Calcium Channel Blocker Therapy: When a Drug Works, it Works. When it Doesn't, it Doesn't

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Calcium channel blocker (CCB) therapy continues to be an element of modern pulmonary arterial hypertension treatment guidelines. However, the true number of patients that can be effectively treated with CCBs is very small. It is important to remember that those who truly retain a long-term benefit are those that tend to have a dramatic initial response to vasodilators and will attain normal or near normal hemodynamics and functional class after starting CCBs. Should a patient do so, they may well enjoy dramatic long-term survival on this regimen. In this article we discuss details and experience with calcium channel antagonists.

Calcium channel blocker (CCB) therapy continues to be an element of modern pulmonary arterial hypertension (PAH) treatment guidelines, although none of these agents have received Food and Drug Administration (FDA) approval for therapy of patients with PAH. Initial experience with these agents emerged almost 40 years ago, during a period when dominant theories of PAH pathogenesis favored an imbalance between vasodilators and vasoconstrictors in the pulmonary arteries as postulated by Wood as early as 1958.[1] Thus, historically it was not surprising then to focus on therapeutic agents that reversed pathogenic vasoconstriction. Short-acting assessments of the vasoreactivity of the pulmonary bed were initially performed and disappointingly revealed significant reversal of vasoconstriction in only a small minority of patients.[2-4] Nonetheless, these patient groups were evaluated further and subsequently found in some cases to display the same significant reversal of pulmonary pressures when calcium CCBs were administered.[5,6] The doses required for this response, however, were often substantially higher than traditionally used to treat systemic hypertension according to their labeled indication.[6] Some fraction of these patients, when placed on these agents long term, retained reversal of elevated pulmonary pressures, with dramatic long-term survival of >90% at 10 years (Figure 1). Remarkably, these patients appeared to achieve normalization or near normalization of pulmonary pressures and functional class.[7] Patients that did not respond in this manner did not display benefit when given these agents.[7,8] Thus, CCB and short-acting vasodilator testing became inextricably linked and incorporated into diagnostic and treatment recommendations for patients with PAH.

The formal recommendations for the sequential application of acute vasodilator testing followed by a trial of calcium channel antagonists have been published—albeit >20 years ago—and articulate 3 critical steps:

1. Evaluation of short-acting vasoreactivity
2. Acute recapitulation of vasodilator response and dose finding of calcium channel antagonist or outpatient uptitration at frequent intervals, with reassessment of clinical response
3. Long-term patient follow-up anticipating normalization or near normalization of pulmonary pressures, echocardiographic abnormalities, and functional class

It is worth noting that many of these data were generated before any therapeutic agents were approved for PAH, and anecdotally it seems that many current practitioners have little or no experience with this rare group of patients. For these reasons, a discussion of the details and experience with calcium channel antagonists seemed appropriate for inclusion in this edition of *Advances*.

SHORT-ACTING VASODILATOR EVALUATION

Although a comprehensive discussion of the critical elements and techniques of acute vasodilator testing is beyond the scope of this article, 2 key elements inherent in this process include agent

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selection and setting of criteria for thresholds of acute response. The former by consensus has involved consideration of inhaled nitric oxide (iNO), epoprostenol, or adenosine. However, some evidence exists which suggests that adenosine and iNO may not be interchangeable in the detection of acute pulmonary vasodilation.[9] Most current testing utilizes intravenous epoprostenol or iNO. The cost, method of administration, resources required, and side effects of these agents are different. Their protocols for administration have been published elsewhere.[10-12]

Threshold criteria for determination of acute vasodilator response in contrast to short-acting testing have evolved in at least 2 different iterations in guidelines. The initial suggestion for threshold of response was a >20% decrease in pulmonary artery pressure (PAP) with unchanged or increased cardiac index in the absence of systemic hypotension.[4] These criteria were modified in 2004.[13] The rationale for modification involved ongoing recognition that meaningful hemodynamic vasodilation and true response typically involved a dramatic decrease in pulmonary pressures. Since most idiopathic PAH (IPAH) patients present with mean PAP >50 mm Hg,[14] modest reductions in PAP that satisfied the 20% criteria did represent populations that were likely to benefit from subsequent administration of CCBs. Table 1 represents the data from selected acute vasodilator responses in the literature.[7] These responses are truly dramatic, and in our experience, represent typical hemodynamic patterns shown upon initial vasoreactivity testing in this unique group of patients.

