Pulmonary Vascular Capacitance as a Predictor of Vasoreactivity in Idiopathic Pulmonary Arterial Hypertension Tested by Adenosine

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Background: Acute pulmonary vasoreactivity testing has been recommended in the diagnostic work-up of patients with idiopathic pulmonary arterial hypertension (IPAH). Pulmonary arteriolar capacitance (Cp) approximated by stroke volume divided by pulmonary pulse pressure (SV/PP) is considered as an independent predictor of mortality in patients with IPAH.
Objectives: We sought to evaluate any differences in baseline and adenosine Cp between vasoreactive and non-vasoreactive IPAH patients tested with adenosine.
Patients and Methods: Fourteen patients with IPAH and a vasoreactive adenosine vasoreactivity testing according to the ESC guidelines were compared with 24 IPAH patients with nonreactive adenosine test results.
Results: There were no statistical significant differences between the two groups regarding NYHA class, body surface area, heart rate, and systemic blood pressure during right heart catheterization. Hemodynamic study showed no statistical significant differences in cardiac output/Index, mean pulmonary artery pressure, pulmonary vascular resistance, and baseline Cp between the two groups. There was a statistical significant but weak increase in adenosine Cp in vasoreactive group compared to non-reactive group (P = 0.04). Multivariable analysis showed an association between Cp and vasoreactivity (Beta = 2, P = 0.04, OR = 0.05 (95%CI = 0.003 - 0.9).
Conclusions: Cp could be considered as an index for the prediction of vasoreactivity in patients with IPAH. Prediction of long-term response to calcium channel blockers in patients with IPAH and a positive vasoreactive test by this index should be addressed in further studies.

Keywords: Artery; Hypertension; Adenosine

1. Background

Pulmonary arterial hypertension (PAH) is defined by conditions including idiopathic forms of the disease, known as idiopathic PAH (IPAH). IPAH is classified as WHO category I-pulmonary arterial hypertension in the Venice 2003 revised classification system (1, 2).

Diagnostic procedures including right heart catheterization (RHC) are required to confirm the diagnosis, predict prognosis and plan for treatments in these patients (3, 4).

Acute pulmonary vasoreactivity test has been recommended in the management strategy of patients with IPAH. The purpose of vasoreactivity test is to identify the small minority of patients who may benefit from an oral calcium channel blocker (CCB) (1, 3, 5-7). It has been found that positive response to pulmonary vasodilator administration is a predictor of better survival in IPAH (1, 3, 5-7).

The hemodynamic characteristics of pulmonary vascular tree and the vasoreactive response to vasodilators are achieved during RHC. However, only the status of stationary component of pulmonary vasculature is assessed by RHC. Pulmonary vascular resistance (PVR) is only one component of afterload and is an assumption of constant blood flow in vascular tree, whereas compliance, capacitance and impedance are more useful to describe pulsatile flow (8-10).

Pulmonary arteriolar capacitance (Cp) reflects the ability of the pulmonary vessels to dilate during systole and recoil during diastole. It is considered as an independent predictor of mortality in patients with idiopathic pulmonary hypertension (9-11). The capacitance is inversely proportional to pulse pressure and approximated by stroke volume divided by pulmonary pulse pressure (SV/PP) (8-10).

The total (rather than local) arterial compliance can be quantified by Cp. Cp shows an average of what is happening in whole pulmonary vasculature and is helpful to detect vascular wall remodeling at early stages (8).

2. Objectives

We sought to evaluate any association between Cp and pulmonary vasoreactivity and whether there were any differences in baseline and adenosine Cp between vasoreactive and non-vasoreactive IPAH patients tested with adenosine.

3. Patients and Methods

3.1. Patients' Selection

In this case-control study, between March 2012 and March 2014, 14 patients with IPAH and a vasoreactive adenosine vasoreactivity testing according to the ESC guidelines (1) were consecutively enrolled. Twenty four patients were randomly selected among IPAH patients with non-reactive adenosine test results as the control group.

The clinical history and physical examination were obtained from all patients and demographic data, echocardiographic findings and NYHA classification were registered.

The study was approved by the institutional ethic committee and an informed consent was obtained from all patients.

