Brief Report

The Long-Term Response to Treatment with Calcium Channel Blockers in Patients with Idiopathic Pulmonary Arterial Hypertension

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Abstract

Background: *Long-term outcomes in patients with idiopathic pulmonary arterial hypertension (IPAH) treated with calcium channel blockers (CCBs) are not well documented. Therefore, this study aimed to determine the long-term response to treatment with CCBs in patients with IPAH.*

Methods: *This retrospective cohort study was performed on 81 patients with IPAH admitted to our center. Vasoreactivity testing with adenosine was performed in all patients. Twenty-five patients showed a positive response to vasoreactivity testing and were included in the analysis.*

Results: *Of 24 patients, 20 (83.3%) were female, and the mean age of the patients was 45.90±10.42 years. Fifteen patients improved after 1 year on CCB therapy (the long-term CCB responders group), and 9 showed no improvement (the CCB failure group). The CCB responders group had a greater proportion of patients in New York Heart Association (NYHA) functional class I or II (93.3%), a longer distance walked, and less severe hemodynamic parameters. At the 1-year evaluation, the long-term CCB responders had more improvements in the mean 6-minute walk test result (437.43±125.32 vs 268.17±130.06; P=0.040), the mixed venous oxygen saturation level (71.84±9.87 vs 59.03±9.95; P=0.041), and the cardiac index (4.76±1.12 vs 3.15±0.90; P=0.012). Additionally, mPAP was lower in the long-term CCB responders group (47.35±12.70 vs 67.23±14.08; P=0.034). Finally, all the CCB responders were in NYHA functional class I or II (P=0.001).*

Conclusion: *Our study illustrated that long-term treatment with oral CCBs was effective in 60% of acute responders and 18.5% of the entire study population.*

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Keywords: *Pulmonary hypertension; Calcium channel blockers; Hemodynamic monitoring; Iran*

Introduction

Pulmonary hypertension (PH) is the presence of an elevated mean pulmonary artery pressure (mPAP) at rest as evaluated by right-heart catheterization. The updated PH classification introduces 5 categories of PH that share similar pathophysiological mechanisms, histological findings, clinical presentation, and management. Group I

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PH corresponds to pulmonary arterial hypertension (PAH), Group II and Group III PH are due to chronic cardiac or lung diseases, Group IV PH corresponds to chronic thromboembolic PH, and Group V is a heterogeneous group of PH due to multiple or unknown mechanisms (eg, patients with PH and sarcoidosis).[1,2]

PAH, as a rare condition with a prevalence rate ranging from 15 to 50 per million in the United States and Europe, denotes the disease of small pulmonary arteries (<500 μm) characterized by a progressive increase in pulmonary vascular resistance, resulting in right ventricular failure and ultimately death. PAH may be idiopathic, heritable, induced by drugs or toxins, or associated with different diseases such as connective tissue disease, congenital heart disease, and portal hypertension. Idiopathic pulmonary arterial hypertension (IPAH) denotes a scenario where no known risk factor is documented.[3, 4]

Calcium channel blockers (CCBs) disturb the movement of calcium (Ca^{2+}) through calcium channels, and they are classified into 2 categories: dihydropyridine and non-dihydropyridine. It is possible to administer CCBs orally or intravenously.[5] Pulmonary vasodilator testing illustrates the relative contribution of reversible vasoconstriction versus fixed stenosis in patients with PAH. If the amount of the reversible vasoconstrictive component is considerable, it recognizes patients who may benefit from long-term CCB therapy.[6] On the other hand, in individuals with a negative pulmonary vasodilator test, CCB therapy may cause adverse effects.[7-9] In 1992, Rich et al.,[9] found that patients with an acute response to CCBs had significantly improved survival compared with patients with no acute response.

Long-term CCB responders have a sustained benefit determined as attaining New York Heart Association (NYHA) functional class I or II with near-normal hemodynamics after at least a 1-year follow-up. Accordingly, in the present study, we aimed to determine the proportion of the long-term response to CCBs in patients with IPAH and to define clinical and hemodynamic characteristics that may help to identify these individuals.

Methods

This retrospective cohort study was conducted at Rajaie Cardiovascular Medical and Research Center, affiliated with Iran University of Medical Sciences (IUMS), Tehran, Iran. This hospital, the main cardiovascular center in the capital of Iran, annually provides more than 2 million people with medical services.

