Congenital heart disease and pulmonary arterial hypertension in South America (2013 Grover Conference series)

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Abstract: South America is a territory of 17,819,100 km², where ~388 million people live in 13 countries. In the region, access to medical assistance (e.g., for treatment of cardiovascular disorders) is relatively easy in metropolitan areas but difficult in remote places such as the Andes and the Amazon. Altitudes up to ~6,700 m influence the prevalence of congenital heart disease (CHD) and pulmonary arterial hypertension (PAH). In tertiary centers, CHD is now treated earlier in life but remains an important etiology of PAH. In adolescents and adults with PAH assisted at institutions devoted to treatment of cardiovascular disorders, the relative frequency of PAH-CHD (~50%–60%) is even higher than that of idiopathic PAH. In one big tertiary center in São Paulo, Brazil, the prevalence of advanced PAH in children and adults with CHD is 1.2% and 4.2%, respectively. In young patients with cardiac septal defects (aged up to 2 years), pulmonary vascular abnormalities are a matter of concern in the decision about operability in 4.9% of cases. Access to specific PAH drugs is not uniform in South America, being unrealistic in remote places. In big cities, there are real possibilities for management of complex CHD, neonatal disorders, and even cardiac transplantation. Research activities have been implemented at clinical, translational, and basic levels. However, because of social and economic inequalities and political issues, access to best standards of medical care remains a problem in the region as a whole.

Keywords: congenital heart disease, pulmonary hypertension, pediatric cardiac surgery, von Willebrand factor, survival.

Pulm Circ 2014;4(3):370-377. DOI: 10.1086/676747.

The region of South America corresponds to a total area of 17,819,100 km² and includes 13 countries. The estimated population of 388 million people is not uniformly distributed. While millions live in industrialized areas or cities (e.g., São Paulo, ~19 million, and Buenos Aires, ~13 million), the population density decreases dramatically in remote areas such as the Amazon. The languages spoken include Spanish, Portuguese, English, French, Dutch, Quechua, Guarani, Aymara, and Nahuatl. The major problems in the region are the heterogeneous distribution of economic activity, social contrasts, inequality, and poverty.¹

In addition to social and economic issues, at least 2 factors seem to play an important role in the prevalence and distribution of cardiovascular disorders. The first corresponds to marked geomorphologic differences, with the lowest places at sea level and altitudes exceeding 4,000 m

in the Peruvian altiplano, in the Andes. Second, the population of South America is a composite of ancestries, ethnic groups, and races with diverse genetic backgrounds (white, mestizo, mulatto, Amerindian, black, and mixed).² These factors are important determinants of the prevalence of cardiovascular disorders, including congenital cardiac anomalies and abnormalities of the pulmonary circulation.

ADULT CONGENITAL HEART DISEASE AND PULMONARY HYPERTENSION

Congenital heart disease (CHD) is an important group of cardiovascular disorders affecting pediatric and adult populations worldwide. Despite the global tendency toward early diagnosis and treatment of anomalies such as atrial septal defect (ASD), aortic coarctation, Ebstein's anomaly of

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Submitted January 14, 2014; Accepted March 10, 2014; Electronically published July 15, 2014.

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the tricuspid valve, and congenitally corrected transposition of the great arteries, these conditions are still frequently diagnosed in adulthood. Furthermore, repaired tetralogy of Fallot is prevalent in adult CHD clinics. Of interest, in terms of pulmonary arterial hypertension (PAH), is the fact that congenital cardiac septal defects (ASDs, ventricular septal defects [VSDs], and atrioventricular septal defects) and communications between the great arteries (e.g., patent ductus arteriosus [PDA]) are prevalent in both pediatric and adult populations and alter pulmonary hemodynamics, leading to pulmonary vascular remodeling in a small but significant percentage of cases.

