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# High Altitude May Protect Against the Early Development of Irreversible Pulmonary Hypertension in Patients With Congenital Heart Disease

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## ABSTRACT

Congenital heart disease (CHD) occurs at increased prevalence at high altitude, but there may be a paradoxical later onset of the development of Eisenmenger syndrome. We hypothesized that congenital heart disease patients at high altitude are protected from an early onset of irreversible pulmonary hypertension. We present a ospective observational case series study, supported by a PVRI grant, of patients in La Paz, Bolivia, located at 3600 m, who underwent surgery for CHD. 10 consecutive patients aged 5 to 29 years (mean 12) with left-to-right shunts and pulmonary hypertension underwent diagnostic catheterization to assess pulmonary pressure pre-operatively and six to 9 months postoperatively, and had a lung biopsy performed at the time of the surgery. Control lung tissue was obtained from patients living at the same altitude who underwent pulmonary hydatid cyst resection. 10 CHD patients and 4 control patients were analyzed. Pre-operatively, the patients had a significant response to hyperoxia with a fall in mean pulmonary pressure (mPAP) from 59.6 mmHg (SD 7.74) to 46.3 mmHg (SD 11.1); ($p < 0.05$). Postoperatively, the patients had an excellent response to surgery, with a mPAP of 26.4 mmHg (SD 6.42) ($p < 0.05$ vs. preoperative pressures). Analysis of the lung histology did not show evidence of pulmonary vascular remodeling in the CHD patients compared to the control patients. During the follow-up in up to 11 years, pulmonary pressure assessed by echocardiography remained normal. In conclusion, chronic hypobaric hypoxemia at high altitude may delay the development of pulmonary vascular disease in CHD patients.

## 1 | Introduction

There is a higher prevalence of congenital heart disease among children born at high altitude, increasing from approximately 1% at sea level [1–4] up to 2.5% at 4000 m elevation [5–9]. Worldwide, 140 million people live at elevations greater than 2500 meters, and thus, there is a significant impact of this increased prevalence. In Bolivia, 60% of the population lives at high altitude [10].

A major consequence of uncorrected CHD with left to right shunting is the development of irreversible pulmonary hypertension called Eisenmenger syndrome: The highly elevated

**Abbreviations:** ASD, atrial septal defect; CHD, congenital heart disease; mPAP, mean pulmonary arterial pressure; NYHA, New York Heart Association; PDA, patent ductus arteriosus; SD, standard deviation; VSD, ventricular septal defect.

pulmonary resistance results in a reversal of shunt direction from systemic to pulmonary to predominantly pulmonary to systemic. Eisenmenger syndrome is a consequence of increased pulmonary blood flow, subsequent increased pulmonary artery pressure and resistance by unfavorable vascular remodeling; the pathophysiology is thought to result from endothelial cell dysfunction, abnormal shear stress, circumferential wall stretch, and an imbalance in vasoactive mediators, promoting vasoconstriction, inflammation, thrombosis, cell proliferation, impaired apoptosis, and fibrosis in the setting of a left to right shunt [11, 12].

The current recommendation is to operate on patients with relevant post tricuspid left to right shunts before 1 year of age [13]. Patients with known left to right shunts that are pressure restrictive and do not result in any or significant pulmonary hypertension do not need to have early surgery. When pulmonary hypertension develops, there is poor exercise intolerance and decrease in the quality of life as well as worse life expectancy. The development of pulmonary hypertension correlates with the pulmonary blood flow volume of left to right shunting and the location and size of the defects. Untreated, the pulmonary resistance rises too and may become irreversible: about 10%–20% of patients with CHD with left to right shunt will develop Eisenmenger syndrome [12, 14–16].