Between January 1, 2000, and December 30, 2019, we retrospectively assessed the medical records of all consecutive adult patients admitted to our institution with a diagnosis of IPAH. PH was defined by a resting mPAP of greater than 25 mmHg during right heart catheterization, with a mean pulmonary wedge pressure of less than 15 mmHg, and a pulmonary vascular resistance level of below 3 Wood units. In this study, patients with connective tissue diseases, congenital heart diseases, portal hypertension, HIV infection, chronic thromboembolic PH, and other chronic respiratory diseases, as well as those with incomplete information, were excluded to eliminate confounding variables. Finally, 81 patients met the criteria of IPAH.

Vasoreactivity testing with adenosine was performed on all the patients during the first hemodynamic evaluation. An acute response to adenosine was defined as a reduction in mPAP of at least 10 mmHg to reach an mPAP of 40 mmHg or less, with an unchanged or increased cardiac output. Twenty-five patients showed a positive response to vasoreactivity testing and were included in the analysis. Out of the 25 patients, 1 patient died due to cardiogenic shock and was excluded from the study.

The drug used was diltiazem (14 patients) or amlodipine (10 patients). Ten patients were initiated with oral doses of amlodipine (10 mg), 3 patients were initiated with oral doses of diltiazem (120 mg), 7 patients were initiated with oral doses of diltiazem (120–240 mg), and 4 patients were initiated with oral doses of diltiazem (>240 mg).

Clinical evaluations, including the NYHA functional class and the 6-minute walk test (6MWT), and baseline hemodynamic measurements, including the mean right atrial pressure (mRAP), mPAP, the cardiac index, and the mixed venous oxygen saturation (SvO_2) level, were performed after 3 months and 1 year of treatment with CCBs.

Demographic, clinical, laboratory, hemodynamic, and echocardiographic data were obtained from the patients' medical records using a checklist and reviewed by a cardiologist.

The data were analyzed using descriptive statistics, including mean±standard deviation, medians, frequencies, and percentages, wherever applicable. Differences between subgroups were assessed using the independent *t* test for continuous and normally distributed variables and the χ^2 test (or the Fisher exact test) for categorical variables. The independent predictors of a long-term favorable response to CCBs were assessed using multivariate logistic regression models. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. A test was considered statistically significant if the probability value (P value) was less than 0.05. All the analyses were carried out using the Stata software, version 14.1 (Stata Corp, College Station, TX, USA).

The Research Ethics Committee of IUMS approved the study protocol (Ethics No. IUMS.REC.). Patient data were kept confidential, with access limited to 2 researchers and the quality control physician.

Results

The assessment of the clinical, functional, and hemodynamic characteristics of the studied patient sample at baseline and 1-year follow-up is shown in Table 1. At baseline, the CCB failure group was more likely to have the NYHA functional class III and IV (88.9% vs 6.7%; *P*=0.001). The CCB failure group had lower 6MWT (*P*=0.049), SvO_2 (*P*=0.045), and cardiac index (*P*=0.047) than the CCB responders group. However, the CCB failure group had higher mRAP (*P*=0.039) and mPAP (*P*=0.048). The CCB failure group was more likely to have severe tricuspid regurgitation (66.7% vs 13.3%; *P*=0.023).

Fifteen patients improved after 1 year on CCB therapy (the long-term CCB responders group), and 9 failed to improve (the CCB failure group). The CCB responders group had less severe disease than the CCB failure group as illustrated by a greater proportion of patients in the NYHA functional class I or II (93.3%), a longer distance walked, and less severe hemodynamic parameters (Table 1). At 1-year evaluation, the long-term CCB responders showed more improvement in the mean 6MWT (437.43±125.32 vs 268.17±130.06; *P*=0.040), SvO_2 (71.84±9.87 vs 59.03±9.95; *P*=0.041), and cardiac index (4.76±1.12 vs 3.15±0.90; *P*=0.012) than the CCB failure group. In addition, mPAP was lower in the long-term CCB responders (47.35±12.70 vs 67.23±14.08; *P*=0.034). At the final evaluation, all the CCB responders were in the NYHA functional class I or II (*P*=0.001) (Table 1).

Table 1. Clinical, functional, and hemodynamic characteristics of the patients (n=24)

