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Original Article

Impact of systemic hypertension on clinical outcome of patients with idiopathic pulmonary arterial hypertension: a retrospective study

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Abstract: It is already reported that patients with pulmonary hypertension can complicated with hypertension, the interactional relationship between systemic and pulmonary hypertension remains unclear. Therefore, we investigated the impact of systemic hypertension (SHT) on clinical outcome of patients with newly diagnosed idiopathic arterial hypertension (IPAH) in the retrospective study. 88 patients with newly diagnosed IPAH were included and divided into non-SHT group and SHT group according to the presence or absence of SHT. In the baseline scenario, the patients with SHT accounted for 23.9% of 88 with newly diagnosed IPAH. They were older compared to the patients without SHT. Hemodynamic results detected by right heart catheterization (RHC) showed that patients in the SHT group had an obviously higher pulmonary vascular resistance (PVR), lower cardiac index (CI) and mixed venous oxygen saturation (SVO2) than those in the non-SHT group. After six months of treatment, patients in the non-SHT group demonstrated decreased serum NT-proBNP level, as well as improvement on World Health Organization function classification (WHO-FC) and exercise capacity, but no similar changes were found in the SHT group. However, there was no statistical significance about survival rate between the two groups. Systemic hypertension has adverse impact on pulmonary hemodynamics of newly diagnosed IPAH patients and patients with SHT had less satisfactory response to specific-PAH therapies. Our study confirmed the deteriorating effect of systemic hypertension on patients with newly diagnosed IPAH.

Keywords: Systemic hypertension, idiopathic pulmonary hypertension, hemodynamics, clinical outcome

Introduction

It is well known that systemic hypertension (SHT) is recognized as a major contributor to coronary artery disease, heart failure, stroke and renal failure. Olivari *et al*. first reported that patients with SHT might complicate with the significant elevations of pulmonary artery pressures in 1978 [1]. A large registered study of 2,967 patients with pulmonary artery hypertension (PAH) from 54 centers in the United States has provided their baseline characteristics, 40.2% of PAH patients combined with systemic hypertension [2]. Despite the growing number of literature has shown that there is a relationship between systemic and pulmonary hypertension, SHT is associated with elevation of pulmonary artery pressure which may be consequence of left ventricular hypertrophy and impairment in left ventricular function [3]. However, it has not been previously well defined the effect of systemic hypertension on clinical outcome of patients with idiopathic pulmonary arterial hypertension (IPAH). Therefore, we illuminated the clinical, echocardiographic, and hemodynamic features of IPAH patients with SHT or not at the baseline and identified the impact of SHT on pulmonary hemodynamics and response to specific-PAH therapies of IPAH patients at the follow-up of 18 months in the retrospective study.

Material and methods

Patients' recruitment

We performed a retrospective analysis of 88 patients with newly diagnosed IPAH from

Table 1. Baseline characteristics of non-SHT group vs. SHT group

Variables	Non-SHT [n=67 (%)]	SHT [n=21 (%)]	*p* value
Age (years)	30.9±10.4	39.3±8.4	0.001
Male	19 (28.4)	9 (42.9)	0.213
WHO functional class			0.520
Class I, II	28 (41.8)	10 (47.6)	
Class III	36 (53.7)	11 (52.4)	
Class IV	3 (4.5)	0 (0)	
Systolic BP (mmHg)	108.08±11.97	126.85±19.27	<0.001
Diastolic BP (mmHg)	75.60±12.04	85.86±15.31	0.002
6-MWT (m)	425.80±93.81	417.60±84.16	0.727
Echocardiography			
LAD (mm)	28.46±3.66	30.24±3.85	0.058
LVEDD (mm)	35.87±5.40	34.76±4.67	0.402
RVEDD (mm)	32.57±6.72	35.05±6.79	0.145
Hemodynamics			
mRAP (mmHg)	61.51±2.17	64.19±2.38	0.516
mRAP (mmHg)	5.57±4.11	6.19±3.97	0.542
PVR (Wood Unit)	14.79±7.05	17.24±3.51	0.038
PAWP (mmHg)	7.92±3.48	7.4±3.30	0.562
CI (L/min/m^2)	2.82±0.85	2.22±0.39	0.002
SvO2 (%)	72.66±7.21	66.25±5.67	<0.001
Positive vasoreactivity	4 (5.97)	0 (0)	<0.001
Endothelin (pmol/ml)	0.86±1.02	0.80±0.54	0.769
NT-proBNP (pg/ml)	1485.9±1043.20	1249.18±692.55	0.333
Serum creatinine (umol/L)	66.245±1.66	78.40±16.04	0.001