Strikingly, at our pediatric cardiac referral hospital located in La Paz, Bolivia with an altitude of 3600 m above mean sea level, in 20 years, we have not seen any Eisenmenger physiology in non-syndromic inhabitants of high altitude, even up to 18 years of age, suggesting that high altitude may be protective against the development of early pulmonary vascular disease and Eisenmenger syndrome in CHD. We thus hypothesized that chronic hypobaric hypoxemia delays the development of severe vascular remodeling and Eisenmenger syndrome in patients with untreated left to right shunts. We conducted a prospective case-control observational study, using a sequential, nonselected series of patients presenting for surgical correction of left to right shunts. As a control group, unaffected lung tissue biopsies from patients living at high altitude with pulmonary hydatidosis who underwent thoracic surgery were also analyzed. We found no significant changes in the pulmonary vascular histopathology in this cohort of patients with left to right shunting at high altitude relative to the controls, as would be expected with similar patients at lower elevation [12].

## 2 | Patients and Methods

This prospective observational study was conducted at Kardiozentrum, La Paz, Bolivia, located at 3600 m and the surgeries in Cochabamba at 2560 m. All the patients included in this series lived in the surrounding area of La Paz at similar elevation (between 3600 and 4000 m). The study was approved by the Ethics Committee at the San Andres University in La Paz, Bolivia and by the Institutional Review Board at the University of Colorado, USA.

### 2.1 | Inclusion and Exclusion Criteria

We included consecutive patients living at high altitude (> 3000 m), parents (or patients if age at least 18 years old) who agreed to informed consent, prior diagnosis of post-tricuspid left to right shunt as ventricular septal defect (VSD) and/or patent ductus arteriosus (PDA), indication for surgical closure, and diagnosis of pulmonary hypertension before the procedure (systolic pulmonary pressure > 40 mmHg) based on interventricular or PDA gradient in echocardiography.

The exclusion criteria were chronic pulmonary disease (such as tuberculosis), pregnancy, or Down syndrome. Patients with a diagnosis of Trisomy 21 were excluded because of the possibility of the development of pulmonary hypertension secondary to chronic lung disease associated with the syndrome, even in the absence of a CHD [13].

### 2.2 | Protocol

Following informed consent, the patients underwent clinical evaluation, measurement of noninvasive oxygen saturation, and echocardiography with an estimation of the pulmonary pressure by the velocity of the flow at the interventricular or PDA shunt level. The heart failure classification was made using the Ross scale for children and the NYHA classification for adults (summarized in Table 1).

### 2.3 | Preoperative Catheterization

After enrollment, the subjects were admitted and underwent diagnostic catheterization in La Paz, including assessment of the flow to the pulmonary circuit in relation with the systemic flow (Qp/Qs) as well as the invasive measurement of the elevated pulmonary pressure and resistance index (Rp/Rs) and their reversibility testing by hyperoxia challenge to establish predicted benefit from surgery by standard guidelines [17]. Preoperative hemodynamic data included invasive measurement of the pulmonary pressure under anesthesia in conditions of ambient air ($FiO_2$ 0.21, percutaneous oxygen saturation approximately 80%) and hyperoxia ($FiO_2$ 1.0, percutaneous oxygen saturation 100%) to establish operative viability (evidence of vasodilation under hyperoxia by change in Qp/Qs, calculated by blood oximetry under both conditions, and decrease of Rp/Rs, calculated by invasive pressures under both conditions). The catheterization was performed under general anesthesia; the oxygen consumption in the calculations was assumed from tables. Once pulmonary vascular reactivity was established, the patient was scheduled for the corrective operation within the next 3 months.

### 2.4 | Corrective Surgery and Biopsy

Corrective surgery was performed by standard surgical techniques under cardiopulmonary bypass in the Hospital Belga in Cochabamba. During the operation a small lung biopsy (ranging in size from 1.5 × 0.6 cm to 0.7 × 0.4 cm) from the right

