Ebstein Repair in a High-Altitude Setting ≥2,500 m: First Experience from Bolivia

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Abstract

Background Contemporary surgical approaches for Ebstein anomaly are based on a paradigm shift towards earlier surgery in order to avoid the deleterious effects of chronic right ventricular (RV) volume overload. In addition, RV dysfunction may worsen in the setting of high altitude, and to date, no results on Ebstein anomaly surgery have been reported from a high-altitude setting.

Methods We herein present first postoperative results from Ebstein anomaly patients who underwent cone reconstruction (with or without bidirectional Glenn anastomosis) in Cochabamba, Bolivia (>2,500 m above sea level) using a specific high-altitude protocol for prophylactic medical treatment of presumed pulmonary hypertension (PH), including sildenafil, iloprost, and higher FiO_2.

Results Four patients underwent surgical correction of Ebstein anomaly (median age 9 years, range 4–12 years, all female). Ebstein anomaly was classified as Carpentier type C in three and as Carpentier Type B in one patient. All patients showed some degree of atrial shunting while one patient exhibited an additional perimembranous ventricular septal defect. All underwent cone reconstruction of the tricuspid valve. Due to massive intraoperative bleeding, which required rethoracotomy, subsequently causing impaired RV function, one patient underwent concomitant "one and a half ventricle" repair. All other patients showed an uncomplicated postoperative course and all were alive with a good and/or improved RV function and only minimal-to-mild tricuspid regurgitation after 1 year.

Discussion Cone reconstruction in children with Ebstein anomaly is feasible in a high-altitude setting when using a dedicated protocol to prophylactically manage PH.

Keywords
- Ebstein anomaly
- cone reconstruction
- bidirectional Glenn anastomosis
- high altitude
- middle- and low-income regions

Introduction

Ebstein anomaly is a rare congenital right heart disease with an incidence of 5.2 per 100,000 live births (1% of all congenital heart defects). The main features of Ebstein anomaly are tricuspid valve (TV) displacement and dysplasia, and a hypoplastic right ventricle (RV).[1] The posterior and septal leaflets of the TV are displaced downwards from the tricuspid annulus

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towards the RV apex. There are several forms with different characteristics due to a wide spectrum varying from a slightly downward location of the septal leaflet and a well-performing RV to a dysplastic valve resulting in a severely dysfunctional RV. Consequently, clinical manifestations and symptoms differ, ranging from asymptomatic patients to those with increasing cyanosis, severe cardiac arrhythmias, and progressive RV failure.[1–3] Ebstein anomaly is recognizable by prenatal ultrasound and usually confirmed by postnatal two-dimensional transthoracic Duplex echocardiography.

Indications and timing of surgical treatment are still a matter of debate, but there is a consensus that surgery may be considered in symptomatic patients with worsening exercise capacity, cyanosis, paradoxical embolism, progressive RV dilation and/or dysfunction, and a new onset of arrhythmias.[2] Contemporary approaches are based on a paradigm shift towards earlier surgery in order to avoid the deleterious effects of chronic RV volume overload and the consecutive development of systolic dysfunction.[4]

Different surgical approaches are described in the literature.[2–5] Standard procedures to reconstruct the TV address the leaflet and annular levels in combination with either horizontal or vertical plication of the atrialized RV, which results in a monocuspid or bicuspid valve. Specific techniques include the *Carpentier–Chauvaud* operation (mobilization and detachment of the anterior and posterior leaflet, longitudinal plication of the atrialized chamber, refixation of the leaflet with a ring to stabilize the valve annulus) and the *Danielson* method (raising of the posterior leaflet to the TV annulus, oblique plication of the atrialized chamber along the TV annulus), among others.[2] In 2004, da Silva and coworkers described the *cone reconstruction* of the TV, which includes complete TV mobilization, clockwise rotation of the inferior leaflet to approximate the proximal edge of the septal leaflet in combination with a thinned longitudinal internal plication of the atrialized RV and plication of the inferior annulus.[5] Nowadays, the cone reconstruction is usually considered the surgical method of choice in most patients with Ebstein anomaly. Depending on the degree of Ebstein anomaly and RV dysfunction, all of the abovementioned reconstructive procedures may be combined with a bidirectional upper cavopulmonary anastomosis (Glenn operation, BDG) in order to facilitate RV volume off-loading in the setting of severe RV dysfunction (so-called "one and a half ventricle" repair).[2–5] In severe neonatal manifestations of Ebstein anomaly, the *Starnes procedure*[6]—which combines subtotal TV closure by leaving a 4-mm fenestration, atrioseptectomy and placement of a modified Blalock–Taussig–Shunt—may be life-saving when TV reconstruction is deemed impossible.[2–5]

