There are different definitions of Latin America, but in a broad sense, the term refers to all of the Americas south of the United States, encompassing English-, French-, Portuguese-, and Spanish-speaking countries, among others (Fig 1). In fact, several other languages are spoken in the region, including Dutch, Quechua, Aymara, Nahuatl, Mayan, Guarani, Haitian, Creole, and Papiamentu. The total area that includes 29 countries is 21,069,501 km$^2$, and the estimated population is 502 million. However, the population distribution is not uniform. Millions live in densely industrialized metropolitan areas or cities, as is the case of Mexico City (19,981,801), São Paulo (19,697,337), and Buenos Aires (~13 million). The population density decreases dramatically in more remote areas, such as the Amazon. The heterogeneous distribution of economic activities, social contrasts, inequality, and poverty constitute major problems in the entire region.  

The percentage of citizens covered by public health systems varies in the region, but in general, many individuals are underinsured. In Chile, for example, the percentage of citizens covered by the public system is relatively high (76.9%) according to data from
mansoni), a known cause of chronic liver disease, portal hypertension, and pulmonary hypertension. Schistosomiasis is a major health problem in Brazil, although not exclusively; it is also seen in Suriname, Venezuela, and the Caribbean. Second, in view of the fact that millions of people live permanently at high altitudes, particularly in the Andean highlands, delayed closure of the ductus arteriosus in children, patent ductus arteriosus, chronic mountain sickness, high-altitude pulmonary hypertension, and pulmonary edema are prevalent disorders that deserve consideration, medical assistance, and governmental attention.

Despite the unavailability of accurate epidemiologic information on pulmonary hypertension, some data now can be obtained from tertiary-care centers located in metropolitan areas. For example, except for regions where schistosomiasis is endemic, idiopathic pulmonary arterial hypertension (IPAH) and pulmonary arterial hypertension associated with congenital heart disease (PAH-CHD) seem to be the predominant etiologies of PAH in Brazil (~30%-40% prevalence each) followed by the form of pulmonary arterial hypertension associated with connective tissue disorders (PAH-CTD). However, in a single center at the northeastern region of the country (293 registered patients with PAH), schistosomiasis is the most prevalent etiology (39%), followed by PAH-CHD (26.9%), IPAH (14.6%), and PAH-CTD (12.2%). Because data from a recently implemented national registry are still preliminary, the relative frequencies of diagnostic categories that can be obtained from individual tertiary centers vary depending on the local specialties. In a recent survey involving 10 institutions (see Acknowledgments) where diverse but predominantly cardiovascular disorders are treated (in six different states), the frequencies of IPAH, PAH-CHD, and other etiologies of pulmonary hypertension were 22.86%, 60.75% and 16.39%, respectively, with a 6.66% to 25% occurrence of PAH-CTD. In four of these centers, which had a total of 568 registered patients with pulmonary hypertension, the frequencies of IPAH and PAH-CHD were 31.37% and 53.13%, respectively.

One possible explanation for this high prevalence of PAH-CHD in local databases is that, quite frequently, patients with congenital cardiac shunts living in distant and underserved regions of the country are referred to tertiary centers late in the course of their illness. In most of these instances, elevated pulmonary vascular resistance associated with advanced pulmonary vasculopathy is detected, and the case is considered inoperable. Not infrequently, the full picture of the Eisenmenger syndrome is present, which is in sharp contrast to the existence of big tertiary-care centers in metropolitan areas where neonates,
Almost 40 years ago, Andrade and Andrade\textsuperscript{11} proposed that in schistosomiasis pulmonary hypertension develops as a result of a massive egg release from adult female worms within the bladder or intestines, with embolization into the lungs. Pulmonary hypertension occurs in the early developmental stages of the disease when worms and eggs are still abundant and the host resistance is low. Repeated but not massive pulmonary egg embolization would match increased host resistance, leading to the formation of small and discrete granulomata. Interestingly, according to some reports, the age distribution of the subpopulation of patients with pulmonary hypertension tends to be different from that of the entire population of patients with schistosomiasis and portal hypertension. Although the latter tends to occur predominantly younger patients (aged \textless 30 years), the former tends to be bimodal.\textsuperscript{12} These observations point toward the hypothesis that in schistosomiasis, there are two distinct subpopulations of patients with pulmonary hypertension. In one, pulmonary vascular lesions probably develop earlier in life due to massive pulmonary egg embolization. In the other, affecting older patients after the third decade of life, pulmonary hypertension might be a result of a more insidious process involving repeated egg embolization.\textsuperscript{12} In any case, the extensive pulmonary vasculopathy contrasts the relatively rare (sometimes absent) granulomata, suggesting that vascular damage may be largely due to inflammatory and immune reactions to substances released by the parasite.