**TABLE 1** | Demographic and clinical characteristics and histology of the lung biopsies.

| SID | Sex | Age (years) | Weight (kg) (*z*-score) | Diagnosis | Dimension of defect (mm) | ROSS/ NYHA | Histology |
|---|---|---|---|---|---|---|---|
| P01 | M | 13 | 33 (−1.95) | VSD | 17 | 3 | Normal |
| P02 | M | 29 | 58 | PDA | 18 | 3 | Slight connective tissue thickening around vessels |
| P03 | F | 11 | 29 (−1.94) | VSD | 20 | 3 | Normal |
| P04 | M | 5 | 19 (−0.16) | VSD | 12 | 2 | Slight thickening of small vessels |
| P05 | F | 9 | 25 (−1.15) | PDA | 15 | 3 | Small vessel thickening |
| P06 | M | 9 | 22.6 (−1.78) | VSD, ISTA | 17.8 | 3 | Inflammation |
| P07 | M | 12 | 33 (−1.18) | VSD | 8.8 | 3 | Normal |
| P08 | M | 12 | 27.5 (−2.45) | PDA, VSD, SAS | 4.6; 10.0 | 2–3 | Prominent vascular thickening |
| P09 | M | 9 | 28 (−1.1) | VSD | 15 | 2 | |
| P10 | M | 6 | 17 (−1.57) | PDA, VSD, ASD | 4.9; 8.7; 6.8 | 3 | |
| C01 | M | 13 | | PHC | | 1 | Normal |
| C02 | M | 8 | | PHC | | 1 | Inflammation with thickening of the arteries and connective tissue |
| C03 | F | 13 | | PHC | | 1 | Inflammation |
| C04 | F | 13 | | PHC | | 1 | Pleuritic, hemorrhage |

Abbreviations: ISTA, Coarctation of the Aorta; PDA, Patent Ductus Arteriosus; PHC, Pulmonary Hydatid Cyst; SAS, Subaortic Stenosis; SID, subject identification: P patient, C control; VSD, Ventricular Septal Defect (all perimembranous).

upper lobe was obtained, formalin fixed, stained by hematoxylin and eosin or elastin, and analyzed in the University of Colorado, USA.

### 2.5 | Control Lung Tissue

For control patients, normal adjacent lung tissue was obtained from patients who were undergoing pulmonary hydatid cyst resection at the Children's Hospital of La Paz. All control subjects underwent echocardiography preoperatively, and had no evidence of either CHD or pulmonary hypertension.

### 2.6 | Postoperative Catheterization

Six to twelve months after surgery, five of the ten patients underwent a second right heart catheterization to assess pulmonary pressure invasively. The parents of the other five patients did not agree to a second invasive diagnostic procedure.

## 3 | Results

Ten CHD patients and four control patients were enrolled. Nine children and adolescents and one young adult were included in the research protocol, two female and eight male patients between 5 and 29 years of age and between 17 and 62 kg in weight (Table 1). All of the patients had a diagnosis of congenital heart disease based on transthoracic echocardiography, and had physical symptoms of elevated pulmonary pressure, such as dyspnea and chest pain during exercise or upon travel to higher elevations. The case subjects had hemodynamically significant post-tricuspid left to right shunting with large (even up to 20 mm) VSD and/or PDA (either isolated or in combination with each other or with other cardiac anomalies, for example, atrial septal defect (ASD)), (Table 1).

All pediatric patients were characterized by failure to thrive. The children and adolescents had an average Ross classification of 2.4 (range: 2–3), the adult patient NYHA class III. All of case subjects had increased diameters of the left atrium and left ventricle and normal biventricular function on echocardiogram. The percutaneous oxygen saturation during the first echocardiography was at least 90% in all patients.

