# The Diagnostic Value of Spectral Doppler echocardiography of the middle Hepatic Vein in Pulmonary Hypertension

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## Abstract

**Background:** Doppler echocardiographic parameters of the middle hepatic vein (MHV)in detecting PHTN. **Methods:** The study comprised 72 patients who were referred for right heart catheterization (RHC) to our department . All patients underwent conventional transthoracic echocardiography (TTE) the day after RHC and Doppler study of the MHV. Based on RHC and TTE results, Patients were divided in three groups 1: patients with PHTN without significant RV dysfunction (n=25), 2: patients with PHTN with significant RV dysfunction (n=22), 3: patients with normal PAP (n=25). **Results:** The analysis revealed a significant relationship between A velocity and PHTN among patients with significant RV dysfunction (p=0.033) and PHTN without significant RV dysfunction (p=0.020). At cut-off value of 39.5 cm/s, A velocity could detect PHTN in patient with significant RV dysfunction with sensitivity and specificity of 77.3% and 56.0%, respectively. At cut-off value of 38.5 cm/s, A velocity could detect PHTN without significant RV dysfunction with sensitivity and specificity of 76.0% and 51.0%, respectively. The ROC curve analysis was performed to assess the sensitivity of the hepatic venous systolic filling fraction in detecting normal SPAP in the study population. The area under curve was 0.718. Considering the cut-off value of 0.535 for the hepatic venous systolic filling fraction, the sensitivity and specificity of S/S+D for detecting normal SPAP were 80% and 64%, respectively . **Discussion:** Doppler echocardiographic parameters of the MHV could be helpful in detecting PHTN. A/S higher than 1 in PHTN was the main finding on HV Doppler assessment in PHT with and without significant RV dysfunction. HV systolic filling fraction more than 0.535 was a sensitive parameter in detecting normal PAP, therefore; HV systolic filling fraction can be used as a screening echocardiographic parameter in ruling out PHTN.

## Introduction

Pulmonary hypertension (PHTN) is a disease of small pulmonary arteries characterized by a progressive increase in pulmonary vascular resistance leading to right ventricular failure. The World Health Organization (WHO) defined a classification for pulmonary hypertension diagnosis , based on the cause of the disease. PHTN is defined as a mean pulmonary artery pressure (mPAP) of 25 mm Hg at rest in Right Heart cath (RHC). PHTN results in right ventricular (RV) pressure overload, which ultimately leads to right-heart failure and death(1,2). The gold standard for the diagnosis of PHTN is right heart catheterization (1). Due to its invasive character and lack of access to the required equipment, RHC cannot be used as a routine screening method. (2, 3).

Echocardiography is an affordable technique and is widely used in diagnosis of cardiac abnormalities in PHTN patients. It has been shown that echocardiography has an acceptable accuracy in detecting mPAP and thus can be used as a screening tool for PHTN in suspicious cases (4). The current advancements in Doppler echocardiography has made it more suitable for the assessment of mPAP (4). The PAP can be determined based on various echocardiographic parameters including pulmonic valvular regurgitation, acceleration time of Pulsed-wave Doppler interrogation of the RV outflow tract and systolic TR jet(which is used to estimate systolic pulmonary artery pressure ,SPAP), too. SPAP is achieved only based on TR jet. TR jet might result in inaccurate SPAP due to trivial regurgitant jet, suboptimal continuous-wave, unclear jet envelope and severe TR, where the peak velocity may not reflect the true RV–right atrial pressure (RAP)gradient because of early equalization of RV pressure and RAP. So, echocardiography was shown to underestimate or overestimate SPAP compared to invasive methods (5). Based on the limitations in the methods for assessing the modalities for detecting PAP, other modalities should be tested to identify PAP with an acceptable accuracy.

