J Bras Pneumol. 2023;49(3):e20220337
https://dx.doi.org/10.36416/1806-3756/e20220337

Loss of response to calcium channel blockers after long-term follow-up treatment in patients with idiopathic pulmonary arterial hypertension

Bruna Piloto[1], Caio Julio Cesar dos Santos Fernandes[1], Carlos Jardim[1], Marcela Castro[1], Jose Leonidas Alves-Jr[1], Rogerio Souza[1]

1. Divisão de Pneumologia, Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.

Submitted: 13 September 2022.
Accepted: 4 February 2023.

Study carried out in the Divisão de Pneumologia, Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.

ABSTRACT

Idiopathic pulmonary arterial hypertension (PAH) patients with a positive response to acute vasodilator challenge and a clinical response to calcium channel blockers (CCBs) for at least one year are traditionally designated true responders. Nevertheless, little is known about a sustained response to CCBs over longer periods of time. We evaluated the loss of response to CCBs after long-term treatment in a cohort of idiopathic PAH patients previously classified as being true responders. Our data suggest that idiopathic PAH patients can lose clinical response to CCBs even after one year of clinical stability, reinforcing the need for constant multidimensional reevaluation to assess the need for targeted PAH therapies and to classify these patients correctly.

Keywords: Pulmonary hypertension; Vasodilator agents; Calcium channel blockers.

Idiopathic pulmonary arterial hypertension (PAH) is a rare condition that is characterized by progressive remodeling of small pulmonary arteries in the absence of associated conditions; this remodeling leads to increased pulmonary vascular resistance and mean pulmonary artery pressure (mPAP), which in turn lead to right heart failure and death.[1-3] Vasoconstriction can play a role in the development of idiopathic PAH in patients who respond to acute vasodilator challenge, characterizing a different phenotype.[4] In a prospective study published in 1992, Rich et al. showed for the first time that idiopathic PAH patients presenting with an acute response to vasodilators could benefit from treatment with calcium channel blockers (CCBs).[5] In a retrospective study published in 2005, Sitbon et al. investigated a cohort of patients with idiopathic PAH and found that 12.6% were responders to acute vasodilator challenge; however, the clinical status of almost half of those patients did not improve with CCB treatment after one year of follow-up.[6] The authors also showed that those who remained responders to CCBs after one year had a better survival rate.[6] Nevertheless, the proportion of patients who remain responsive to CCBs after periods longer than one year remains unknown. The objective of the present study was to evaluate a sustained clinical response to CCBs in patients with idiopathic PAH.

We evaluated retrospective data obtained from the medical records of all consecutive patients diagnosed with idiopathic PAH and responding to acute vasodilator challenge between January of 2003 and December of 2018 at a referral center for PAH. Baseline data included New York Heart Association (NYHA) functional class, brain natriuretic peptide (BNP) levels, the six-minute walk distance (6MWD), and hemodynamic parameters. There are new criteria for the diagnosis of idiopathic PAH.[7] However, because of the retrospective nature of the present study, we defined idiopathic PAH as an mPAP ≥ 25 mmHg, a normal pulmonary artery wedge pressure of ≤ 15 mmHg, and a pulmonary vascular resistance > 3 Wood units in the absence of other causes of precapillary pulmonary hypertension.[8] All patients underwent right heart catheterization in accordance with standard techniques, and all vasodilator challenges were performed in accordance with the same protocol during the study period, with inhaled nitric oxide for 10 min. The test was considered positive if there was a decrease in mPAP of at least 10 mmHg to an absolute mean of < 40 mmHg without a decrease in cardiac output.[9,10]

After a positive response to vasodilator challenge, patients were started on treatment with CCBs. Short-term responders were defined as those who failed to reach or maintain NYHA functional class I or II, or those in whom BNP levels remained elevated and/or the 6MWD remained short during the first year of treatment with CCBs. True responders were defined as those who achieved or remained in NYHA functional class I or II after treatment with CCBs for at least one year,[6] with improvements in BNP levels and the 6MWD, remaining clinically stable during the follow-up period. Loss of response to CCBs after long-term treatment was defined as any worsening of NYHA functional class, the 6MWD, and/or BNP levels followed by prescription of specific PAH therapy after one year of treatment with CCBs, at the discretion of the attending physician. The one-year mortality risk

Correspondence to:
Rogerio Souza. Divisão de Pneumologia, Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, Avenida Dr. Enéas de Carvalho Aguiar, 44, CEP 05403-000, São Paulo, SP, Brasil.
Tel./Fax: 55 11 2661-5695. E-mail: rogerio.souza@fm.usp.br
Financial support: None.

was assessed in accordance with criteria described elsewhere,[11] being classified as low or not low at baseline, 3-6 months after initiation of treatment with CCBs, and before initiation of targeted PAH therapies. Because these were not the criteria that were classically used at the time in order to define response to CCBs, we used them exclusively to reinforce the need for multidimensional assessment.

