

# Acute Vasodilator Testing in PAH

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Vasoconstriction of pulmonary arteries is recognized as an important component of the pathogenesis of pulmonary arterial hypertension (PAH). Pure vasodilators alleviate vasoconstriction with little effect on the fibrotic and proliferative changes that frequently predominate over vasoconstriction in PAH. Uncontrolled studies have suggested that long-term administration of calcium-channel blockers (CCBs) prolongs survival in the rare subset of responsive patients (representing around 10% of patients referred to pulmonary vascular centers), compared with unresponsive patients. Therefore, the question of the overall efficacy of administering CCBs is still of concern, as well as the way of safely identifying the patients who may benefit from long-term oral treatment. Unfortunately, any clinical or hemodynamic parameter can predict acute and chronic responses to CCBs in patients with PAH. It is generally accepted that patients who may benefit from long-term use of CCBs can be identified by an acute vasodilator challenge performed during right heart catheterization in specialized pulmonary vascular units.

The magnitude of acute vasodilator response that predicts a favorable outcome with long-term CCB therapy remains poorly defined. Until recently, a reduction of both mean artery pulmonary pressure (mPAP) and of pulmonary vascular resistance (PVR) by at least 20% was used as the criterion for the initiation of oral CCB therapy. A drop in mPAP by more than 10 mm Hg without decrease in cardiac output could be the minimum acceptable response. A decrease in PVR of 50% relative to baseline value and an mPAP lower than 30 mm Hg could indicate better clinical outcome. However, these definitions do not discriminate between patients with a sustained benefit from CCBs (defined as being in NYHA functional class I or II with near-normal hemodynamics after at least one year follow-up) and those whose condition will fail to improve. In our experience, only 7% of patients referred to a specialized pulmonary vascular center with idiopathic PAH will have a sustained benefit from treatment with CCBs. During acute vasodilator challenge, these rare patients markedly improve their pulmonary hemodynamics, achieving an mPAP less than 40 mm Hg, and



associated with a normal or high cardiac output. We therefore consider that a positive response to acute vasodilator challenge is defined by a substantial reduction in mPAP (decrease exceeding 10 mm Hg to reach an mPAP lower than 40 mm Hg) with a normal or high cardiac output. The occurrence of severe life-threatening hemodynamic compromise during acute vasodilator challenge with CCBs is an obvious risk, even when conventional doses of CCBs are used. Therefore, there is a need for a safe, potent, and short-acting vasodilator having limited side effects during acute testing to accurately identify patients who may benefit from long-term CCB therapy. In the therapeutic approach of patients with PAH, numerous vasodilator agents have been used on a short-term basis to evaluate the capacity of the pulmonary vascular bed to vasodilate. Among them, prostacyclin, adenosine, and nitric oxide are the most widely used drugs. Recent data suggest that inhaled iloprost may be more effective than nitric oxide to decrease PVR. However, no information is available regarding acute response to iloprost as a predicting factor to long-term efficacy of CCB therapy.

With emerging potent oral and inhaled drugs combining vasodilatory and antiproliferative properties, the issue of invasive testing for pulmonary vasoreactivity in selecting treatment may lose its importance. It should be easy to prescribe oral therapies such as an endothelin receptor antagonist (bosentan), a prostacyclin analogue (beraprost), or a phosphodiesterase inhibitor (sildenafil) to all PAH patients whatever their functional class (except for class IV) and acute pulmonary vasoreactivity. Although it is reasonable to think that patients who respond to intravenous prostacyclin, adenosine, or inhaled nitric oxide are able to respond to such oral therapies, no study has evaluated the acute and chronic response to these drugs in vasoreactive patients. In addition, the cost of these therapies could be a limitation to their prescription in some PAH patients.

In conclusion, the drugs of choice for testing vasoreactivity are short-acting agents, intravenous prostacyclin, adenosine, or inhaled nitric oxide. Long-term treatment with oral CCBs will be considered only in responders to one of these three drugs. ■