Correlation between Degrees of Pulmonary Hypertension and Findings in Complementary Tests

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Abstract

Introduction: **Pulmonary hypertension is potentially fatal and courses with important day-to-day limitation. While the treatment is capable of slowing the disease's progression, increase in life expectancy is directly linked to early diagnosis and treatment.**

Objectives: **To analyze the relation between alterations detectable on routine exams performed on pulmonary hypertension patients (echocardiography, electrocardiography and computerized tomography) and increases on pulmonary artery systolic pressure.**

Methods: **We analyzed the recordings of patients presented with pulmonary hypertension, and separated them in two groups based on their echocardiography-estimated pulmonary artery systolic pressure. Group 1 was composed of patients with pulmonary artery systolic pressure between 35 mmHg and 65 mmHg, and Group 2 of patients with pulmonary artery systolic pressure > 65 mmHg. We analyzed the prevalence of alterations suggestive of pulmonary hypertension on echocardiography, electrocardiography and computerized tomography. A descriptive analysis of the findings was conducted, followed by comparative analysis between the groups.**

Results: **We analyzed 101 patients (43 from Group 1 and 58 from Group 2). Most were women (82). Higher pulmonary artery systolic pressure values were correlated with right-heart dilation on echocardiography ($p < 0.001$). Electrocardiography findings revealed that right-heart hypertrophy and ventricular strain pattern were more common on Group 2 ($p < 0.05$). Computerized tomography analysis showed Group 2 patients had superior pulmonary artery diameters ($p < 0.05$). There was correlation between high pulmonary artery systolic pressure and clinical progression of the disease measured via the NYHA score ($p < 0.05$).**

Conclusion: **It is possible to make use of clinical examination and a simple electrocardiography to stratify the severity of a pulmonary artery patient. Computerized tomography and echocardiography should be used to confirm these findings. (Arq Bras Cardiol: Imagem cardiovasc. 2018;31(3):175-182)**

Keywords: **Hypertension, Pulmonary; Echocardiography/methods; Electrocardiography; Tomography, X-Ray Computed; Diagnostic Imaging; Blood Pressure; Pulmonary Arterial.**

Introduction

Pulmonary hypertension (HP) is a disease defined by the presence of mean pulmonary artery pressure ≥ 25 mmHg.[1] This condition has been considered a disease of young women, but it is now known to affect the all sorts of age groups and ethnic groups. This is due to the different mechanisms that can cause it, such as congenital heart diseases of pulmonary hyperflow, pulmonary and cardiac pathologies, infectious diseases and idiopathic forms.

Today, HP is ranked according to the decisions of the Fifth World Symposium on Pulmonary Hypertension, held in Nice, France, in 2013. According to this classification,[2] there is a division of five groups, corresponding to the following basic etiologies: class I, idiopathic; class II, associated with diseases of the left heart; class III, associated with pulmonary diseases; class IV, associated with pulmonary thromboembolism; and class V, multifactorial.

Its prevalence in the general population is not well established yet. However, there are statistics corresponding to the groups, in which the prevalence of the condition is evaluated in specific populations.[3] In the case of class I, which is more widely studied, some data show a prevalence of around 15 per 1 million patients.[4] In class II, studies focus on populations with heart problems, and the prevalence is proportional to the progression of left ventricular (LV) dysfunction.

Studies estimate that about 60% of patients with LV systolic dysfunction develop PH.[5] In addition to that, nearly all patients with symptomatic severe aortic insufficiency have some degree of PH,[6] and about 65% of patients with symptomatic aortic stenosis also have some degree of PH.[7]

In class III, a prevalence of about 35% was observed in patients with interstitial pulmonary disease.[8] In patients with severe chronic obstructive pulmonary disease (COPD), there

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is a prevalence of PH > 50%.[9] A study conducted at the COPD clinic of Hospital de Clínicas da Universidade Federal do Paraná found a prevalence of 63%.[10] Data on class IV report a prevalence of 3.8% in patients with pulmonary thromboembolism.[11] Class V does not have its prevalence estimated, as it involves conditions that are too heterogeneous and difficult to account for.