It was previously reported that flow velocity, waveform morphology of middle hepatic vein (MHV) and inferior vena cava (IVC) were significantly related to RA pressure (6). The hepatic vein has a smaller angle compared to the IVC (6). Therefore, echocardiographic parameters pertaining to hepatic vein may serve as easy measures for assessing right atrial (RA) pressure (3, 7). It was previously shown that chronic pulmonary hypertension increases the sensitivity of HV systolic filling fraction in detecting cardiac chamber dysfunction (8, 9). The aim of this study was to identify the proper hepatic vein Doppler echocardiographic parameters in predicting PHTN.

**Methods**

This cross-sectional study was conducted in National Center for Cardiovascular Diseases and a university hospital from November 2019 to January 2020. Seventy-two Patients (mean age: 40.90 ± 13.28), )21 patient :29.1 % male gender) who underwent right heart catheterization (RHC) were enrolled in this study. This study was approved by the Ethical Committee of the University of Medical Sciences .

Exclusion criteria were poor image quality, history of liver disease, tricuspid stenosis, equal or more than moderate TR, pericardial disease and presence of any type of arrhythmia or heart block. Patients were divided in two groups with PHTN and with normal PAP .Patients with PHTN were subdivided in two sub-groups based on the presence or absence of significant RV dysfunction. Significant RV dysfunction was defined as RV fraction area change(FAC)<20% and by visual assessment(10, 11). All patients had LVEF > 50% and were in sinus rhythm.

RHC was performed in the cardiac catheter laboratory under radiographic guidance (Siemens Medical Solutions, Erlangen, Germany). PHTN was defined as mPAP greater than or equal to 25 mmHg in RHC (12).

All subjects underwent transthoracic echocardiography (TTE) using Phillips iE33 ultrasound device equipped with an S5-1 transducer by an expert echocardiologist who was blinded to RHC results the day after RHC. An electrocardiogram and spirogram were recorded during TTE. After a complete conventional TTE, the spectral Doppler of the MHV was obtained via subcostal view. A 2-mm Pulse Wave sample volume was placed 1 to 2 cm into the MHV, proximal to its junction with the IVC. Color Doppler flow was used to obtain good alignment of ultrasound beam to the MHV flow. The velocity filter was adjusted to optimize the quality of the spectral display and to allow visualization of low-velocity waveforms. Data derived from recording of several respiratory cycles using speed of 25 mm/s. To obtain accurate morphology and measurements of HV waveform, Doppler data were traced at the speed of 75 mm/s (6,7). The measured parameters in spectral Doppler of the HV included maximal S ,V ,D and A wave velocities, the systolic velocity time integral (S VTI), diastolic VTI (D DVTI) and atrial reversal VTI (A AVTI) waves. Furthermore, time to peak and duration of all the waves were measured separately. All parameters were obtained in several respiratory cycle and averaged in five cardiac cycles during end inspiration. Furthermore, the hepatic venous systolic filling fraction [S/(S+D)], S/D and A/S ratios were also calculated.

Statistical analysis

Statistical analysis was performed using the statistical package for social sciences (SPSS) software version 16 (IBM Inc, Chicago, Il). The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess the normality distribution of continuous data. If the number of cases was larger than 30, the Kolmogorov-Smirnov test was used, while the Shapiro-Wilk test was used for data of less than 30 subjects. Normally distributed data were presented using mean and standard deviation (SD), while non-normally distributed data were presented using median and interquartile range (IQR). Comparison of normally distributed continuous variables between groups was performed using one-way analysis of variance (ANOVA) with Bonferroni post hoc test. Non-normally distributed variables were compared between groups using the Kruskal-Wallis test and Mann-Whitney test for comparing variables between two groups.

## Results

A total of 72 patients undergoing RHC were included in this study. Patients included 34 cases of atrium septal defect (ASD), 24 cases of ventricular septal defect (VSD) and 14 cases of patent ductus arteriosus (PDA).

