Correlation of 6-minute-walking test with echocardiographic pulmonary arterial stiffness in patients with pulmonary hypertension

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Abstract

Introduction:

Pulmonary arterial stiffness (PAS) has been shown to be related to pulmonary artery pressure (PAP) in patients with pulmonary artery hypertension (PAH). The aim of this study was to determine the correlation between functional capacity and echocardiographic indices of PAS in patients with PAH.

Materials and methods

This cross sectional study was performed on patients with PAH were confirmed by right heart catheterization who referred to Imam Reza PAH clinic for routine follow up between November 2019 and January 2020. All patients underwent echocardiography and the maximum Doppler frequency shift, pulmonary acceleration time, peak velocity of the pulmonary flow and velocity time integral, as well as PAS were measured. All patients performed 6-minute walk test.

Results

Fifty patients with the mean age of 41.90 ± 14.73 years old participated in this study. Majority of the patients were female (74%). The most common cause of PAH was idiopathic (74%). There was a significant correlation between PAS and PASP (r = 0.302, P = 0.041), \( V_2 \) (r=-0.461, P = 0.003), \( T_2/V_1 \) (r=-0.311, P = 0.037) and \( Z_3 \) ratio (r=-0.346, P = 0.023). There was no significant correlation between PAS and 6MWT, PVR and TAPSE (P > 0.05). There was a significant correlation between \( V_2 \) and PVR (r = 0.359, P = 0.049).

Conclusions

PAS and \( V_1 \) are simple, non-invasive, available tools for evaluation of pulmonary vascular bed and early diagnosis of pre-symptomatic clinical status in patients with PAH.

Background

Pulmonary arterial hypertension (PAH) is defined as mean pulmonary arterial pressure (mPAP) greater than or equal to 25 mmHg at rest (1). PAH is a progressive disorder, primarily results from extensive pulmonary vascular remodeling over time (2). PAH is a complex disorder and can be the end result of a variety of different underlying disorders. Pulmonary arterial stiffness (PAS) is a strong determinant of right ventricular (RV) functions (3). PAS is mainly due to endothelial dysfunction and inflammation (4). Elevated PAS leads to a higher right ventricle workload and enhances energy transmission to small pulmonary vessels, which results in further vascular damage (1, 5). Increased stiffness is associated with
reduced functional capacity (6) and higher mortality (7). This association is independent of pulmonary artery pressures or pulmonary vascular resistance (7). So far, PAS and response to treatment have been assessed through invasive hemodynamic assessment (8–10). Non-invasive imaging modalities have also been used to measure PA distensibility for the assessment of PA stiffness and risk stratification in patients with PAH (11). Many studies demonstrate that PAS is correlated with right ventricular dysfunction and disease severity in PAH regardless of the etiology (12, 13).

Despite a good correlation between mean pulmonary artery pressure (PAP) and pulmonary artery acceleration time (AT), some errors exist in noninvasive estimation of mPAP using pulmonary AT by Doppler echocardiography (14). Studies found a correlation between pulmonary artery elasticity and PAP (15). This indicates that PAS parameters can be used to determine PAH and to evaluate of RV function.

In this study, we aimed to determine the correlation between Six Minute Walk Test (6MWT), as an indicator of functional capacity, with echocardiographic indices of PAS in patients with PAH.

**Methods**

**Subjects**

This cross sectional study was performed on patients referred to Imam Reza PH clinic for routine follow up (including 6MWT) between November 2019 and January 2020.

**Eligibility**

Patients with confirmed diagnosis of PAH based on right heart catheterization within the past 12 months were enrolled in this study. PAH was defined as mPAP greater than 25 mm Hg, pulmonary artery wedge pressure (PAWP) ≤ 15 mmHg at rest. We included patients younger than 65 years old who were diagnosed with PAH within the past 12 months. Subjects with diabetes mellitus, chronic kidney disease, ischemic heart disease, and peripheral vascular disease or history of stroke and significant anemia were excluded. We also excluded patients with moderate or severe mitral and aortic regurgitation or stenosis, tricuspid stenosis, previous aorta or mitral valve operation or valvuloplasty, clinical, electrocardiographic or angiographic evidence for coronary artery disease; wall motion abnormality, and bundle branch block and arrhythmia.