Alternatively, there is a separation based on the value of estimated or measured pulmonary artery systolic pressure (PASP), which includes three groups. Patients with PASP > 35 mmHg and < 45 mmHg are considered to have mild PH. Patients with 45 mmHg to 65 mmHg are considered moderate and > 65 mmHg are considered severe.[3] This classification is subject to age, and values older than that standard may be tolerated in elderly patients.

There is also the functional classification of PH, which separates patients according to the influence that the disease has on their daily activities. The division is organized by the New York Heart Association (NYHA), into 4 classes, including I for patients with PH without limitation of daily activities; II, appearance of symptoms in common daily activities and absence of symptoms at rest; III, presence of symptoms in minimal daily activities and absence of symptoms at rest; and IV, persistence of symptoms, even at rest.[1]

Increase in the prevalence of heart diseases in the last decades, due to life habits and increased longevity of the population, combined with an increase in smoking-related pulmonary conditions, such as COPD, increase the need for studies aimed at diagnosis and treatment of PH.

In addition to the statistical significance of the disease, it is worth mentioning that this is a potentially fatal, progressive condition with great impact on the patient's quality of life.[1]

Treatment of PH is very complex because the disease has several different causes. The primary cause is treated first (except in class I cases), with specific medications for the causing condition. If the response is insufficient, a treatment is added to PH itself.[12] In Class I situations, PH is treated directly.

Treatment may change the disease progression, but improvement in quality of life and increased survival are related to early diagnosis and therapy,[12,13] and it is necessary to be attentive to symptoms suggestive of PH. Therefore, the details of findings suggestive of PH in the tests, as well as their prognostic value, should be studied in depth.

Comparing the findings of tests between patients with mild and severe PH, we hope to contribute to the early diagnosis and evaluation of the severity of the case using these diagnostic methods.

The method of choice for following up PH routinely used in outpatient clinics is transthoracic echocardiography because it is a non-invasive procedure and does not pose risks to the patient, as opposed to direct measurement of pulmonary pressures by cardiac catheterization with all the risks that are common to the interventionist method. Ultrasound allows the examiner, to evaluate the cardiac changes that usually occur with PH and to estimate PASP. This estimate is done using a formula that relates the tricuspid regurgitation velocity and the maximum pressure gradient between the right atrium and the right ventricle (RV),[1] with the pressure gradient being equal to four times the squared the maximum velocity. This gradient, added to the right atrial estimated pressure, infers the PASP.

In addition to this extremely important variable, echocardiography identifies findings related to PH, notably the increase between RV/LV ratio, right chamber dilation and interventricular septal bulging.[1]

In addition to echocardiography, other tests are used to evaluate progression parameters and increase the severity of the disease, such as electrocardiography (ECG) and computed tomography (CT).

ECG is commonly done routinely in cases of PH, to produce data that indicate the progression and cardiac complication of the disease. This complication results, in the test, as signs of RV hypertrophy,[1] which suggest chamber pressure overload, presence of P *pulmonale* wave and QT interval prolongation, which in some studies was indicated as a predictor of mortality in patients.[14] The presence of ventricular strain pattern is also considered a sign of PH.[15]

Chest tomography can also be used to monitor patients with PH, as it provides high-resolution data of the heart, pulmonary vessels, and the lung itself. The most significant CT findings are an increase in the caliber of the trunk and pulmonary vessels, as well as right chamber dilation. CT may also clarify the baseline cause of PH in cases in which abnormalities in the vasculature (Class IV) or pulmonary parenchyma (class III) cause the disease.[16]

By associating the severity of PH with test findings (CT, ECG and echocardiography) and functional class, we hope to determine the absence or presence of a relationship between increased PASP and progression of anatomical and functional abnormalities in patients.

Methods

A retrospective study was conducted at the PH outpatient clinic of a university hospital. By reviewing medical charts, the study included patients who were regularly seen at the service, with a record of echocardiography, chest CT and ECG data. Patients who did not have echocardiograms, patients without PASP estimate and under 18 years of age were excluded. There was no intervention in the management of these patients. This study was approved by the Research Ethics Committee on March 2017, under CAAE no. 61977716.7.0000.0096.

