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RESEARCH ARTICLE

Pulmonary Hypertension in Hispanics: An Update on Treatment Options and Possible Causes

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ABSTRACT

Pulmonary arterial hypertension, a form of pulmonary hypertension (PH), is a rare but serious disease. This condition carries significantly increased risk of morbidity and mortality, associated with progressive elevations of pulmonary pressures and the subsequent development of right heart failure. PAH can also be very difficult to diagnose primarily because the initial symptom of shortness of breath can be very nonspecific and similar to other diseases. There are certain medications used to target obesity that have been associated with the development of pulmonary hypertension. Aminorex, commonly used in Europe in the 1960s, has been grossly tied with PAH. Additionally, Flenfluramine both on its own and used in combination with Phentermine, as appetite-suppressant medications, were associated with Primary Pulmonary Hypertension and valvulopathies. We believe the widespread use of weight loss medications in Latin America remains a risk factor for PH development in the Hispanic population. The NIH and the REVEAL registries in the United States provide the most information for different races/ethnicities in patients with the diagnosis of PAH. Both NIH and the REVEAL registries in the United States show a lower prevalence of PH than the expected prevalence of 11.5% in the Hispanic population. The underdiagnosis of PH in the Hispanic population can be explained by several causes such as lack of awareness of disease, access to healthcare, and tolerance to symptoms. Remarkable efforts in medicine have been made to better treat patients with this condition in the past few years, with the introduction of combination therapy in treatment-naive patients, which has changed the guidelines for treatment of PAH. Furthermore, recent clinical trials have shown promissory results with initiation of dual or even triple therapy instead of a step up approach in therapeutics. However, the majority of these therapies are indicated for PAH and PH related to connective tissue disease and come with a high financial burden to patients, especially minority patients such as Hispanics.

Introduction and Background

Pulmonary hypertension is a pathophysiological process that involves a combination of cardiovascular and pulmonary manifestations, where elevated pressures in the pulmonary vessels are observed. Pulmonary hypertension can be divided into two mechanisms, primary elevations in the pulmonary arterial system (pre-capillary) vs primary elevations in the pulmonary venous system (post-capillary) (1).

Pulmonary Hypertension is divided into five different subgroups as defined by the World Health Organization criteria, given that different etiologies are responsible for the development of elevated pulmonary pressures Table 1 (2). Group 1 is pulmonary arterial hypertension (PAH), defined by the remodeling of the resistant pulmonary arteries, ultimately leading to right ventricular failure and increased mortality (1). The hemodynamic definition of PAH is Mean Pulmonary artery Pressure (PAP) $\geq$ 20 mm Hg, pulmonary capillary wedge pressure (PCWP) $<$ 15 mm Hg, Pulmonary vascular resistance (PVR) $\geq$ 2 Wood units. PAH etiology is thought to be related to heritable causes, or associated with other conditions such as connective tissue disease, congenital heart disease, portal hypertension, human immunodeficiency virus (HIV) infection, anorexigen exposure, or schistosomiasis. However, the main etiology for PAH is an idiopathic cause and still an enigma for clinicians up to this date. Regarding the epidemiology of PAH, registries such as the REVEAL registry have collected characteristic of patient such as sex, ethnicity, and age to better understand this pathology. As a result, there has been shown to be an underrepresentation of Hispanic diagnosed with PAH. For example, looking at the REVEAL data the patient distribution was 72.8% Caucasians, 12.2 % African Americans, 8.9% Hispanics, 3.3 % Asians or Pacific Islanders, and 2.8% other or unknown (3). The amount of Caucasian registered correlated with the expected number, whereas the number of African Americans was overrepresented. However, Hispanics were underrepresented as well as Asian and Pacific Islanders (3).