In a survey that was carried out in the European Union,³ ASDs and VSDs were present in 48% and 38% of 1,877 adults with CHD, while cyanotic defects were detected in only 7% of patients. Among patients with ASD, PAH was present in 12% and 34% of those with repaired and unrepaired defects, respectively. Among patients with VSD, PAH was diagnosed in 13% and 28% of those with repaired and unrepaired communications, respectively. The overall prevalence of the Eisenmenger syndrome (the most

advanced form of pulmonary vascular disease and PAH in CHD) was 12% in this survey. This is in contrast with the reported prevalence of ~4% among adults with CHD followed up in specific tertiary centers in London, Toronto, and Zurich.⁴

Numbers may be different if one considers developing nations, particularly underserved areas. Estimates for South America are difficult to obtain, in particular because big registries are lacking. However, institutional data may help in understanding what goes on at the populational level. The Heart Institute (InCor) in São Paulo, Brazil, is a referral tertiary center where patients from distant regions in the country are assisted. In 2012, 7,320 patients (most with CHD) were seen on an ambulatory basis at the Department of Pediatric Cardiology and Adult Congenital Heart Disease. The relative frequencies of specific anomalies in the adult population (~46% of subjects seen as outpatients) are depicted in Figure 1. Of the acyanotic defects, ASD was the most prevalent (35% of all anomalies). Because this center was probably the only one in the country managing cyanotic CHD in the past, tetralogy of Fallot appears in

Figure 1. Relative frequencies of specific congenital cardiovascular anomalies in adults followed as outpatients at the Heart Institute (InCor), University of São Paulo School of Medicine, São Paulo, Brazil. The listed anomalies are represented in the graph in a clockwise fashion.

the second position (18%, mostly repaired defects). Among the adults (3,344 patients), 140 (4.2%) had advanced PAH. Most of them were either cyanotic, presenting the typical features of the Eisenmenger syndrome, or still acyanotic but definitely inoperable ("pre-Eisenmenger syndrome"). A few had postoperative PAH. In the pediatric group (3,976 patients), 48 individuals (1.2%) had advanced PAH and were considered unsuitable for repair of their cardiac anomalies.

In tertiary centers in privileged areas, the incidence of late referral is decreasing. Years ago, the issue of operability (decision about surgery in subjects with cardiac shunts associated with moderate to severe pulmonary hypertension) was discussed for older children (4–15 years of age) with relatively simple lesions that could have been repaired earlier. At present, in most instances this kind of discussion is carried out for subjects in the age range of 0–2 years. In the pediatric population, we estimate that 2.5%–10% of patients require some discussion about the state of the pulmonary circulation before assignment to surgery. This includes not only patients with shunts and elevated pulmonary vascular resistance but also those with systemic-to-pulmonary connections in pulmonary atresia and related anomalies and candidates for cavopulmonary anastomosis who have inappropriate pulmonary vascular beds. Thus, in the age range of 0–2 years, where most patients are now investigated, the problem of late referral still remains, but in many instances early development of pulmonary vasculopathy that precludes surgery is the most relevant issue. Although early diagnosis and treatment constitute quite a real scenario in privileged communities/areas, late referral is still a major problem in underserved regions of Brazil and South America in general. Unfortunately, exact numbers are not available.

Congenital communications between the systemic and pulmonary circulation remain an important etiology of PAH in South America. In Brazil, idiopathic PAH and PAH associated with CHD (PAH-CHD) are the most frequent presentations (each represents 30%–40% of all etiologies), followed by PAH associated with connective-tissue disorders. These overall statistics correspond to tertiary care centers located in metropolitan areas, except for regions where schistosomiasis is endemic. Data collected from 10 tertiary institutions where diverse but predominantly cardiovascular disorders are treated (in 6 different states in the country) indicated that the relative frequencies of idiopathic PAH, CHD, and other etiologies of PAH were 22.9%, 60.7%, and 16.4%, respectively. In 4 of these centers (big ones, with a total of 568 registered PAH patients), the frequencies of idiopathic PAH and PAH-CHD were 31.4% and 53.1%, respectively.⁵ In one center located in an area where schistosomiasis is endemic (northeastern region of Brazil; 293

PAH patients evaluated), this etiology appears in the first position (39% of cases), followed by CHD (26.9%), idiopathic PAH (14.6%), and connective-tissue disease (12.2%).⁵ Thus, at least in centers devoted to the management of cardiovascular disorders, the relative frequency of CHD as an etiology of PAH is even higher when compared with the idiopathic form of the disease.

