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Relationship between Myocardial Right Ventricular Relaxation Time and Pulmonary Artery Pressure in Patients with Pulmonary Arterial Hypertension

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ABSTRACT

Introduction: Recent developments in echocardiography made assessing pulmonary arterial hypertension (PAH) in the heart, a suitable choice. This study aimed to investigate the association of myocardial right ventricular relaxation time and systolic pulmonary artery pressure (SPAP) in PAH patients.

Materials and Methods: The present study evaluated 74 patients with PAH (n=49) and age- and sex-matched healthy controls (n=25). All patients underwent transthoracic echocardiography. We evaluated the right ventricular (RV) function's echocardiographic parameters, including IVRT, IVCT, S, E, A, S', E', A', ET, DT, TAPSE, FAC, and SPAP.

Results: We found no significant differences in age and gender between the two studied groups (p>0.05). However, we observed a significant difference in IVRT, IVCT, E', A' (p=0.004), A, S', DT, TAPSE, FAC and SPSP (p<0.001 for all cases) between two studied groups. Unlike the control group, we revealed a significant correlation between S' and E' (r=0.45, p=<0.001), S' and A' (r=0.66, p=<0.001), S' and FAC (r=0.3, p=0.035), A and A'(r=0.4, p=0.004), TAPSE and FAC (r=0.82, p=<0.001), TAPSE and SPAP (r= -0.43, p=0.002), MPI and A (r= -0.35, p=0.013), MPI and ET (r= -0.72, p=<0.001), E/A and E/E'(r=0.47, p=<0.001), and BSA and S' (r= -0.3, p=0.011). In addition, no meaningful association was found between SPAP and IVRT and IVCT (p>0.05) .

Conclusion: Our findings revealed that IVRT and IVCT might not be affected by the SPAP and, therefore, could be used in the assessment of right ventricular function in patients with PAH.

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Introduction

Pulmonary hypertension (PHTN) is considered a common cause of morbidity and mortality worldwide. PHTN is manifested as propagation of the pulmonary circulation pressure. PHTN is present in some disorders, such as chronic obstructive pulmonary disease (COPD), acute or chronic pulmonary embolism, autoimmune diseases, and idiopathic pulmonary hypertension (1, 2). PHTN has five subgroups, among which pulmonary arterial hypertension (PAH) is considered type 1 PHTN according to WHO classification. It has been emphasized that small pulmonary arteries are damaged through pulmonary vascular lesions following PAH. Furthermore, PAH is associated with a broad spectrum of injuries, including medial hypertrophy, intimal proliferation and fibrosis, adventitial thickening along with inflammatory infiltrates, complex lesions, and thrombotic lesions (3,4).

In previous years, PAH was named as an incidental disease impressing few individuals and was therefore ignored by physicians. Later on, some important findings of this rare condition improved the knowledge about PAH (5,6). The prevalence and annual incidence of PAH were estimated to be 15.0 cases/million and 2.4 cases/million, respectively. PAH cases are comprised of Idiopathic (39.2%), familial (3.9%), anorexigen-induced (9.5%), and patients with confirmed comorbidities, including connective tissue disease (15.3%), congestive heart disease (11.3%), and portal hypertension (10.4%), as well as HIV infection (6.2%) (7). However, the exact prevalence of PAH is unknown due to different diagnostic thresholds (8).

PAH is described as mean pulmonary artery pressure (mPAP) greater than 25 mmHg determined by invasive cauterization of the right heart at rest (9). Increased pulmonary vascular resistance results in elevated mPAP and, consequently, right ventricular dilatation, right ventricular failure, and dilated pulmonary arteries (8, 10). Furthermore, the left ventricle is also affected by preload due to reduced right ventricular end-diastolic volume (8). In order to assess PAH in a non-invasive approach, transthoracic echocardiography with Doppler and tissue Doppler imaging is beneficial (11, 12). There are controversy in different studies about the accuracy of right ventricle isovolumic relaxation time (IVRT) and isovolumic contraction time (IVCT) in predicting PAH (8). This study aimed to measure the association of myocardial right ventricular isovolumic relaxation time and PAP in patients with PAH.