Group 2 is secondary to left-sided heart disease meaning heart failure with reduced ejection fraction, heart failure with preserved ejection fraction or valvular disease. This entity has been divided into two subclasses isolated post-capillary PH (Ipc-PH) in which mPAP is elevated solely from passive transmission of increased left-sided filling pressure to the pulmonary circulation and combined post- and precapillary PH (Cpc-PH) in which mPAP is elevated from passive transmission of increased left-sided filling pressures with superimposed pulmonary vascular disease (4). The diagnosis of these two different entities is complex and requires right heart catheterization along with consideration of other clinical causes. Since the development of Group 2 PH has been directly linked to heart diseases, researchers have tried with several randomized clinical trials to determine if treating PH with conventional treatments for PAH would lead to better clinical outcomes for this patient selection. Unfortunately, clinical trials such as the ENABLE trial in which Bosentan, endothelin 1 receptor antagonist, was used in patients with HFrEF failed to show an improved clinical outcome (5). Similarly, SIOVAC trial had the aim to determine whether Sildenafil use would improve the clinical outcomes of patient with persistent pulmonary hypertension after valvular repair. Patients were randomized to 40 mg sildenafil 3 times daily (n=104) versus placebo (n=96) for 6 months (6). The results of this study did not reach statistical significance and there was no obvious clinical benefit. In summary, the clinical consensus continues to be to treat the underlying cardiac etiology for Group 2 PH patients and not to use PAH specific therapies due to the lack of clinical benefit.

Group 3, the second most common form of PH, is secondary to chronic lung disease such as COPD, ILD, and OSA. In the case of COPD, there is usually a correlation between the severity of COPD and the presence of PH in these patients (7). In the case of the hypoxic lung, there is a loss of pulmonary vessels and as a result pulmonary vasculature is unable to dilate to accommodate increased cardiac output (8). In the advanced stages of pulmonary hypoxia, release of vasoconstrictors such as endothelin leads to hypertrophy of pulmonary vasculature contributing to the development of PH (9).

Group 4 is due to chronic thromboembolic disease (Chronic Thromboembolic Pulmonary Hypertension, CTEPH), and is possibly the only pulmonary hypertension group with a cure available. CTEPH is directly related to the occurrence of pulmonary embolism (PE), although not completely clear as to why some patients with PE develop CTEPH and others do not. As to this reason, clinicians have moved beyond the idea of thrombosis in order to find possible causes of CTEPH. Studies have shown

common diseases found in patients with CTEPH such as infections, small vessel diseases, right ventricular dysfunction but no clear link consistently has been found (10). The prevalence of CTEPH after PE ranges from 0.4 to 9% in several reports with great variations between studies (11). The imaging standard test to diagnose CTEPH has been determined to be a Ventilation/perfusion (VQ) scan with a sensitivity of 90–100% and a specificity of 94–100% (12). The gold standard for definitive diagnosis remains to be a catheter pulmonary angiography although less used now due to its invasive nature and other emerging non-invasive imaging modalities (13). Fortunately, there is a curative treatment option for CTEPH which consists of pulmonary endarterectomy especially for proximal lesions (14). Mortality of the procedure itself is low being less than 5% and haemodynamics after the procedure has been shown to normalize with significant functional improvement (14). Almost 40% of patients with CTEPH are deemed ineligible for surgery and are being managed with anticoagulation and supplemental oxygen as needed. Newer studies have shown some benefit to use PAH specific therapies, such as Riociguat, in patients with CTEPH although more extensive clinical studies are needed in this field (15).

Finally, group 5 pulmonary hypertension is composed of several complex medical disorders such as hematologic conditions (chronic myeloproliferative disease, post-splenectomy, sickle cell disease, hemolytic anemia), sarcoid, thyroid disease, Glycogen storage diseases, chronic renal disease (16). Treatment is also guided to the underlying conditions and early referral to a pulmonary hypertension center is crucial for better clinical outcomes.