PEDIATRIC PULMONARY HYPERTENSION AND MANAGEMENT OF CHD

In South America, children with pulmonary hypertension are assisted at institutions with different characteristics, depending on the country and the etiology of the disease. For example, in Colombia and Ecuador, similarly to other countries, children with pulmonary hypertension (including those with PAH-CHD) are generally assisted at institutions devoted to the management of pediatric disorders. As a consequence, the relative frequencies of neonatal and respiratory disorders as etiologies of pulmonary hypertension are high. In Colombia, the average frequencies of neonatal pulmonary hypertension (formerly primary pulmonary hypertension of the newborn), idiopathic PAH, PAH-CHD, and other etiologies (including lung disease and bronchopulmonary dysplasia) are 19.5%, 27.5%, 11%, and 42%, respectively (G. F. Diaz, personal communication). In one referral institution for treatment of pediatric diseases in Ecuador (Patronato Municipal San Jose Sur, in Quito), 25% of naive patients seen by the pediatric cardiologist have pulmonary hypertension. Among these, the relative frequencies of neonatal pulmonary hypertension, idiopathic PAH, PAH-CHD, and other etiologies (including bronchopulmonary dysplasia, diaphragmatic hernia, prematurity, and meconium aspiration) are 15%, 0.3%, 25%, and 59.7%, respectively (P. C. Flores, personal communication). In Brazil, it is difficult to compute the frequency of PAH-CHD relative to other etiologies of pulmonary hypertension in the pediatric population, as these patients are generally treated (and subjected to surgery) at institutions devoted to the management of cardiovascular disorders, where adults are assisted, too. However, it is possible to find numbers for PAH-CHD within the specific group of pediatric CHD patients. In 2012, 739 open cardiac operations were performed at InCor in São Paulo for repair of congenital cardiac anomalies, the majority pediatric cardiac operations (645 procedures). Of these, 244 operations were for treatment of patients in the range of 0–2 years of age. In at least 12 of these patients (4.9%), changes in the pulmonary circulation were considered as a matter of concern in the decision to operate. That is, these patients were considered "at risk" for immediate postoperative complications (pulmonary hypertensive crises, right heart failure)

and/or persistence of PAH following repair of their anomalies. They have been included in a specific study that is being developed in the institution⁶ as a research activity of the Pulmonary Vascular Research Institute (<http://www.pvri.info>). This percentage of 4.9% is within the range of 2%–10% accepted by pediatric cardiologists as the percentage of patients with CHD who deserve special attention in terms of diagnosis and treatment in order to prevent complications of PAH.

As a general rule, in terms of the management of pediatric CHD (and PAH-CHD) in South America, tertiary centers in metropolitan areas and big cities may be considered adequately structured to offer medical and surgical treatment, even to patients with complex anomalies, neonates, and candidates for cardiac transplantation. However, as a consequence of the social and economic scenario, in addition to overall politics of health, relevant problems remain to be solved, such as late diagnosis and referral, particularly in remote areas; specific diagnostic and therapeutic limitations (inhaled nitric oxide is expensive and unavailable in many regions); and difficult access to medications, as is the case of new drugs for the management of PAH. There have been initiatives to overcome some of these problems. In Ecuador, for example, there are programs where doctors move from their institutions to small satellite centers for screening of CHD in underserved populations (P. C. Flores, personal communication).

HIGH ALTITUDE AND PULMONARY HYPERTENSION

An interesting geomorphologic characteristic of South America is the existence of high altitudes. This makes the region similar to the Himalayas and the Tibetan Plateau in many aspects. Although Lima, the capital of Peru, is localized at sea level, quite high altitudes may be found in the country, such as Huancayo (3,200 m), La Groya (3,700 m), Cerro de Pasco (4,300 m), Morococha (4,540 m), and Nevado Huascaran (6,768 m). In La Paz, the capital of Bolivia, ~1 million inhabitants live at altitudes in the range of 3,200–4,050 m. In other regions of the country, there are ~3 million people living between 3,000 and 5,500 m. This is relevant in terms of pulmonary hypertension in general, not specifically PAH.