High Altitude and Congenital Heart Defects

The physiological changes due to high altitude are well understood in healthy individuals. Even for young healthy individuals, altitude can cause problems in the cardiopulmonary system.[7,8] The effect on those with cardiovascular disease[5] is increasingly studied because of the availability of altitude simulation in a safe and controlled environment.[8,9] Especially, RV dysfunction in the setting of hypoxia and/or pulmonary hypertension (PH) is influenced by high altitude.[10–13] Hypoxia at high altitude is associated with increased pulmonary vascular resistance (PVR) and myocardial work. While these findings are relevant even to healthy individuals, their impact on those with a higher likelihood of right heart failure may be detrimental. In particular, patients with a passive pulmonary circulation, such as Fontan patients, may exhibit lower exercise capacities at high altitude.[12] In addition, Fontan surgery at higher altitudes may be associated with an increased risk of perioperative complications, which is why some groups perform routine fenestration in order to avoid the deleterious effects of sudden increases in PVR.[14] Data on other congenital heart defect repairs at high altitude are sparse. While an Indian study showed that patent ductus arteriosus ligation can safely be performed at high altitude,[15] a Chinese study suggested a higher risk of postoperative cardiac dysfunction in children with congenital heart disease who underwent operation in a high-altitude setting as compared to a matched control group from a lower altitude region.[16] Specifically, patients at high altitude required more FiO_2, inotropic support, pulmonary vasodilators, and had a longer intensive care stay. To date, no study specifically addressing primary RV pathology repair, including Ebstein anomaly, has been reported from a high-altitude setting.

We herein present the first early postoperative and 12-month follow-up results from Ebstein anomaly patients who underwent cone reconstruction (with or without bidirectional Glenn physiology [BDG]) at >2,500 m above sea level using a specific high-altitude protocol for prophylactic medical treatment of presumed PH, including sildenafil, iloprost, and higher fraction of inspired oxygen (FiO_2).

Methods

Setting

In March 2020, four consecutive patients with Ebstein anomaly underwent cone reconstruction of the TV at the Bolivian Belga-Hospital, Cochabamba, Bolivia (2.560 m above sea level). The hospital has a special focus on pediatric cardiovascular medicine and cardiothoracic surgery. Echocardiography was performed preoperatively to determine the type and severity of the disease, TV anatomy and annular dimension, and RV morphology. Postoperative echocardiography was performed daily until discharge. Ebstein anomaly was preoperatively categorized according to Carpentier's classification as type A, B, C, or D, and staged according to the Great Ormond Street Echo Score (GOSE Score[15]; ►**Fig. 1**).

Surgical Technique—Cone Reconstruction ± "One and a Half Ventricle" Repair

Cardiopulmonary bypass (CPB) was established by aortic and selective cannulation of both caval veins. The cone procedure was performed as previously described.[2,4,5] Due to insufficient leaflet structures, autologous pericardial patch augmentation was applied in all cases to achieve TV annulus diameters within normal ranges (according to z-scores). The atrialized RV and inferior annulus were longitudinally plicated from the inside of the RV, and no prosthetic materials, such as rings, were used. In one case, an additional superior