Symptoms and Diagnosis

The cardinal symptom of PH is progressively worsening dyspnea on exertion. Further symptoms are related to worsening right ventricle dysfunction (28) . As with any disease entity, there are early and late identifiable manifestations. The early symptomatology includes shortness of breath, dyspnea on exertion, fatigue and rapid exhaustion, bendopnea, palpitations, hemoptysis, syncope- which can be nonspecific for PH and differentials remain broad for several pulmonary and cardiovascular etiologies (28). Late symptoms, related to pulmonary artery dilation, can be exhibited by exertional chest pain, hoarseness due to compression of surrounding nerve structures, wheezing/atelectasis due to compression of surrounding bronchi. The physical exam, performed thoroughly, can key a physician into suspecting and subsequently diagnosing pulmonary hypertension.

Once the history and physical exam point clinicians towards suspecting a diagnosis of PH, diagnostic testing should be used to confirm the diagnosis and identify potential etiologies. Assessing for evidence of connective tissue disorders, history of smoking/chronic lung diseases, prior use of appetite suppressant medications, HIV, liver disease and history of thromboembolic disease are important to identify in order to properly guide management.

Transthoracic echocardiography is usually the initial diagnostic work up when suspecting PH. Several findings on echocardiography have been found to be present in pulmonary hypertension, especially when there is right ventricle involvement. Regarding ventricles, a finding of flattening of the interventricular septum (left ventricle eccentricity index (LVEI) >1.1 in systole and/or diastole) , tricuspid annular plane systolic excursion/systolic pulmonary arterial pressure (TAPSE/sPAP ratio <0.55 mm/mmHg), and RV/LV basal diameter/area ratio >1.0 are suggestive of pulmonary hypertension among other signs (E). More specifically for the diagnosis of CTEPH, the use of V/Q scan remains essential although a newer imaging modality called Dual-energy CT (DECT) angiography and iodine subtraction mapping that might increase the sensitivity to detect CTEPH looks promising to increase sensitivity and accuracy in diagnosing CTEPH (28). The gold standard for diagnosis of Pulmonary Hypertension remains to be right heart catheterization for a complete assessment of cardiopulmonary values and to assess patients with a favorable response to calcium channel blockers with a vasoreactivity test (28). There are specific criteria for patient selection to undergo a vasoreactivity test which are beyond the scope of this manuscript. The use of other imaging modalities such as computer tomography of the chest serve to evaluate underlying causes of PH such as ILD, sarcoid, or other conditions affecting lung parenchyma.

The WHO-FC is is one of the strongest predictors of survival, both at diagnosis and follow up- where worsening WHO-FC is a poor predictor of survival and signifies disease progression.

Table 1. World Health Organization classification of functional status of patients with pulmonary hypertension

Class	Description
WHO-FC I	Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain, or near syncope
WHO-FC II	Patients with PH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain, or near syncope
WHO-FC III	Patients with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain, or near syncope
WHO-FC IV	Patients with PH with an inability to carry out any physical activity without symptoms. These patients manifest signs of right HF. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity

PH, pulmonary hypertension; WHO-FC, World Health Organization functional class.

a

Functional classification of PH modified after the New York Heart Association functional classification according to the World Health Organization 1998.147

PAH and the Hispanic population

The prevalence of pulmonary hypertension is higher than what is listed in and what is available for review regarding the hispanic population. Most of the accessible data comes from registries in Latin American countries: Argentina, Chile, and Brazil. Additionally, even between different hispanic countries, there are differing etiologies of PAH. For instance, connective tissue disease is the underlying driver for PAH in Brazil but not frequently seen in Chile and Argentina (17). In the US, the NIH and the REVEAL (The Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management) registries do provide information about hispanic patients diagnosed with PAH, however both registries under-represent hispanic and asian patients(3). In the Pulmonary Arterial Hypertension category in the US, hispanics represented 2.3% of the NIH registry at a time when it represented 6% of the US population (17).