Materials and Methods

Ethical statements

The ethics committee of Mashhad University of Medical Sciences approved this study (code. IR.MUMS.MEDICAL.REC.1398.856).

Study design

This cross-sectional study was conducted on patients with PAH who were referred to the Imam Reza Hospital, Mashhad, Iran, from July 2018 to January 2020. Patients with documented PAH based on cardiac catheterization were included in the study as a PAH group. PAH is defined as mPAP higher than 25 mmHg measured by invasive cauterization of the right heart at rest (9). Group 1 (PAH), 4 (PH due to pulmonary artery obstructions), and 5 (PH with unclear and/or multifactorial mechanisms) patients of classification of pulmonary hypertension were only included in this study (13). Right heart catheterization was done through the femoral vein using Right Judkin or Multipurpose catheter. The catheter was introduced to the main pulmonary artery through the femoral vein, inferior vena cava, right atrium, and ventricle. The systolic pulmonary artery pressure (SPAP) was then measured.

In addition, we choose healthy age- and sex-matched controls from the patients referred to the same hospital for echocardiography due to suspected cardiac abnormalities, but their echocardiography assessment revealed neither structural heart disease nor cardiac abnormalities.

Exclusion criteria were lack of good quality echocardiography images, any arrhythmia or bundle branch block in ECG, valvular diseases, coronary artery disease (CAD), dilated cardiomyopathy , group 2 of PH

classification (pulmonary hypertension due to left heart disease) and group 3 of PH classification (pulmonary hypertension due to lung disease) (13), severe tricuspid regurgitation (TR) and severe right ventricle (RV) dysfunction.

Evaluation of outcomes

All subjects underwent echocardiography by one echocardiography subspecialist using Philips iE33 (Philips Healthcare, Best, The Netherlands) device with an S5 probe. The assessed echocardiographic parameters included right ventricle isovolumic relaxation time (IVRT), isovolumic contraction time (IVCT), ejection time (ET) derived from tissue Doppler study of TV, and peak velocity of early diastolic trans tricuspid flow (E), early diastolic tricuspid annular motion (E'), late diastolic trans tricuspid flow (A), diastolic tricuspid annular motion (A'), systolic tricuspid flow (S), deceleration time of early diastolic trans tricuspid flow (DT), systolic tricuspid annular motion (S'), tricuspid Annular Plane Systolic Excursion (TAPSE), and fractional area change (FAC). These parameters were then used to calculate E/E', E/A, and MPI, defined as (IVRT+IVCT)/ET. All data used in the analysis in this study were derived from echocardiography assessment except for SPAP, which was derived from right heart catheterization.

Statistical analysis

Data analysis was done using the SPSS software version 16. First, we assessed the normality of data using the Kolmogorov-Smirnov test. After that, normally distributed data were showed using mean ± standard deviation (SD) and were compared using the independent t-test. However, non-normally distributed data were presented as median and interquartile range (IQR) and were compared using the Mann-Whitney tests. Furthermore, the chi-square test was performed for analyzing categorical markers. Correlation between continuous data was evaluated using the Pearson and Spearman correlation coefficients accordingly. P-value less than 0.05 was considered statistically significant.

Results

Demographic characteristics

A total of 74 subjects (49 cases and 25 controls) participated in the present study. The majority of subjects in the PAH (35, 71.4%) and control (19, 76.0%) groups were female. There was no significant difference in gender distribution between two studied groups (p=0.675). The mean age of the PAH and control group subjects were 42.29 ± 14.63 and 40.72 ± 13.13 years old, respectively. In addition, we found no meaningful difference in age between the PAH and control groups (p=0.654).

