Assessment of Pulmonary Arterial Stiffness in Patients with Cirrhosis: A Prospective Cohort Study

Ahmet Öz[1], Tufan Çınar[2], Ebru Tas[1], Suleyman Efe[3], Burak Ayca[1], and turgut karabag[4]

[1]Istanbul Egitim ve Arastirma Hastanesi
[2]Affiliation not available
[3]Kartal Kosuyolu Yuksek Ihtisas Heart-Education and Research Hospital
[4]Istanbul Education and Research Hospital

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Abstract

Introduction In the current literature, several studies show that pulmonary artery stiffness (PAS) is associated with right ventricular (RV) dysfunction, pulmonary arterial hypertension (PAH), and disease severity in patients with structural heart disease, human immunodeficiency virus (HIV), and chronic lung disease. Hence, in this study, we aimed to use PAS to show the early changes in the pulmonary vascular bed in patients with cirrhosis. Material and Methods In this prospective, cross-sectional study, 39 subjects who were being followed up with cirrhosis and 41 age- and sex-matched healthy participants were enrolled. For each case, the PAS value was calculated by dividing mean peak velocity of the pulmonary flow by the pulmonary flow acceleration time (PfAT). Results The measured PAS was 23.62 ± 5.87 (Hz/msn) in cirrhotic patients and 19.09 ± 4.16 (Hz/msn) in healthy subjects ($p < 0.001$). We found a positive statistical significance between PAS and systolic pulmonary arterial pressure (sPAP) ($r = 0.378$; $p = 0.001$). PAS was an independent predictor that was associated with cirrhosis disease according to multivariate logistic regression analysis (OR: 1.209; 95% CI: 1.059–1.381; $p = 0.005$). Conclusion Based on the study results, we consider that PAS may help in the early detection of changes in the pulmonary vascular bed, even if the RV function parameters or sPAP are within the normal range.

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Ahmet Öz, MD, Istanbul Training and Research Hospital, Department of Cardiology, Istanbul/TURKEY drozahmet@gmail.com

Tufan Çınar, MD, Sultan Abdulhamid Han Training and Research Hospital, Department of Cardiology, Istanbul/TURKEY drtufancinar@gmail.com

Ebru Taş,MD , Istanbul Training and Research Hospital, Department of Gastroenterology, Istanbul/TURKEY ebrutas7498@hotmail.com

Süleyman Çağan Efe, MD, Istanbul Training and Research Hospital, Department of Cardiology, Istanbul/TURKEY scaganefe@gmail.com

Burak Ayça, MD, Istanbul Training and Research Hospital, Department of Cardiology, Istanbul/TURKEY drburakayca@yahoo.com.tr

Turgut Karabağ, MD, Istanbul Training and Research Hospital, Department of Cardiology, Istanbul/TURKEY turgutkarabag@yahoo.com

Corresponding author

Ahmet Öz MD

E-mail

drozahmet*@gmail.com*

Address

Kasap İlyas Mah, Org. Abdurrahman Nafiz Gürman Cd./34098/Fatih/İstanbul/Turkey

Phone : +905332075510

Abstract

Introduction

In the current literature, several studies show that PAS (pulmonary artery stiffness) is associated with RV (right ventricular) dysfunction, PAH (pulmonary arterial hypertension), and disease severity in subjects with structural cardiac disease, HIV (human immunodeficiency virus), and chronic lung disease. Hence, our main aim was to use PAS to show the early changes in the pulmonary vascular region in subjects with cirrhosis.

Material and Methods

In this prospective, cross-sectional study, 39 subjects who were being followed up with cirrhosis and 41 age- and sex-matched healthy subjects were included in this study. For each case, the PAS value was obtained by dividing mean peak velocity of the pulmonary flow by the PfAT (pulmonary flow acceleration time).

Results

The measured PAS was 23.62 ± 5.87 (Hz/msn) in cirrhotic participants and 19.09 ± 4.16 (Hz/msn) in healthy cases ($p < 0.001$). We found a positive statistical significance between PAS and sPAP (systolic pulmonary arterial pressure) ($r = 0.378$; $p = 0.001$). PAS was an independent predictor that was associated with cirrhosis disease according to multivariate LR (logistic regression) analysis (OR: 1.209; 95% CI: 1.059–1.381; $p = 0.005$).