An element not discussed above is the inclusion recommendation of vasodilator testing for all classes of PAH, although non-IPAH patients rarely, if ever, display short-acting vasodilator responsivity,[14,15] and if they do, they do not appear to benefit long term from CCB therapy.[16,17] This has led several practitioners to question the continued inclusion of a recommendation for inclusive testing for all PAH patients. Nonetheless, insurance approval for current PAH medications almost uniformly continues to require documentation of either failure of short-acting vasodilator trials or CCB trials in all groups of PAH patients.

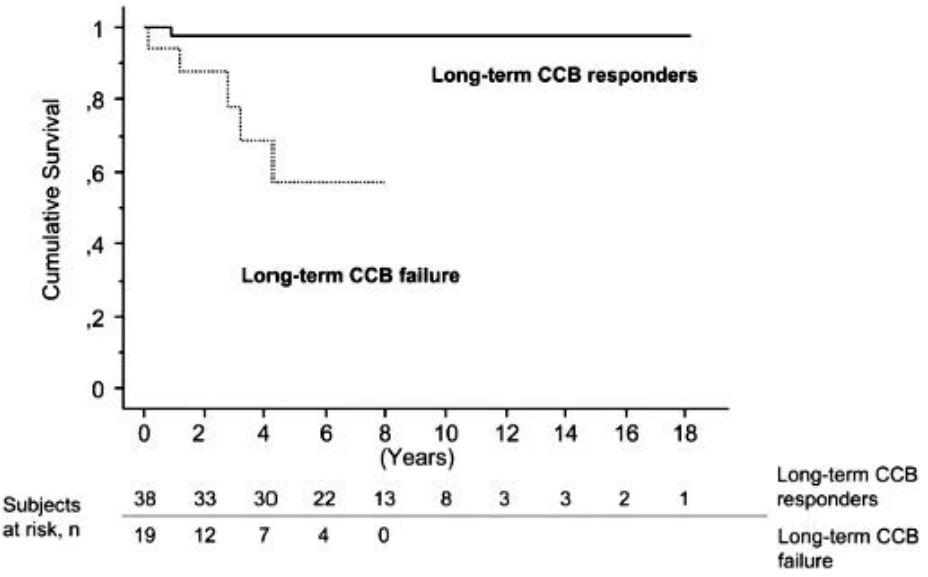

Figure 1: Survival of long-term calcium channel blocker responders.
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ACUTE RECAPITULATION OF THE VASODILATOR RESPONSE AND DOSE FINDING VS OUTPATIENT UPTITRATION

The next step in the classic description of response to calcium channel antagonists involves recapitulating the initial acute vasodilator response with home-going oral medications. Nifedipine and diltiazem (not verapamil) were typically used in the initial descriptions of this step based on heart rate < or >100 beats per minute.[6]

Two approaches have been described. The first: a direct attempt at recreation of the acute vasodilator response by CCBs. Briefly, patients demonstrating vasoreactivity in response to short-acting vasodilators were taken to an intensive care unit for continuous hemodynamic monitoring. Efficacy of CCB was assessed by continued hemodynamic monitoring while sequential doses of CCB were given at 15 to 30 minutes. Simultaneous continuous monitoring of systemic blood pressure and cardiac index is necessary, as these agents could negatively impact one or both.[6]

Acute CCB trials are halted either with successful reproduction of the short-acting vasodilator response (a positive response) or with limiting decreases in either systemic blood pressure or cardiac index. Importantly, absence of systemic hypotension and maintenance or improvement of cardiac index is important. These agents can lead to dangerous decrease in systemic blood pressure, which may be particularly devastating in a PAH patient, and CCB trials have been reported to be associated with infrequent mortality.[2,4] It is generally felt that patients with significant elements of right heart failure or depressed cardiac index should not undergo acute CCB trials for this reason.