The patients were initially divided into two groups according to their PASP estimated on echocardiography. Patients with PASP between 35 mmHg and 65 mmHg were part of Group 1 (mild-moderate), and patients with PASP > 65 mmHg, Group 2 (severe).

After separating into groups, the patients' following general data were recorded: age, sex, disease duration and NYHA symptomatology scale. In the echocardiography test, three abnormalities were chosen for PH assessment: dilation of right chambers, interventricular septal bulging and increased RV/LV ratio. Besides, the percentage of LV ejection fraction was collected. In chest CT, Pulmonary Artery Trunk (PAT) dilation, dilation of direct chambers and PAT size in millimeters were considered. On ECG, signals of RV overload, P *pulmonale* and ventricular *strain* pattern were evaluated.

The descriptive statistical analysis of the data collected in this study was made by means of relative frequency, absolute frequency, mean and median. Mann-Whitney test, chi-square test and Fisher's exact test were used for the inferential statistical analysis. The study considered $p \leq 0.05$ or 5% as a rejection level for null hypothesis.

Results

This study included 101 patients, including 82 females. The average age was 45.9 years of age, with minimum 18 and maximum 80 years, and standard deviation of 16.3. Group 1 included 43 patients, while Group 2 included 58 patients. The minimum PASP value was 35 mmHg and the maximum value was 156 mmHg, with a mean of 74.4 and a standard deviation of 26.6. The disease duration, in years, ranged from 1 year to 43 years, with an average of 7.4 and a standard deviation of 9.29. As to the NYHA index, 17 patients of class I, 29 of class II, 34 of class III and 19 of class IV were evaluated. LV ejection fraction had a mean of 68.43%, with a minimum of 21%, maximum of 83% and standard deviation of 8.93%. Only 41 of the 101 patients evaluated had a documented ECG. Of these, 27 had signs of RV overload, and 14 did not. P *pulmonale* wave was present in three patients and absent in 38 of them. Ventricular strain pattern was found in 12 and was absent in 29 patients. In chest tomography, mean PAT was 35.76 mm, with a minimum of 24 mm, maximum of 70 mm and standard deviation of 7.41 mm.

Group 1 had a minimum PASP of 35 mmHg, maximum of 64 mmHg, mean of 50.48 and standard deviation of 10.5 mmHg. Patients were, on average, 51.43 years, with a minimum of 18, maximum of 80 and standard deviation of 16. The disease duration, in years, had an average of 7.4 and standard deviation of 9.29 years. As to the NYHA index, 12 patients of class I, 13 of class II, 12 of class III and 4 of class IV were evaluated. LV ejection fraction had a mean of 69.55%, minimum of 21%, maximum of 83%, and standard deviation of 10.48%. In the chest tomography, the mean PAT was 34.24 mm, with minimum of 24 mm, maximum of 70 mm and standard deviation of 8.59 mm.

Group 2 had a minimum PASP of 65 mmHg, maximum of 156 mmHg, mean of 92.7 and standard deviation of 19.7 mmHg. The patients were, on average, 42 years old, with minimum of 18, maximum of 73 and standard deviation of 15.5. The disease duration, in years, had an average of 8.6 and standard deviation of 10.1 years. As to the NYHA index, five patients of class I, 16 of class II, 22 of class III and 15 of class IV were evaluated. LV ejection fraction had a mean of 67.5%, with minimum of 44%, maximum of 80%, and standard deviation of 7.4%. In chest tomography, the mean PAT was 37.1 mm, with minimum of 26 mm, maximum of 50 mm and standard deviation of 6 mm.

The echocardiographic, electrocardiographic and tomographic variables are shown in Tables 1, 2 and 3, respectively.

The comparison between the ages of Groups 1 and 2 revealed that, on average, severe patients were younger than mild-moderate patients (Figure 1), with $p < 0.01$. The disease time was not inconsistent between the two groups.