**6MWT**

The 6MWT was carried out by a trained technician on a 20-m corridor with no prior practice walks. Patients were instructed to walk and cover as much distance as possible in 6 minutes. Standardized encouragement was given at 1-min intervals as per guideline (16).

**Transthoracic echocardiography**
Trans-thoracic echocardiography was performed by an experienced echocardiography specialist the day before or after 6MWT using the Philips Echocardiography system iE33 equipped with S5 probe in left lateral decubitus position. The recordings were performed in five cardiac cycles. Measurements were adjusted to obtain maximal frequency shift. Doppler signals were recorded at the speed of 100 mm/second. The maximum Doppler frequency shift, pulmonary acceleration time, peak velocity of the pulmonary flow and velocity time integral were measured from the parasternal short-axis view using pulsed Doppler ultrasound with the sample volume placed in the pulmonary artery just 1 cm below to the pulmonary valve annulus. Pulmonary artery stiffness was calculated by dividing MFS by PAT.

**Measurements**

The echocardiographic measurements were performed based on Fig. 1. Definition of the measurement parameters are presented in Table 1.

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Definition/ Calculation</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAT (ms)</td>
<td>Time from onset of pulmonary flow ejection to V₁</td>
</tr>
<tr>
<td>V₁ (ms/s)</td>
<td>First pulmonary valve pulse Doppler velocity</td>
</tr>
<tr>
<td>V₂ (ms/s)</td>
<td>Second pulmonary valve pulse Doppler velocity</td>
</tr>
<tr>
<td>V₃ (ms/s)</td>
<td>Third pulmonary valve pulse Doppler velocity</td>
</tr>
<tr>
<td>PAS</td>
<td>MFS / PAT</td>
</tr>
<tr>
<td>T₂ (ms)</td>
<td>Time from onset of pulmonary flow ejection to V₂</td>
</tr>
<tr>
<td>Z₁</td>
<td>T₂ / V₁</td>
</tr>
<tr>
<td>Z₂</td>
<td>T₂ / V₂</td>
</tr>
<tr>
<td>Z₃</td>
<td>(PAT + T₂ / 2) / V₁</td>
</tr>
</tbody>
</table>

**Ethics**

Written informed consent was obtained from all patients. This study was approved by the local ethics committee of the Mashhad University of Medical Sciences (Code: IR.MUMS.MEDICAL.REC.1399.437) in compliance with Declaration of Helsinki.

**Statistics**

Data were entered in the statistical package for social sciences (SPSS) software (SPSS, Ver. 18.0, 2018, SPSS Inc., Chicago, IL, USA). Qualitative variables were presented as percent and frequency and percentage. Continuous quantitative variables were reported as mean and standard deviation (SD).
Correlation between quantitative variables was evaluated by Spearmen or Pearson tests. For categorical variables, Chi square or Fisher's exact tests were used. Relationship between echocardiographic parameters and 6MWT was assessed using linear regression. P value less than 0.05 was considered as statistical significant.

Results

Fifty patients enrolled in this study. The mean age of the patients was 41.90 ± 14.73 years old. Majority of the patients were female (37, 74%). The most common cause of pulmonary hypertension was idiopathic (37, 74%). The mean wedge pressure measured by right heart catheterization was 8.02 ± 3.21 cmHg. Table 2 shows the demographic, clinical and general information of the study patients.

Echocardiographic parameters in the study patients are presented in Table 3. Echocardiographic As it is shown in Table 4 there was a significant correlation between PAS and PASP (r = 0.302, P = 0.041), but there was no significant correlation between PAS and 6MWT, PVR and TAPSE (P > 0.05).

