifestyle factors specific to high-altitude populations.

Current evidence on the efficacy and safety of conventional cardiovascular pharmacological and non-pharmacological therapies under hypobaric hypoxic conditions remains limited. Addressing this knowledge gap requires the promotion of



ABPM: Ambulatory Blood Pressure Monitoring.

Figure 3. Ambulatory blood pressure monitoring (ABPM) curve of a 35-year-old woman, born in Juliaca, Puno (3860 m.a.s.l.), currently working in La Rinconada (5300 m.a.s.l.), diagnosed with hypertension 1 year ago, treated with enalapril 10 mg twice daily, haemoglobin 23.2 g/dL.



ABPM: Ambulatory Blood Pressure Monitoring.

Figure 4. Ambulatory blood pressure monitoring (ABPM) curves of a 65-year-old woman, born in Juliaca, with a 6-year history of hypertension, obesity, and treated with telmisartan 80 mg and amlodipine 10 mg. She reports that her blood pressure "drops significantly" when travelling to Lima. She usually resides 1 month at high altitude and 15 days at sea level. **A)** 24-hour ABPM performed at high altitude. **B)** 24-hour ABPM performed 3 days after arrival at sea level. **C)** 24-hour ABPM in Juliaca, on the third day after returning to high altitude by air.

epidemiological studies that examine the prevalence, clinical characteristics, genetic factors, and biomarkers associated with cardiovascular diseases in high-altitude populations, particularly in the Peruvian Andes. Furthermore, it is essential to investigate the impact of climate change, migration, environmental pollution, and the urbanisation of high-altitude rural areas on cardiovascular risk and disease expression. Such efforts are crucial to generate local evidence that supports the development of clinical guidelines tailored to the Andean context.

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.

Table 2. Recommendations for patients with HTN travelling to high altitude [38]

Recommendations	Class of recommendation	Level of evidence
Patients with moderate to severe HTN and moderate-to-high cardiovascular risk should monitor blood pressure before and during their stay at altitude.	IIa	B
Patients with controlled or mild HTN may ascend to high altitude (>4000 m) with appropriate medical treatment.	I	C
Patients with uncontrolled or severe HTN should avoid exposure to high altitude to prevent target organ damage.	I	C
In patients with moderate to severe HTN, or those with moderate-to-high cardiovascular risk planning prolonged stay at altitude, appropriate adjustment of antihypertensive therapy should be considered in collaboration with their physician.	IIa	C

HTN: hypertension.

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