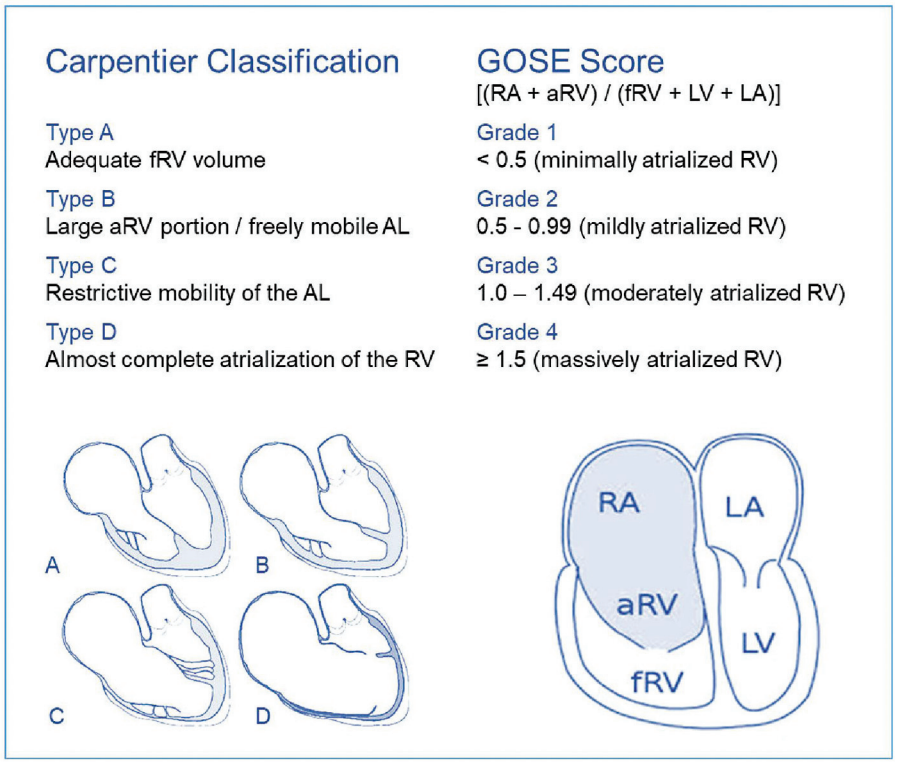

Fig. 1 Carpentier classification of Ebstein anomaly and Great Ormond Street Echocardiographic (GOSE) Score. (Adapted and modified in part from Burri and Lange.[2]) aRV, atrialized RV; fRV, functional RV; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

BDG anastomosis (PCPC, partial cavopulmonary connection) was performed ("one and a half ventricle" repair). Finally, atrial septal defect (ASD) size was reduced in diameter while a patent foramen ovale (PFO) was routinely left open to allow some degree of right-to-left shunting. Intraoperative findings, aortic cross-clamp (ACC) time, and CBP times were documented.

Postoperative Care and Follow-Up

All patients were followed up by direct postoperative echocardiography and clinical examination, which was regularly repeated during the pediatric intensive care unit (PICU) stay. If feasible, a "fast-track" concept with early extubation either in the operating room or directly after admission to the PICU was implemented. All patients underwent a 12-month follow-up examination at 1 year after the operation. The follow-up assessed clinical symptoms, degree of cyanosis, ECG, and echocardiographic analysis, including diameter of the TV and grade of TV regurgitation (TR). All patients underwent prophylactic measures to decrease PVR/RV afterload, including sildenafil, iloprost, and higher FiO_2 after surgery—a strategy that is also used for other congenital heart surgery patients, including children with simple shunt defects.

Results

A total of four patients underwent surgical correction of Ebstein anomaly in March 2020. The patients' median age was 9 ± 3.83 years (ranging from 4 to 12 years), and all patients were female. While cyanosis (peripheral oxygen saturation [SpO_2] <85%) at rest was present in one of the patients, all patients showed mild desaturations (ranging from 86 to 92%). Ebstein anomaly was classified as Carpentier type C in three and as Carpentier type B in one patient. All patients showed some degree of atrial shunting (three type II ASD, one PFO), with one patient having an additional perimembranous ventricular septal defect, which was partially covered by accessory TV tissue. At the time of preoperative presentation, three patients were in sinus rhythm, and one exhibited a high degree (grade II–III) non-reversible atrioventricular block, which resulted from prior electrophysiological studies with radiofrequency ablation of atrial flutter (►**Table 1**). In this patient, implantation of an epicardial dual-chamber pacemaker was performed in addition to Ebstein surgery. All four patients underwent a cone procedure.

Three of the four patients could be treated according to the *fast-track concept* and were extubated in the operation theatre or directly after admission to the PICU. In these three patients, vasopressor and/or inotropic support (epinephrine, noradrenaline, and/or milrinone) was discontinued after less than 48 hours. There was no major postoperative bleeding in these patients. One of the three fast-track patients received a red blood cell (RBC) transfusion due to a hemoglobin level <10 g/dL.