Conclusion

Based on the study results, we consider that PAS may help in the early detection of findings in the pulmonary vascular area, even if the RV function findings or sPAP are within the normal range.

Keywords: Cirrhosis, pulmonary artery stiffness, pulmonary arterial hypertension, early

Introduction

Cirrhosis usually results from the conversion of normal liver architecture into structurally abnormal nodules due to tissue fibrosis. According to the current knowledge, cirrhosis's 1-year mortality rate may range from 1% to as high as 57%, and it is a leading cause of morbidity and mortality, especially in developed nations (1). Alcoholic liver disease and chronic infections due to hepatitis-B and -C viruses constitute the leading causes of liver cirrhosis worldwide (2). Clinically, cirrhosis is categorized into two configurations: either as compensated or decompensated. Although compensated cirrhosis is difficult to distinguish from chronic hepatitis infection, decompensated cirrhosis is easily diagnosed because it has several specific clinical and laboratory findings, such as ascites, hepatic encephalopathy, gastrointestinal bleeding, thrombocytopenia, and hypoalbuminemia. In addition, cirrhotic patients can be classified into two configurations based on the absence or presence of PH (portal hypertension) (3), a condition characterized by a hepatic venous pressure gradient of [?]5 mmHg and the main mechanism leading to mortality in cirrhotic patients (4).

PAH (pulmonary arterial hypertension) is categorized into five major forms based on the WHO (World Health Organization) recommendation, and PAH due to portal hypertension, which is termed PoPH (porto-pulmonary hypertension), is included in group I. PoPH is most commonly found in cases with cirrhosis, and it develops in approximately 1-5% of subjects with PH (5, 6). Hence, PoPH screening is crucial in subjects with chronic liver disease; TTE (transthoracic echocardiography) is the best non-invasive applicable tool for such screening (7).

PAS (pulmonary artery stiffness) is a simple, easily measurable echocardiographic variable that can be obtained by dividing the peak velocity of the pulmonary flow by the PfAT (pulmonary flow acceleration time). A prior clinical study found that echocardiographically-obtained PAS parameters were well correlated with the measurements obtained from right heart catheterizations (8). Moreover, PAS can represent early changes in the pulmonary vascular region in congenital cardiac disease cases without significant PAH (8). In the current literature, several studies show that PAS is linked with RV (right ventricular) dysfunction, PAH, and disease severity in subjects with structural cardiac disease, HIV (human immunodeficiency virus), and chronic lung disease (8-12). However, to our knowledge, no prior research has evaluated PAS in cirrhotic patients. Hence, our main aim was to use PAS to show the early changes in the pulmonary vascular region in subjects with cirrhosis.

Materials and Methods

Data collection

In total, consecutive 39 subjects with cirrhosis who were being followed up at the Istanbul Training and Research Hospital in the Gastroenterology department between December 2019 and February 2020 were enrolled in this prospective, cross-sectional study. The control cohort was composed of 41 age- and sex-matched healthy participants. In the study, the exclusion principles were as the following: patients with a known congenital cardiac disease, connective tissue disorders, HIV, LV (left ventricular) systolic or diastolic ($>$ grade II) dysfunction, moderate-to-severe heart valve disorders, chronic lung disorder, chronic thromboembolic PAH, chronic renal disorder, atherosclerotic cardiovascular disease, insufficient imaging quality, and were using medical treatment or illegal drugs accused of PAH etiopathogeneses. Baseline clinical properties, such as age, gender, and BMI (body mass index), and the etiology of cirrhosis for all patients were recorded. For each patient, we calculated the severity of cirrhosis using the MELD (Model for End-Stage Liver Disease), MELD-Na and CTP (Child-Turcotte-Pugh) scores (**Table 1**). The clinical conditions of all cases (whether clinically compensated or decompensated) were noted.

This prospective, cross-sectional study protocol was approved by the Institutional Ethics Committee. A written informed consent form was obtained from all subjects.