Table 2
General Characteristics of the Study patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± S.D) years</td>
<td>41.90 ± 14.73</td>
</tr>
<tr>
<td>Sex (n, %)</td>
<td>Female (37, 74), Male (13, 26)</td>
</tr>
<tr>
<td>Etiology of pulmonary hypertension (n, %)</td>
<td>AP window (1, 2)</td>
</tr>
<tr>
<td></td>
<td>ASD (4, 8)</td>
</tr>
<tr>
<td></td>
<td>Idiopathic (37, 74)</td>
</tr>
<tr>
<td></td>
<td>Lupus (1, 2)</td>
</tr>
<tr>
<td></td>
<td>PDA (2, 4)</td>
</tr>
<tr>
<td></td>
<td>PTE (1, 2)</td>
</tr>
<tr>
<td></td>
<td>Scleroderma (1, 2)</td>
</tr>
<tr>
<td></td>
<td>TA (1, 2)</td>
</tr>
<tr>
<td></td>
<td>VSD (2, 4)</td>
</tr>
<tr>
<td>BSA (m2) (Mean ± S.D)</td>
<td>1.72 ± 0.15</td>
</tr>
<tr>
<td>6MWT (m) (Mean ± S.D)</td>
<td>400.14 ± 79.53</td>
</tr>
</tbody>
</table>

Table 3
Echocardiographic parameters

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>E/E’ ratio</td>
<td>7.66 ± 3.83</td>
</tr>
<tr>
<td>PAS (kHz/sec)</td>
<td>41.2 ± 5.38</td>
</tr>
<tr>
<td>TAPSE (cm) (Mean ± S.D)</td>
<td>1.34 ± 0.23</td>
</tr>
<tr>
<td>mPAP (mmHg) (Mean ± S.D)</td>
<td>68.95 ± 18.25</td>
</tr>
<tr>
<td>PASP (mmHg) (Mean ± S.D)</td>
<td>109.53 ± 27.39</td>
</tr>
<tr>
<td>FAC</td>
<td>22.40 ± 5.09</td>
</tr>
</tbody>
</table>

SD = standard deviation; PASP = pulmonary artery systolic pressure; TAPSE = tricuspid annular plan systolic excursion; E/E’m = ratio of early diastolic trans tricuspid flow velocity to early diastolic peak myocardial velocity; PAS = pulmonary artery stiffness; FAC = fractional area change

Table 4
Correlation between PAS and other factors

<table>
<thead>
<tr>
<th></th>
<th>6MWT</th>
<th>PASP</th>
<th>PVR</th>
<th>FAC</th>
<th>TAPSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correlation Coefficient</td>
<td>0.040</td>
<td>0.302</td>
<td>0.045</td>
<td>-0.042</td>
<td>-0.111</td>
</tr>
<tr>
<td>P value</td>
<td>0.392</td>
<td>0.041</td>
<td>0.420</td>
<td>0.390</td>
<td>0.230</td>
</tr>
</tbody>
</table>

There was a significant correlation between V₁ and 6MWT (r = 0.259, P = 0.036) (Fig. 2). There was a significant correlation between PASP and V₂ (r=-0.461, P = 0.003), T₂/V₁ (r=-0.311, P = 0.037) and Z₃ ratio (r=-0.346, P = 0.023). There was also a significant correlation between V₂ and PVR (r = 0.359, P = 0.049). There was no significant correlation between 6MWT with PASP (r = 0.067, P = 0.353), PVR (r=-0.069, P = 0.381) and PAS (r = 0.04, P = 0.392). Multivariate regression analysis showed that, PAS and V₁ could significantly predict functional capacity assessed by 6MWT (Table 5).

Table 5
Multivariate logistic regression analysis for 6MWT

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>P value</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAS</td>
<td>0.738</td>
<td>0.008</td>
<td>-349.20 - -60.00</td>
</tr>
<tr>
<td>PV 1</td>
<td>0.599</td>
<td>0.027</td>
<td>0.54 - 7.95</td>
</tr>
</tbody>
</table>

Discussion
The main finding in our study was that V1 could significantly predict functional capacity in patients with PAH but PAS was not significantly correlated with 6MWT. We also found some new indices that were correlated with PASP in our study population.