In Brazil, schistosomiasis is endemic in at least five states, including two large states in terms of land size (Bahia and Minas Gerais), but is also found in other regions. Estimates indicate that 8 to 12 million people are infected by schistosomiasis in the country, whereas 35 million are at risk. Controversy remains about the prevalence of pulmonary hypertension in patients with schistosomiasis, with frequencies ranging from 6.5\% to 20\% to 30\%. The variability is essentially related to differences in patient population, sample size, and the method used to diagnose pulmonary hypertension. Taking into consideration only studies where the diagnosis was based on cardiac catheterization, Bertrand and colleagues\textsuperscript{13} reported that in 37 patients from a hospital population there was a 21.6\% prevalence of pulmonary hypertension. This finding is in contrast with the 13.0\% prevalence reported by Guimarães,\textsuperscript{14} who studied 141 patients from a rural population who came to the hospital specifically for investigation. Lapa and coworkers\textsuperscript{15} reported a 7.7\% frequency of pulmonary hypertension in 65 patients from a hospital population outside the endemic areas of schistosomiasis in Brazil. After \textgreater 20 years of schistosomiasis control programs in Brazil, chemotherapy has been considered...
one of the most important tools for control of morbidity and for decreasing the prevalence and incidence of the disease in endemic areas. However, long-term measures are needed in terms of sanitation, water supply, sewage draining, and health education. Until the disease can be completely eradicated, attention must be paid to the management of the systemic complications, such as chronic liver disease, portal hypertension, and PAH, in view of their impact on mortality.

High-Altitude Pulmonary Hypertension

The existence of high altitudes in South America, particularly in the Andes, makes the region similar to the Himalayas and the Tibetan plateau in many aspects. In fact, the Andean region includes very high places, such as Nevado Huascaran (6,768 m) in Peru. In Bolivia, ~3 million people live at altitudes between 3,000 m and 5,500 m. In La Paz, the capital of Bolivia, it is estimated that 1 million inhabitants live between 3,200 m and 4,050 m. Although Lima, the capital of Peru, is localized at sea level, very high places are found in the country, as is the case of Huancayo (3,200 m), La Oroya (3,700 m), Cerro de Pasco (4,300 m), and Morococha (4,540 m). Several investigators have been working and describing features of high-altitude disorders within these regions for >80 years. Undoubtedly, the most well-known high-altitude disorder is Monge disease, or chronic mountain sickness, which is an association of excessive polycythemia (erythrocytosis), fatigue, dyspnea, headache, digestive complaints, sleep, and neurologic disturbances described by Carlos Monge Medrano in 1925. Pulmonary hypertension frequently is associated with Monge disease, leading to cor pulmonale and cardiac failure.

Although hypoxia is a strong stimulus for pressor response in the pulmonary circulation, differences in ancestry and genetic background account for a non-homogeneous propensity to development of pulmonary hypertension. For a long time, it has been acknowledged that the llama and other camelids in the Andes, similar to the yak in the Himalayas, have thin-walled pulmonary arteries. Heath and coworkers reported years ago that the mestizo citizens of La Paz (~3,600 m) do not have a tendency to pulmonary arteriolar muscularization. Therefore, these adapted and acclimatized species can survive and live together very successfully at high altitudes. In contrast, Arias-Stella and Saldana observed that the Quechua Indians of the Peruvian altiplano, the direct descendants of the Incas, have muscularized pulmonary arterioles, including 30-μm diameter precapillary vessels. Thus, some native highlanders who have lived at altitudes exceeding 4,000 m for a long time lose their natural acclimatization and develop Monge disease.

High-altitude pulmonary edema also is seen in the Andes. However, reascent (reentry) pulmonary edema after returning from a short stay at lower altitudes is even more frequent than ascent pulmonary edema, particularly in young people. The main findings are exaggerated pulmonary vasoconstriction and hypoxemia associated with increased pulmonary capillary pressure, whereas the pulmonary capillary wedge pressure remains normal. The degree of high-altitude ancestry affects the susceptibility to reentry high-altitude pulmonary edema. For example, in the Qinghai-Tibetan plateau (3,000-5,000 m), the longest-residing high-altitude population, the prevalence is considerably low (0.7%) compared with the Andes and Colorado in the United States. By contrast, in the same region the prevalence of ascent high-altitude pulmonary edema in Chinese children of Han origin from lower places is ~1.5%. This condition is called subacute mountain sickness and is the human counterpart of cattle brisket disease.