The clinical worsening measured by the NYHA scale was correlated ($p < 0.05$) with high PASP. In Group 1, there was a higher prevalence of NYHA I and II and, in Group 2, there was a higher prevalence of NYHA III and IV (Chart 1).

Echocardiography showed a significant relationship between PH severity and right chambers dilation ($p < 0.001$), RV/LV increase ($p < 0.001$) and ventricular septal bulging ($p < 0.05$). LV ejection fraction did not have any statistical relevance.

The ECG showed a positive correlation with RV hypertrophy ($p < 0.01$) and the presence of ventricular strain pattern ($p = 0.01$). The presence of p *pulmonale* wave was not statistically relevant.

Table 1 – Echocardiographic variables

ECHO	Mild-moderate group (n = 43)		Severe group (n = 58)		p
	Absent	Present	Absent	Present	
RV increase	23	20	12	46	p < 0.001
Bulged septum	40	3	43	15	p = 0.01
RV/LV increase	31	12	17	41	p < 0.001

LV: Left ventricle; RV: Right ventricle.

Table 2 – Echocardiographic variables

ECG	Mild-moderate group (n = 16)		Severe group (n = 25)		p
	Absent	Present	Absent	Present	
RV hypertrophy	15	1	12	13	p = 0.002
P pulmonary wave	16	0	22	3	p = 0.28
Strain standard	15	1	14	11	p = 0.01

RV: Right ventricle.

Table 3 – Tomographic variables

TOMOGRAPHY	Mild-moderate group (n = 43)		Severe group (n = 58)		p
	Absent	Present	Absent	Present	
RV increase	33	10	39	19	p = 0.29
PAT increased	13	30	13	45	p = 0.37

RV: Right ventricle; PAT: Pulmonary artery trunk.

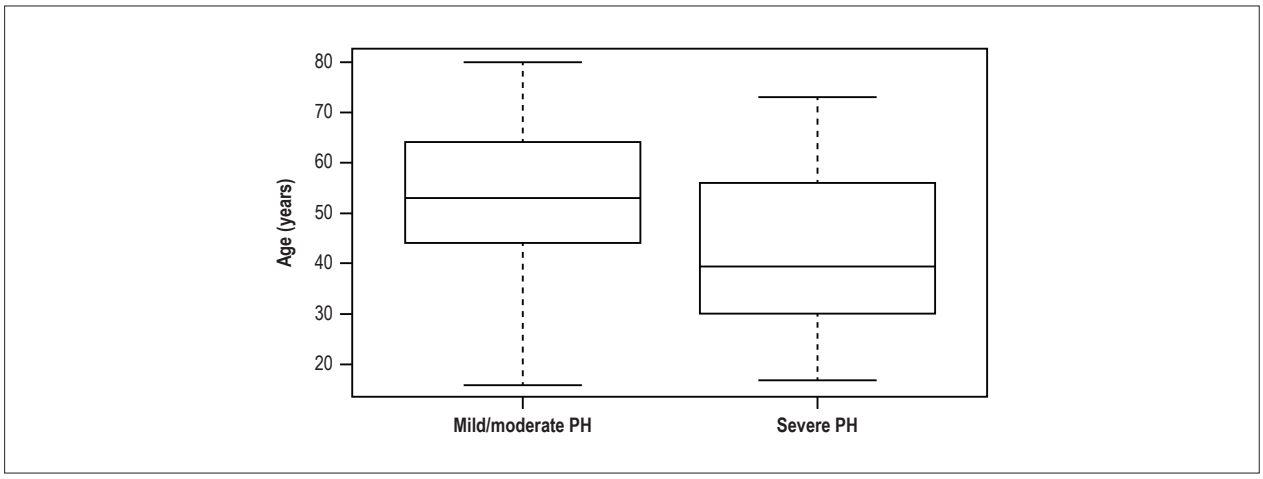

Figure 1 – *Patient's age in years x mild-moderate and severe PH. PH: Pulmonary hypertension.*

As for the chest CT, a positive correlation was derived from the comparison between the severity of PH and the PAT size in millimeters (p = 0.01). Patients from Group 2 had a higher size compared to Group 1, as observed in Figure 2.

