

Flow-Mediated Dilation, a Marker of Endothelial Cell Dysfunction, in Patients with Pulmonary Hypertension

Ahmad Mirdamadi¹, Mohammad Shirzad²,
Raana Abrishamkar², Mohaddeseh Behjati³

¹ Department of Cardiology, Najafabad Branch, Islamic Azad University, Najafabad, Isfahan, Iran, ² Najafabad Branch, Islamic Azad University, Najafabad, Isfahan, Iran, ³ Rajaie Cardiovascular, Medical and Research Center, Iran University of Medical Sciences, Tehran, Iran.

Received: 5 October 2020

Accepted: 3 April 2021

Correspondence to: Abrishamkar R

Address: Najafabad Branch, Islamic Azad University, Isfahan, Iran

Email address: Raana.abrishamkar@gmail.com

Background: Flow-mediated dilation (FMD) is considered a marker of endothelial cell dysfunction (ECD) and has been mostly evaluated in coronary artery disease. The role of ECD in the pathogenesis of pulmonary hypertension (PH) is not well-known. This study sought to evaluate the relationship between FMD and PH.

Materials and Methods: In this cross-sectional study, the FMD of the brachial artery was measured in 40 confirmed PH patients. Meanwhile, echocardiographic findings, the 6-minute walk test (6MWT), and serum pro-brain natriuretic peptide (pro-BNP) level were evaluated. Overall, 20 patients accomplished all evaluations, and their data were analyzed using SPSS software (version 23).

Results: There was an inverse relationship between pro-BNP and 6MWT ($r < 0$, $P < 0.05$). A significant direct relationship was observed between left ventricular ejection fraction and FMD ($P = 0.031$). Right ventricular (RV) dilation was significantly correlated with pro-BNP ($P = 0.046$). There was a significant direct correlation between RV function and FMD and a significant inverse relationship between pro-BNP and FMD ($P = 0.05$). The independent t-test showed no relationship between FMD and syncope ($P = 0.75$).

Conclusion: Endothelial cell function, which can be evaluated by FMD, was involved in patients with PH. The FMD and 6MWT were helpful as objective prognostic markers in PH. Furthermore, pro-BNP was a noninvasive indicator in the diagnosis of RV systolic dysfunction.

Key words: Pulmonary Hypertension (PH); 6-Minute Walk Test (6MWT); Flow-Mediated Dilatation (FMD); Endothelial Cell Dysfunction (ECD)

INTRODUCTION

Pulmonary hypertension (PH) is defined as increased pressure in the lung arteries (1). The PH symptoms include shortness of breath, syncope, fatigue, chest pain, swelling, and increased heart rate (2). Although the exact incidence of this condition is unknown, it is estimated that approximately 1,000 new cases will occur in the United States each year (3). The onset of the disease is usually

within 20-60 years, and females are more affected than males (3).

The molecular mechanisms of PH have not been well-known yet; however, currently, some major signaling pathways are supposed to be involved in its pathogenesis. Endothelial cell dysfunction (ECD) with the reduced synthesis of endothelium-derived vasodilators, such as nitric oxide and prostacyclin, is one of them (4). Regardless of pathogenesis, the risk of mortality is high in cases with

PH (1). Therefore, it is essential to obtain an index to determine these individuals' morbidity and mortality rates and the severity of their condition. Currently, one of the approved prognostic tests in PH cases is the 6-minute walk test (6MWT).

Endothelial dysfunction is an important physiological mechanism leading to coronary artery disease (CAD) and other cardiovascular diseases (4-6). It has also been shown to be of particular independent prognostic importance in predicting vascular events, such as stroke and myocardial infarction (6-8). Currently, the role of flow-mediated dilation (FMD) in PH is not fully defined. One of the suggested methods for the measurement of ECD is FMD. Recent years have also shown the feasibility of translating this measure into clinical trials (6). The baseline size of the artery, which is part of the test to calculate the percentage of vascular dilatation (% FMD), is of potential prognostic value for the early detection of cardiovascular disease.

Considering the important role of ECD in the pathogenesis of PH and the role of FMD in the identification of ECD at earlier stages, this study aimed to determine the relationship between FMD and 6MWT with pulmonary artery pressure (PAP) in different types of PH. This study also evaluated the prognostic role of FMD in PH cases.

MATERIALS AND METHODS

This cross-sectional study was performed on 40 known patients of PH who had already been registered in a PH clinic in Isfahan, Iran. The PH was already confirmed in all patients by right heart catheterization. The exclusion criteria included patients with any pulmonary diseases, such as chronic obstructive pulmonary disease, diabetes mellitus, dyslipidemia, collagen vascular diseases, atherosclerotic cardiovascular disease, and heavy smoking, and patients with unstable conditions, such as septic shock. The participants were enrolled after obtaining signed informed consent and then underwent new evaluation by physical examination, echocardiography, 6MWT, and FMD (by a qualified expert with knowledge of the procedure).

Blood pressure, 25-hydroxy (OH) vitamin D3 level, thyroid function test, and serum pro-brain natriuretic peptide (pro-BNP) level were also measured.

For the 6MWT, the patient was asked to walk through a flat, hard path for 6 minutes at maximum speed. At the end of the 6th minute, the traveled distance was calculated and expressed in meters. Echocardiography was performed, and all echocardiographic data were re-evaluated, such as PAP, right ventricular (RV) dimensions, tricuspid annular plane systolic excursion (TAPSE) as an indicator of RV function, and left ventricular function.