Pulmonary Hypertension in Children

In institutions where predominantly cardiovascular disorders are treated, the prevalence of PAH-CHD among the etiologies of PAH tends to be at least twice that of IPAH. In some tertiary centers, the observed ratios are approximately 4:1. This is seen, for example, in big institutions in the city of Sao Paulo, Brazil. Late diagnosis of congenital heart disease in children from underserved regions accounts for these numbers. By contrast, these same centers perform pediatric cardiac surgery, with >500 open heart surgeries per year. Patients with congenital cardiac anomalies can be operated on early in life (even neonates). In this scenario of early repair, similar to developed countries, pulmonary circulation is a matter of concern in only 5% to 10% of all patients with congenital septal defects, in those with single ventricle physiology, and in those with major aortopulmonary collateral vessels.

Pulmonary hypertension associated with rheumatic valvular disease occurs in the pediatric population. However, with improvement of postoperative care in tertiary centers, only rarely would a child with valvular disease be considered inoperable based on elevated pulmonary artery pressure. In <5% of children with dilated cardiomyopathy, pulmonary hypertension represents a major problem for assignment to cardiac transplantation. However, although the exact numbers are not available, restrictive cardiomyopathy in children generally is associated with accelerated pulmonary vasculopathy. In institutions devoted to general pediatric care, chronic lung
disease and hematologic disorders (mainly sickle cell anemia) are important etiologies of pulmonary hypertension.

Of interest in Latin America, particularly South America, is pulmonary hypertension in children living at high altitudes. In contrast with sea level, pulmonary artery pressure fails to drop rapidly after birth. As a result, mean pulmonary arterial pressures of 45 mm Hg may be observed in healthy children aged 1 to 5 years. Pressure levels tend to decrease progressively but remain mildly elevated (~28 mm Hg), even in older children and adolescents. Because of a mixture of ancestries, many children have a cardiovascular developmental pattern similar to that seen at sea level, without evidence of pulmonary hypertension. Some become symptomatic or even develop pulmonary edema, but in terms of the pediatric population, this is more frequently observed in individuals who return to high altitudes after a short stay at lower places (reentry pulmonary edema).

It has been demonstrated that some congenital cardiac anomalies are more prevalent in pediatric populations living at high altitudes compared with those living at sea level, such as atrial septal defects and patent ductus arteriosus. When different regions of Latin America are compared, the prevalence of patent ductus arteriosus increases exponentially as a function of the altitude. Decreased oxygen concentration in the atmosphere and elevated pulmonary artery pressure account for delayed closure of the ductus and its persistent patency. The prevalence is < 0.1% at sea level and > 0.2% in Mexico City (2,200 m). Decades ago, epidemiologic data from 5,000 school children born and living between 3,500 m and 5,000 m in the Peruvian Andes showed a prevalence of 1.0%, that is, 30 to 40 times that observed at sea level. Based on hemodynamic data collected at high altitude (Cerro de Pasco, Peru, 4,340 m), it has been assumed that in children with patent ductus arteriosus heightened pulmonary artery pressure is a result of increased pulmonary blood flow (pulmonary-to-systemic blood flow ratio, > 2.0) and vascular resistance (5-6 Wood units). However, the relative role of hypoxia and the genetic background in determining the magnitude of pulmonary vascular abnormalities remain to be determined. According to the expert opinion of pediatric cardiologists living and working in Quito, Ecuador (~3,000 m), and in contrast to the expectations of others, some children with very large ductus arteriosus (diameter ≥ 10 mm) can be operated on successfully without any clinically relevant residual increase in pulmonary artery pressure. If so, it could be hypothesized that because of ancestry and genetic background some mestizo children living at these altitudes are relatively protected from the severe pulmonary vasculopathy frequently associated with unoperated large left-to-right congenital cardiac shunts. This hypothesis requires further investigation to be proven.

Medical Education, Early Diagnosis, and Availability of New Treatments

Early detection of pulmonary hypertension and access to treatment are still challenges in most countries of Latin America. In past decades, several programs of medical education in this particular field have been implemented in the region. Some of them are now being developed in collaboration with local universities and medical societies. Additionally, there have been academic endeavors involving international organizations aimed at increasing awareness about the disease and improving education and research methods. As a result of these joint efforts, considerable headway has been made in education and the creation of new reference centers.

Despite the existence of tertiary-care centers where patients can be assisted according to good standards of medical practice (Buenos Aires, Mexico City, São Paulo, and other cities), early diagnosis and treatment of pulmonary hypertension are still unrealistic in the distant regions of all countries. Most patients with functional class III or IV seek medical assistance late, which is a problem considering that IV drugs for treatment of pulmonary hypertension are available only in specific countries and not included in any governmental health programs.