Patients were divided in three groups based on mPAP and RV function as follows; group 1: patients with PHTN without significant RV dysfunction (n=25), group 2: patients with PHTN with significant RV dysfunction (n=22), group 3: patients with normal PAP (n=25). Mean age of the subjects was $40.90 \pm 13.28$ years old. There was no significant difference between groups in terms of age (p=0.726). Majority of subjects were female (51, 70.8%). There was no significant difference between groups in terms of gender distribution (p=0.553). Comparison of the echocardiographic findings of the study subjects are presented in Table 1. There was a significant difference in terms of A/S ($p<0.001$) between group 1 and 3. There was a significant difference in terms of S velocity(p=0.021), D (p=0.010), S/(S+D) ($p<0.001$), S/D ($p<0.001$) and S/D ($p<0.001$) between group 2 and 3. There was a significant difference in terms of S velocity ($p<0.001$), D velocity (p=0.010), S/(S+D) ($p<0.001$), and S/D between group 1 and 2.

The multinomial logistic regression was used to assess the relationship between PHTN and echocardiography parameters with control group as reference. The analysis revealed a significant relationship between A velocity and PHTN among patients with significant RV dysfunction (p=0.033) and PHTN without significant RV dysfunction (p=0.020). At cut-off value of 39.5 cm/s, A velocity could detect PHTN with significant RV dysfunction with sensitivity and specificity of 77.3% and 56.0%, respectively. At cut-off value of 38.5 cm/s, A velocity could detect PHTN without significant RV dysfunction with sensitivity and specificity of 76.0% and 51.0%, respectively.

The ROC curve analysis was performed to assess the sensitivity of systolic filling fraction (S/S+D )in detecting normal SPAP in the study population. The area under curve was 0.718. Considering the cut-off value of 0.535 for systolic filling fraction, the sensitivity and specificity of S/S+D for detecting normal SPAP were 80% and 64%, respectively (Figure 1).

## Discussion

The role of echocardiography in detecting cardiovascular abnormalities is increasing worldwide (4, 13). Considering the cost effectiveness of non-invasive echocardiography modality , it could be an alternative screening tool in detecting or excluding PHTN if it is proven to have acceptable adequacy (4). The aim of this study was to assess the properties of the hepatic vein Doppler signal as an echocardiographic parameter in detecting PHTN. Because hepatic vein is affected by RV function besides PHT; we divided our PHTN patients into two groups based on RV dysfunction, including PHTN with significant RV dysfunction and PHTN without significant RV dysfunction

The normal flow-pattern in the middle HV is phasic, in which the most predominant velocities are antegrade. Pulsed-wave Doppler assessment describes 3–4 distinct waveforms after atrial contraction: (1) large systolic antegrade wave (negative velocity) (S-wave); (2) small retrograde late systolic wave (positive velocity) (V-wave), (3) early to mid-diastolic antegrade wave (D-wave), (4) late diastolic retrograde wave (A-wave) (14).

In our study 13 cases in normal group, 16 cases in PHTN without significant RV dysfunction and 11 cases in PHT with significant RV dysfunction had all 4 distinct waveforms and 12 cases in normal group, 11 cases in PHT without significant RV dysfunction and 11 cases in PHT with significant RV dysfunction had 3 distinct waveforms (absent V wave). The findings of the current study revealed that A velocity , A/S were significantly higher in PHT group with and without significant RV dysfunction compared to normal group, while S/S+D and S/D were significantly higher just in PHT with significant RV dysfunction compared to normal group.

It was previously reported that the systolic wave is diminished in PHT and therefore S is reduced. A/S, A/(S+D), AVTI/(SVTI+DVTI) were positively correlated with mPAP (3). It was previously shown that PHT group had higher A velocity ;VTI A ;VTI A/VTI S+VTI D were higher in PHTN patients compared to healthy controls (14). Inclusion of patients with PHTN with and without significant RV dysfunction in this study enabled us to evaluate the effect of RV dysfunction on PHTN.