Echocardiographic findings

Echocardiographic parameters in the PAH and control groups are illustrated in Table 1. We revealed a notable difference in IVRT (P<0.001), IVCT (p<0.001), E' (p<0.001), A' (p=0.004), A (p<0.001), S' (p<0.001), DT (p=0.013), TAPSE (p<0.001), FAC (p<0.001) and SPSP (p<0.001) between the two studied groups (Table 1).

In addition, Table 2 presented the correlation between study parameters among the PAH group. We found a remarkable correlation between IVRT and IVCT, A' and E', S' and E', S'and A', A and A', FAC and S', FAC and TAPSE, SPAP and TAPSE, BSA and S', MPI and IVRT, MPI and IVCT, MPI and ET, MPI and A, E/E' and E', E/E' and A', E/E' and S', E/E' and E, E/A and ET, E/A and E, E/A and A, E/A and MPI, E/A and E/E', E/A and DT, and E/A and A' in the case group.

Table 3 illustrated the correlation between study parameters in the control group. In the control group, we measured a notable correlation between IVCT and IVRT, A' and E', A and IVCT, A and E, DT and ET, SPAP and A', age and S', MPI and IVRT, MPI and IVCT, MPI and ET, MPI and DT, E/E' and E', E/E' and A', E/E' and E, and E/E' and A, E/A and E, and E/A and A.

Discussion

Our findings indicated a remarkable difference between PAH patients and healthy controls in IVRT, IVCT, E', A', A, S', DT, TAPSE, FAC and SPAP between PAH patients. These findings were in line with the findings of previous studies (14, 15).

The results of our study showed no meaningful correlation between IVRT, IVCT, and SPAP. In contrast, some past studie supported the significant correlation between these parameters (16, 17). The reason for no correlation in our results might be due to the use of crude IVRT values in the current study. This finding might also be due to the observation that IVRT is affected by increased right atrial pressure and tricuspid regurgitation (18). Therefore the presence of valvular disorders, including tricuspid regurgitation (TR) and RV dysfunction, can affect IVRT (18). Previous studies did not exclude patients with severe TR or severe RV dysfunction. Therefore, a reason for this difference may be the exclusion of patients with severe TR from the current study. Due to the exclusion of patients with other etiologies of increased right atrial pressure, the non-significant correlation between SPAP and IVRT might be attributed to increased right atrial pressure due to PAH. In other words, IVRT and IVCT are not affected by changes in SPAP and the main cause of finding this relationship in previous studies was their patient selection policy. It was previously reported that correcting IVRT for HR results has a moderate (but not significant) correlation between IVRT and invasive SPAP measurements, which again, patients with severe TR and severe RV dysfunction were not excluded (19). Therefore, it would be better if IVRT was corrected based on HR. Only the crude IVRT measurements were used in the current study.

In contrast to the control group, the current study revealed a markedly association between S' and E', A', and FAC; A and A', TAPSE and FAC, and SPAP; MPI and A, E/A, E/E' and S', and ET; E/A and E/E', and BSA and S'. FAC is an indicator of RV systolic function and was found to be correlated with RVEF (20). TAPSE is also an easy method for assessing RVEF and FAC (21). Among the echocardiographic assessments, S' is more similar to TAPSE (21). MPI is an indicator of both systolic and diastolic function of RV (21).

Table 1. Comparison of echocardiographic parameters between study groups

Variable	Case (n=50)		Control (n=25)		P-value
IVRT (ms)	73.35	20.39	48.40	20.74	<0.001*†
IVCT (ms)	63.00	28.00	13.00	7.00	<0.001*ǂ
ET (ms)	234.98	47.40	208.75	70.31	0.108†
E' (cm/s)	8.41	2.88	16.40	4.78	<0.001*†
A' (cm/s)	11.68	4.23	15.00	5.24	0.004*†
E (m/s)	57.24	20.39	54.36	12.47	0.454†
A (m/s)	62.16	19.13	43.63	12.26	<0.001*†
S' (cm/s)	9.00	2.60	15.00	5.75	<0.001*ǂ
DT (ms)	166.29	54.36	208.75	70.31	0.013*†
TAPSE (mm)	1.40	0.30	21.00	5.50	<0.001*ǂ
FAC (%)	22.45	5.98	47.54	8.02	<0.001*†
SPAP (mmHg)	95.71	26.36	16.24	5.55	<0.001*†
BSA (m^2)	1.72	0.16	1.69	0.17	0.414†