3.2. Right Heart Catheterization

All patients were assessed in the catheterization laboratory with 7F balloon-tipped, triple lumen thermodilution catheters (Edwards life sciences, Irvine, CA) and Vigilance (VGSVSYS) monitors (Edwards life science). All measurements were performed with patients at rest in the supine position while breathing room air. The pressures were all averaged in three consecutive heart beats at end expiration. The following variables were measured for each patient: mean right atrial pressure, systolic and end-diastolic right ventricular (RV) pressures, systolic, diastolic and mean pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP), mixed venous oxygen saturation and cardiac output by thermodilution technique. The transpulmonary gradient was calculated by subtracting the mean PAP from PCWP. PVR was calculated by dividing the transpulmonary gradient (TPG) by cardiac output and Cp was calculated by dividing the stroke volume (SV) by pulmonary artery pulse pressure (PP).

3.3. Vasoreactive Challenge Test

We use only adenosine for vasoreactive challenge test in our center because of some limitations in providing other agents such as nitric oxide and prostaglandins. The protocol used for adenosine vasoreactive challenge test was according to the European society of cardiology (ESC) guidelines (1, 3) for diagnosis and treatment of pulmonary hypertension. Vasoreactivity is assessed by intravenous infusion of adenosine, starting at 50 micro/kg/min followed by 50 micro/kg/min increase every 2 minutes and stopping at 350 micro/kg/min or when side effects are intolerable for patient. A positive acute vasoreactive response is defined as a reduction of mean PAP by more than 10 mmHg and absolute mean PAP of less than 40 mmHg with an increased or unchanged cardiac output.

Using the standard protocol, adenosine vasoreactive challenge test (AVRT) was performed after baseline RHC in all patients.

3.4. Statistical Analysis

Patients were defined to be vasoreactive or non-vasoreactive based on their vasoreactive test result. All statistical analyses were conducted using IBM SPSS Statistics 19.0 for Windows (IBM Corp., Armonk, NY, USA). All data were initially analyzed for normal distribution by Kolmogorov-Smirnov test. Categorical variables were presented as numbers and percentages and quantitative variables as mean (standard deviation) for normally distributed variables and median (interquartile range) for non-normally distributed variables. Categorical data were compared by chi square test and quantitative variables by Student t-test or Mann-Whitney test as appropriate. The correlation between Cp and PVR was assessed by linear regression methods and binary logistic regression model was used for multivariate analysis. P values less than 0.05 was considered as significant.

4. Results

A total of 38 patients (4 males and 34 females), mean age of 35.5 (12.1) years, with a diagnosis of IPAH were included in this study (14 patients with IPAH and a vasoreactive AVRT and 24 IPAH patients with a non-reactive AVRT).

Table 1 depicts baseline characteristics of the study population. There was no statistically significant difference between the two vasoreactive and non-vasoreactive groups for sex, age, NYHA class and echocardiographic findings (Table 2).

Table 1. Descriptive Statistics in the Study Participants (n = 38) [a,b]

Characteristic	Values [b]
Age, y	35.5 (12.2)
Gender, No. (%)	
Female	34 (89)
Male	4 (11)
BSA, m^2	1.64 (0.15)
NYHA Class, No. (%)	
I, I-II	25 (66)
II, II-III	13 (34)
Vasoreactive	
Yes	14 (37)
No	24 (63)
SBP, mmHg	116.9 (15.7)
DBP, mmHg	75.3 (12.3)
HR, BPM	85 (12)
LVEF, %	52.1 (2.1)
TAPSE, mm	17.3 (2.9)
RVSm, cm/s	9.8 (2.2)
RVEDD, mm	36.4 (11.5)
RAA index, mm^2/m^2	12.6 (3.8)

[a] Abbreviations: BSA, body surface area; DBP, diastolic blood pressure; HR, heart rate; LVEF, left ventricular ejection fraction; RAA, right atrium area; RVEDD, right ventricular end diastolic diameter; RVSm, right atrium area; SBP, systolic blood pressure; BPM, beat per minutes.
[b] Data are presented as mean (SD) for quantitative and count (%) for qualitative variables.