The differences between the findings of our study and previous studies is may be due to dividing the PHT patients based on RV function and also exclude patients with severe TR(table2). Based on the findings of our study, it can be hypothesized that increase in SPAP increased RV afterload, which may lead in chamber remodeling and increased in muscle mass. Increased RV end diastolic pressure (RVEDP) is the hemodynamic consequence of RV hypertrophy. As RA pressure is not reduced at this point, the duration of backflow in IVC and the HV persists will be longer compared to the backflow across the Tricuspid valve. Therefore, a large A-wave in terms of duration and velocity is observed in HV Doppler assessment. Therefore, A/S also increases to values higher than 1 in PHTN even at early stages. This pattern was the main finding on HV Doppler assessment in PHT with and without significant RV dysfunction(table2). When RV longitudinal motion is significantly reduced, the S wave is blunted or reduced in HV Doppler with consequent re-emergence or increase in D velocity .Therefore, S/S+D and S/D could only differentiate normal PAP from PHT with significant RV dysfunction and thus may not be useful in differentiating normal SPAP from PHT without RV dysfunction that is not an issue in previous echo study. Furthermore, as evidenced by the findings of the current study, increased D and decreased S values in PHT patients with RV dysfunction magnifies the changes due to RV function and the S/D might detect significant RV dysfunction earlier compared to other echocardiographic parameters(table2).

The findings of this study revealed that A wave velocity and duration could be a predictor for PHT patients regardless of RV dysfunction although the result for the A wave duration was not statistically significant in PHT patients. It was previously reported that in PHTN patients, the peak A wave velocity significantly increases compared to healthy individuals, which was in line with the findings of the current study (7). As A velocity is a determinant of RV filling function, combination of RV dysfunction and PHTN will result in significant change in A velocity that may make it a better marker for determining RV function in PHTN patients compared to other echocardiographic parameters in the current study (table2) (15). It was previously shown that the use of parameters that are calculated based on dividing A, S, and D including A/S, A/(S+D) and AVTI/(SVTI+DVTI) could be more sensitive in detecting PHTN compared to A, S, and D alone (6, 16, 17). This finding was in line with the finding of the current study.

The findings of this study also revealed that hepatic venous systolic filling fraction had an acceptable sensitivity in detecting normal SPAP patients from PHT patients (80%), while its specificity was low (64%). Similar sensitivity and specificity were found hepatic venous systolic filling fraction in detecting normal RV function in PHT patients (table2). It was previously reported that hepatic venous systolic filling fraction less than 55% had 86% sensitivity and 90% specificity in detecting PHTN (7). The difference between the findings of this study and the finding of latter studies may be due to the effect of RV function and TR severity on echocardiographic parameters(table2). The high sensitivity of hepatic venous systolic filling fraction in detecting normal PAP indicates that this marker can be appropriate in ruling out PHTN but due to its low specificity, this marker could not be used as a diagnostic marker for PHT. There is a need for further studies to confirm these findings.

**Study limitations**

Since the current study was cross-sectional, no matching was performed on the subjects; therefore, the heterogeneity in the findings resulted in the use of non-parametric tests. Thus, small number of subjects in each study group could be considered as a limitation of the current study. The overall effect size for one-way ANOVA test ranged from 0.59 to 0.71 and ranged from 0.29 to 0.79 for Kruskal-Wallis test. The effect size indicates that there is a high possibility that the comparison of A velocity and S/D between groups differ if the sample size is increased. It is suggested that further studies include larger samples of patients with any of the conditions. The strength of the current study was the assessment of hepatic venous systolic filling fraction in PHT patients with and without significant RV dysfunction and also remove patients with severe TR and arrhythmia in our study.

**Conclusions**

The findings of this study showed that Doppler echocardiographic parameters of the middle hepatic vein could be helpful in detecting PHTN .This was due to the effect of PHTN on A wave and the resultant changes in the relationship between A and S wave. Therefore, A/S is increased to values greater than 1 in PHTN, while the A/S values were smaller than 1 in patients with normal PAP. A wave velocity and duration were found to be related to PHTN in PHTN patients with and without RV dysfunction. HV systolic filling fraction more than 0.535 was a sensitive parameter in detecting normal PAP, therefore; HV systolic fraction index can be used as a screening echocardiographic parameter in ruling out PHTN.