### 3.1 | First Catheterization

At the preoperative cardiac catheterization, the patients had moderate to severe pulmonary hypertension at room air and a significant response to hyperoxia. During the first catheterization, the pulmonary artery pressures were assessed under ambient air (the oxygen saturation decreased under

anesthesia < 85%, typically 80%) and hyperoxia conditions with $FiO_2$ 1.0, with oxygen saturations measured > 95% (typically 100%). Blood samples were obtained from the right atrium, right ventricle, pulmonary artery and aorta in VSD and PDA patients, and additionally from the superior and inferior vena cava in patients in which an ASD was present to calculate the venous mixed oxygen saturation. The relative index of pulmonary to systemic resistance Rp/Rs was calculated by invasive pressure measurement. The sample collection protocol was repeated under room air and hyperoxia conditions. All patients showed reactivity in the severity of pulmonary hypertension, with enhancement of the Qp/Qs index under hyperoxia and decrease of the Rp/Rs index (Table 2 and Figure 1). There was a significant response to hyperoxia with a fall in mPAP from 59.6 (SD 7.74) to 46.3 mmHg (SD 11.1; $p < 0.05$).

### 3.2 | Surgery

At surgery, the congenital heart defects were corrected. None of the patients died during surgery or afterwards until the present time (up to 11 years follow-up). There were no other major complications. There were several minor complications, including one small pericardial effusion, which resolved with pharmacological conservative management; one postoperative pneumothorax resolved by tube thoracotomy; one case of left ventricular dysfunction, which recovered under pharmacological therapy after several months (in the one adult patient); two transient AV-blocks which spontaneously disappeared without treatment; and two small residual shunts, both of which closed spontaneously.

### 3.3 | Second Catheterization

At the postoperative cardiac catheterization in La Paz, the patients had persistent lower pulmonary artery pressures with a mean pulmonary artery pressure of 26.4 mmHg (SD 6.42) versus preoperative pressures ($p < 0.001$; Table 3 and Figure 2).

### 3.4 | Analysis of Histopathology

A small lung biopsy was obtained during the corrective surgery from eight subjects, per our study protocol. Control lung tissue was obtained at the time of resection of hydatid cyst from four subjects at similar ages, which were living at similar geographical elevation as the patients.

A summary of the histopathology from each case and control is presented in Table 1, with representative images in Figure 3. The biopsy of case subject 7 was the smallest ($0.7 \times 0.4$ cm), and the largest vessel observed was 100 μm diameter without a connective tissue layer, limiting analysis of larger vessels in this specimen. Overall, analysis of the lung histology did not reveal evidence of significant pulmonary vascular remodeling in the CHD patients in comparison to the control patients. All vascular remodeling observed was in the medial and adventitial compartments. In the control subjects, a notable finding was increased vessel thickness in control subject C02, consistent with elevated baseline pulmonary pressure likely due to chronic high-altitude exposure.

## 4 | Discussion

The first description of chronic hypobaric hypoxia was made in 1590 by Father José de Acosta, who described air at 4000 m as "subtle and thin and as not compatible with human life." No wonder, since all babies born to Spaniards died during the first years of the colonization of Potosi, mining city in Bolivia [18]. Babies born to pregnancies at high altitude are exposed to hypoxia in a higher degree as fellows at sea level. Arterial oxygen tension of the cord blood at sea level is 35.1 mmHg and at 3600 m is 14.8 mmHg (own not published data).

Overall, we did not find evidence of Eisenmenger syndrome in patients with CHD who were born and live at high altitude, as suggested by three key results of this study:

**TABLE 2** | Preoperative hemodynamic data. Including invasive measurements of pulmonary pressure under room air (80% oxygen saturation) and hyperoxia (100% oxygen saturation) conditions.

| SID | Age (years) | sPAP room air | dPAP room air | mPAP room air | Qp/Qs room air | Qp/Qs hyperoxia | Rp/Rs room air | Rp/Rs hyperoxia |
|---|---|---|---|---|---|---|---|---|
| P01 | 13 | 80 | 52 | 61 | 2.3 | 5.4 | 0.4 | 0.1 |
| P02 | 29 | 60 | 39 | 46 | 2.7 | 3.2 | 0.3 | 0.2 |
| P03 | 11 | 96 | 59 | 71 | 2.4 | 4.4 | 0.5 | 0.1 |
| P04 | 5 | 81 | 46 | 58 | 1.4 | 4.0 | 0.6 | 0.3 |
| P05 | 9 | 83 | 45 | 58 | 2.6 | 5.8 | 0.6 | 0.1 |
| P06 | 9 | 89 | 32 | 51 | 3.5 | 5.3 | 0.2 | 0.1 |
| P07 | 12 | 81 | 43 | 56 | 4.4 | 5.7 | 0.1 | 0.1 |
| P08 | 12 | 88 | 51 | 63 | 1.4 | 3.0 | 0.8 | 0.3 |
| P09 | 8 | 96 | 61 | 73 | 2.2 | 5.9 | 0.5 | 0.1 |
| P10 | 6 | 84 | 47 | 59 | 2.6 | 5.8 | 0.6 | 0.1 |