A second approach consists of initial dosing with 10 mg of nifedipine or 60 mg of diltiazem TID with uptitration to 20 mg or 120 mg respectively if tolerated initially, with further dose increases as an outpatient according to tolerance.[8] It bears re-emphasis that both approaches are only used in patients who have met the criteria for acute vasoreactivity. Empiric use of CCB in PAH patients is strictly forbidden. Indeed, CCB-induced systemic hypotension or fluid retention may be detrimental or dangerous in these patients. Regardless of the strategy, final daily doses of either approach were at or above typical dosing for patients

receiving these drugs for labeled indications.

LONG-TERM PATIENT FOLLOW-UP

Short-term response to acute vasodilators and a positive initial response to a CCB trial does not guarantee a durable response. Patients need to be followed closely to ensure that their functional status, echocardiograms,[18] and hemodynamics continue to improve over the months up to a year. There may be a substantial number of patients that fail to improve or initially have some benefit, which wanes in ensuing months. It is recommended that these patients be followed initially at 1- to 3-month intervals with assessments of exercise tolerance, physical examination, and echocardiography. True CCB responders will continue improvement toward normal. Failure to continue improvement or any deterioration should signal the need for alternate therapies. It is estimated that almost half the patients originally responsive to CCB therapy will fail in the first year.[8] In this study, the patients who had the most robust response had a lower greater absolute drop during acute vasodilator testing and a lower mean pulmonary pressure compared to those who failed CCB therapy. As previously noted, however, continued improvement with ultimate normalization or near normalization does occur and is accompanied by a dramatic long-term survival eclipsing any other typical groups of patients receiving modern therapies.[19]

UNRAVELING THE BASIS OF CCB RESPONSIVENESS

A great deal of speculation regarding the mechanism of CCB sensitivity has occurred since the original recognition of this phenomenon. Theories have been advanced regarding aberrant smooth muscle contraction or alterations in calcium utilization, but heretofore have been unexplored or remain unsubstantiated. Certainly, understanding this uniquely favorable course in an otherwise fatal disease process may provide important insight, perhaps allowing other patients with PAH to benefit from cellular or genetic modifications or manipulations that could provide such a benefit.

Several recent studies have levered modern techniques of molecular characterization in the investigation of the CCB responder. Microarray analysis of polymerase chain reactions from peripheral lymphocytes identified unique expression profiles of vasoreactive IPAH patients, which could then be used in decision trees to identify vasoreactive patients in a validation cohort.[20] A pathway-based analysis of whole exome sequencing (WES) was employed by Hemnes et al in the analysis of vasoreactive variants of IPAH compared to nonresponsive IPAH patients.[21] Analysis demonstrated genetic variants representing cellular pathways such as cytoskeletal function and Wnt signaling. Vascular smooth muscle contraction–related genes were enriched in vasoreac-

Table 1. Baseline Values and Early and Late Effects of Calcium Channel Blockers on Mean Hemodynamic Variables in Patients Who Responded to Treatment

