Cardiac arrhythmias in highlanders with a diagnosis of chronic cor pulmonale

Arritmias cardíacas en habitantes de gran altura con diagnóstico de corazón pulmonar crónico

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Abstract

Background: Chronic cor pulmonale (CPC), with increased presentation in high-altitude inhabitants. **Objectives:** The objectives of the study were to investigate the frequency of cardiac arrhythmias and risk factors for its development. **Methods:** A descriptive, cross-sectional study, the inpatient registry of the Department of Cardiology of the National Institute of Thorax, La Paz-Bolivia, from January 2017 to June 2018 was reviewed, all were incorporated with the diagnosis of CPC, defined by clinical criteria, electrocardiographic and echocardiographic, 162 patients who met the criteria were taken, the Student's t-test and ANOVA were used for the analysis. **Results:** Arrhythmias: atrial fibrillation (AF) 125 (75%), atrial flutter (AA) 17 (10.5%), atrial tachycardia (AT) 17 (10.5%), and extrasystoles 3 (1.9%). Univariate analysis of factors related to the development of arrhythmias: erythrocytosis: FA, RR: 1.33, other arrhythmias RR: 1.67, $p = 0.0001$, pulmonary arterial hypertension: FA, RR: 3.10, other arrhythmias RR: 3.21, $p = 0.0001$, right atrial dilation (AD): FA, RR: 1.92, other arrhythmias RR: 2.13, $p = 0.0001$, obesity: FA, RR: 3.47, $p = 0.001$, other arrhythmias RR: 3.70, $p = 0.001$, systemic arterial hypertension: FA, RR: 3.10, $p = 0.001$, and other arrhythmias RR: 3.21, $p = 0.001$. Multivariate analysis: erythrocytosis (RR: 2.2), AD dilation (RR: 1.2), $p = 0.0001$. **Conclusions:** AF was found more frequently in patients with CPC, the risk factors with the greatest statistical significance for presentation were erythrocytosis and AD dilation.

Key words: Atrial fibrillation. Pulmonary arterial hypertension. Erythrocytosis.

Resumen

Antecedentes: El corazón pulmonar crónico (CPC) muestra un incremento en habitantes que viven en grandes altitudes. **Objetivo:** Investigar la frecuencia de arritmias cardíacas y factores de riesgo para su desarrollo. **Métodos:** Estudio descriptivo y transversal; se revisó el registro de pacientes internados del Departamento de Cardiología del Instituto Nacional de Tórax, La Paz, Bolivia, entre enero de 2017 y junio de 2018; se incorporó a todos los individuos con diagnóstico de CPC, definido por criterios clínicos, electrocardiográficos y ecocardiográficos; se incluyó a 162 pacientes que cumplieron los criterios en el análisis; se utilizaron la t de Student y ANOVA. **Resultados:** Arritmias: fibrilación auricular (FA), 125 (75%); aleteo auricular (AA), 17 (10.5%); taquicardia auricular (TA), 17 (10.5%); extrasístoles, 3 (1.9%). Según el análisis univariado, los

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factores relacionados con el desarrollo de arritmias fueron: eritrocitosis: FA, RR: 1.33, otras arritmias (RR: 1.67), $p = 0.0001$; hipertensión arterial pulmonar: FA, RR: 3.10, otras arritmias (RR: 3.21), $p = 0.0001$; dilatación de aurícula derecha (AD): FA, RR: 1.92, otras arritmias (RR: 2.13), $p = 0.0001$; obesidad: FA, RR: 3.47, $p = 0.001$, otras arritmias (RR: 3.70), $p = 0.001$; hipertensión arterial sistémica: FA, RR: 3.10, $p = 0.001$, otras arritmias (RR: 3.21), $p = 0.001$. Según el análisis multivariado: eritrocitosis (RR: 2.2), dilatación de AD (RR: 1.2), $p = 0.0001$. **Conclusiones:** Se encontró FA con mayor frecuencia en los pacientes con CPC; los factores de riesgo con mayor significancia estadística para su presentación fueron la eritrocitosis y la dilatación de la AD.