The underlying etiology for developing PAH has been proposed to differ by location in the world. For example, the proportion of patients who developed PAH with congenital heart disease reported in Argentina was 28%, which is higher than what was reported in North America and Europe (both below 15%). (23) In Brazil, the incidence of schistosomiasis is particularly high with millions of people affected, this data suggests that schistosomiasis is one of the prevalent causes of PAH for this particular hispanic population (24). The most commonly reported subtype of PAH is Idiopathic Pulmonary Arterial Hypertension (IPAH) in Hispanic countries. The percentage of IPAH is higher in Latin American countries when compared to European studies and the REVEAL registry in the United States. (Fig2, R23). This also varies by country; for instance, in Brazil IPAH was lower than in other hispanic countries. This can be explained by the high percentage of other etiologies in Brazil like the previously described PAH due to schistosomiasis. (26)

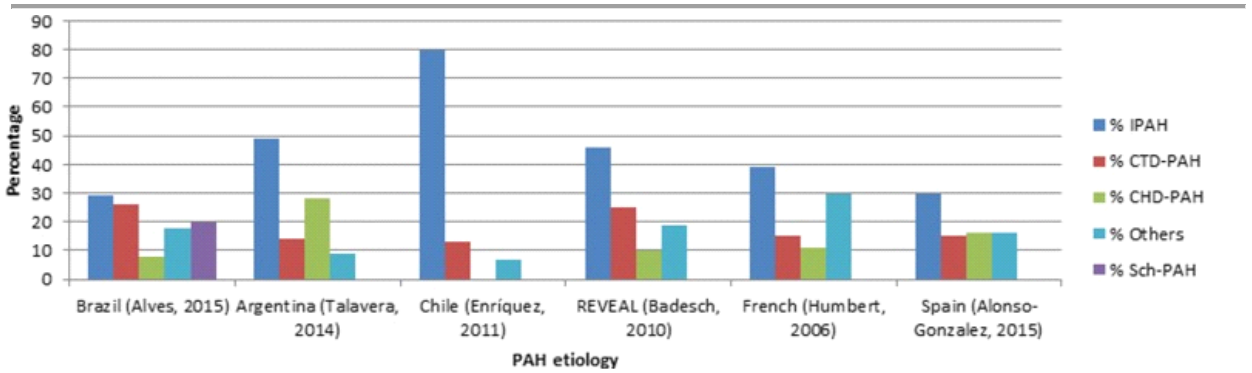

Fig 2: (Valverde AB, Soares JM, Viana KP, Gomes B, Soares C, Souza R. Pulmonary arterial hypertension in Latin America: epidemiological data from local studies. BMC Pulm Med. 2018 Jun 26;18(1):106. doi: 10.1186/s12890-018-0667-8. PMID: 29940945; PMCID: PMC6019295.)

Appetite suppressant medications are popularly used as weight loss adjuncts in the general population, most commonly in the hispanic population. Several anti-suppressant medications are target-marketed to the Latin American population, mainly because they are easily available over the counter. In a study performed by Julia et. al, Latin American students had a 30%–40% higher odds of past-30-day diet-pill use than their White peers (22). Drugs such as Aminorex, Fenfluramine, and Dexfenfluramine have long been associated with the development of PAH. The proposed theory of serotonin signaling is believed to be responsible for the association between these medications and PAH, where anorexigens increase free serotonin which activates serotonin receptors and causes pulmonary artery vasoconstriction in addition to pulmonary artery smooth muscle proliferation. Another drug, Norfenfluramine has direct activity on serotonin 2B receptors (21). Also proposed is internalization of the drugs via serotonin transporter which disrupts internal serotonin storage and can subsequently lead to pulmonary artery smooth muscle proliferation (19). The serotonin hypothesis has been revised and revisited over the years, but still remains intact.

Measurement of N-terminal Pro-BNP is an important parameter used in the assessment of patients with PAH. It has been reported that hispanic individuals have a baseline lower NT-ProBNP level than do caucasian counterparts. Khatab et al (27) performed a study which suggests that NT-ProBNP is a valid biomarker to predict time to clinical worsening (TTCW) in hispanic patients with PAH. TTCW was defined as a decrease of more than 15 % in 6 minute walk tests, escalation of therapy, hospitalization for right heart failure, referral for lung transplant, and death related to right heart failure. Patients in this study with NT-ProBNP levels below 300 had excellent 1 year prognosis while those with levels >1,400 had overall clinical worsening. This data suggests that NT-ProBNP can be used to risk stratify Hispanic PAH patients (27).