WHO, world health organization; BP, blood pressure; 6-MWT, 6-minute walking test; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; RVEDD, right ventricular end-diastolic diameter; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; PVR, pulmonary vascular resistance; PAWP, pulmonary artery wedge pressure; SVO2, mixed venous oxygen saturation; CI, cardiac index; SHT, systemic hypertension.

Pulmonary Vascular Disease Center of Fuwai Hospital between January 2013 and December 2014. The diagnosis of IPAH was established according to the 2015 ESC/ERS guidelines [4]. All the patients were the first time admitted to our PH expert center and had never received PAH-specific drug therapy. Patients with the following diseases were excluded: lung diseases (i.e. greater than mild COPD and/or emphysema), obstructive sleep apnea, end stage renal disease (defined as estimated glomerular filtration rate [eGFR] <15 ml/min), significant valvular disease, ischemic heart disease and other cardiomyopathies.

Study design

As routine in our center, all patients underwent detailed evaluation and hemodynamic assessment. Baseline demographic characteristics, medical histories (including World Health Organization function classification [WHO-FC], PAH-specific medications, and the presence of other comorbidities) and laboratory test results (including serum creatinine [sCr] and plasma brain natriuretic peptide [BNP] values) were collected. Exercise capacity was evaluated by 6-minute walking test (6-MWT). Right heart catheterization (RHC) was performed using a standard protocol. Inhaled 20 μg iloprost within 15 min was used to assess acute vasodilator response. A positive acute response is defined as reduction of the mean pulmonary artery pressure (mPAP) ≥10 mmHg to reach an absolute value of mPAP ≤40 mmHg with an increased or unchanged cardiac output.

The patients were divided into two groups according to the presence or absence of SHT: non-SHT group and SHT group. SHT was defined by systolic blood pressure of >140 mmHg and/or diastolic blood pressure of >90 mmHg recorded in more than two measurements, by physician-documented history of hypertension, or by chronic use of antihypertensive medications.

All the patients had been followed up by telephone contact from the date of visiting our center every three months. In the 88 patients initially enrolled, 55 patients returned visit our center after about six months. We also reviewed the data and compared their response to treatment. Improvements on treatment were defined as an improvement of WHO-FC plus an increase in 6-MWT of ≥15% compared with baseline. Worsening on treatment was defined as deterioration of WHO-FC after treatment plus a decrease in 6-MWT of ≥15% or increase of the PAH-specific drug dosages and/or classes.

Table 2. Pulmonary arterial hypertension medications

Treatment	Non-SHT [n=67 (%)]	SHT [n=21 (%)]	*p* value
Monotherapy	58 (86.6)	18 (85.7)	1.0
Combination therapy	2 (2.99)	1 (4.8)	0.563
CCB	4 (6.0)	0	0.57
No PAH-specific drugs	3 (4.48)	2 (9.5)	0.589

CCB, Calcium channel blockers; SHT, systemic hypertension; PAH, pulmonary arterial hypertension; SHT, systemic hypertension.

Table 3. Response to pulmonary arterial hypertension drug therapy

	Non-SHT [n=40 (%)]	SHT [n=15 (%)]	*p* value
Improvement	16 (40.0)	2 (13.3)	0.040
Stable	21 (52.5)	10 (66.7)	
Worsening	3 (7.5)	3 (20.0)	

SHT, systemic hypertension.

Statistical analysis

Data are presented as mean ± standard deviation for continuous variables and as percentage for discrete variables. Student's *t*-test for independent samples was applied to compare the mean values of continuous variables and Mann-Whitney U test for ordered variables. Chi-square statistics were used to assess the differences between proportions. Survival was estimated from the time of IPAH diagnosis until followed up for 18 months or all-cause mortality. A two-sided *p* value <0.05 was considered statistically significant. All of the analyses were performed using Statistical Package for the Social Sciences software (SPSS, version 20.0).