All statistical analyses were performed with the IBM SPSS Statistics software package, version 26 (IBM Corporation, Armonk, NY, USA). Continuous variables are expressed as mean ± standard deviation, whereas categorical data are expressed as proportions. Differences between groups were analyzed by means of the Student's t-test or the chi-square test, as appropriate. A value of $p < 0.05$ was considered statistically significant.

We collected data on 26 patients presenting with a positive response to acute vasodilator challenge, those patients corresponding to 16.1% of all patients diagnosed with idiopathic PAH during the study period. All 26 patients met the criteria for an acute vasodilator response (Figure 1). Baseline clinical, demographic, and hemodynamic characteristics are presented in Table 1. Four patients (2.4%) had a positive response to acute vasodilator challenge but showed no clinical improvement after treatment with CCBs, therefore being classified as short-term responders. Twenty-two patients (13.6% of the total of patients diagnosed with idiopathic PAH during the study period) met the criteria for response to CCBs over the course of at least one year of treatment. However, only 11 (6.8% of the total of patients diagnosed with idiopathic PAH during the study period) remained stable for periods longer than one year, without the need for specific PAH therapy, and were therefore classified as true responders to treatment with CCBs. The group of 11 patients who responded to treatment with CCBs for more than one year but later showed no clinical response (6.8% of the total of patients diagnosed with idiopathic PAH during the study period) did so after a mean follow-up period of 47 months and were then prescribed specific PAH therapy. At diagnosis, there were no significant differences in clinical, hemodynamic, and functional characteristics between the group of true responders and that of those who lost response after long-term follow-up.

After initial treatment with CCBs, only 27% of the patients who later had a loss of response to CCBs did not meet the criteria for a low mortality risk in one year. Those patients were reassessed before initiation of targeted PAH therapies, and 82% were classified as not being at a low mortality risk.

We had four deaths in our cohort. Two deaths occurred in the group of patients who lost response to CCBs, and two occurred in the group of patients who were still receiving treatment with CCBs at the time of analysis. Three deaths occurred because of infections followed by right ventricular failure. One death occurred in the postoperative period after lung transplantation, in a patient in whom treatment with CCBs had failed.

We found that one year of clinical response to CCBs might be insufficient to predict a long-term clinical benefit and a favorable outcome in patients with idiopathic PAH. Approximately 50% of patients with a positive clinical response for one year showed clinical and functional worsening and required specific PAH therapy after approximately four years of follow-up.

In contrast with our findings, Sitbon at al.[6] reported that all but one idiopathic PAH patient who had at least one year of clinical benefit with CCBs after a positive response to acute vasodilator challenge had an excellent prognosis after seven years of follow-up and did not require add-on therapy for the treatment of PAH. However, our results show that this phenotype of idiopathic PAH is not absolute, and a one-year follow-up period may not be enough to identify patients who will have a favorable outcome while on treatment with CCBs exclusively. Genetic evaluation of idiopathic PAH patients, comparing vasodilator-responsive with vasodilator-nonresponsive patients, showed that multiple genetic variants are present in the same individual.[12] Therefore, it is quite possible that an acute vasodilator response and a one-year response to treatment with CCBs encompass multiple genotypic features, resulting in similar, although not identical, phenotypic patterns.

The concept of risk stratification is recent[11,13,14] and has not been used in order to determine response to CCBs. According to Sitbon et al., long-term responders are those who are in NYHA functional class I or II and show a sustained hemodynamic improvement without the need for specific therapy.[6] Although these were the criteria that were used at our institution in the last decade, it is of note that evaluation by risk stratification also reflected the loss of response. Although this is apparently obvious, it had not been previously demonstrated and reinforces the need for multidimensional reassessment in patients deemed to be responders.