New National Registries are being implemented to improve the lack of available data regarding Pulmonary Hypertension in the hispanic population. An international multicenter registry "Registro Latinoamericano de Hipertensión Pulmonar" (REHLAP) was launched in 2014. This registry primarily collects medical data, diagnostic workup, and management of patients with PH under optimal medical care. Although these are all steps in the right direction, further efforts are still needed to fill the existing gap on limited available data in hispanics with PH (23).

Hispanics face a variety of barriers to obtain access to healthcare, both financial and nonfinancial. Even in the United States, hispanics are are substantially more likely to be uninsured than the white population. In 2004, about 36% of Hispanics under 65 did not have access to health insurance as compared to 15 % in whites (25). In addition, hispanics are much less likely to receive health insurance as a benefit from their employers than their white counterparts. It is known that hispanics have lower access to healthcare than do non-hispanic whites. When it comes to diseases such as pulmonary hypertension, this issue becomes remarkably more important. This, in combination with the non-specific symptoms of shortness of breath, makes it significantly more difficult to diagnose and manage hospanic patients with PH.

Data regarding prevalence, etiology, and survival for hispanic patients living in the United States remains limited. Limitations are observed due to several reasons; including the lack of data

imported from Latin American countries, low percentage of patients in these countries enrolling in treatment and clinical trials in the US, as well as socioeconomic status. Minority populations tend to have lower socioeconomic status due to complex cultural factors (25). Further studies performed regarding PAH should pay close attention to socioeconomic status as a possible confounder to the results, given that limited access to healthcare and resources can significantly affect the prognosis of any patient with any given disease. The lack of access to healthcare and resources in hispanic populations leads to delay in diagnosis and treatment- which can be observed in all diseases but is particularly important in PAH because delay in diagnosis can be very detrimental for survival.

Treatment Options

The management strategies of individuals who have been diagnosed with Pulmonary Hypertension will inherently depend on the type or Group they fall into, based on the underlying etiology as previously discussed. In this section, we will briefly discuss some of the therapies available to clinicians to treat pulmonary hypertension.

The guidelines for diagnosis and treatment have been recently updated and can help guide clinicians on choosing the best regimen for PAH (28). When discussing Group 1, Pulmonary Arterial Hypertension, the efficacy of drugs has only been approved for patients with mPAP>25 and PVR >3 WU. In addition to prescribing medications, the care will consist of a multidisciplinary approach. A combination of specialized rehab programs, avoiding fluid retention with diuretics and restriction of fluid intake, ambulatory oxygen when there is symptomatic benefit, routine vaccination, psychosocial support, and possible consideration for anticoagulation due to the procoagulant state. Drug classes available to clinicians include calcium channel blockers, endothelin receptor antagonists, phosphodiesterase 5 inhibitors, guanylate cyclase stimulators, prostacyclin analogues, and prostacyclin IP receptor agonists (28). From this latter class, there are studies in phase 3 with Ralenipag, which has shown better pharmacology than similar agents of its class.

Overall the most important factor that affects the overall prognosis of patients with Pulmonary Hypertension is their adherence to medication and management along with early detection and referral to a pulmonary hypertension center.

Conclusion

The lack of awareness of pulmonary hypertension as a disease and the non-specific components of the presenting symptoms in the hispanic population is ultimately what leads to under diagnosis and delay in care. The PH guidelines have been updated in August of 2022, detailing diagnosis and treatment of Pulmonary Hypertension. This update provides access to the most recent recommendations aiming to guide health professionals towards the best management strategies.

Nevertheless, educating patients in both primary physician and specialist clinics can help bring awareness on PH. The primary goal is to raise early suspicion for PH in patients with a high likelihood of disease and ensure they are appropriately evaluated at a PH center. Ultimately identifying their underlying etiology will help guide management.

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