Results

Baseline characteristics of non-SHT group versus SHT group

In the total of 88 patients with IPAH, 21 patients (23.9%) simultaneously suffered from systemic hypertension. There were significant differences between the non-SHT and SHT groups (**Table 1**). Patients in the SHT group were significantly older than those in the non-SHT group (30.9±10.4 years *vs.* 39.3±8.4 years, P=0.001). There was no statistical significance on WHO-FC, 6-minute walking distance and echocardiographic measurements between the two groups. An analysis of invasive hemodynamic variable showed that patients in the SHT group had higher pulmonary vascular resistance (PVR) (14.79±7.05 *vs.* 17.24±3.51, P=0.038), lower cardiac index (CI) (2.82±0.85 *vs.* 2.22±0.39, P=0.002) and lower mixed venous oxygen saturation (SVO2) (72.66±7.21 *vs.* 66.25±5.67, P<0.001) compared with those in the non-SHT group. Four patients in the non-SHT group were of positive in acute pulmonary vasodilation testing, but no patient in the SHT group. On the basis of supported therapy, including diuretics, digoxin, oral anticoagulants and other cardiovascular drugs, 60 patients in the non-SHT group accepted PAH-specific drug therapy and four patients accepted CCB. 19 patients in the SHT group accepted PAH-specific drug therapy. There was no difference in terms of PAH-specific drugs (**Table 2**). Monotherapy was defined as using one of the specific drugs, including bosentan, ambrisentan, sildenafil and inhaled iloprost, and combination therapy was defined as using two classes of specific drugs simultaneously. Calcium channel blockers (CCB) only were used in the patients who had positive response in acute vasodilation testing. For 21 IPAH patients with SHT, antihypertensive drugs including angiotensin converting enzyme inhibitors (ACEI) and CCB were given to achieve target blood pressure of 140/90 mmHg.

Response to treatment

55 patients (15 with SHT) returned visit our center after about six months. Differences in response to treatment were significant between the two groups, and **Table 3** showed more improvement in the non-SHT group than in the SHT group (40.0% *vs.* 13.3%, P=0.04). NT-proBNP level of patients in the non-SHT group decreased after treatment (1482.54±1048.66 *vs.* 1046.48±880.61, P=0.047), but the similar change was not observed in the SHT group (1262.36±656.07 vs. 1185.73±1146.45, P=0.824). Moreover, no significant differences in echocardiography measurements and serum creatinine were found between the two groups (**Table 4**).

After followed up for 18 months, there were 2 deaths in the 67 IPAH patients without SHT and 2 deaths in the 21 IPAH patients with SHT. In

Table 4. Changes after treatment for about 6 months

Variables	Non-SHT (n=40)		*p* value	SHT (n=15)		*p* value
	Baseline	6 months		Baseline	6 months	
Echocardiography						
LVEDD (mm)	35.55±5.86	37.28±6.19	0.204	34.6±4.31	35.67±5.21	0.546
LVEF (%)	64.05±6.33	66.05±8.51	0.235	62.75±4.31	64.01±5.34	0.483
RVEDD (mm)	33.0±7.13	32.23±6.93	0.623	35.60±7.09	35.67±10.54	0.984
sCr (umol/L)	66.90±14.87	67.61±12.69	0.818	77.55±14.97	79.65±15.88	0.712
NT-proBNP (pg/ml)	1482.54±1048.66	1046.48±880.61	0.047	1262.36±656.07	1185.73±1146.45	0.824

LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; RVEDD, right ventricular end-diastolic diameter; sCr, serum creatinine; SHT, systemic hypertension.

the 21 IPAH patients with SHT, the estimated mortality rate of 18 months showed a higher trend, although there was not statistically significant (P=0.236) compared with 67 IPAH patients without SHT.

Discussion

Systemic hypertension is the most common cardiovascular disease risk factor. Previous investigators have reported the relationship between systemic and pulmonary hypertension. Many studies have shown that PH in patients with SHT was associated with LV diastolic dysfunction and heart failure of preserved ejection fraction (HFPEF) [5-7]. We extended the study to observe which impact that SHT lack of diastolic dysfunction and heart failure having on patients with IPAH. This retrospective study showed 23.9% IPAH patients coexisted with SHT in the study cohort. All patients with SHT in our study had normal left atrial dimensions and were lack of left ventricular hypertrophy, enabling us to rule out diastolic dysfunction as the reason of pulmonary hypertension.