Characteristic	Total	Baseline		*P*	1-Year Evaluation		*P*
		CCB Responders Group (n=15)	CCB Failure Group (n=9)		Long-Term CCB Responders Group (n=15)	CCB Failure Group (n=9)	
Age (y)	45.90±10.42	44.83±9.51	45.30±10.18	0.923	45.73±9.60	46.45±10.03	0.945
Sex							0.571
Male	4 (16.7)	3 (20.0)	1 (11.1)	0.571	3 (20.0)	1 (11.1)	
Female	20 (83.3)	12 (80.0)	8 (88.9)		12 (80.0)	8 (88.9)	
Hypothyroidism	10 (40.0)	8 (53.3)	2 (22.2)	0.933	8 (53.3)	2 (22.2)	0.933
NYHA class							0.001
I or II	15 (62.5)	14 (93.3)	1 (11.1)		15 (100)	1 (11.1)	
III	6 (25.0)	1 (6.7)	5 (55.6)	0.001	0 (0)	4 (44.4)	
IV	3 (12.5)	0 (0)	3 (33.3)		0 (0)	4 (44.4)	
History of syncope	8 (33.3)	6 (40.0)	2 (22.2)	0.371	6 (40.0)	2 (22.2)	0.371
N-terminal pro-BNP (pg/mL)	906.81±179.45	795.63±180.72	910.80±168.19	0.228	281.80±98.45	308.23±102.71	0.624
Six-minute walk test (m)	299.25±121.71	399.83±150.10	248.16±120.94	0.049	437.43±125.32	268.17±130.06	0.040
Right atrial pressure (mmHg)	11.30±5.15	6.72±5.97	12.93±5.05	0.039	5.61±4.28	10.74±5.39	0.103
SvO_2 (%)	67.80±8.43	69.81±9.67	57.10±10.18	0.045	71.84±9.87	59.03±9.95	0.041
Cardiac index (L/min/m^2)	2.91±0.76	4.18±0.63	2.93±0.90	0.047	4.76±1.12	3.15±0.90	0.012
mPAP	51.33±13.71	53.18±14.72	69.82±13.17	0.048	47.35±12.70	67.23±14.08	0.034
Pericardial Effusion							0.187
None	21 (87.5)	14 (93.3)	7 (77.8)	0.264	15 (100)	8 (88.9)	
Minimal	3 (12.5)	1 (6.7)	2 (22.2)		0 (0)	1 (11.1)	
Tricuspid Regurgitation							0.060
Mild	8 (33.3)	7 (46.7)	1 (11.1)	0.023	9 (60.0)	2 (22.2)	
Moderate	8 (33.3)	6 (40.0)	2 (22.2)		5 (33.3)	3 (33.3)	
Severe	8 (33.3)	2 (13.3)	6 (66.7)		1 (6.7)	4 (44.4)	
RV Dysfunction							0.621
Mild	3 (12.5)	2 (13.3)	1 (11.1)		4 (26.7)	1 (11.1)	
Moderate	5 (20.8)	3 (20.0)	1 (11.1)	0.824	5 (33.3)	3 (33.3)	
Severe	16 (66.7)	10 (66.7)	7 (77.8)		6 (40.0)	5 (55.6)	
Systolic PAP (mmHg)	59.16±14.42	56.36±14.27	64.77±14.55	0.291	43.06±13.15	59.67±13.54	0.024

CCB, Calcium channel blocker; NYHA, New York Heart Association; SvO_2, Mixed venous oxygen saturation; mPAP, Mean pulmonary artery pressure; RV, Right ventricle

Table 2. Hemodynamic effects of long-term CCB therapy in the CCB responders group (n=15)

Characteristic	Baseline	1-Year Evaluation	*P*
Right atrial pressure (mmHg)	6.73±5.90	5.61±4.24	0.001
SvO_2 (%)	69.88±9.63	71.84±9.87	0.001
Cardiac index (L/min/m^2)	4.12±0.66	4.72±1.14	0.001
mPAP (mmHg)	53.13±14.74	47.37±12.72	0.001

CCB, Calcium channel blocker; SvO_2, Mixed venous oxygen saturation; mPAP, Mean pulmonary artery pressure; RV, Right ventricle

Table 3. Predictors of a long-term favorable response to CCBs

Predictors	OR	95% CI	*P*
Age <40 (y)	1.15	0.88-2.01	0.128
Male	1.46	0.78-2.48	0.248
History of hypothyroidism (No)	1.10	0.72-1.98	0.253
History of connective tissue disease (No)	1.50	0.98-2. 81	0.338
NYHA class I or II	2.98	1.15-3.56	0.003
History of syncope (None)	1.34	0.68-1.90	0.121
N-terminal pro-BNP <300 (pg/mL)	2.60	1.13-3.10	0.045
Six-minute walk test >440	4.25	2.10-5.01	0.001
Right atrial pressure <8	1.90	0.95-2.18	0.098
SvO_2 >65 (%)	6.50	3.58-7.12	0.001
Cardiac index >2.5	2.40	1.54-3.78	0.030
mPAP <25	4.65	2.84-5.90	0.001
History of pericardial effusion (No)	1.18	0.56-1.93	0.285
History of tricuspid regurgitation (Mild)	1.74	0.92-2.15	0.685
History of RV dysfunction (Mild)	1.65	0.99-2.03	0.058
Systolic PAP <30	3.50	1.85-4.01	0.001