**Statement of competing interests**

The author has no conflicts of interest or financial interest to disclose.

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Table 1. Comparison of the echocardiographic parameters between study groups

| Variable | Total N= 72 | PHTN with significant RV dysfunction n= 22 | PHTN without significant RV dysfunction n= 25 | Control n= 25 | P |
|---|---|---|---|---|---|
| BSA ($m^2$) | 1.71±0.15 | 1.71±0.14 | 1.70±0.16 | 1.70 (0.17) | 0.736 |
| S (m/s) | 57.81±22.34 | 43.00 (21.75)[ab] | 58.71±18.82[b] | 59.50 (33.00)[a] | 0.003* |
| D (m/s) | 49.15±19.46 | 51.50 (23.75)[cd] | 44.32±18.89[d] | 46.16±21.01[c] | 0.008* |
| A (m/s) | 42.11±12.76 | 45.59±10.04[e] | 48.84±11.37[ef] | 30.00 (8.50)[f] | <0.001* |
| S/S+D | 0.54±0.11 | 0.44±0.07[gh] | 0.57±0.11[h] | 0.60±0.08[g] | <0.001*+ |
| S/D | 1.31±0.55 | 0.83±0.23[ij] | 1.48±0.57[j] | 1.56±0.47[i] | <0.001*+ |
| A/S | 0.80±0.34 | 1.04±0.32[k] | 0.89±0.27 [l] | 0.50 (0.17)[kl] | <0.001* |
| A DURATION(m/s) | 0.86±0.07 | 0.82±0.07 | 0.91±0.03 | 0.87±0.12 | <0.054 |

PHTN: pulmonary artery hypertension, RV: right ventricle, antegrade wave during systole (S-wave), retrograde wave in late systole (V-wave), antegrade wave in early-mid diastole (D-wave), and retrograde wave in late diastole (A-wave)., BSA: body surface area, m: meter, s: second,

Median and interquartile range (IQR) were presented for non-parametric variables and the Kruskal-Wallis test was used for comparison. Comparison between two groups were performed using the Mann-Whitney test.

+ Mean and standard deviation were presented for normally distribute variables and one-way analysis of variance (ANOVA) was used for the comparison. The Bonferroni test was used as post hoc test.

[a] p=0.021, [b] p=0.001,[c] p=0.005, [d] p=0.010,[e] p<0.001, [f]p<0.001, [g] p<0.001,[h] p<0.001, [i]p<0.001, [j] p<0.001,[k] p<0.001, [l]p<0.001

Table 2. Relationship between HV echocardiographic parameters in PHTN and RV dysfunction with healthy controls as reference

| Group | Variable | p | OR | 95% CI for OR | 95% CI for OR |
|---|---|---|---|---|---|
| | | | | Lower | Upper |
| PHTN + significant RV dysfunction | S | 0.502 | 0.891 | 0.638 | 1.247 |
| | D | 0.237 | 0.821 | 0.592 | 1.138 |
| | A | 0.033* | 1.911 | 1.052 | 3.473 |
| | S/S+D | 0.560 | 1.657E-18 | 2.816E-78 | 9.747E+41 |
| | S/D | 0.494 | <0.001 | 2.203E-14 | 3866247.996 |
| | A/S | 0.190 | 4.803E-7 | 1.692E-16 | 1363.531 |

| Group | Variable | p | OR | 95% CI for OR | 95% CI for OR |
|---|---|---|---|---|---|
| | A DURATION(m/s) | 0.051 | 0.887 | 0.750 | 0.896 |
| PHTN without significant RV dysfunction | S | 0.117 | 0.820 | 0.640 | 1.051 |
| | D | 0.404 | 0.881 | 0.655 | 1.186 |
| | A | 0.020* | 1.996 | 1.113 | 3.579 |
| | S/S+D | 0.133 | 1.183E-34 | 5.798E-79 | 24146733112.88 |
| | S/D | 0.056 | 20426.163 | 0.786 | 531096291.454 |
| | A/S | 0.195 | 6.662E-7 | 3.028E-16 | 1465.967 |
| | A DURATION(m/s) | 0.052 | 0.965 | 0.746 | 0.912 |