Abbreviations: dPAP, diastolic pulmonary artery pressure; mPAP, mean pulmonary artery pressure; Qp/Qs, pulmonary-to-systemic flow ratio; Rp/Rs, pulmonary-to-systemic resistance ratio; SID, subject identification; sPAP, systolic pulmonary artery pressure.

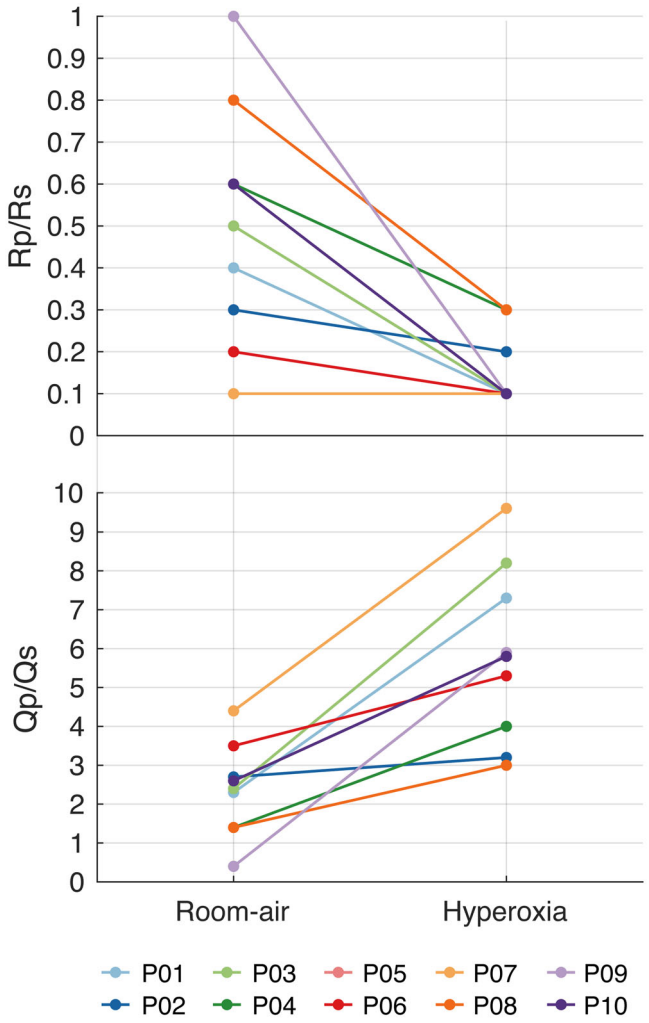


**FIGURE 1** | Change in Rp/Rs (top) and Qp/Qs (bottom) between room-air and hyperoxia exposures during the first catheterization.

**TABLE 3** | Postoperative hemodynamic data. Invasive measurements of pulmonary pressure under room air.

| SID | Months after correction | sPAP mmHg | dPAP mmHg | mPAP mmHg |
|---|---|---|---|---|
| P01 | 6 | 30 | 12 | 18 |
| P02 | 11 | 36 | 13 | 21 |
| P03 | 7 | 41 | 17 | 25 |
| P04 | 9 | 38 | 11 | 20 |
| P05 | 6 | 43 | 24 | 30 |

Abbreviations: dPAP, diastolic pulmonary artery pressure; mPAP, mean pulmonary artery pressure; SID, subject identification; sPAP, systolic pulmonary artery pressure.