Abbreviations: IVRT: Isovolumic Relaxation Time; **ET:** Ejection Time; **E':** Peak velocity of early diastolic mitral annular motion; **A':** Peak velocity of diastolic mitral annular motion; **E:** Peak velocity of early diastolic transmitral flow; **A:** Peak velocity of late diastolic transmitral flow; **S':** Peak velocity of systolic mitral annular motion; **DT:** Deceleration time of early diastolic transmitral flow; **TAPSE:** Tricuspid Annular Plane Systolic Excursion; **FAC:** Fractional area change; **SPAP:** Systolic pulmonary artery pressure; **BSA:** Body surface area; **SD:** Standard deviation; **m:** meter, **s:** second; **ms:** millisecond; **cm:** centimeter; **mm:** millimeter.

† Mean and SD were presented, and Independent t-test was used to compare the case and control groups.

ǂ Median and interquartile range were shown, and the Mann-Whitney test was used to compare the case and control groups.

* Significant difference

Table 2. Correlation between study parameters among case group.

Variable		IVRT†	IVCT	ET†	E'†	A'†	S'ǂ	E†	A†	DT†	TAPSEǂ	FAC†	SPAP†	Age†	BSA†	MPI†	E/E'†	E/A†
IVRT	**r**																	
	p																	
IVCT	**r**	0.442																
	P	0.001*																
ET	**r**	-0.02	-0.09															
	P	0.886	0.541															
E'	**r**	-0.17	0.08	-0.07														
	p	0.24	0.59	0.62														
A'	**r**	-0.27	-0.2	0.07	0.51													
	p	0.06	0.14	0.63	<0.001*													
S'	**r**	-0.07	-0.19	0.16	0.45	0.66												
	p	0.58	0.17	0.24	<0.001*	<0.001*												
E	**r**	-0.32	0.17	-0.33	0.13	-0.1	-0.1											
	p	0.02*	0.24	0.01	0.36	0.49	0.3											
A	**r**	-0.28	-0.03	0.29	0.08	0.40	0.05	0.10										
	p	0.05	0.83	0.03	0.57	0.004*	0.7	0.46										
DT	**r**	0.09	0.06	0.00	-0.09	0.21	0.1	-0.24	0.26									
	p	0.52	0.65	0.97	0.51	0.13	0.2	0.09	0.06									
TAPSEǂ	**r**	0.08	0.07	0.25	0.12	0.04	0.2	-0.24	0.04	-0.1								
	p	0.54	0.61	0.07	0.39	0.77	0.1	0.09	0.73	0.3	.							