TTE evaluation

In this research, TTE was performed by two experienced echocardiographers who were unaware of the patients' medical data. For all measurements, a Vivid S70N TTE device (GE-Vingmed-Ultrasound) and M5Sc (1–5 MHz) ultrasound probe was applied. The biplane Simpson method was used to measure the LV ejection fraction for each participant, while the LV measurements were determined with using the M-mode method obtained from the parasternal long-axis window. In order to record either mitral or tricuspid flow velocities, the sample volume was oriented at the tip of both valve leaflets in an apical 4-chamber window by applying the pulsed Doppler method. From this window, the peak A (atrial) flow velocity and the peak E (early) diastolic flow velocity were recorded. To obtain the LV and RV tissue Doppler variables using the pulsed wave Doppler method, the sample volume was oriented either on the mitral lateral annulus or the tricuspid lateral annulus in the apical 4-chamber window. Both peak E' (early diastolic) and peak A' (late diastolic) cardiac velocities were recorded from this view. The RV MPI (myocardial performance index) was obtained using the following equation: tricuspid valve closure to opening time – RV-ET (ejection time)/RV-ET. RV mid and annular diameters were obtained at the end-diastole from the apical 4-chamber window. By accommodating a 2D cursor at the tricuspid lateral annulus on the apical 4-chamber window, the TAPSE (tricuspid annular plane excursion) was recorded for each case. The simplified Bernoulli formula

was performed to determine the sPAP (systolic pulmonary artery pressure) (13).

Measurement of PAS

First, in the parasternal short axis window, we obtained the pulmonary artery. Thereafter, the pulmonary blood flow Doppler recordings were measured under the semilunar pulmonic valve. The MFS (maximum frequency shift) of the pulmonary flow was recorded for at least 5 succeeding beats. The PfAT, which is described as the distance between the starting of systolic pulmonary artery flow and peak flow rate, was measured for at least 5 succeeding beats. The PAS value was then obtained by dividing average MFS by average PfAT (**Fig. 1**). Intra- and inter-observer agreements were 0.97 and 0.93 for PAS measurements, respectively ($p < 0.001$).

Laboratory examination

Patients' blood values, including albumin, INR (international normalized ratio), and CRP (C-reactive protein), were obtained following 8 hours of overnight fasting. A haematology analyser (Beckman Coulter LH 780, FL, USA) was carried out to obtain the results of the complete blood samples, while CRP was measured using a biochemical analyser (Beckman Coulter AU 680).

Statistical Analysis

SPSS statistical software version 22.0 (IBM, Chicago, IL, USA) was conducted to analyse the data. To test the normality of the data, Kolmogorov-Smirnov tests were used. To express quantitative variables, the mean +- standard deviation (SD) was used, while the numbers and percentages were used to express the categorical variables. When the parameters had normal distributions, the independent t-tests were applied to compare the groups. On the other hand, the parameters without normal distributions, the Mann-Whitney U tests were applied to compare the groups. Either Chi-square tests or Fisher's exact tests were applied to determine the dissimilarities for categorical variables. To assess the correlation between the parameters, we applied a Spearman's correlation test. To identify independent relations in patients with cirrhosis, probable parameters obtained in univariate analyses were included into multivariate LR (logistic regression) analysis. A $p$value of < 0.05 indicated statistical significance.

Results

In the current study, 39 cirrhotic patients and 41 age- and sex-matched healthy participants were studied. **Table 2** is a presentation of the demographic features and laboratory findings for the patients with cirrhosis and healthy subjects. Both groups were not dissimilar regarding the clinical properties. In terms of laboratory findings, white blood cell count, haemoglobin, platelet count, creatinine, sodium, and albumin were significantly decreased in the cirrhotic cases, while their alanine transaminase, aspartate transaminase, total bilirubin, indirect bilirubin, and prothrombin time were significantly elevated ($p < 0.05$, for each parameter). The other laboratory results were fairly similar for each group. We noted that no significant differences were present between each group in the many standard echocardiographic parameters in which the diameter and functions of the right and left spaces were evaluated (**Table 3**). However, PAS was measured as 23.62 +- 5.87 (Hz/msn) in the cirrhotic cases and 19.09 +- 4.16 (Hz/msn) in the healthy subjects ($p < 0.001$). Fifteen cirrhotic patients (%38.4) were clinically decompensated in the study, but there was no statistically significant dissimilarities in terms of echocardiographic parameters for compensated or decompensated cirrhotic patients (**Table 4**).