In the fourth patient, the postoperative course was complicated due to massive intraoperative bleeding, which required rethoracotomy, subsequently causing impaired RV function with concomitant "one and a half ventricle" repair. The same patient received a dual-chamber pacemaker as

Table 1 Patient characteristics

Patient	I	II	III	IV
Age (years)	4	7	11	12
Gender (F/M)	F	F	F	F
Height (cm)	87	120	141	152
Weight (kg)	10	27	32	51
SpO_2 (%)	92	80	86	94
Ebstein classification	Carpentier C GOSE III TR grade I	Carpentier C GOSE III TR grade III	Carpentier C GOSE III TR grade III	Carpentier B GOSE II TR grade II
Pulmonary valve	Normal	Minimal PR	Normal	Vena contracta 4 mm
RVSP (mm Hg)	28	26	35	n/a
ASD/PFO (mm)	5 (bidirectional)	4 (predominantly R/L shunt)	13 (bidirectional)	2 (predominantly L/R shunt)
VSD (mm)	–	5	–	–
LV-EF (%)	57	55	58	55
TAPSE (z-score)	+0.5	−0.7	−0.6	+0.8
WHO-FC	I	II	I-II	II
History of arrhythmia	–	–	–	AVB grade II–III AFlut (s/p EP study)

Abbreviations: AFlut, atrial flutter; ASD, atrial septal defect; AVB, atrioventricular block; EP, electrophysiology; GOSE, Great Ormond Street Echocardiographic Score; L/R, left-to-right; LV-EF, left ventricular ejection fraction; PFO, persistent foramen ovale; PR, pulmonary regurgitation; RVSP, right ventricular systolic pressure; s/p, status post; SpO_2, peripheral oxygen saturation; TAPSE, tricuspid annular systolic plane excursion; TR, tricuspid regurgitation; VSD, ventricular septal defect; WHO-FC, World Health Organization Functional Class.

described above. The patient experienced transient postoperative renal failure (without the need for renal replacement therapy), required mechanical ventilation and inotropic support for 3 to 4 days, and received several RBC and fresh frozen plasma transfusions due to significant fluid loss. Despite this complication, the patient could be transferred from intensive care after 4 days.

All patients were perioperatively treated with inhalative iloprost as long as they were intubated and/or received inotropic support (median 32.5 hours, range 2.5–72 hours). Supplemental oxygen and sildenafil (1–2 mg/kg/d) were administered as long as the patients required intensive care (median 2 days, range 2–4 days). Patients were transferred to the regular ward if (a) SpO_2 levels at rest were >94% (without PCPC) or >90% (with PCPC), (b) no significant atrial right-to-left shunting was detected, and (c) tricuspid annular systolic plane excursion (TAPSE) values indicated appropriate RV function.

All patients showed normal sinus rhythm or proper dual-chamber pacemaker function (atrial sensing, ventricular pacing), respectively. We did not observe any cardiac arrhythmias requiring medical and/or electrical cardioversion. Postoperative results by echocardiography demonstrated adequate RV function and absence of high-grade TR in all cases. The intra- and postoperative findings (duration of ACC, CBP time, etc.) are summarized in ►**Table 2**. At 12-month follow-up, all four patients were alive and showed good and/or improved RV function with only minimal-to-mild TR (►**Table 3**). One patient developed ventricular bigeminy and was successfully treated with propranolol (due to a limited local availability of selective beta-blockers). None of the patients developed malignant supraventricular or ventricular tachyarrythmias.

Discussion

Currently, the cone reconstruction of the TV, which is associated with the advantages of decreased reoperation, morbidity, and mortality rates in adults, is the surgical therapy of choice in adult Ebstein patients.[5,17,18] In addition, cone repair can be performed with low early mortality and excellent durability at short-term follow-up in children and young adults with Ebstein anomaly.[19,20]

We herein show that cone-type surgical repair of Ebstein anomaly is feasible in a high-altitude setting and can safely be performed with/without PCPC (Glenn anastomosis) according to the individual anatomic and hemodynamic conditions. Cone reconstruction may exhibit additional beneficial effects on RV function as reduced functional RV volume, improved RV global synchronization, and restored RV geometry, resulting in improved RV performance and improved long-term prognosis.[17] Thus, although cone repair is nowadays considered the standard procedure for Ebstein anomaly, the optimal timing is a matter of ongoing debate. A recently published large cohort from the Mayo Clinic suggests optimal results in patients with good/stable RV

Table 2 Intra- and perioperative data

Patient	I	II	III	IV
Cone procedure (Yes/No)	Yes	Yes	Yes	Yes
Glenn (bidirectional; Yes/No)	No	No	No	Yes
ACC time (minutes)	78	106	120	125
CPB time (minutes)	109	131	186	262
ICU stay (days)	2	2	2	4
Inotropic support (hours)	2.5	47	18	72
Minimum Hb (g/dL)	10.1	12.1	9.9	9.8
Erythrocyte transfusion (Yes/No)	No	No	Yes	Yes
Drainage loss (mL)	124	265	550	>2,000
Pulmonary VTI (cm)	16.9	13.3	19.2	19.5
Cardiac rhythm	Sinus	Sinus	Sinus	Pacemaker
TV anulus diameter (z-score)	+0.8	+0.9	+1	+0.9
RVSP (+CVP) (mm Hg)	16 (+10)	16 (+10)	13 (+10)	16 (+12)
Comment	- Normal renal and hepatic function - Fast track	- Normal renal and hepatic function - Fast track	- Normal renal and hepatic function - Fast track	- Rethoracotomy after bleeding - Pacemaker upgrade to 2C-PM due to SSS - Transient renal failure - Extubation on postoperative day 4