Palabras clave: Fibrilación auricular. Hipertensión arterial pulmonar. Eritrocitosis.

Introduction

The cities of La Paz and El Alto are at 3,577 and 4,050 MASL¹, respectively, and, together, they have a population of 2,904,996 inhabitants, out of whom half is spread at different ecological levels of the La Paz department; barometric pressure at this altitude is 490 mmHg and FiO₂, 0.21 (21%), with very special climatic variations and cold and dry temperatures.

As a chronic acclimatization mechanism, natives to this height have higher pulmonary pressure values than those who live at sea level, with normal pulmonary pressure for the altitude¹.

Chronic cor pulmonale (CCP) is a right ventricular (RV) structural alteration (hypertrophy or dilatation) and functional impairment resulting from pulmonary pressures elevation in relation to diseases of the lung parenchyma and its vascularization, of the upper respiratory tract, or chest wall. RV dysfunction due to the left-sided heart disease or congenital heart disease is not regarded as CCP².

In the field of work, this population is found in, CCP is a common heart condition^{3,4}, as an effect of alterations that occur with hypoxemia or pulmonary vascular-arterial obstruction. It has a solid connection with chronic obstructive pulmonary disease, pulmonary tuberculosis chronic sequelae, and pulmonary thromboembolic disease.

CCP incidence and prevalence are variable due to the diversity of entities that trigger it and, consequently, its epidemiology is linked to the causes that originate it.

Material and Methods

This study is of descriptive and cross-sectional nature and was performed from January 2017 to June 2018. Its purposes were to determine which cardiac arrhythmias are the most common in CCP diagnosed patients admitted to the Cardiology Department of the National Thorax Institute of La Paz, Bolivia, and to find

out the predisposing risk factors for the development of cardiac arrhythmias. For data collection, the medical records of patients admitted to this hospital were reviewed; the inclusion criteria asked for patients with CCP established diagnosis through clinical (increased second heart sound, presence of tricuspid regurgitation murmur or pulmonary insufficiency, and systemic venous congestion), electrocardiographic (RV Sokolow-Lyon > 11 mm, and Lewis indices < -14 mm), and echocardiographic criteria, with RV dimensions and systolic pulmonary artery pressure (sPAP) determination being obtained by this same method (RV free wall thickness > 5 mm increase, RV basal segment dilatation > 42 mm, RV length > 86 mm, tricuspid regurgitation, sPAP > 35 mmHg, and right atrium (RA) dilatation > 18 cm²), with permanent residence in the cities of La Paz and El Alto, with patients with diseases other than pulmonary hypertension (hypertensive heart disease, ischemic heart disease, and rheumatic heart disease) being excluded.

The risk factors that were found were high altitude pathological erythrocytosis (hemoglobin > 17 g/dL for women and > 18 g/dL for men, and hematocrit > 62.1%)⁵, dyslipidemia (total cholesterol > 200 mg/dL and HDL-C < 70 mg/dL)⁶, high blood pressure (systolic blood pressure > 130 mmHg and diastolic pressure > 80 mmHg)⁷, established and controlled type 2 diabetes mellitus (HbA_{1c} < 7.0%)⁸, obesity (BMI > 25 kg/m²)⁸, and smoking.

Supraventricular arrhythmias such as atrial fibrillation (AF), atrial flutter (AFL), atrial tachycardia (AT), and ventricular and supraventricular extrasystoles were identified; no ventricular arrhythmias were identified. As ECG data of AF characteristics, an average heart rate of 78 bpm and presence low voltage in the frontal plane were assumed to probably be attributed to overweight or lung disease and right bundle branch block in a 70-year-old patient, without left bundle branch block being found.