A positive statistical relevance was found between PAS and sPAP ($r = 0.378$; $p = 0.001$), and a negative statistical relevance was found with PfAT and sPAP (r = -0.314; $p = 0.005$). An elevated PAS values was positively associated with sPAP ($p < 0.05$) (**Fig. 2**). The interactions of the echocardiographic parameters with age, BMI, disease period, and PAS in cirrhotic patients are shown in **Table 5** .

The independent effects of probable demographic and echocardiographic parameters associated with cirrhosis disease were evaluated by univariate and multivariate LR analysis. Following applying of the univariate analysis, five parameters were statistically significance with cirrhosis disease (sPAP, PAS, LA diameter, RV

annular diameter, and E/e'); the variables, which were applied into the multivariate analysis, are shown in **Table 6** . The multivariate analysis found that PAS (OR: 1.209; 95% CI: 1.059–1.381; $p = 0.005$), sPAP (OR: 1.201; 95% CI: 1.057–1.365; $p = 0.005$), and LA diameter (OR: 1.396; 95% CI: 1.079–1.805; $p = 0.011$) were independently linked with cirrhosis disease.

Discussion

In the present research, we observe that cirrhotic patients without PAH have higher PAS values than healthy subjects, which may indicate an early change in the pulmonary vascular bed among these cases. To our knowledge, this should be the first study demostarating higher PAS values in cirrhotic patients.

Nowadays, the average life expectancy of cirrhotic patients is prolonged due to early diagnosis and effective treatment modalities. However, complications related to portal hypertension, which is the main cause of mortality, are frequently observed. (1-4). Portal hypertension is included in the WHO PAH group I; PAH caused by portal hypertension is termed PoPH. Even though the underlying pathophysiologic mechanisms of PoPH are somewhat complex and not fully understood, it is hypothesized that the passage of some vasoconstrictive substances, mainly serotonin and endothelin-1, into the lung circulation with portosystemic collaterals and shunts is the main mechanism of developing PoPH (14). Another possible explanation is that thrombi caused by venous thromboembolism can enter the lung circulation through shunts, thereby resulting in PAH (15, 16). Furthermore, hyperdynamic circulation in cirrhotic patients can cause excessive blood flow to the lung circulation, which may promote PAH formation (15). All in all, it is still not clear why PoPH develops in a small proportion of cirrhotic cases with PH.

In previous studies, although different rates have been reported, PoPH was detected in 1-2% of cases with PH and in 5-10% of cases who were candidates for liver transplantation (7, 16). These findings highlight that cirrhotic patients should be evaluated more carefully for the development of PoPH and that a screening plan is needed. In a recent analysis, the importance of early recognition for PAH was noted, and some echocardiographic parameters, including PfAT, RV isovolumic relaxation time and Tei index, were suggested (17). However, measuring such parameters is quite time consuming. In a prospective study that included patients waiting for liver transplantation, 7 out of 17 patients with an echocardiographic diagnosis of PAH were demonstrated by right heart catheterization (RHC) to not show PoPH. In that study, there was a 10 mmHg greater difference between RHC and echocardiographic sPAP (18). In this reseach, there was also no significant dissimilarities between the groups in terms of sPAP. Because the pulmonary vascular bed has high capacitance property, sPAP does not usually develop until the loss in microcirculation reaches 60-70%. After this threshold is exceeded, clinical findings occur and sPAP increases (19). Therefore, we consider that using only echocardiographic measurements of sPAP may be misleading for early diagnosis among these patients.

PAS, which is a simple and easy echocardiographic parameter to determine, is found to be linked with a worse survival in PAH patients (20). In addition, an independent and significant relationship between PAS and RV dysfunction has been demonstrated (21). Previously, PAS was shown to be an significant determinant in the occurrence of PAH in subjects with chronic lung disease (10), as well as an early prognosticator of RV dysfunction in patients with systemic lupus erythematosus and HIV (9,12). However, to our knowledge, no prior research has examined the PAS in cirrhotic patients. This might be the first study to show that the PAS values are significantly elevated in subjects with cirrhosis comparing in healthy participants. Moreover, PAS was an independent predictor that was associated with cirrhosis disease according to multivariate logistic regression analysis. Additionally, we detected a positive correlation between PAS and sPAP values and a negative correlation between PfAT and sPAP values, while observing that there was no difference in terms of PAS values between clinically compensated and decompensated cirrhotic patients.