Our study has limitations that are inherent to its retrospective nature, such as a small sample size. Furthermore, hemodynamic variables such as cardiac index and stroke volume were not available to refine risk assessment, and neither was hemodynamic reassessment at follow-up. In addition, no specific thresholds were used in order to determine CCB response, and neither was it a multidimensional assessment. Nevertheless, our findings raise questions that merit further investigation in prospective and controlled cohorts to validate the latest changes in the classification of PAH,[15] which now includes CCB responders as a separate subgroup of PAH patients.

In conclusion, our data suggest that idiopathic PAH patients can lose clinical response to CCBs even after one year of clinical stability, reinforcing the need for constant multidimensional reevaluation to assess the need for targeted PAH therapies and to classify these patients correctly.

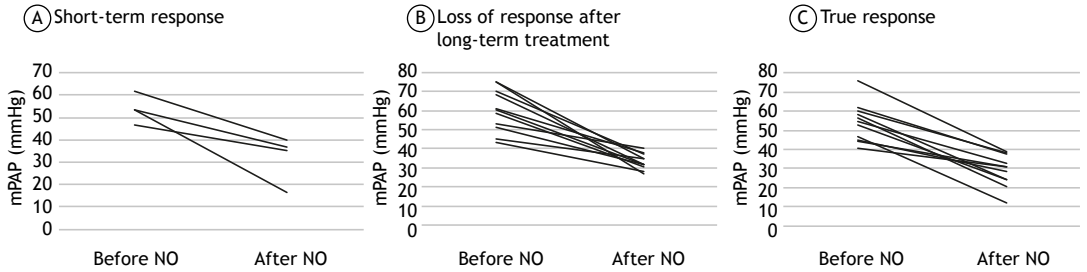

Figure 1. Mean pulmonary artery pressure (mPAP) reached during acute vasodilator testing with inhaled nitric oxide (NO) in the 4 patients who lost response to calcium channel blockers (CCBs) in less than one year (in A), in the 11 patients who lost response to CCBs after long-term treatment with CCBs (in B), and in the 11 patients who remained responders to CCBs after long-term treatment with CCBs (in C).

Table 1. Baseline characteristics of patients at diagnosis of idiopathic pulmonary arterial hypertension, by type of response to treatment with calcium channel blockers.[a]

Characteristic	Short-term response (n = 4)	Loss of response after a long-term response (n = 11)	True response (n = 11)	p*	Total (N = 26)
Female sex	4 (100)	10 (91)	9 (81)	0.53	23 (88)
Age, years	34.2 ± 12.9	33.6 ± 9.8	33.7 ± 13.9	0.98	33.8 ± 11.7
NYHA functional class	-	1 (11.1)	1 (9.1)	0.54	2 (9.1)
I	2 (100)	5 (55.6)	6 (54.5)		13 (59.1)
II	-	3 (33.3)	2 (18.2)		5 (22.7)
III	-	-	2 (18.2)		2 (9.1)
IV					
BNP, pg/dL	128.5 ± 72.8	155.7 ± 153.8	47.0 ± 45.4	0.11	98.3 ± 111.7
6MWD, m	435 ± 77	475 ± 61	458 ± 94	0.69	463.7 ± 77.0
Hemodynamic parameters					
RAP, mmHg	5.8 ± 5.7	10.0 ± 3.6	9.0 ± 4.7	0.61	8.8 ± 4.5
mPAP, mmHg	53.7 ± 6.1	60.2 ± 11.1	54.2 ± 10.1	0.19	56.6 ± 10.2
PAWP, mmHg	9.8 ± 2.9	10.2 ± 2.5	9.2 ± 3.2	0.44	9.7 ± 2.8
Cardiac output, L/min	4.0 ± 1.4	3.7 ± 0.9	4.4 ± 1.2	0.18	4.0 ± 1.1
PVR, Wood units	11.6 ± 2.2	14.0 ± 3.9	11.3 ± 5.4	0.20	12.5 ± 4.4
mPAP after NO, mmHg	32.0 ± 10.4	33.2 ± 4.1	28.9 ± 8.3	0.14	31.2 ± 7.1
Cardiac output after NO, L/min	4.6 ± 1.2	4.2 ± 1.0	4.6 ± 1.2	0.46	4.4 ± 1.1
Not at low risk	2 (50)	7 (64)	6 (55)	0.65	15 (58)
Mean follow-up period, months	77.5 ± 81.1	117.1 ± 38.8	75.0 ± 52.6		93.2 ± 54.2
Time to loss of response, months	4.9 ± 2.7	47.2 ± 37.6	-		-