FAC	**r**	-0.07	-0.01	0.14	0.19	0.10	0.3	-0.22	0.09	-0.1	0.82							
	p	0.63	0.93	0.30	0.17	0.48	0.035*	0.12	0.51	0.2	<0.001*							
SPAP	**r**	-0.07	0.10	-0.17	0.07	0.03	-0.05	0.17	-0.08	0.2	-0.43	-0.28						
	P	0.605	0.486	0.234	0.603	0.802	0.6	0.226	0.587	0.06	0.002*	0.04						
Age	**r**	0.20	-0.04	0.001	-0.19	-0.05	-0.058	-0.27	-0.07	0.2	-0.04	-0.16	-0.121					
	P	0.15	0.760	0.994	0.191	0.695	0.7	0.060	0.610	0.13	0.74	0.24	0.4					
BSA	**r**	0.07	0.17	-0.12	-0.00	-0.29	-0.3	0.12	-0.06	-0.27	0.23	0.12	-0.045	0.007				
	p	0.63	0.22	0.40	0.96	0.04	0.011*	0.38	0.65	0.057	0.10	0.40	0.761	0.96				
MPI	**r**	0.60	0.57	-0.72	0.01	-0.22	-0.208	0.11	-0.35	0.083	-0.06	-0.12	0.092	0.15	0.21			
	p	<0.001*	<0.001*	<0.001*	0.93	0.13	0.152	0.44	0.013*	0.569	0.66	0.39	0.530	0.30	0.14			
E/E'	**r**	-0.20	-0.04	-0.21	-0.57	-0.33	-0.46	0.64	0.03	-0.111	-0.26	-0.290	0.069	-0.10	-0.05	0.025		
	p	0.16	0.78	0.13	<0.001*	0.020*	0.001*	<0.001*	0.79	0.4	0.06	0.04	0.6	0.45	0.70	0.864		
E/A	**r**	-0.14	0.08	-0.50	0.06	-0.34	-0.06	0.67	-0.58	-0.31	-0.14	-0.24	0.268	-0.07	0.14	0.31	0.470	
	p	0.33	0.54	<0.001*	0.65	0.01*	0.666	<0.001*	<0.001*	0.028*	0.34	0.09	0.063	0.60	0.32	0.03*	0.001*	

Abbreviations: IVRT: isovolumic relaxation time; **ET**: ejection time; **E':** peak velocity of early diastolic mitral annular motion; **A':** peak velocity of diastolic mitral annular motion; **E:** peak velocity of early diastolic transmitral flow; **A:** peak velocity of late diastolic transmitral flow; **S':** peak velocity of systolic mitral annular motion; **DT:** deceleration time of early diastolic transmitral flow; **TAPSE:** tricuspid Annular Plane Systolic Excursion**; FAC:** fractional area change; **SPAP:** systolic pulmonary artery pressure**; BSA:** body surface area; **SD:** standard deviation; **m:** meter; **s:** second; **ms:** millisecond; **cm:** centimeter; **mm:** millimeter.

† Pearson correlation coefficient was used.

ǂ Spearman correlation coefficient was used

* Significant correlation

Table 3. Correlation between study parameters among the control group.

Variable		IVRT†	IVCT‡	ET†	E'†	A'†	S'†	E†	A†	DT†	TAPSE†	FAC†	SPAP†	age†	BSA†	MPI†	E/E'†	E/A†
IVRT	**r**																	
	p																	
IVCT	**r**	0.51																
	P	0.008*																
ET	**r**	-0.08	-0.182															
	P	0.69	0.4															
E'	**r**	-0.10	0.153	-0.09														
	p	0.60	0.465	0.66														
A'	**r**	-0.09	0.383	-0.04	0.63													
	p	0.67	0.059	0.83	0.001*													
S'	**r**	0.27	-0.138	-0.003	-0.22	-0.4												
	p	0.19	0.5	0.98	0.28	0.1												
E	**r**	0.13	0.06	0.11	-0.33	-0.142	0.073											
	p	0.51	0.75	0.58	0.1	0.5	0.7											
A	**r**	0.15	0.43	0.07	-0.26	-0.08	0.03	0.51										
	p	0.47	0.035*	0.75	0.22	0.7	0.88	0.01*										
DT	**r**	-0.08	-0.18	1.00	-0.09	-0.045	-0.003	0.11	0.069									
	p	0.69	0.4	<0.001*	0.66	0.8	0.9	0.58	0.7									
TAPSE	**r**	-0.09	-0.06	-0.05	-0.17	-0.186	0.1	-0.06	0.015	-0.06								
	p	0.64	0.7	0.78	0.39	0.4	0.67	0.76	0.9	0.8								