Discussion

HP is a progressive — often irreversible — disease that causes severe limitation to the patient's activities.[1] The prevalence of this condition is markedly higher in women,[4,17] with up to 3.6:1 compared to men with the same age and symptoms. This study strengthened this information, since 82 of the patients were women and only 19 were men (W:M ratio of 4.3:1). The reasons for this discrepancy are still unknown. Some authors have suggested the higher mortality found in male patients,[17] but even the analysis of new cases of PH still prevails, with about 80% of cases in women.[17]

In this study, Group 2 patients had a lower age (mean 42 years) than those in Group 1 (mean 51.4 years). The main reason listed for this pattern is the difference between the etiologies of PH in young and old patients. While young patients have a higher incidence of PH type I (idiopathic) and IV (secondary to PTE),[1,18] which usually present with rapidly progressive pathology and high PASP, elderly patients develop the disease mainly from chronic cardiac and pulmonary conditions, with a longer course.[18] Although young people have higher PASP and more hemodynamic complications, the elderly have a higher mortality, possibly due to comorbidities.[18]

The therapy of PH is very complex, due to the multiple pathologies that can cause it. As the treatment is capable of changing the disease progression, improvement in the quality of life and increase in survival are related to early diagnosis.[12,13] After a suspected diagnosis of PH, it is necessary to quantify its symptoms in order to determine the accuracy of the severity of the condition.[1] The higher prevalence of classes III and IV in the NYHA classification in Group 2 (63% vs. 37% in Group 1) as found in this study reinforces the importance of the symptomatology approach in clinical practice, to better stratify the patient's risk.

Echocardiography is one of the main tools in the diagnosis of PH and its cardiac complications and is considered a routine follow-up test.[1,15,16] In addition to being able to estimate PASP, the possibility of detecting right ventricular dysfunctions is an important parameter in the stratification of PH severity. In this study, the prevalence of RV dilation was 46% in Group 1 patients and 79% in Group 2 patients. Moreover, the change in the RV/LV ratio is also a faithful marker of the presence of severe PH, possibly because it increases in direct proportion to the RV size.[15] Finally, the paradoxical movement of the interventricular septum is also considered a sign of PH,[1] as instead of moving to the right during systole (because of the LV pressure that is physiologically higher than that of the RV), the interventricular septum moves to the left or remains rectified upon increased pressure in pulmonary circulation. This was also relevant in our study, with 25% of the Group 2 patients presenting this abnormality vs. 7.5% of Group 1 patients. We also believe

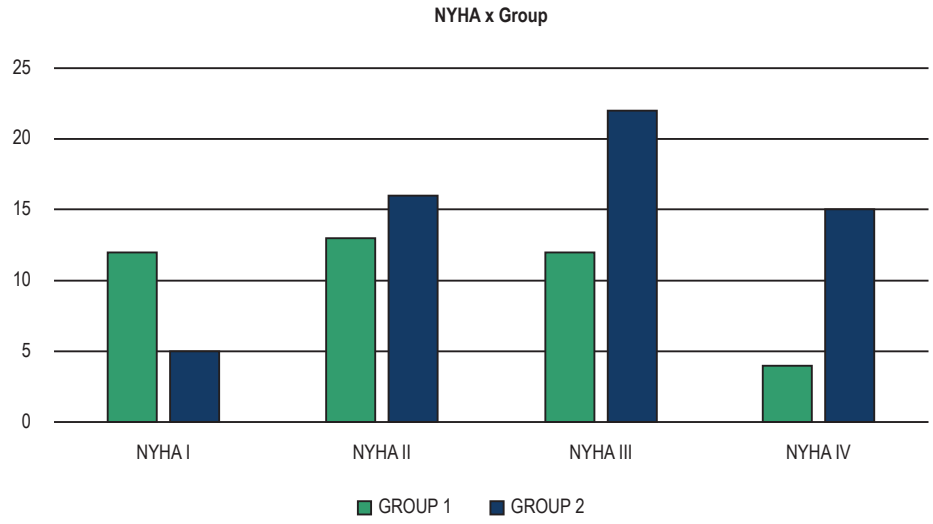

Chart 1 – *Correlation between NYHA and mild-moderate (1) and severe (2) PH. PH: Pulmonary hypertension; NYHA: New York Heart Association.*