At this stage, FMD was performed in a laid position. The brachial artery diameter was first measured by ultrasound above the elbow. A mercury sphygmomanometer cuff inflated at 30 mmHg above patients' systolic blood pressure in the proximal part of the forearm to induce congestion hyperemia. Five minutes later, the maximum diameter of the brachial artery was measured again at the peak of the systole, using the same ultrasound technique. The percentage of the size difference of the brachial artery was also calculated. Overall, 20 patients accomplished all these evaluations, and their data were expressed as means±standard deviation and analyzed by SPSS software (version 23) using Pearson coefficient correlation and independent t-test.

RESULTS

In this study, 20 out of 40 patients were eligible for data analysis based on the inclusion and exclusion criteria. Furthermore, 85% and 15% of the patients were female and male, respectively. The percentage of participants in different PH subtypes according to the World Health Organization classification (i.e., 1-5 types of PH) were determined as follows (10):

- 10 cases (50%) with type 1 (idiopathic pulmonary artery hypertension)
- 6 cases (30%) with type 4 (chronic thromboembolic pulmonary hypertension)
- 4 cases (20%) with Eisenmenger syndrome
- 0 case with type 2, 3, or 5

The mean values of serum pro-BNP level, 6MWT, and left ventricular ejection fraction (LVEF) were 3268.4 pg/ml, 333.23 m, and 56.25%, respectively. Abnormal 25(OH) vitamin D3 level, abnormal thyroid function, and hypertension were also observed in 10.5%, 5.3%, and 5% of patients, respectively. The RV dysfunction (50%) and enlargement (70%) were observed mostly in patients with severe PH. Severe PH considered systolic PAP higher than 60 mmHg by echocardiography. In addition, 30% of patients had a history of syncope.

The obtained data demonstrated an inverse relationship between serum pro-BNP level and 6MWT, in which pro-BNP level decreased; however, 6MWT was increased ($r < 0$, $P < 0.05$). This study also showed a significant direct relationship between LVEF and FMD ($P = 0.031$). The RV size was significantly correlated with serum pro-BNP level ($P = 0.046$); nevertheless, there was no significant relationship between systolic and mean PAP with the serum pro-BNP level ($P > 0.05$). There was a significant direct correlation between TAPSE, as an indicator of RV function, and FMD ($P = 0.05$). The TAPSE had an inverse relationship with serum pro-BNP level ($P = 0.05$). There was also no relationship between FMD and syncope ($P > 0.05$). The independent t-test also showed no relationship between FMD and syncope occurrence ($P = 0.75$).

DISCUSSION

The most important result of this study was finding a significant direct relationship between FMD, as a marker of ECD, and RV function. The RV function usually is measured by TAPSE. The RV size was also significantly correlated with the serum pro-BNP level and was inversely related to FMD. This study did not find any significant association between 6MWT and FMD. There was also no association between FMD and syncope.

Philpott et al. (9) showed that FMD and physical tests, including 6MWT, are functional methods for the

measurement of cardiovascular risk factors, especially in patients with PH. The results of another study conducted by Yazdanyar et al. indicated that the risk of mortality from cardiovascular diseases was not significant among those with 6MWT higher than 290 m. This study demonstrated that 6MWT was independently associated with all causes of cardiac mortality and is a useful prognostic tool in patients with PH, especially older adults (10). Another study conducted by Zelniker et al. on 2391 patients showed that 6MWT is a prognostic factor in patients with PH (11). In the present study, although 6MWT was a valuable prognostic variable, it was not significantly correlated with FMD. No significant relationship was observed between these two important prognostic factors, which might be due to the small sample size of the present study.

There was a significant inverse correlation between serum pro-BNP level and FMD. Another study performed by Hijmering et al. investigated the variability of FMD and its consequences for clinical application. They showed that FMD is a trusted method of the assessment of RV function (12). The aforementioned results are consistent with the findings of the current study. The present study showed a significant direct correlation between FMD and RV function in patients with PH. Peled et al. also showed peripheral endothelial dysfunction in patients with PH, which might increase cardiovascular risks. They also showed that RV function in these patients is directly related to FMD, which is similar to the findings of the current study (13). Van Wolferen et al. in a study on the relationship between RV size and structure (RV size and function) with survival in patients with idiopathic pulmonary artery hypertension, showed dilated right ventricle, worsened RV function, and decrease in end-diastolic volume as the strongest predictors of mortality (14). The aforementioned data are also in line with the data of the current study.

A study conducted by Blyth et al. demonstrated a significant correlation between serum N-terminal pro-brain

natriuretic peptide (NT-pro-BNP) level and RV systolic dysfunction. In addition, the serum level of NT-pro-BNP over 1,685 ng·L⁻¹ was related to increased RV systolic dysfunction and mortality. Therefore, serum NT-pro-BNP level was a noninvasive marker of RV systolic dysfunction in patients with PH (15). In the aforementioned study, FMD values were significantly related to syncope in patients with PH, which was not obtained in the present study (16). Consequently, the relationship between FMD and RV function in cases with PH might be a potential diagnostic and prognostic marker in these patients. However, this finding needs further investigation to determine the diagnostic and prognostic value of FMD as a ubiquitous marker in PH.

CONCLUSION

The FMD as a marker of ECD has attracted special attention in CAD; nevertheless, it is also valuable in PH. This study showed that ECD is related to RV dysfunction, and this viewpoint on ECD in PH might help better understand and manage the disease. The FMD is particular prognostic value as 6MWT and serum pro-BNP emphasizes its importance.

Limitation of study

This study can be done on a larger scale with a larger sample size to obtain more accurate information about the available variables.

Acknowledgment

We would like to express our great appreciation to research unit in School of Medicine of Islamic Azad University, Najafabad Branch for helping us during the planning and development of this research.

Conflict of Interest

Authors have no conflict of interests.

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