Our study results are important and valuable in terms of clinical perspectives. Because most cirrhotic patients are usually asymptomatic at the time of recognition of PAH, early diagnosis facilitates treatment as well as reduces the mortality risks in such patients. Similarly, no clear PAH was observed among the cases we investigated; however, the cirrhosis group had higher PAS values. Therefore, we believe that PAS may

show us transitions in the pulmonary vascular region before the development of significant PAH.

Limitations

Our study has the following limitations. First, a limited number of cases included in the study were a main limitation. Thus, multi-centre studies with large cohort of subjects are needed to confirm our study results. The anohter limitation was that there were no patients diagnosed with PoPH. Therefore, it is necessary to examine the predictive value of PAS in cirrhotic patients with PoPH. Finally, the average follow-up time of cirrhotic cases included in the study was relatively short. Because this period was not sufficient to demonstrate some transitions in the pulmonary vascular region, studies involving a longer study cohort are necessary.

Conclusion

In this research, we demonstrated that the PAS values were significantly increased in cirrhotic cases. Based on the study results, we believe that since the PAS measurement is an inexpensive and easily applicable echocardiographic method, it may help us detect transitions in the pulmonary vascular region early, even if RV function variables are within the normal range.

Conflict of interest

Not declared.

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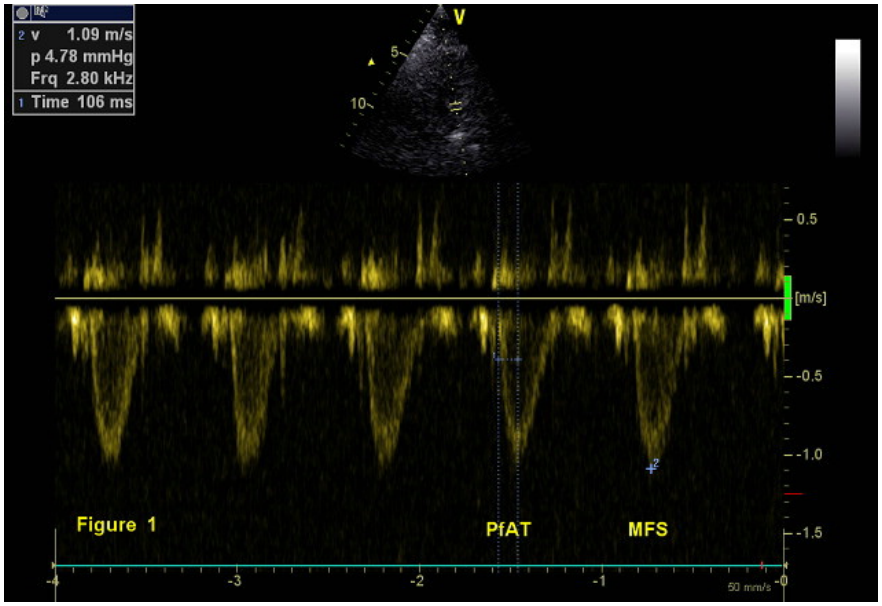

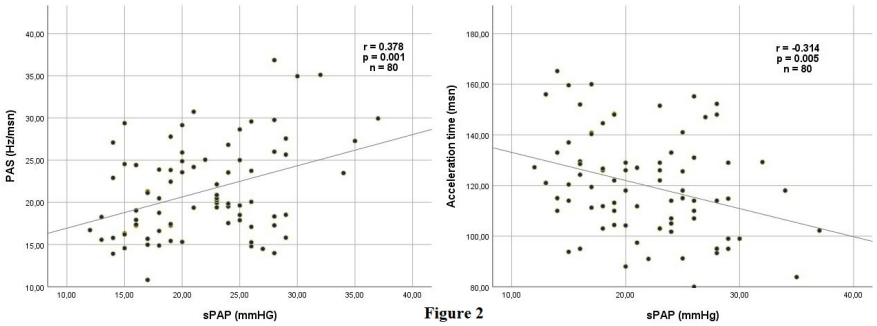

Figure 2