Arterial stiffness is a well-known risk factor for cardiovascular events and the secondary target for pharmacological treatment (17). Endothelial dysfunction is one of the main factors associated with the development of both the PAH (18, 19) and systemic hypertension (20, 21). Pulmonary artery is a low pressure, high distensible system which transforms the highly pulsatile right ventricular output into the near steady flow at the capillary level (22). The distal pulmonary vascular bed is also comprised of highly distensible vessels. Distension and recruitment of this microvascular bed can accommodate large increases in volume such as during exercise. This response is the opposite of that experienced in the systemic circulation where exercise induces vasoconstriction in majority of the vascular tree other than the vessels supplying muscles. This inbuilt reserve means that resting pulmonary arterial pressures will rise relatively late in a disease process only when 60–70% of the bed is obstructed (13).

PAH is a rare but fatal disease worldwide that can be due to many causes ranging from idiopathic to secondary to many underlying pathologies, including congenital heart diseases. Several prognostic indicators, including NYHA functional class, 6MWT and echocardiographic and hemodynamic parameters, are used for routine follow up of the disease. Right heart catheterization (RHC) is pivotal in the evaluation of patients with PAH. This invasive test is used for both diagnosis and determination of the prognosis of PAH (19). However, the most widely used method in routine practice is Doppler echocardiography. RHC may not be suitable for routine evaluation due to its invasiveness. On the other hand, echocardiography has some limitation sin the diagnosis of PAH. For instance, systolic PAP cannot be estimated in echocardiography based on modified Bernoulli equation in the absence of tricuspid regurgitation. Therefore, it is necessary to develop new noninvasive methods. Studies found a correlation between pulmonary artery elasticity and PASP. Studies have demonstrated that PAS parameters, which are derived by CMR, can be used in determination of PAH (15). In this investigation, we decided to assess the relationship between PAS and 6MWT in patients with PAH. To the best of our knowledge, no similar study has yet been conducted on this topic. Nevertheless, the findings of our study were in line with the findings of some investigations. Ragab and Mahfouz assessed the impact of PAS by echocardiography on the long-term right ventricular (RV) function and tricuspid regurgitation (TR) changes after percutaneous balloon mitral valvuloplasty (PBMV). They showed that patients with mitral stenosis (MS) had significantly higher PAS compared with control subjects. They also showed that PAS was significantly low in patients with progressive RV function improvement and regression of TR. They showed that PAS was significantly correlated with the degree of PASP, tricuspid annular plane systolic excursion (TAPSE), and E/E’m ratio (11). We did not find any significant relationship between PAS and PASP, TAPSE and E/E’ ratio.

It is believed that vasoconstriction develops in the early stages of PAH and that increase in vasoconstriction leads to endothelial dysfunction. Elastic and collagen fibers are important components of the arterial wall that determine the extensibility of the great arteries (23). Pulmonary artery and
vascular bed changes occur before the development of overt PAH. Therefore, remarkable increase in PAS might be a predictor for the onset of changes in pulmonary vascular bed (24). Previous studies have shown that emphasis on the increase in PASP may result in failure to diagnose these early changes. Our study demonstrated a significant correlation between PAS and PASP, which can be useful for early diagnosis of PAH especially in patient with predisposing underlying diseases. Weir-McCall et al. reviewed the role of PAS in COPD patients. They showed that PAS increases with the severity of COPD, and correlates well with the presence of exercise induced pulmonary hypertension. They reported a curvilinear relationship exists between PA distensibility and mPAP and PVR with a marked loss of distensibility followed by a rapid rise in mPAP and PVR that occur with the resultant right ventricular failure. Weir-McCall et al. concluded that PAS can be a promising biomarker for early detection of pulmonary vascular disease, and can play a role in right ventricular failure in COPD (13). Ozkececi et al. evaluated PAS and cardiac function in sixty newly diagnosed patients with obstructive sleep apnea syndrome (OSAS) and 30 healthy controls. They analyzed the relationship between OSAS severity and PAS. Positive correlations were observed between apnea hypopnea index and total oxygen desaturation with PAS and mean PAP. They mentioned that PAS and mPAP increased in patients with OSAS and pulmonary vascular bed, which may be affected by PAP fluctuation during day and night time (25).