Table 1. Patient general characteristics

	Overall (162)
Age	68.7 ± 12
Gender	
Males	77 (47.5%)
Females	85 (52.5%)
Pulmonary arterial hypertension	
Mild pulmonary arterial hypertension (PAP, 35-50 mmHg)	27 (16.7%)
Moderate-to-severe pulmonary arterial hypertension (PAP, 51-70 mmHg)	135 (83.3%)
Erythrocytosis	95 (56.8%)
Smoking	41 (25.3%)
Obesity	34 (24%)
High blood pressure	63 (38.9%)
Dyslipidemia	56 (34.6%)
Diabetes mellitus	8 (4.9%)
Right atrial dilatation	
Mild dilatation (area < 18 cm ²)	27 (16.7%)
Moderate to severe dilatation (area, 18-26 cm ²)	135 (83.3%)
Right ventricular dilatation	162 (100%)

For analysis, the SPSS statistical package, version 23.0, was used, and absolute frequencies, relative frequencies, and contingency tables were obtained; for related factors' analysis, Student's t-test was used for univariate analysis and the ANOVA test for multivariate analysis; in both analyses, related factors' relative risk (RR) was calculated.

Results

A total of 224 patients were analyzed; 62 did not meet the study inclusion criteria and 162 met the clinical, electrocardiographic, and echocardiographic inclusion criteria, with an average age of 68.7 ± 12 years (52.5% females); patient general characteristics are described in [table 1](#).

Most common arrhythmias were identified to be AF, with 125 (77%); AFL, with 17 (11%); AT, with 17 (10%); and ventricular and supraventricular extrasystoles, with 3 (2%); no ventricular tachycardia episodes were identified ([Fig. 1](#)).

In the univariate analysis ([Table 2](#)), the main factors related to the development of arrhythmias were erythrocytosis, moderate pulmonary arterial hypertension, moderate and severe RA dilatation, obesity, and high

Table 2. Univariate analysis

	AF and other arrhythmias (n = 162)	Relative risk (95% CI)	p-value
Erythrocytosis			
AF	83 (87.4%)	1.33	0.0001
Other arrhythmias	12 (12.6%)	1.67	0.0001
Pulmonary arterial hypertension			
AF	125 (77.2%)	3.10	0.0001
Other arrhythmias	37 (22.8%)	3.21	0.0001
Moderate-to-severe right atrial dilatation			
AF	94 (75.2%)	1.92	0.0001
Other arrhythmias	30 (18.5%)	2.13	0.0001
Obesity			
AF	30 (18.5%)	3.47	0.001
Other arrhythmias	4 (2.46%)	3.70	0.001
High blood pressure			
AF	50 (30.8%)	3.10	0.001
Other arrhythmias	13 (8%)	3.21	0.001

AF: Atrial fibrillation.

blood pressure. When the multivariate analysis was performed ([Table 3](#)), a higher statistical significance was observed for erythrocytosis and moderate-to-severe RA dilatation as supraventricular arrhythmias development promoting factors, in particular AF.

Discussion

The cities of La Paz and El Alto (Bolivia) have a numerous high-altitude native population, which makes for patients with arrhythmias in this population to be of particular interest; some of the pathophysiological aspects that are involved in their development differ from those in the rest of populations that live at lower altitudes¹.

Natives residing at high altitudes actually have higher pulmonary pressure in comparison with those who live at sea level¹; this, added to the high incidence of lung disease and tuberculosis present in this setting, contributes for the incidence of CCP to be very high³.

In addition, due to various factors, CCP patients have been observed to tend to develop cardiac arrhythmias, especially of the supraventricular type⁹, including RA dilatation¹⁰, which is secondary to the severe pulmonary hypertension associated with this disease, and both trigger an alteration in atrial remodeling¹¹.