In terms of pulmonary vascular reactivity to the hypoxic environment, there are striking differences between species and ethnicities. Since the first description in 1925 (by Carlos Monge Medrano), the so-called Monge disease (chronic mountain sickness) has been largely shown to be associated with pulmonary hypertension and sometimes cor pulmonale and heart failure.^{7,8} High-altitude pulmonary edema (with exaggerated pulmonary vasoconstriction,

increased pulmonary capillary pressure, and normal wedge pressure)^{9,10} is also seen in the Andes. However, reascent (reentry) pulmonary edema, after a short stay at low altitudes, is even more frequent than ascent pulmonary edema, particularly in young people.¹¹ Although hypoxia is a strong stimulus for pulmonary vasoconstriction, differences in genetic background may account for a non-homogeneous propensity to develop sustained pulmonary hypertension. For example, like the yak in the Himalayas, the llama and other camelids in the Andes have thin-walled pulmonary arteries. Furthermore, Heath and colleagues^{12,13} reported years ago that mestizo citizens living in La Paz (~3,600 m) do not have a propensity for pulmonary arteriolar muscularization. Thus, different species can live successfully at high altitudes, well adapted and acclimatized. On the other hand, the Quechua Indians of the Peruvian altiplano were shown to have muscularized pulmonary arterioles,¹⁴ indicating that some native highlanders living at altitudes above 4,000 m for a long time lose their natural acclimatization and become susceptible to the development of Monge disease.

In terms of the pediatric population, it has been shown that pulmonary artery pressure fails to drop rapidly after birth. A mean pulmonary arterial pressure of ~45 mmHg may be observed in healthy children aged 1–5 years, and levels may remain mildly elevated (~28 mmHg) even in older children and adolescents.¹⁵ Depending on their ancestry, many children have a cardiovascular pattern similar to that seen at sea level, with no evidence of pulmonary hypertension.^{16,17} Others become symptomatic or develop pulmonary edema but do so more frequently when returning to high altitudes after a short stay in low places.

HIGH ALTITUDE AND CHD

For a long time, it has been acknowledged that the prevalence of certain congenital cardiac anomalies is higher in the pediatric population living at high altitudes than in that at sea level. This is particularly so for ASD and PDA.^{18,19} Previous data from children living at 3,500–5,000 m in the Peruvian Andes showed a prevalence of PDA 30–40 times higher than that observed at sea level.²⁰ Hemodynamic data obtained at Cerro de Pasco (~4,300 m) showed that in children with PDA, pulmonary artery pressure was elevated as a result of increased pulmonary blood flow (greater than 2 : 1, relative to the systemic blood flow) and vascular resistance (~5–6 Wood units).¹¹

The relative roles of hypoxia and genetic background in determining the severity of pulmonary vascular abnormalities in children with PDA (and other anomalies) living at high altitudes remain to be investigated. Observations from pediatric cardiologists in Ecuador (P. C. Flores,

Table 1. Data from Ecuadorian children (Indians) with patent ductus arteriosus living at high altitudes

Patient	Altitude, m	Age, years	Sex	Sat. O ₂ , %	DA diameter, mm	LA : aorta	PAP, systolic, mmHg	SAP, systolic/diastolic, mmHg
1	2,853	13	M	95	20	1.36 : 1	52	100/50
2	3,500	10	M	93	10	1.23 : 1	35	90/60
3	3,500	4	F	94	7	1.20 : 1	24	80/60
4	3,500	5	M	94	10	1.48 : 1	35	80/60
5	2,853	8	M	95	10	1.36 : 1	40	100/70

Note: Normal or only mildly elevated levels of pulmonary artery pressure are shown, relative to patient's age and size of the ductus arteriosus (DA). Sat. O₂: peripheral oxygen saturation; LA : aorta: relative diameter of the left atrium; PAP and SAP: pulmonary arterial pressure (echocardiography) and systemic arterial pressure, respectively.

personal communication) indicate that some children with very large ductus arteriosus (Table 1; Fig. 2) can be operated on successfully without any clinically relevant residual increase in pulmonary artery pressure. This is particularly so for children coming from Zumbahua (~3,500 m), a region of Indians in the south of Ecuador, where PDA figures as the most prevalent anomaly (95% of cases). In Quito, these children undergo successful surgical closure of the ductus (on a day-hospital basis), and 90% of them have normal postoperative pulmonary artery pressure. Of course, data on long-term follow-up of these patients are needed. Anyway, it could be hypothesized that in view of ancestries and genetic backgrounds, some mestizo or Indian children living at high altitudes are “protected” from development of severe pulmonary vasculopathy, a complication that is frequently observed in association with large systemic-to-pulmonary communications.