FAC	**r**	-0.13	0.2	-0.02	0.07	0.08	-0.2	0.06	0.024	-0.02	-0.21						
	p	0.54	0.4	0.93	0.72	0.7	0.2	0.76	0.9	0.9	0.31						
SPAP	**r**	0.15	0.35	0.22	0.17	0.41	-0.2	0.16	0.25	0.22	-0.15	0.1					
	P	0.46	0.08	0.29	0.40	0.04*	0.3	0.42	0.2	0.3	0.47	0.6					
Age	**r**	-0.03	0.09	-0.11	-0.18	-0.09	-0.44	-0.09	-0.06	-0.1	-0.22	0.2	0.3				
	P	0.87	0.6	0.58	0.38	0.6	0.033*	0.65	0.7	0.6	0.27	0.3	0.16				
BSA	**r**	0.12	0.2	-0.04	0.10	0.017	-0.187	-0.03	0.07	-0.045	-0.17	0.12	0.115	0.1			
	p	0.55	0.2	0.83	0.60	0.9	0.4	0.89	0.7	0.8	0.41	0.5	0.5	0.5			
MPI	**r**	0.72	0.55	-0.65	-0.02	-0.011	0.1	0.11	0.2	-0.66	-0.12	0.009	0.115	0.1	0.04		
	p	<0.001*	0.005*	0.001*	0.90	0.9	0.6	0.58	0.2	0.001*	0.56	0.9	0.5	0.4	0.82		
E/E'	**r**	0.12	-0.07	0.17	-0.8	-0.4	0.2	0.72	0.4	0.1	-0.01	-0.04	0.004	0.1	-0.2	0.04	
	p	0.56	0.7	0.42	<0.001*	0.036*	0.2	<0.001*	0.035*	0.4	0.95	0.8	0.9	0.6	0.32	0.84	
E/A	**r**	-0.03	-0.3	0.11	-0.09	-0.1	-0.02	0.40	-0.5	0.1	-0.16	0.2	-0.1	0.1	-0.1	-0.1	0.27
	p	0.86	0.09	0.61	0.67	0.5	0.9	0.05*	0.008*	0.6	0.44	0.3	0.6	0.6	0.5	0.4	0.2

Abbreviations: IVRT: isovolumic relaxation time; **ET**: ejection time; **E':** peak velocity of early diastolic mitral annular motion; **A':** peak velocity of diastolic mitral annular motion; **E:** peak velocity of early diastolic transmitral flow; **A:** peak velocity of late diastolic transmitral flow; **S':** peak velocity of systolic mitral annular motion; **DT:** deceleration time of early diastolic transmitral flow; **TAPSE:** tricuspid Annular Plane Systolic Excursion**; FAC:** fractional area change; **SPAP:** systolic pulmonary artery pressure**; BSA:** body surface area; **SD:** standard deviation; **m:** meter; **s:** second; **ms:** millisecond; **cm:** centimeter; **mm:** millimeter.

† Pearson correlation coefficient was used.

ǂ Spearman correlation coefficient was used

* Significant correlation

The current study's findings indicate that MPI was correlated with TAPSE and S', which were also indicators for RV performance. Our results indicated that SPAP was only correlated with TAPSE among RV function indicators in PAH patients. This might suggest that regardless of the high difference in SPAP between study groups, TAPSE measures RV function without being influenced by other confounders, including image quality and heart rate.

It can be noted that the strength of our study was using the combination of various echocardiographic parameters, which provided the opportunity to assess the correlation of different measures of right heart in patients with PAH. A limitation of this study could be the lack of data correction based on time as IVRT, ET, and IVCT are affected by HR. The other limitation was the lack of a control group, including PAH patients with RV dysfunction, to evaluate the effect of RV function on the relationship between SPAP and IVRT and IVCT. Therefore, it is recommended for further research studies to include three-arm studies on PAH patients and healthy subjects in order to better identify the predictors for PAP at different stages of PAH.

Conclusion

Our findings showed no significant association between SPAP and crude IVRT and IVCT values. Considering previous studies and their case selection, this finding might indicate that these parameters could not be used in PAH patients without correction for HR. Furthermore, the mentioned correlation in their studies is not helpful without deleting cases with severe TR and severe RV dysfunction. Therefore, there is a need for further investigations prior to making any recommendations.

Conflict of interests

The authors have no conflicts of interest to declare.

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