Very few studies in the world describe the relationship with these aspects; most correspond to descriptions of

Table 3. Multivariate analysis (ANOVA) of risk factors for the development of arrhythmias

Risk factors	Relative risk (RR)	p
Erythrocytosis	2.2	0.0001
Right atrial dilatation	1.2	0.0001
Pulmonary arterial hypertension	1.01	0.001

Figure 1. Arrhythmias frequency.

isolated reports on the incidence of cardiac arrhythmias at high altitude.

In the presence of chronic hypoxia-associated RA dilation, the most common cardiac arrhythmias that are to be expected include AFL, supraventricular extrasystoles, and AT; however, in this protocol, the main cardiac arrhythmia in patients with CCP was observed to be AF in a large percentage (77%) and, much less frequently, AFL (11%); this entails that, in addition to factors such as pulmonary hypertension and right cavities' dilatation secondary to chronic hypoxemia, factors that generate supraventricular arrhythmias, including erythrocytosis, may intervene.

In the multivariate analysis, the presence of erythrocytosis was found to be the most important risk factor for the development of AF (RR, 2.02; $p = 0.0001$) and, to a lesser extent, right atrial moderate dilatation (RR, 1.02).

One of the causes of pulmonary artery hypertension is chronic altitude sickness (defined as a loss of adaptation to high altitudes), which can be primary or an effect of lung disease, obesity, sleep apnea, and old age. As a consequence, a compensatory response is activated, and erythropoietin secretion and erythrocyte load are increased¹²; the presence of secondary pulmonary hypertension increases mortality so that these

cases are related to high RV hypertrophy, distal pulmonary arteries excessive muscularization, and adventitial thickening¹³.

It has been postulated that chronic hypoxia at high altitudes, added to a chronic loss of acclimatization to altitude (chronic altitude sickness) and chronic inflammation, might favor the establishment of a pathophysiological substrate, known as triple hypoxia, and influence on high-altitude pathological erythrocytosis accelerated development¹³.

The development of secondary erythrocytosis in a patient with CCP living at high altitudes is, therefore, an adverse prognostic factor that predisposes to the development of AF, which, in turn, contributes to hemodynamic deterioration of these patients^{9,11}.

In addition, the probability of developing cardiovascular episodes in the ensuing 10 years has been observed to be higher in subjects with erythrocytosis, in comparison with patients without it, and this probability is higher in the subgroup of individuals with moderate-to-severe pulmonary arterial hypertension¹⁴.

A hypothesis that may explain the pathophysiology of AF indicates that, initially, high-altitude hypoxia occurs and, in some cases, it can be added to a chronic loss of acclimatization to altitude, which causes chronic alveolar hypoventilation¹⁵, followed by an increased stimulation of erythropoietin production¹⁶, which increases the production of red blood cells.

Once pathological erythrocytosis is established, a chronic inflammatory state and vascular rheology alteration due to higher blood viscosity are produced, which, in turn, predisposes to high blood pressure¹⁷ and also leads to decreased tissue oxygenation, with endothelial dysfunction appearance.

Chronic heart disease, a constant inflammatory state, and endothelial dysfunction are substrates that are characteristically described as predisposing factors for AF genesis^{18,19}, as also high blood pressure has²⁰, but not erythrocytosis.

Inflammation partly causes atrial structural and electrical remodeling; in its presence, atrial conduction heterogeneity is accentuated by altering the expression of connexins, a factor that alters intercellular coupling²¹.

Once AF is chronically established, it worsens the clinical state of the patient with CCP⁹ and, in turn, it increases patient hemodynamic deterioration. For this reason, the development of erythrocytosis becomes an important risk factor in the genesis of AF and, therefore, for poor prognosis in patients with CCP.

Conclusions

The most common arrhythmia in high-altitude inhabitants with CCP is AF. The risk factors for the development of cardiac arrhythmias, especially AF, in patients with CCP who live at high altitudes, are erythrocytosis and RA severe dilatation.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this research.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained informed consent from the patients or subjects referred to in the article. This document is in the possession of the corresponding author.

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