CCBs, Calcium channel blockers; NYHA, New York Heart Association; N-terminal pro-BNP, N-terminal prohormone of brain natriuretic peptide; SvO_2, Mixed venous oxygen saturation; mPAP, Mean pulmonary artery pressure

All the CCB responders showed a sustained improvement in hemodynamics parameters, with an mRAP of 5.61±4.24 mmHg, an mPAP of 47.37±12.72 mmHg, a mean cardiac index of 4.72±1.14 L.min-1. m^2, and a mean SvO_2 of 71.84±9.87% (*P*=0.001) (Table 2).

Table 3 summarizes the results of the univariate analysis applied to find the predictors of the long-term favorable response to CCBs. The most significant factors that increased the long-term favorable response to CCBs were an SvO_2 level exceeding 65 (OR, 6.48; 95% CI, 3.57 to 7.12; *P*=0.001), an mPAP of below 25 (OR, 4.65; 95% CI, 2.84 to 5.90; *P*=0.001), a 6MWT result exceeding 440 (OR, 4.25; 95% CI, 2.10 to 5.01; *P*=0.001), a systolic PAP below 30 (OR, 3.50; 95% CI, 1.85 to 4.01; *P*=0.001), NYHA class I or II (OR, 2.95; 95% CI, 1.15 to 3.54; *P*=0.003), an N-terminal pro-BNP level of below 300 (OR, 2.56; 95% CI, 1.03 to 3.10; *P*=0.045), and a cardiac index exceeding 2.5 (OR, 2.40; 95% CI, 1.54 to 3.78; *P*=0.030) (Table 3).

Discussion

Early experimental documents in rat lungs demonstrated that CCBs inhibited hypoxic pulmonary vasoconstriction.[10] Shortly thereafter, a study found that CCBs might be beneficial in patients with IPAH.[11] Subsequently, CCBs were considered the first therapy capable of improving survival in patients with IPAH.[12, 13] Therefore, in the current study, we aimed to determine the proportion of the long-term response to CCBs in patients with IPAH and to define clinical and hemodynamic characteristics that may help to identify these individuals.

It is well known that the initial response to acute pulmonary vasodilator testing detects patients with PAH likely to respond to CCBs. When applying the criteria of the positive response to vasoreactivity testing (a reduction in mPAP of at least 10 mmHg to reach an mPAP of 40 mmHg or less, with an unchanged or increased cardiac output), we

found that only 25 among 81 patients (30.9%) demonstrated an acute vasodilator response, leading to the initiation of long-term CCBs. Out of the 25 patients, 1 patient died due to cardiogenic shock and was excluded from the study. Among these acute responders, only 15 patients (ie, 60% of the acute responders and 18.5% of the whole study population) had a sustained long-term benefit with CCBs. It is unknown why some patients may have an initial positive vasodilator test but fail in CCB therapy.

Sitbon et al[14] reported that only 38 patients (ie, 54% of acute vasodilator responders and 6.8% of the entire studied patient sample) had a sustained long-term benefit with oral CCBs. Rich et al[9] reported that 26.6% of their patients benefited from CCBs. Rong Zuo et al[15] reported that 5.8% of their patients with IPAH had a sustained long-term benefit with CCBs.

Nonetheless, acute CCB responders have less severe disease as shown by a higher proportion of patients in the NYHA functional class I or II; a better 6MWT, SvO_2, and CI; and a lower RAP and mPAP. Likewise, we reported a higher proportion of previous syncope in acute CCB responders, although the differences were not statistically significant, probably due to the fact that these patients have less severe disease and are able to do more heavy activities.

Our study has several limitations. Firstly, the nature of the study design (retrospective nature) is the salient limitation of the present study. Secondly, some patients with a good response to CCBs may have been treated experimentally and never referred. Thirdly, only patients showing an acute response to adenosine were treated with CCBs, precluding the assessment of the effects of CCBs in patients not showing acute pulmonary vasodilatation because they never received this treatment. Fourthly, the small sample size is another limitation of the current study. Fifthly, only IPAH was assessed in this study. Nevertheless, acute vasoreactivity testing in PAH associated with other conditions, including connective tissue diseases, HIV infection, portal hypertension, and left-to-right congenital shunts, indicates that the acute response to adenosine is less common than in IPAH. Finally, our data were derived from a single center; thus, our findings may not be generalizable to other racial/ethnic populations.