Abbreviations: ACC, aortic cross-clamp; CPB, cardiopulmonary bypass; CVP, central venous pressure; Hb, hemoglobin; ICU, intensive care unit; LV-Fx, left ventricular function; RVSP, right ventricular systolic pressure; SSS, sick sinus syndrome; SVT, supraventricular tachycardia; TR, tricuspid regurgitation; TV, tricuspid valve; VTI, velocity time integral; 2C-PM, dual-chamber pacemaker.

Table 3 12-Month follow-up after cone reconstruction

Patient	I	II	III	IV
TR (grade)	None	I	Minimal	I
TAPSE (z-score)	0.3	1.1	−0.5	0.2
LV-EF (%)	60	58	62	60
SpO_2 (%)	96	97	96	91
SVT (Yes/No)	No	No	No	No
Premature beats >5% (Yes/No)	No	No	No	No
Exercise capacity (parental assessment)	Improved, no symptoms of clinical heart failure	Improved, no symptoms of clinical heart failure	Improved, no symptoms of clinical heart failure	Improved, but still mildly impaired as compared to peers

Abbreviations: LV-EF, left ventricular ejection fraction; SpO_2, peripheral oxygen saturation; SVT, supraventricular tachycardia; TAPSE, tricuspid annular systolic plane excursion; TR, tricuspid valve regurgitation.

function in the absence of cyanosis and clinical signs of heart failure.[18] In addition, the authors suggest waiting until the age of 4 years since this was associated with reduced rates of postoperative complications and a minimized need for PCPC in their cohort. Other authors reported similar findings and showed that cone reconstruction before the age of 4 years was associated with a shorter time to TV reoperation.[19] However, cone repair may be considered at an earlier age in selected cases under the assumption that surgery at a younger age may help preserve RV function, but these findings require confirmation from larger cohorts.[20] Even neonatal cone reconstruction has been described in patients with severe TR due to either neonatal Ebstein anomaly or TV dysplasia with associated pulmonary atresia.[21] However, in their cohort, Mizuno et al. report that only three out of five newborns survived a biventricular approach, thus the Starnes operation is now currently applied in symptomatic neonatal Ebstein patients.[6,21] Of note, all survivors showed a TR jet velocity of greater than 3 m/s, which may serve as an indicator of successful biventricular repair.[21]

In the cohort reported herein, all patients were at least 4 years of age and therefore were not considered to belong to the high-risk group. However, the high-altitude setting represents a significant challenge, as lower partial oxygen pressures under extreme altitude are known to adversely affect RV function and (passive) pulmonary blood flow.[7–13] In general, living at high altitude has adverse effects on patients with single ventricle hemodynamics and may be associated with decreased SpO_2, increased pulmonary artery pressures, and the development of complications such as pulmonary edema or protein-losing enteropathy.[7,8] In a mathematical model study to investigate the effect of high-altitude exposure to BDG, high altitude was associated with increases in PVR and heart rate, which negatively impacted cardiac index, end-diastolic volume, systemic blood flow split (between the upper and lower circulations), ventricular efficiency (Ea/Ees), and oxygen extraction ratio.[9]

Thus, whether Glenn anastomosis is applied or not, postoperative measures to decrease pulmonary resistance should be employed to reduce RV workload. In addition, for the abovementioned reasons, patients with Glenn anastomosis should be advised to move to areas closer to sea level, which represents a significant socioeconomic challenge to the whole family. Despite these considerations, we decided to perform PCPC in one case based on postoperative risk assessment (severely impaired RV function).[2] However, we observed good/improved RV function and increased SpO_2 levels postoperatively and stable results during 12-month follow-up in all four patients.