RESEARCH ACTIVITIES: POSSIBILITIES AND LIMITATIONS

The impressive number of patients and the diversity of diseases, at least in big centers of metropolitan areas, make the idea of research activities very attractive in South America. In a single academic institution in Brazil (InCor, in São Paulo), 1,338 studies have been produced and published in international journals in the past 5 years. In the specific setting of pulmonary vascular disease and pulmonary hypertension, many tertiary centers in Brazil and several other countries in South America have participated in most of the recent clinical trials designed to test the efficacy of the so-called new specific therapies. Limitations still remain and must be solved. Some of the most important ones are the recruitment and transportation of patients from remote areas to referral centers and the governmental bureaucracy that results in delay in the approval

of study protocols involving pharmaceutical companies (this is particularly so in Brazil).

In terms of academic research, there have been governmental initiatives in different countries, but the number of agencies and their budgets are still limited. Therefore, investments of this kind are warranted and should be strongly encouraged. Just to mention examples, in Argentina, the National Administration of Laboratories and Health Institutes is connected to the Interinstitutional Council of Science and Technology, which is linked to the Ministry of Science, Technology, and Productivity Innova-

Figure 2. Chest computed tomography showing a huge patent ductus arteriosus (arrows, 20-mm diameter) in a 13-year-old Indian adolescent successfully operated on in Quito, Ecuador (2,853 m altitude). Image courtesy of P. C. Flores.

tion. In Brazil, the National Council for Scientific and Technologic Development (CNPq) is a federal agency that provides institutions and students with grants and scholarships all over the country.

Still in the setting of academic studies, to mention an example of translational research, over the past 2 decades we have attempted to characterize the structure, function, and circulating levels of von Willebrand factor (VWF) as a marker of microvascular dysfunction in PAH (Fig. 3). Sequential studies on this subject²¹⁻²⁶ have been supported by the Foundation for Research Support of the State of São Paulo (FAPESP), an excellent governmental agency now connected with many institutes and universities in North America and Europe. An interesting observation of ours, with clinical implications, was the association of increased plasma levels of VWF with poor short-term outcomes in patients with PAH.^{24,25} More recent data of ours suggest that heightened circulating levels of VWF are associated with decreased medium-term survival in the specific subgroup of patients with PAH-CHD (Fig. 4).²⁶ Similar observations have been reported for patients with other forms

of PAH (idiopathic, familial, or associated with anorexigen use).²⁷ Since in these studies statistical analyses were performed in such a way as to eliminate possible confounders, data suggest that plasma VWF is an independent predictor of prognosis in patients with PAH.

PERSPECTIVES

Much has been done, and much remains to be done in South America. Early detection, prompt patient referral to tertiary centers, and assistance according to the best standards of medical practice remain important goals to be achieved in the management of CHD in many areas. In the management of PAH-CHD, availability of PAH drugs is not uniform in the region. Access to PAH therapies is unrealistic in remote places. However, even in the era of new, specific PAH therapies, it is largely acknowledged that the best strategy to prevent the development of pulmonary vasculopathy in CHD is early repair of systemic-to-pulmonary shunts. Yet pulmonary artery banding remains a common strategy for patients with late presentation and elevated pulmonary vascular resistance, despite the fact