1. The pulmonary vasculature was reactive to hyperoxia preoperatively, as evidenced by decreases in Rp/Rs and increases in Qp/Qs.
2. All the patients had excellent hemodynamic response to the corrective surgery, despite ages much older than that generally recommended for surgery (< 1 year old).

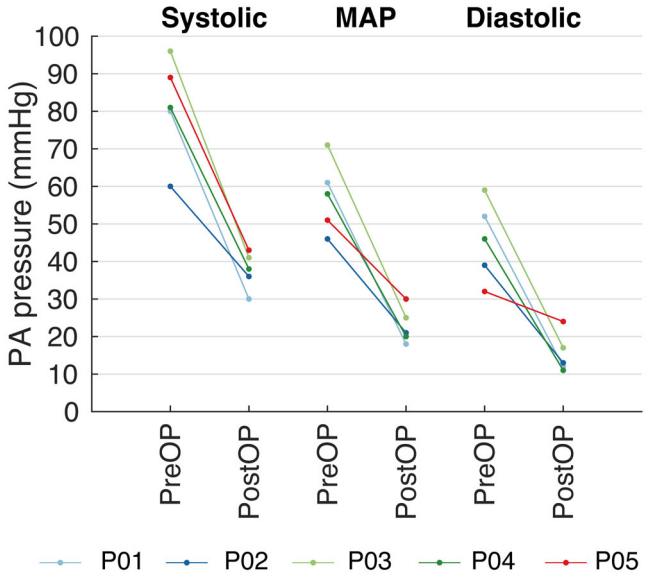


**FIGURE 2** | Comparison of the pulmonary pressures on the pre-op catheterization and post-op control: systolic, mean (MAP) and diastolic arterial pressure.

3. There was no to minimal evidence of pulmonary vascular remodeling in the lung biopsies collected from the CHD subjects, comparable to the findings in the control subjects living at similar altitude.

The mechanism for this observed protection is unclear but may be related to the known elevated pulmonary artery pressures at high altitude, which persist after birth, with an increased pulmonary vascular media thickness that does not regress as fast as at sea level. We speculate that this increased vascular thickness could be protective against further vascular remodeling in the setting of increased shear stress which occurs in CHD patients with left to right shunt resulting in excessive pulmonary vascular flow [19].

The strengths of our study include the assessment of both pre- and postprocedure heart catheterization with invasive measurement of the pulmonary pressures, the analysis of lung biopsies, which was analyzed by pulmonary pathologists (RT, BG) as compared to control tissue obtained from individuals living at the same geographical elevation, and the follow-up from up to 11 years without clinical or echocardiographic data of pulmonary hypertension. The limitations of our study include a small number of subjects, the absence of data or lung biopsies from CHD patients who live at sea level, and relatively small lung biopsies that limit extrapolation to the entire vascular tree.

In conclusion, we found that CHD patients who are born and still live at high altitude may be protected against the early development of irreversible pulmonary hypertension. There are two primary implications of our findings: The first is that CHD patients living at high altitude may have a better prognosis than similar CHD patients living at sea level. The second is that operations which occur later than the standard guidelines (which recommend operation before 1 year of age) may still result in good outcomes in CHD patients living at high geographical elevation.