PHTN: pulmonary artery hypertension, RV: right ventricle, OR: odds ratio, CI: confidence interval, antegrade wave during systole (S-wave), retrograde wave in late systole (V-wave), antegrade wave in early-mid diastole (D-wave), and retrograde wave in late diastole (A-wave)* Significant relationship

**Figure legends**

Figure 1. ROC curve for S/S+D in detecting normal SPAP

Figure 2. ROC curve for S/S+D in detecting normal RV function in PHTN patients

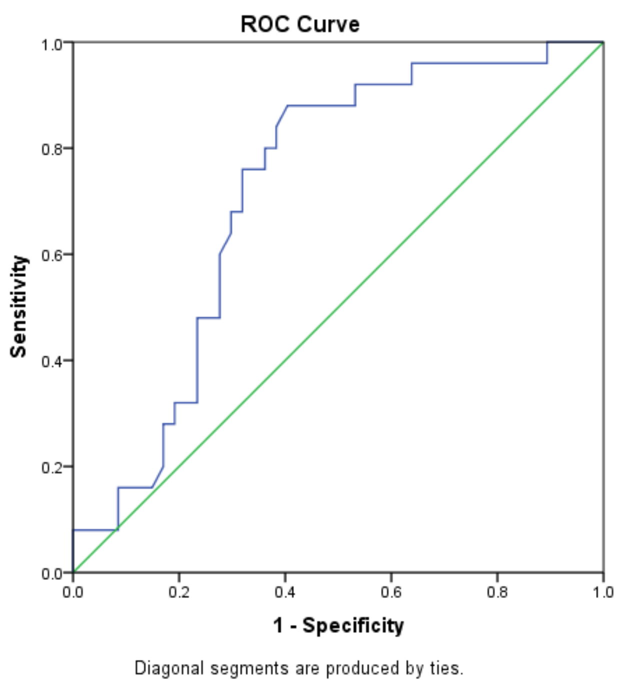


Figure 1. ROC curve for S/S+D in detecting normal SPAP

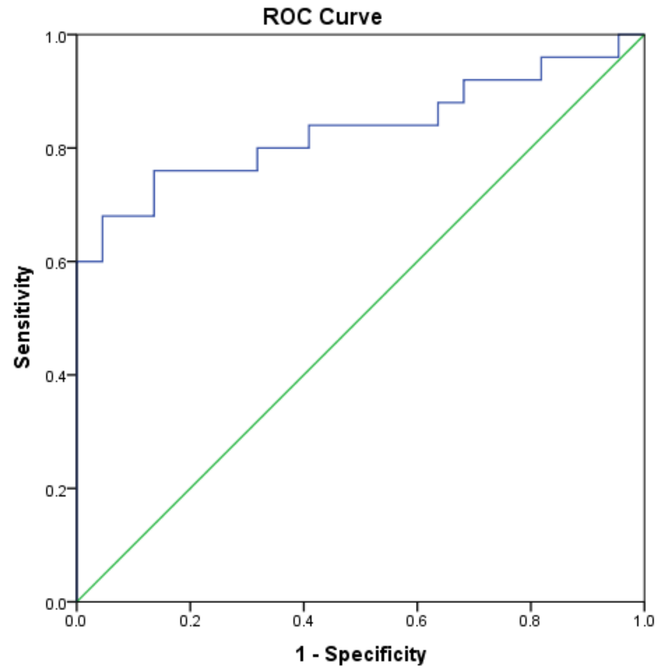


Figure 2. ROC curve for S/S+D in detecting normal RV function in PHTN patients