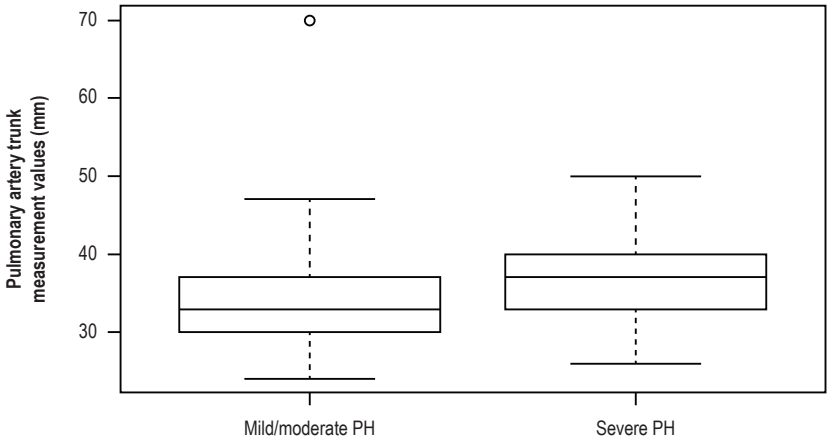

Figure 2 – *PAT size (mm) x group in the research. PH: Pulmonary hypertension.*

that the prevalence of the paradoxical movement of the septum is underestimated, since the medical records often omitted information about whether the septum was abnormal or if it remained normal. Ignorance of the importance of this finding and the overloaded service routine are factors that have possibly influenced this omission.

The PASP estimate accuracy using echocardiography has been recently questioned, mainly in the monitoring of severe pulmonary diseases. A study conducted by Alcasoy et al.[19] found discrepancies greater than 10 mmHg in about 52% of the patients evaluated, compared to the PASP estimated by echocardiography and the one measured by catheterization. Another study, conducted by Fisher et al.,[20] obtained an even weaker correlation. Some possible reasons for these differences are in technical flaws in professional estimates and the time difference between the estimate and the direct measurement.[21] Amsallen et al.[21] conducted a recent study with a bigger number of participants (n = 704), in which there was a good correlation between measured and estimated data. The echocardiographer's level of experience was one of the distinguishing features in this relationship. More experienced examiners obtained more reliable results. Additionally, some technical parameters in the detection of tricuspid reflux have been pointed out as possible factors that may underestimate or overestimate PASP.[21] Other recent studies[22,23] also observed a good correlation between both methods of evaluating PASP.

It should be noted, however, that even when performed by an experienced professional, with attention to technique and good infrastructure, the PASP estimation by echocardiography may not be reliable in up to 40% of the

cases, especially when tricuspid reflux cannot be measured with a sufficient signal.[1,21] This impossibility to establish PASP impairs the diagnostic routine and follow-up of these cases by echocardiography, so direct PASP measurement by cardiac catheterization is mandatory for determination of diagnosis and evaluation of treatment.[1,21]

Also regarding the limitations of the echocardiographic study, we should consider primary PH in a separate group. In cases where HP-compatible symptomatology is associated with risk factors for type 1 hypertension (pulmonary or primary hypertension), it is mandatory to investigate the pressures by direct catheter.[1] Such approach is necessary because there is a higher incidence of discrepancy between estimated and measured PASP in these cases.[1,21,22] Cardiac catheterization, in these situations, is also fundamental in the evaluation of the treatment to be used, thanks to the possibility of a vasoreactivity testing.[23] When PASP is reduced with vasodilator drugs, type I PH patients are candidates to long-term vasodilator use.[1]

Despite its limitations in certain cases, the value of echocardiography cannot be underestimated yet,[21] when performed by a properly trained professional, especially in services that do not have routine catheterization, as it is only used in complex cases.