Patient No.	Base-Line Values				Early (24 hr) Effects				Late Effects				
	RA	PA	CI	PVRI	RA	PA	CI	PVRI	RA	PA	CI	PVRI	year
	mm Hg		liters/min/m²	units	mm Hg		liters/min/m²	units	mm Hg		liters/min/m²	units	
1	6	62	2.5	22.1	8	39	3.8	9.0	2	39	3.9	9.5	5
2	3	41	2.9	11.7	1	22	4.0	3.7	3	26	5.2	3.1	1
3	13	60	3.7	35.4	4	38	2.8	11.5	3	38	4.2	7.1	5
4	2	41	2.8	13.0	5	31	3.3	7.8	4	47	3.6	11.3	3
5	0	47	2.6	17.3	1	20	3.4	5.1	6	19	4.1	1.9	3
6	11	77	1.9	34.3	3	47	2.1	21.9	15	49	2.9	12.0	5
7	0	34	3.9	8.1	1	24	4.2	5.3	6	24	3.2	4.0	3
8	7	75	2.8	22.7	5	30	4.5	5.9	7	32	5.2	9.2	5
9	10	61	1.7	32.8	6	47	2.4	16.8	16	67	2.0	31.3	3
10	6	48	3.2	12.4	2	27	2.8	8.4	2	36	4.9	5.7	1
11	4	53	1.5	32.5	4	37	1.7	19.9	7	24	2.7	5.2	3
12	11	77	2.7	29.2	7	32	2.7	9.1	3	30	3.1	7.0	5
13	7	69	2.9	21.4	2	33	2.0	14.7	1	27	2.2	5.3	1
14	7	77	1.5	49.4	2	55	2.2	22.8	—	—	—	—	—
15	14	48	3.0	11.8	16	39	3.3	6.8	—	—	—	—	—
16	7	70	2.7	22.2	4	44	4.3	8.9	—	—	—	—	—
17	5	51	1.7	25.6	14	38	1.7	19.7	—	—	—	—	—
Mean ±SD†	6.6±4.2	58.3±14.2	2.6±0.7	23.6±11.0	5.0±4.3	35.5±9.5	3.0±0.9	11.6±6.4	—	—	—	—	—
Mean ±SD‡	6.0±4.1	56.9±14.1	2.6±0.7	26.6±10.9	3.8±2.3	33.2±8.4	3.0±0.9	11.2±6.7	5.8±4.7	35.2±13.1	3.6±1.1	8.7±7.5	—

*RA denotes right atrial pressure, PA pulmonary-artery pressure, CI cardiac index, PVRI pulmonary-vascular-resistance index, and year year of most recent catheterization study.
†Mean data on all patients. ‡Mean long-term data on 13 patients.

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tive IPAH, suggesting a unique genetic predisposition in these patients. In that study, Wnt signaling was also shown to be increased in general in lung fibroblasts from PAH patients.

In another study utilizing proteomics, several groups of patients with and without PAH were compared, including CCB responders.[22] Metabolites that were shown to discriminate PAH from normal patients were evaluated in CCB responders. These metabolites most closely resembled that of normal patients consistent with their essentially normal functional status and hemodynamics. Distinguishing expressions of the vasoreactive phenotype were not evident from this analysis.

The implications favor the theory that the vasoreactive patient may have a substantially different genetic basis, where specific gene expression may be utilized to identify these patients prospectively. Pathway analysis of WES suggests future areas for investigation both to better understand pathogenesis of PAH, vasoreactive phenotypes, and potential therapeutic targets.

CCB THERAPY IN OTHER TYPES OF PULMONARY HYERTENSION

WHO Group 2 Patients

Arguably the most common cause of elevated pulmonary pressures is left-sided heart disease. Elevated pulmonary pressure in both systolic and diastolic heart failure is common[23,24] and remains a poor prognostic sign.[25,26] A discussion of pulmonary hypertension (PH) in heart failure is beyond the scope of this article, but has been concisely reviewed.[27] Despite considerable attention to PH in heart failure over decades, including assessment of vasodilators in the treatment of heart failure, current guidelines for the management of heart failure have no recommendations for the use of CCB in the specific treatment of PH related to heart failure.[28,29] Treatment strategies specifically targeting pulmonary pressures have proven almost exclusively unrewarding in large controlled trials.[29] This is likely due to the primary etiology of pulmonary vascular changes in heart failure—high left-sided filling pressures. Increased interest in the evaluation of PH in heart failure with preserved ejection fraction due to frequent association with PH in these groups has revealed infrequent vasoreactivity with acute testing and a potential to increase pulmonary capillary wedge pressure.[30,31] Furthermore, vasoreactivity in heart failure with preserved ejection fraction, in contrast to PAH, does not appear to confer an outcome advantage.[32] While CCBs may be employed for control of systemic hypertension or heart rate control, there is currently no role in the use of CCB for specific treatment of PH associated with heart failure.