4.1. Catheterization Measurements

RHC was performed in all patients successfully with no complication. AVRT was safely and feasibly performed and no complications or significant adenosine side effects were occurred during the test.

Table 3 depicts hemodynamic measures in the two vasoreactive and non vasoreactive groups.

There were no statistical significant differences in cardiac output/Index, mean PAP, PVR and baseline Cp between the two groups (P > 0.05). There was a statistical signifi-

cant but weak increase in adenosine Cp in vasoreactive group compared to nonreactive group (P = 0.04).

Multivariable logistic regression analysis was performed to investigate the associations between vasoreactivity and baseline Cp. After adjustment of other variables, cardiac output [ß = 3.7, P = 0.02, odd ratio = 41.6 (95% confidence interval = 0.003 - 0.9)] and baseline Cp [ß = 2.9, P = 0.04, odd ratio = 0.05 (95%confidence interval = 1.5-1186)] showed significant association with vasoreactivity (Table 4).

Table 2. Comparing Demographic and Clinical Data Between Vasoreactive and Non- Vasoreactive Groups [a,b]

Variables	Vasoreactive		P Value
	Yes (n = 14)	No (n = 24)	
Age, y	35.7 (14.1)	35.3 (10.1)	0.9
Gender, No. (%)			0.9
Female	12	22	
Male	2	2	
BSA, m^2	1.6 (0.13)	1.6 (0.15)	0.7
NYHA class			
I ,I-II	7	18	0.8
II,II-III	7	6	0.9
SBP, mmHg	114 (16)	118 (15)	0.5
DBP, mmHg	73.1 (13)	76.5 (11)	0.4
HR BPM	83 (8)	86 (13)	0.3
LVEF, %	52.7 (2.2)	51.5 (2.5)	0.6
TAPSE, mm	18.3 (2.5)	16.7 (2.9)	0.09
RVSm, cm/s	10.3 (2.1)	9.5 (2.3)	0.3
RVEDD, mm	37.2 (11)	35.1 (13)	0.4
RAA index, mm^2/m^2	12.9 (4)	12 (2.9)	0.3
TRG	76.9 (16.4)	88.6 (24)	0.1

[a] Abbreviations: BSA, body surface area; DBP, diastolic blood pressure; HR, heart rate; LVEF, left ventricular ejection fraction; NYHA, New York heart association; RV Sm; right ventricular systolic tissue velocity, RVEDD; right ventricular end diastolic diameter, RAA, right atrium area; SBP, systolic blood pressure; TAPSE, tricuspid annular plane systolic excursion; TRG, tricuspid regurgitation gradient.
[b] Data are presented as Mean (SD) or number (%).

Table 3. Hemodynamic Measures of the Study Participants (n = 38) [a,b]

	Vasoreactive		P Value
	Yes (n = 14)	No (n = 24)	
Mean RAP, mmHg	9.4 (3.4)	10.4 (4.6)	0.4
SPAP, mmHg	78.7 (21.5)	87.9 (30.7)	0.3
DPAP, mmHg	42.3 (10.4)	50.1 (16.1)	0.1
Mean PAP, mmHg	54.6 (13.4)	62.1 (19.5)	0.2
PCWP, mmHg	9.9 (3.3)	11.7 (5.1)	0.3
CO, Lit/min	4.5 (0.7)	4.2 (0.8)	0.3
CI, L/min/m^2	2.7 (0.4)	2.6 (0.5)	0.4
PVR, wood unit [c]	10.6 (6.4-14.3)	10.1 (7.4-17.8)	0.3
SV, mililiter	55.3 (11.4)	49.7 (12.1)	0.2
Cp baseline, mL/mmHg	1.8 (0.98)	1.7 (0.96)	0.7
Cp End	2.4 (1.03)	1.7 (0.96)	0.04

[a] Abbreviations: Cp, pulmonary artery capacitance; CI, cardiac index; CO, cardiac output; DPAP, diastolic pulmonary artery pressure; PAP, pulmonary artery pressure; SPAP, systolic pulmonary artery pressure, PCWP; pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; SV, stroke volume.
[b] Data are presented as Mean (SD).
[c] PVR as median (Interquartile range).