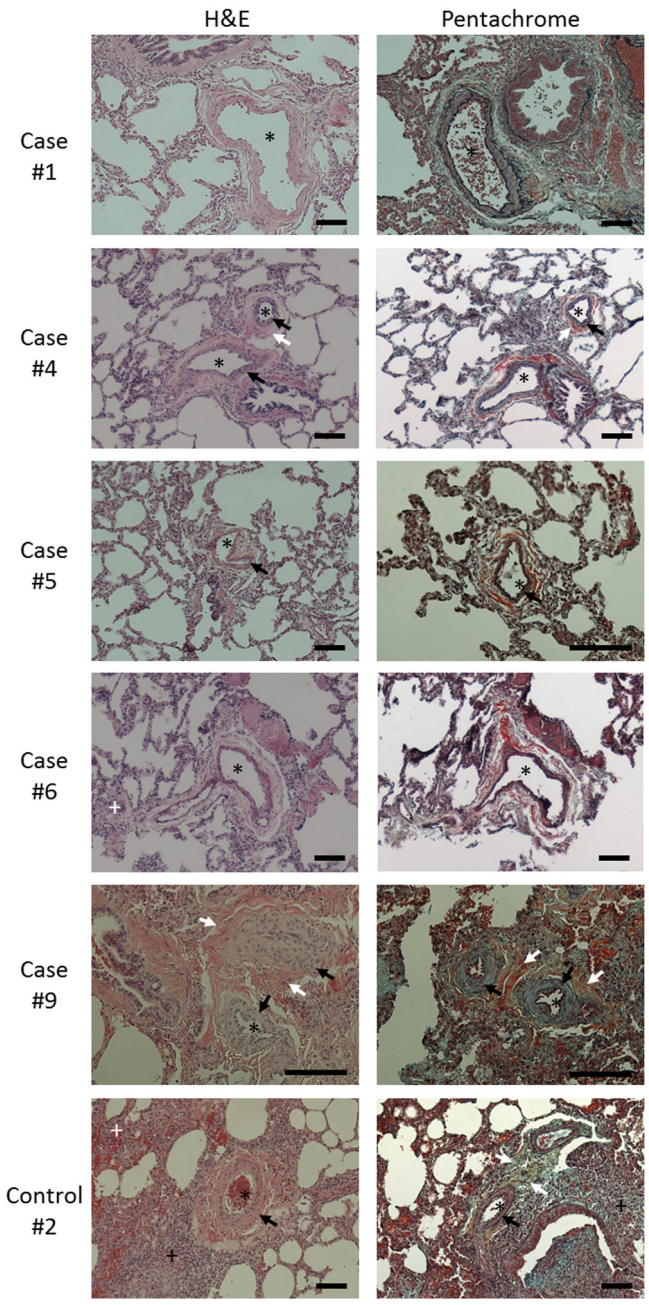


**FIGURE 3** | Representative histopathology from lung biopsies, stained with H&E and pentachrome stains, from 5 cases and 1 control as labeled. All scale bars are 100 μm. All stars mark vessel lumens. Black arrows indicate thickened media layers. White arrows indicate thickened connective tissue layers. Black plus signs indicate areas of adventitial inflammation. White plus signs indicate areas of parenchymal inflammation.

### Author Contributions

Alexandra Heath and Inge von Alvensleben had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Alexandra Heath and Franz Freudenthal designed the study. Alexandra Heath and Franz Freudenthal conducted the heart catheterizations. Carlos Brockmann and Ericka Pérez performed the surgeries. Inge von Alvensleben and Ximena Vicente obtained the biopsies and coordinated the processing of the tissue specimens. Brian Graham and Rubin Tuder contributed to the data analysis including biopsy analysis. Inge von Alvensleben and Alexandra Heath drafted the manuscript. Alexandra Heath and Brian Graham contributed equally to the revision of the manuscript. Gustavo Balanza contributed to the design and presentation of the article. All authors approved the final manuscript. Guarantor statement: Alexandra Heath and Inge von Alvensleben are responsible for the content of the manuscript, including the data and analysis.

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### Ethics Statement

The study was approved by the Ethics Committee for Investigation of the National Committee for Bioethics of Bolivia (CEI-CNB), and informed consent was obtained from the children's guardians or the patients, respectively. The study complied with the Declaration of Helsinki.

### Conflicts of Interest

The only funds came from the PVRI and the foundation Herzverein e.V., registered in Germany. No property or tested technology was purchased, borrowed, or donated to the study. In addition, the authors state that they had full control of the design of the study, methods used, outcome parameters, analysis of data, and production of the written report.

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