WHO Group 3 Patients

PH in chronic obstructive pulmonary disease (COPD) patients is generally mild and occurs primarily in those with severe hypoxemia. Severe PH (mean PAP ≥40 mm Hg) is seen in a very small percentage (1%) of patients with COPD and may represent a different entity.[33] The role of acute vasoreactivity testing has not been studied in COPD; however, the effect of CCBs in COPD patients with precapillary PH has been described.[34] Short-term administration of felodipine or amlodipine led to 20% and 17% reductions in PAP as estimated by Doppler ultrasound. The mean pulmonary systolic estimated pressures pretreatment, however, was mild (approximately 40 mm Hg). Another study of long-term administration of amlodipine in patients with COPD and mild PH, however, did not change pulmonary pressures.[35] CCB treatment or vasoreactivity in patients with severe PH and COPD has not been reported to our knowledge. A universal concern for any vasodilator in COPD is the potential deleterious effect on gas exchange. In aggregate, there is no evidence of substantial vasoreactivity or utility of CCB therapy in the treatment of PH associated with COPD.

WHO Group 4 Patients

The pathogenesis of chronic thromboembolic pulmonary hypertension (CTEPH) includes failed resolution of clot leading to large vessel occlusion and small vessel remodeling. The small vessel component of CTEPH is indistinguishable from vascular lesions seen in PAH.[36] Evaluation of vasoreactivity in CTEPH, however, has mixed results. Halliday et al found no significant response (change >10 mm Hg) to iNO administration among patients with CTEPH.[17] Conversely, Skoro-Sajer et al[37] demonstrated some degree of vasoreactivity in 80 of 103 (77.7%) patients with CTEPH in response to iNO. However, only 8 of these patients fulfilled typical PAH vasodilator response of >10 mm Hg and resting mean PAP <40 mm Hg. These 8 patients underwent pulmonary endarterectomy, and thus no information is available on any potential impact of CCB in this population. Most recently, acute vasoreactivity evaluation of 175 CTEPH patients was reported.[38] Twenty-five of 175 patients demonstrated vasoreactivity as is conventionally defined (>10 mm Hg decrease and final PAP <40 mm Hg). Fourteen of these 25 patients underwent nonoperative treatment with CCB and "conventional therapy" defined as digoxin, diuretics, and anticoagulation. Their overall survival was not statistically different from patients receiving conventional therapy only. Overall, it does not appear that vasoreactivity testing to guide CCB therapy has a role in the treatment of CTEPH.

WHO Group 5 Patients

In general, WHO Group 5 PH patients represent a very diverse collection of (often rare) causes of PH. For this reason, little is published about vasoreactivity or CCB treatment of these patients. Sarcoid is likely the most common of these, and treatment of patients with sarcoid-associated PH has been reported. Few include acute vasodilator testing results. Preston et al report the evaluation and treatment of 8 patients with sarcoid-associated PH using intravenous epoprostenol, iNO, or CCB. All patients had advanced sarcoidosis (chest x-ray stages 3-4) and severe PH (average mean PAP 55 mm Hg). The acute response in mean PAP was greater for those receiving iNO (decrease of 18±4%) compared to patients that received epoprostenol at doses of 2-8 ng/kg/min (6±2% decrease). Note that neither of these responses would satisfy current vasodilator responsiveness

guidelines of >10% and final mean PAP <40 mm Hg. No patients had an acute response with nifedipine.[39]

CONCLUSION

Although included in all current guidelines, the true number of patients that can be effectively treated with CCBs is very small and essentially limited to IPAH patients, genetically associated PAH, or anorexigen-induced PAH. There is no role for empiric CCB treatment of PAH patients, and indeed hypotension or fluid retention may be detrimental or dangerous in these patients. It is important to remember that those who truly retain a long-term benefit are those that tend to have a dramatic initial response to vasodilators and will attain normal or near normal hemodynamics and functional class after starting CCBs. Should a patient do so, they may well enjoy dramatic long-term survival on this regimen.

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