Some studies have demonstrated that increased PAS is a predictor of decreased functional capacity. Kang et al. showed that non-invasive CMRI-derived PA distensibility index correlates with PA stiffness and can predict functional capacity with 6MWT in patients with PAH (6). The 6MWT is an important functional test in the assessment functional capacity in PAH patients. It is an important parameter for clinical surveillance of disease progression and treatment effect. In this study, there was no significant correlation between PAS and 6MWT. We used novel parameter to assess the relationship between echocardiography and 6MWT. $V_1$ as defined in the methods section, was found to have a significant positive correlation with 6MWT. We also demonstrated in multivariate regression analysis that PAS and $V_1$ significantly predicted the 6MWT. 6MWT is a primary endpoint of many clinical investigations related to PAH. Therefore, these variables can be used for future clinical studies in the evaluation of PAH severity and response to treatment.

PA distensibility index using non-invasive methods such as echocardiography or computed tomography were introduced to easily measure PA stiffness. These methods have some limitations, including reproducibility and variability and lack of data to compare with invasive hemodynamic parameters (26, 27).

**Conclusion**

To best of our knowledge this study was the first study that assessed the relationship between functional capacity and PAS and $V_1$ in PAH patients with any underlying predisposing factors. These parameters are simple, non-invasive, available and easy to measure tools for evaluation of pulmonary vascular bed and early diagnosis of pre-symptomatic clinical status in patients with PAH. Large-scale multi-centric studies in this issue can be helpful to identify the power of these factors.
Abbreviations

PAS = Pulmonary arterial stiffness
PAP = pulmonary artery pressure
PAH = pulmonary artery hypertension
PVR = Pulmonary vascular resistance
RV = right ventricular
AT = acceleration time
6MWT = Six Minute Walk Test
PAWP = pulmonary artery wedge pressure
MFS = maximal frequency shift
SPSS = statistical package for social sciences
SD = standard deviation
NYHA = New York Heart Association
RHC = Right heart catheterization
TR = tricuspid regurgitation
PBMV = percutaneous balloon mitral valvuloplasty
MS = mitral stenosis
TAPSA = tricuspid annular plane systolic excursion
COPD = Chronic obstructive pulmonary disease
CMRI = Cardiac magnetic resonance imaging

Declarations

Ethics approval and consent to participate

Publishing this case presentation is performed according to ethical guidelines of Mashhad University of Medical Sciences. Patient was evaluated for his problem and fulfilled informed consent for participation.
Consent for publication

We obtained consent for publication from patients.

Availability of data and material

The data that support the findings of this study are available from Ghaem Hospital, Mashhad University of Medical Sciences, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the corresponding author.

Competing interests

The authors declare that they have no competing interests.

Funding

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Authors’ contributions

Leila Bigdelu and Sara Afshar analyzed and interpreted the patient data regarding the cardiovascular disease and managed patients. Hedie Alimi, Hoorak Poorzand, Fereshteh Ghaderi and Afsoon Fazlinezhad helped in data gathering and diagnosis patients in echocardiographic evaluation. Farveh Vakilian helped in patients’ management. Faeze Keihanian helped in management of patients, diagnosis and contributor in writing the manuscript. Zahra Abbasi Shaye helped in statistical analysis. All authors read and approved the final manuscript.

Acknowledgements

We all thank nursed of Ghaem Hospital helped us in different stages of patient evaluations.

References


**Figures**

**Figure 1**

The ratio of maximal frequency shift (MFS) to acceleration time (PAT) gives us pulmonary artery stiffness (PAS)
Figure 2

The correlation between V1 and 6MWT