Table 4. Association Between Baseline Pulmonary Artery Capacitance and Vasoreactivity Adjusted by Other Variables [a]

	coefficient	P Value	Odd Ratio	95%CI
NYHA, class	1.8	0.1	6.07	0.6 - 60
CO	3.7	0.02	41.6	1.5 - 1186
MEANPAP	3.9	0.1	54	0.4 - 7266
PVR	0.4	0.07	1.5	0.9 - 2.4
PA O2 SATURATION	0.2	0.06	1.2	0.9 - 1.5
BASELINE CP	2.9	0.04	0.05	0.003 - 0.9
TRG	0.1	0.1	0.9	0.8 - 1.03

[a] Abbreviations: CO, cardiac output; Cp, pulmonary artery capacitance; NYHA, New York heart association; PA, pulmonary artery; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; TRG, tricuspid regurgitation gradient.

5. Discussion

Our study demonstrated that PAP, PVR and baseline Cp are not different between patients with and without vasoreactivity. However, vasoreactive group had higher adenosine Cp than non-reactive group and in multivariable analysis baseline Cp and cardiac output had association with vasoreactivity, which means that Cp could be considered as an index for prediction of vasoreactivity in IPAH patients scheduled for vasoreactive test.

The pulmonary vascular properties such as capacitance, stiffness and impedance and their prognostic significance in patients with pulmonary hypertension have been investigated in many studies (8-12).

Grignola et al. demonstrated that local PA stiffness indexes normalized by pulse pressure correlated with global capacitance and resistance properties of the pulmonary arterial tree (13). Pulmonary vascular capacitance has been considered a strong predictor of mortality in patients with IPAH and adds prognostic value to conventional risk markers and remarks an index of vascular remodeling in pulmonary vasculature (8-13). Mahapatra et al. followed up 104 IPAH patients for four years and concluded that the capacitance index is a strong independent predictor of mortality in patients with IPAH (9, 14). Dupont et al. (11) reviewed 724 patients with heart failure who underwent right heart catheterization and concluded that pulmonary arterial capacitance is correlated with pulmonary vascular resistance and wedge pressure with RV function and has a significant association with RV dysfunction, poor long-term prognosis and response to therapy. Sajan et al. (15) demonstrated that pulmonary arterial capacitance is correlated with functional capacity and survival in children with idiopathic pulmonary arterial hypertension and PAH associated with congenital heart disease.

Vasoreactivity testing is indicated in patients with IPAH to detect patients who can be treated with high doses of calcium channel blockers (1, 2, 6, 7). It has been shown that IPAH patients with positive pulmonary vasodilator response have better prognosis and vasoreactivity predicts improved survival (6, 7, 16). We demonstrated in multivariable analysis that baseline Cp is correlated with vasoreactivity and can be considered as a predictor for vasoreactivity. Up to our knowledge, only a few studies investigated this association. Cp reflects the ability of pulmonary vessels to dilate during systole and recoil during diastole, a dynamic component of pulmonary circulation. The association between Cp and vasoreactivity shows that presence of a more dynamic pulmonary artery might increase the probability of a positive pulmonary vasodilator test and Cp can be considered as an index of vascular remodeling in patients with pulmonary hypertension. However, it should be clarified in other studies whether Cp is an independent predictor of response to CCBs in long-term in patients with positive vasoreactive test. It has been shown that hemodynamic responders to pulmonary vasoreactive tests may not have a true vasodilation on intravascular ultrasound studies (13, 17). This would explain the long-term clinical benefit of CCBs in only 50% of patients with positive vasoreactive test.

5.1. Study Limitation

Lack of follow-up data was the main limitation of our study.

5.2. Conclusion

Regarding our findings, Cp could be considered as an index for the prediction of positive pulmonary vasoreactive test. Further studies are needed to clarify whether this index can predict long-term response to CCBs.

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Authors' Contributions

Davood Shafie: Collecting data, interpretation the results and drafting the manuscript. Abolfazl Dohaei: drafting the manuscript. Ahmad Amin: Collecting data, interpretation

the results, revising the manuscript. Sepideh Taghavi: Collecting data, interpretation the results. Nasim Naderi: Concept, study design, statistical analyses, interpretation the results and final revision the manuscript.

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