NYHA: New York Heart Association; BNP: B-type natriuretic peptide; 6MWD: six-minute walk distance; RAP: right atrial pressure; mPAP: mean pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; PVR: pulmonary vascular resistance; and NO: nitric oxide. [a]Values expressed as n (%) or mean ± SD. **For the comparison between true response and loss of response after a long-term response.*

AUTHOR CONTRIBUTIONS

BP, JLAJ, and RS: study design, data collection, data analysis, drafting of the manuscript, and approval of the final version of the manuscript. CJCSF and CJ: data analysis, drafting of the manuscript, and approval of the final version of the manuscript. MC: data collection, data analysis, drafting of the manuscript, and approval of the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Humbert M, Sitbon O, Simonneau G. Treatment of pulmonary arterial hypertension. N Engl J Med. 2004;351(14):1425-1436. https://doi.org/10.1056/NEJMra040291
2. Alves JL Jr, Gavilanes F, Jardim C, Fernandes CJCDS, Morinaga LTK, et al. Pulmonary arterial hypertension in the southern hemisphere: results from a registry of incident Brazilian cases. Chest. 2015;147(2):495-501. https://doi.org/10.1378/chest.14-1036
3. Montani D, Savale L, Natali D, Jaïs X, Herve P, Garcia G, et al. Long-term response to calcium-channel blockers in non-idiopathic pulmonary arterial hypertension. Eur Heart J. 2010;31(15):1898-1907. https://doi.org/10.1093/eurheartj/ehq170
4. Langleben D, Orfanos SE, Giovinazzo M, Schlesinger RD, Hirsch AM, Blenkhorn F, et al. Acute vasodilator responsiveness and microvascular recruitment in idiopathic pulmonary arterial hypertension. Ann Intern Med. 2015;162(2):154-156. https://doi.org/10.7326/M14-1402

5. 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(2):76-81. https://doi.org/10.1056/NEJM199207093270203
6. Sitbon O, Humbert M, Jaïs X, Ioos V, Hamid AM, Provencher S, et al. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. Circulation. 2005;111(23):3105-3111. https://doi.org/10.1161/CIRCULATIONAHA.104.488486
7. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2022;43(38):3618-3731. https://doi.org/10.1093/eurheartj/ehac237
8. Lau EM, Tamura Y, McGoon MD, Sitbon O. The 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: a practical chronicle of progress. Eur Respir J. 2015;46(4):879-882. https://doi.org/10.1183/13993003.01177-2015
9. Alves JL Jr, Oleas FG, Souza R. Pulmonary Hypertension: Definition, Classification, and Diagnosis. Semin Respir Crit Care Med. 2017;38(5):561-570. https://doi.org/10.1055/s-0037-1606577
10. Costa EL, Jardim C, Bogossian HB, Amato MB, Carvalho CR, Souza R. Acute vasodilator test in pulmonary arterial hypertension: evaluation of two response criteria. Vascul Pharmacol. 2005;43(3):143-147. https://doi.org/10.1016/j.vph.2005.05.004
11. Hoeper MM, Pittrow D, Opitz C, Gibbs JSR, Rosenkranz S, Grünig E, et al. Risk assessment in pulmonary arterial hypertension. Eur Respir J. 2018;51(3):1702606. https://doi.org/10.1183/13993003.02606-2017
12. Hemnes AR, Zhao M, West J, Newman JH, Rich S, Archer SL, et al. Critical Genomic Networks and Vasoreactive Variants in Idiopathic Pulmonary Arterial Hypertension. Am J Respir Crit Care Med. 2016;194(4):464-475. https://doi.org/10.1164/rccm.201508-1678OC
13. Hoeper MM, Pausch C, Olsson KM, Huscher D, Pittrow D, Grünig E, et al. COMPERA 2.0: a refined four-stratum risk assessment model for pulmonary arterial hypertension. Eur Respir J. 2022;60(1):2102311. https://doi.org/10.1183/13993003.02311-2021
14. Hoeper MM, Kramer T, Pan Z, Eichstaedt CA, Spiesshoefer J, Benjamin N, et al. Mortality in pulmonary arterial hypertension: prediction by the 2015 European pulmonary hypertension guidelines risk stratification model. Eur Respir J. 2017;50(2):1700740. https://doi.org/10.1183/13993003.00740-2017
15. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53(1):1801913. https://doi.org/10.1183/13993003.01913-2018