Disorders revealed at ECG in PH are a frequent finding[24,25] and often underestimated, as observed in this study, in which only 41 of the 101 patients had the test done. The most common abnormalities are signs of RV hypertrophy, presence of P pulmonale wave, QT interval enlargement and ventricular strain pattern (repolarization disorders, notably T-wave inversion).[1,18,24,25] The prevalence of RV hypertrophy detectable on ECG was significantly higher in patients in the severe group (52%) compared to the mild-moderate group (6%). The presence of P pulmonale wave was rare in both groups; the strain pattern was more common in Group 2 patients (11 of the 25 cases; 44%), whereas only one of the 16 patients in Group 1 (6%) presented it. This demonstrates the value that the ECG can provide at a first moment of investigation, since it is an inexpensive test that is easy to conduct. This information can be used to encourage the use of this type of test, in order to better study its cost-effectiveness.

Chest CT is of great importance in the diagnostic routine of PH, since it can provide information regarding the heart (dilation of right chambers and PAT) and lung (detection of the underlying disease) condition.[1,15,16,26] This study did not show any significant difference between the two groups regarding the presence of right chambers dilation. In Group 1, it was present in 23% of patients and 32% in Group 2. However, these data may be underestimated, since most CT medical record reports only presented information about pulmonary disorders and PAT diameter. The presence or not of PAT dilation was not relevant, as it was prevalent in both groups. This may be due to the fact that the CT scan performed a high-definition analysis with high sensitivity to detect this type of disorder, even if it was minimal.[26] The PAT measurement in millimeters, in contrast, was larger in Group 2, with a mean of 37 mm vs. 34 mm of Group 1. Studies have shown that dilations > 34 mm may have specificity sensitivity of 90 to 100% for the diagnosis of PH.[15,16,26] CT scan can and should be used to quantify both pulmonary and cardiac disorders in a complementary way.

The main limitation of this study is the difficulty in obtaining standardized records of patients within a strictly retrospective study. While all cases were collected in the same sector, with a standard form, there is a significant discrepancy in the way professionals fill it. It is also necessary to indicate that, because the groups were based on the PASP estimated by echocardiography, there is possibly a case-by-case loss regarding the percentage of errors in this method (up to 40%). Multiple cases without the documented ECG tests also weaken the possible correlation with this test, although the statistical relevance was maintained.

It is also important to highlight the strengths of this study. We sought to provide incentives for research in national centers, and the collection and analysis were carried out in public service centers. Besides, the search for patterns suggestive of clinical severity and in noninvasive testing is of paramount importance within the context of a developing country in which complex and costly procedures may not be routinely available.

Conclusion

NYHA classification can be easily applied during anamnesis to quantify symptoms and determine the severity of the condition. NYHA III and IV patients are more likely to have high pulmonary artery systolic pressure. Similarly, the electrocardiography should be used in the initial approach of the patient, since it is a simple, fast and inexpensive test, and has relevant signs of gravity, such as right ventricular hypertrophy and ventricular strain pattern. We suggest a study with a greater number of patients with electrocardiography recorded to avoid the bias of only 40% of patients having done it, in order to establish this relationship more deeply.

Complementary evaluation by echocardiography is indispensable in cases of suspected pulmonary hypertension, once it has been shown to be superior in the risk stratification through the analysis of cardiac disorders, such as chamber dilation and anomalous movement of the interventricular septum.

Finally, computed tomography should be used in a second moment, in a complementary way, both for the search for specific pulmonary hypertension disorders, as demonstrated in the pulmonary artery abnormal diameter, and for the search of pulmonary causes for the disease.

The correct association of these diagnostic methods is of paramount importance in the management of a case of pulmonary hypertension, to allow early identification and stratification of the disease, as well as to optimize the treatment.

Authors' contributions

Research creation and design: Camarozano AC; Data acquisition: Pazello JA; Data analysis and interpretation: Camarozano AC; Statistical analysis: Pazello JA; Manuscript drafting: Pazello JA; Critical revision of the manuscript as for important intellectual content: Camarozano AC.

Potential Conflicts of Interest

There are no relevant conflicts of interest.

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Academic Association

This study is not associated with any graduate programs.

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