Figure 3. Summary of biological mechanisms underlying the mobilization of endothelial von Willebrand factor (VWF) and P-selectin, likely present in pulmonary vascular disease. P-selectin and VWF are stored in Weibel-Palade bodies. In addition, VWF serves as an adhesion molecule for endothelial cells via the vitronectin receptor (ultralarge multimers at the basement membrane). Under a number of stimuli, including inflammatory mediators, coagulation factors, hypoxia, and shear stress, endothelial Weibel-Palade bodies are moved onto the inner side of the plasma membrane and release their contents via secretion pores. Once in circulation, newly secreted VWF either becomes attached to the surface of endothelial cells via interaction with P-selectin or undergoes limited proteolysis by the action of ADAMTS-13 metalloproteinase. Endothelial VWF and P-selectin play an important role in the recruitment of platelets and polymorphonuclear leucocytes (PMN), respectively, thus representing markers of endothelial cell activation/dysfunction. ADAMTS-13: a disintegrin-like and metalloproteinase with thrombospondin type 1, motif 13; IFNγ: interferon γ; IL: interleukin; TNFα: tumor necrosis factor α. A color version of this figure is available online.

Figure 4. Association of plasma von Willebrand factor antigen (VWF:Ag) with survival in pulmonary arterial hypertension (PAH). A, B, Short-term survival (1 year) in patients with PAH associated with congenital heart disease (CHD-PH) or the idiopathic form of PAH (formerly primary pulmonary hypertension, PPH). C, Medium-term survival in patients with pulmonary hypertension associated with CHD. Reproduced with permission from Lopes et al.²⁵ (A, B) and Lopes et al.²⁶ (C).

that “deremodeling” of pulmonary arteries^{28,29} has not been definitely demonstrated in humans. On the other hand, not all patients subjected to early repair of their cardiac anomalies will become free of pulmonary vascular disease and PAH.³⁰ Continued knowledge is needed about the mechanisms underlying the progression and regression of pulmonary vascular remodeling in PAH-CHD, especially now that specific PAH treatments are available. Of course, there is room for initiatives in terms of clinical, translational, and even basic research in many centers in South America. Educational investments aimed at increasing the number of new investigators and development of continuous international collaborative work are fully warranted and recommended.

Source of Support: Nil.

Conflict of Interest: None declared.

REFERENCES

- United Nations Department of Economic and Social Affairs, Statistics Division. Population and vital statistics report. Statistical Papers Ser. A, Vol. 53, p. 4. <http://unstats.un.org/unsd/demographic/products/vitstats/default.htm>. Published January 2013. Accessed August 5, 2013.
- Lizcano Fernández F. Composición étnica de las tres áreas culturales del continente Americano al comienzo del siglo XXI. *Convergencia* 2005;12(38):185–232.
- Engelfriet PM, Duffels MG, Möller T, Boersma E, Tijssen JGP, Thaulow E, Gatzoulis MA, Mulder BJM. Pulmonary arterial hypertension in adults born with a heart septal defect: the Euro Heart Survey on adult congenital heart disease. *Heart* 2007;93(6):682–687.
- Oeschlin EN, Harrison DA, Connelly MS, Webb GD, Siu SC. Mode of death in adults with congenital heart disease. *Am J Cardiol* 2000;86(10):1111–1116.
- Lopes AA, Bandeira AP, Flores PC, Santana MVT. Pulmonary hypertension in Latin America. *Chest* 2010;137(6 suppl.):78S–84S.
- Lopes AA, Thomaz AM, Aiello VD, Kajita LJ, Galas FRB, Zorzanelli L, Jatene MB, Bydlowski SP. Drug therapy and surgery in congenital heart disease with pulmonary hypertension. Clinical trial NCT01548950. <http://www.clinicaltrials.gov/ct2/show/NCT01548950>.
- León-Velarde F, Maggiorini M, Reeves JT, Aldashev A, Asmus I, Bernardi L, Ge R-L, et al. Consensus statement on chronic and subacute high altitude diseases. *High Alt Med Biol* 2005;6(2):147–157.
- Peñaloza D, Arias-Stella J. The heart and pulmonary circulation at high altitudes: healthy highlanders and chronic mountain sickness. *Circulation* 2007;115(9):1132–1146.
- Maggiorini M, Mélot C, Pierre S, Pfeiffer F, Greve I, Sartori C, Lepori M, Hauser M, Scherrer U, Naeije R. High-altitude pulmonary edema is initially caused by an increase in capillary pressure. *Circulation* 2001;103(16):2078–2083.
- Maggiorini M. High altitude-induced pulmonary oedema. *Cardiovasc Res* 2006;72(1):41–50.
- Peñaloza D, Sime F, Ruiz L. Pulmonary hemodynamics in children living at high altitudes. *High Alt Med Biol* 2008;9(3):199–207.
- Heath D, Smith P, Rios Dalenz J, Williams D, Harris P. Small pulmonary arteries in some natives of La Paz, Bolivia. *Thorax* 1981;36(8):599–604.
- Heath D. Missing link from Tibet. *Thorax* 1989;44(12):981–983.