It is well known that the incidence of certain congenital heart diseases, for example, patent ductus arteriosus, increases with altitude, which is (at least in part) due to a lower partial oxygen pressure at high altitude.[22] In fact, partial arterial oxygen pressures at sea level are approximately 100 mm Hg, which decrease to 60 mm Hg at 3,600 m. Usually, several physiological mechanisms, which include lower pCO_2, subsequent metabolic/renal adaptations, higher hematocrits, and an increased mitochondrial enzyme activity, among others, compensate for some of these impairments after chronic adaptation to hypoxia.[23,24] While these chronic adaptations (in contrast to acute exposure to high altitude) allow for a (near-)normal cardiorespiratory exercise capacity in healthy individuals, cardiorespiratory alterations, even if chronically present, constitute significant challenges after cardiac surgery. Due to a physiologically elevated pulmonary arterial pressure at high altitude (i.e., 32 ± 6.4 mm Hg at 3,600 m in healthy individuals), right heart adaptation after cardiac surgery is associated with a higher risk of postoperative PH.[25] Although at high altitude, simple shunt closures are often possible later in life (due to a prolonged physiologic postnatal decline in PVR), sudden and/or chronic increases in pulmonary artery pressures may cause significant challenges during postoperative care.[25] Furthermore, right heart performance after complex valvular surgery, as in cone reconstruction, with relatively longer CPB times (as compared to simple shunt closures) may further predispose to RV failure. We, thus, implemented a postoperative protocol with prophylactic sildenafil, iloprost, and higher FiO_2 after surgery—a strategy that is also used for other congenital heart surgery patients, including children with simple shunt defects. Of note, inhaled nitric oxide (iNO) support is currently unavailable in Cochabamba, Bolivia.

Sildenafil is known to significantly reduce RV pressure load at rest and exercise in normobaric and hypobaric hypoxia in individuals without congenital heart disease. While in hypobaric or normobaric hypoxia, sildenafil had no significant effects on SpO_2, heart rate, or cardiac output during exercise,[26] experimental data suggest an increased RV contractility at hypoxic exercise with the administration of sildenafil as compared to placebo.[27] In addition, sildenafil usage and efficacy have recently been reported in adults with PH from Quito, Ecuador (located at 2,840 m)[28] and in children with PH (some associated with congenital heart disease) from Bogota, Colombia (located at 2,640 m).[29] While these observations provide a rationale for using PH-targeted therapies at high altitude, systematic evaluations of perioperative PH-targeted therapies for children with congenital heart disease in this setting are still lacking. Of note, our postoperative strategy focused on prophylactically addressing potential hypobaric pulmonary vasoconstriction at high altitude (and thereby decreasing RV afterload) and was not aimed at long-term treatment of PH (as often required after shunt closure). In addition to PH-targeted therapies, catecholamine usage was minimized to not further increase myocardial oxygen consumption, while milrinone was routinely applied. In addition, fast-track extubation as described above was used whenever possible to decrease RV workload.

Of note, in our cohort, all patients underwent patch augmentation of the anterior and/or septal leaflet. As reported in the literature,[30] this technique may be applied when the height of the leaflet is considered "shallow" (there is a distance between annulus and leaflet leading edge). In a recent analysis, the necessity of cone modification (including patch augmentation and Glenn procedure) was not associated with rates of reoperation or progression to greater than mild-to-moderate TR.[31]

Our observations require confirmation from larger cohorts, ideally from prospective observations, which should include patients with and without the need for additional cavopulmonary connections. In addition, long-term outcomes can currently not be assessed in our cohort. However, we hypothesize that early cone reconstruction in childhood will be associated with significant improvements in RV function by avoidance of RV volume overload.[19] Of note, congenital heart disease patients from several high-altitude regions worldwide have only limited access to follow-up care. While these services are principally available in Bolivia, life-long access to follow-up care—including specialists for grown-ups with congenital heart disease (GUCH), arrhythmia/electrophysiology, congenital cardiac surgery, and others[32–34]—cannot be guaranteed in all settings, and treatment decisions must consider these issues.

Conclusion

Cone reconstruction in children with Ebstein anomaly can be performed without early–midterm mortality and excellent durability in a high-altitude setting if appropriate measures are undertaken to prophylactically address perioperative PH. Cone reconstruction nowadays is considered the standard procedure for Ebstein anomaly and, in our opinion, represents the optimal surgical approach for most young patients in order to prevent RV volume overload and subsequent systolic RV failure. Additional cavopulmonary anastomosis function (in "one and a half ventricle" cases) may be negatively impacted by high altitude and should only be considered as a surgical bailout. Further studies on Ebstein pathophysiology and treatment under high-altitude conditions are required to improve the outcome of this challenging condition worldwide.

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Conflict of Interest
None declared.

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