Conclusion

In summary, the administration of CCBs in IPAH patients with a positive pulmonary vasodilator test is suggested. Our study illustrated that long-term treatment with oral CCBs was effective in 60% of acute responders and 18.5% of the entire studied patient sample. These patients can be detected by acute pulmonary vasoreactivity testing. During the acute vasodilator challenge, these patients show a marked decrease in mPAP. Patients that are started on CCB therapy should be carefully monitored both clinically and hemodynamically to assure a long-term CCB response. Finally, a multicenter prospective investigation with a greater sample size should be performed to prove these findings in the future.

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References

1. Galiè N, McLaughlin VV, Rubin LJ, Simonneau G. An overview of the 6th World Symposium on Pulmonary Hypertension. Eur Respir J 2019;53:1802148.
2. Akbar M, Mohammad Yusof Aarabi M, Paridokht Nakhostin D, Akbar S, Mahmood M. Validity of Sildenafil Test in Patients with Pulmonary Arterial Hypertension Associated with Congenital Heart Disease According to Clinical and Echocardiographic Parameters. J Tehran Heart Cent 2009;4:103-108.
3. Rubin LJ. Primary pulmonary hypertension. N Engl J Med 1997;336:111-117.
4. Humbert M, Nunes H, Sitbon O, Parent F, Hervé P, Simonneau G. Risk factors for pulmonary arterial hypertension. Clin Chest Med 2001;22:459-475.
5. Galiè N, Torbicki A, Barst R, Dartevelle P, Haworth S, Higenbottam T, Olschewski H, Peacock A, Pietra G, Rubin LJ, Simonneau G, Priori SG, Garcia MA, Blanc JJ, Budaj A, Cowie M, Dean V, Deckers J, Burgos EF, Lekakis J, Lindahl B, Mazzotta G, McGregor K, Morais J, Oto A, Smiseth OA, Barbera JA, Gibbs S, Hoeper M, Humbert M, Naeije R, Pepke-Zaba J; Task Force. Guidelines on diagnosis and treatment of pulmonary arterial hypertension. The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology. Eur Heart J 2004;25:2243-2278.
6. Groves BM, Badesch DB, Turkevich D, Ditchey RV, Donnellan K, Wynne K, et al. Correlation of acute prostacyclin response in primary (unexplained) pulmonary hypertension with efficacy of treatment with calcium channel blockers and survival. In: Weir EK., Hume JR., Reeves JT, eds. Ion Flux in Pulmonary Vascular Control. NATO ASI Series, vol 251. Boston, MA. Springer US; 1993. p. 317-330.
7. Sitbon O, Humbert M, Jagot JL, Taravella O, Fartoukh M, Parent F, Herve P, Simonneau G. Inhaled nitric oxide as a screening agent for safely identifying responders to oral calcium-channel blockers in primary pulmonary hypertension. Eur Respir J 1998;12:265-270.
8. Badesch DB, Abman SH, Simonneau G, Rubin LJ, McLaughlin VV. Medical therapy for pulmonary arterial hypertension: updated ACCP evidence-based clinical practice guidelines. Chest 2007;131:1917-1928.
9. Rich S, Kaufmann E, Levy PS. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. N Engl J Med 1992;327:76-81.
10. McMurtry IF, Davidson AB, Reeves JT, Grover RF. Inhibition of hypoxic pulmonary vasoconstriction by calcium antagonists in isolated rat lungs. Circ Res 1976;38:99-104.
11. Kambara H, Fujimoto K, Wakabayashi A, Kawai C. Primary pulmonary hypertension: beneficial therapy with diltiazem. Am Heart J 1981;101:230-231.
12. Weir EK, Rubin LJ, Ayres SM, Bergofsky EH, Brundage BH,

Detre KM, Elliott CG, Fishman AP, Goldring RM, Groves BM, et al. The acute administration of vasodilators in primary pulmonary hypertension. Experience from the National Institutes of Health Registry on Primary Pulmonary Hypertension. Am Rev Respir Dis 1989;140:1623-1630.

13. Barst RJ, Maislin G, Fishman AP. Vasodilator therapy for primary pulmonary hypertension in children. Circulation 1999;99:1197-1208.
14. Sitbon O, Humbert M, Jaïs X, Ioos V, Hamid AM, Provencher S, Garcia G, Parent F, Hervé P, Simonneau G. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. Circulation 2005;111:3105-3111.
15. Zuo XR, Zhang R, Jiang X, Li XL, Zong F, Xie WP, Wang H, Jing ZC. Usefulness of intravenous adenosine in idiopathic pulmonary arterial hypertension as a screening agent for identifying long-term responders to calcium channel blockers. Am J Cardiol 2012;109:1801-1806.