14. Arias-Stella J, Saldaña M. The terminal portion of the pulmonary arterial tree in people native to high altitudes. *Circulation* 1963;28(5):915–925.
15. Sime F, Bancho N, Peñaloza D, Gamboa R, Cruz J, Marticorena E. Pulmonary hypertension in children born and living at high altitudes. *Am J Cardiol* 1963;11(2):143–149.
16. Huicho L, Niermeyer S. Cardiopulmonary pathology among children resident at high altitude in Tintaya, Peru: a cross-sectional study. *High Alt Med Biol* 2006;7(2):168–179.
17. Huicho L. Postnatal cardiopulmonary adaptations to high altitude. *Respir Physiol Neurobiol* 2007;158(2–3):190–203.
18. Miao C-Y, Zuberbuhler JS, Zuberbuhler JR. Prevalence of congenital cardiac anomalies at high altitude. *J Am Coll Cardiol* 1988;12(1):224–228.
19. Chen QH, Wang XQ, Qi SG. Cross-sectional study of congenital heart disease among Tibetan children aged from 4 to 18 years at different altitudes in Qinghai Province. *Chin Med J (Engl)* 2008;121(24):2469–2472.
20. Peñaloza D, Arias-Stella J, Sime F, Recavarren S, Marticorena E. The heart and pulmonary circulation in children at high altitudes: physiological, anatomical and clinical observations. *Pediatrics* 1964;34(4):568–582.
21. Lopes AAB, Maeda NY, Aiello VD, Ebaid M, Bydlowski SP. Abnormal multimeric and oligomeric composition is associated with enhanced endothelial expression of von Willebrand factor in pulmonary hypertension. *Chest* 1993;104(5):1455–1460.
22. Lopes AAB, Maeda NY. Abnormal degradation of von Willebrand factor main subunit in pulmonary hypertension. *Eur Respir J* 1995;8(4):530–536.
23. Lopes AA, Souza BF, Maeda NY. Decreased sialic acid content of plasma von Willebrand factor in precapillary pulmonary hypertension. *Thromb Haemost* 2000;83(5):683–687.
24. Lopes AA, Maeda NY, Bydlowski SP. Abnormalities in circulating von Willebrand factor and survival in pulmonary hypertension. *Am J Med* 1998;105(1):21–26.
25. Lopes AA, Maeda NY, Gonçalves RC, Bydlowski SP. Endothelial cell dysfunction correlates differentially with survival in primary and secondary pulmonary hypertension. *Am Heart J* 2000;139(4):618–623.
26. Lopes AA, Barreto AC, Maeda NY, Cícero C, Soares RP, Bydlowski SP, Rich S. Plasma von Willebrand factor as a predictor of survival in pulmonary arterial hypertension associated with congenital heart disease. *Braz J Med Biol Res* 2011;44(12):1269–1275.
27. Kawut SM, Horn EM, Berekashvili KK, Widlitz AC, Rosenzweig EB, Barst RJ. Von Willebrand factor independently predicts long-term survival in patients with pulmonary arterial hypertension. *Chest* 2005;128(4):2355–2362.
28. Wagenvoort CA, Wagenvoort N, Draulans-Noë Y. Reversibility of plexogenic pulmonary arteriopathy following banding of the pulmonary artery. *J Thorac Cardiovasc Surg* 1984;87(6):876–886.
29. O'Blens SB, Fischer S, McIntyre B, Keshavjee S, Rabinovitch M. Hemodynamic unloading leads to regression of pulmonary vascular disease in rats. *J Thorac Cardiovasc Surg* 2001;121(2):279–289.
30. Lopes AA. Is surgical treatment the cure for patients with congenital heart disease? *Pulmonary Circulation* 2012;2(3):273–274.