The present study found that although mPAP was not significantly different between the two groups, patients with SHT demonstrated higher PVR and poorer response to vasodilator. These findings are consistent with previous reports [1, 8, 9], suggesting increased vasoreactivity of pulmonary and systemic vascular beds. These observations, as well as our study support that SHT associated with PAH not only resulted in pulmonary venous hypertension and HFPEF but might also result in adverse pulmonary remodeling and elevated pulmonary vascular resistance. A recent clinical research also found that resting and exercise PVR were increased in uncomplicated SHT, without being related to increased pulmonary venous pressure [10].

Evaluation of severity in PAH patients included several approaches, such as clinical parameters, imaging, hemodynamics, exercise capacity and biochemical markers. In our study, patients in the two group demonstrated similar WHO-FC and exercise capacity, but hemodynamics assessed by RHC showed lower CI and SvO2 in patients with SHT after adjustment for age. Previous studies have reported that RA pressure, CI and SvO2 are the most robust indicators of RV function and prognosis [11-13]. Therefore, we confirmed that IPAH patients with SHT in the present study had diminished cardiac function compared to patients without SHT.

This study also compared difference in the response to PAH therapies between IPAH patients with or without SHT. Results showed that IPAH patients with SHT have a less satisfactory response to therapy than those without SHT in terms of WHO-FC and exercise capacity after treatment for about six months, but no changes were observed in the echocardiography parameters. In this study all the patients in the SHT group had accepted antihypertensive therapies and their blood pressure were decreased to less than 140/90 mmHg, so higher blood pressure was unlikely to explain the difference. Cardiac function is one of affecting factors of the treatment effect in PAH patients. The trials of bosentan on patients with left ventricular systolic dysfunction have shown negative or no effect on clinical outcomes [14, 15]. Another randomized clinical trial suggested that chronic phosphodiesterase type-5 inhibitor therapy with sildenafil did not alter exercise capacity or clinical status compared to placebo in patients with heart failure and preserved

ejection fraction [16]. All the patients in this study did not reveal left ventricular dysfunction, but RV function is a key determinant of exercise capacity and outcome in patients with PH, worse RV function in IPAH patients with SHT consistent with the worse response of treatment. One possible mechanism for the association of SHT and IPAH is an increased endothelial response to vasoconstrictor stimuli existing in both the systemic and pulmonary vasculature of hypertensive patients [8, 17]. Worse function of vascular endothelial cells and of pulmonary vasculature may be another explanation for the poor response of PAH therapy in IPAH patients with SHT.

As have been shown, lower CI predicts poorer prognosis. In addition, clinical research supported that patients with PAH who improve from WHO-FC III to I/II have better survival compared to patients who failed to improve [18]. In this study, although IPAH patients with SHT showed a trend of poor survival, there was no significant difference. We had followed up all the patients for 18 months, and this time is shorter than previous studies, for this reason future studies should confirm this result through longer time observation.

Our study has a number of limitations. First, it is a single-center, retrospective study, and for this reason we recognized that the findings required further verification in larger and multicenter patient cohorts. Second, all the patients with systemic hypertension had accepted antihypertensive treatment, but impact of different antihypertensive therapies was not well defined in this study. Future research should attempt to elucidate the role of aggressive blood pressure control. Finally, we followed up for 18 months, the number of events limited further survival analysis as Kaplan- Meier curve, long-term observation should be considered in the future study.

In conclusion, systemic hypertension had adverse impact on pulmonary hemodynamics of IPAH patients, who were lack of left ventricular dysfunction. Despites similar use of disease-specific therapies for PAH, IPAH patients with systemic hypertension had less satisfactory response to the therapies. However, survival appeared no significant difference among patients with systemic hypertension, maybe because of the small sample size and shorter time of follow up. Future study should attempt to confirm long-term survival of those patients. Overall, our study recognized the deteriorating effect of systemic hypertension on patients with newly diagnosed IPAH patients.

Disclosure of conflict of interest

None.

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