Until recently, only patients included in clinical studies had access to medication in Mexico. Similarly, in Brazil, hundreds of patients with PAH associated with schistosomiasis had no access to the drugs; bosentan and sildenafil are now available in some states, but there are no federal programs in this way. Besides bosentan and sildenafil, inhaled iloprost is available in the region but only in a restricted number of countries (eg, Argentina). In the past few years, there has been increasing interest in the inclusion of Latin American countries in clinical trials. Pharmaceutical companies have approached physicians and institutions, and patients have been included in multicenter randomized trials. In many instances, these trials are an important source of medication and sometimes, the only source. Yet, the number of patients with undiagnosed conditions that are not being treated is still large. In Brazil, it is estimated that 60% to 70% of PAH cases remain undiagnosed and untreated. Conceivably, it is the same for the majority of countries in Latin America.
Pulmonary hypertension is neither a single and simple disease nor a rare disorder as previously imagined. As different (and new) etiologies are better explored and studied in underserved countries and areas, the number of patients who need medical attention increases. A logical approach to this condition should not just include new drugs and new diagnostic tools. In underserved areas, which include many regions of Latin America, a successful approach should include measures to improve social and economic conditions of the affected populations. In Brazil, there are ongoing projects for the control or eradication of S mansoni. Awareness should be improved not only in areas of intense economic activities but also among physicians and other health professionals involved in primary care in distant regions where early diagnosis is wanting or not made at all. Distances should be shortened by improving transportation between remote areas and the reference centers. Patients living at high altitudes (especially children) should be offered facilities to move to at sea level. Subjects with residual postoperative pulmonary hypertension following repair of congenital cardiac defects usually improve dramatically when they are encouraged to do so, and this is true for persons with IPAH. Finally, much remains to be done in terms of improving communication between the academic and governmental authorities. For example, a governmental program for access to medication is in the final stage of preparation in Brazil.54 There are three key issues to be prioritized by governmental health authorities: (1) awareness about the disease, which involves medical education; (2) access to early diagnosis, which involves awareness; and (3) access to medication. This prioritization may best be facilitated by nonprofit, nongovernmental organizations that have as members of their boards persons known for their involvement in humanitarian work. In terms of research, there is room for clinical studies as mentioned previously. Many centers in Latin America are now prepared, some have already been involved, and new ones can be included in training programs. There also is room for translational research, and some work in this area has been done in past decades. In sum, considerable headway has been made at social, medical, and investigational levels, but much work remains to be done.

ACKNOWLEDGMENTS

Financial/nonfinancial disclosures: The authors have reported to the CHEST the following conflicts of interest: Dr Lopes has received speaking fees from Actelion and Pfizer. Dr Bandeira has received speaking fees from Pfizer. Drs Flores and Tavares Santana have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Other contributions: We thank the following institutions in Brazil that contributed local data for the overall picture of pulmonary hypertension etiologies presented in this review: Instituto do Coração (InCor)-HCFMUSP, Instituto Dante Pazzanese de Cardiologia, Santa Casa de Misericórdia de São Paulo, and Hospital do Coração (HCor), São Paulo, SP; Pronto-Socorro Cardiológico-Hospital das Clínicas-UFPF, Recife, PE; Hospital das Clínicas-UFMG, Belo Horizonte, MG; Hospital Messejana, Fortaleza, CE; Hospital Infantil Joana de Gusmão, Florianópolis, SC; Instituto do Coração Dr Elias Antonio–Hospital Evangélico, Cachoeiro do Itapemirim, ES; Hospital Ana Neri, Salvador, BA; and Hospital Municipal Mario Gatti, Campinas, SP.

REFERENCES

19. Arias-Stella J, Saldaña M. The terminal portion of the pulmonary arterial tree in people native to high altitudes. 
21. Maggiorini M, Mélot Ch, Pierre S, et al. High-altitude pulmonary edema is initially caused by an increase in capillary 
22. Maggiorini M. High altitude-induced pulmonary oedema. 
   S, Nakashima M, eds. Progress in Mountain Medicine and High Altitude Physiology. Matsumoto, Japan: Dogura and 
24. da Silva CH. Rheumatic fever: a multicenter study in the state of São Paulo. Pediatric Committee—São Paulo Pediatric 
   and living at high altitudes. Am J Cardiol. 1963;11(2):143-149.
29. Chen QH, Wang XQ, Qi SG. Cross-sectional study of congenital heart disease among Tibetan children aged from 4 
30. Peñaloza D, Arias-Stella J, Sime F, Recavarren S, Marticorena E. The heart and pulmonary circulation in children at high altitudes: physiological, 