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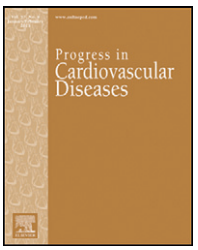

Role of Vasodilator Testing in Pulmonary Hypertension

Abhishek Sharma[a,*], *Chukwudi Obiagwu*[b], *Kenechukwu Mezue*[c], *Aakash Garg*[d], *Debabrata Mukherjee*[e], *Jennifer Haythe*[f], *Vijay Shetty*[b], *Andrew J. Einstein*[g]

[a]*Division of Cardiology, Department of Medicine, State University of New York Downstate Medical Center, NY, USA*
[b]*Department of Medicine, Maimonides Medical Center, NY, USA*
[c]*Department of Medicine, Einstein Medical Center, PA, USA*
[d]*Department of Medicine, Saint Peter's University Hospital, NJ, USA*
[e]*Division of Cardiology, Department of Medicine, Texas Tech University, El Paso, TX, USA*
[f]*Division of Cardiology, Department of Medicine, Columbia University Medical Center, New York, NY, USA*
[g]*Division of Cardiology, Department of Medicine and Department of Radiology, Columbia University Medical Center, New York, NY, USA*

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ABSTRACT

Pulmonary hypertension is clinically defined by a mean pulmonary artery (PA) pressure of 25 mm Hg or more at rest, as measured by right heart catheterization. To identify patients who are likely to have a beneficial response to calcium channel blockers (CCBs) and therefore a better prognosis, acute vasodilator testing should be performed in patients in certain subsets of pulmonary arterial hypertension (PAH). A near normalization of pulmonary hemodynamics is needed before patients can be considered for therapy with CCBs. Intravenous adenosine, intravenous epoprostenol, inhaled nitric oxide, or inhaled iloprost are the standard agents used for vasoreactivity testing in patients with idiopathic PAH. In this review we describe the various aspects of vasodilator testing including the rationale, pathophysiology and agents used in the procedure.

Pulmonary hypertension (PH) is clinically defined by a mean pulmonary artery (PA) pressure (PAP) of 25 mm Hg or more at rest, as measured by right heart catheterization (RHC).[1] PH is characterized by a progressive increase in pulmonary vascular resistance (PVR) causing right ventricular (RV) failure (RVF) and even death.[1] With advances in treatment and patient support strategies, the median survival time for patients with PH now exceeds 7 years.[2] Bearing in mind the diverse processes involved in the pathology of the pulmonary vasculature, the 5th World Symposium on PH in Nice, France (2013) recommended classifying PH into five groups: (1) Pulmonary arterial hypertension (PAH); (2) PH due to left-sided heart disease (LSHD); (3) PH due to chronic lung disease and/or chronic hypoxia; (4) chronic thromboembolic PH; and (5) PH with unclear or multifactorial mechanisms (see Table 1).[3]

PAH refers to a subgroup of PH (Group 1 PH), defined hemodynamically as PA wedge pressure (PAWP) less than or equal to 15 mm Hg and PVR > 3 wood units.[4] PAH is made of several subsets, one of which is idiopathic PAH (IPAH). To identify patients who are likely to have a beneficial response to calcium channel blockers (CCBs) and therefore a better prognosis, acute vasodilator testing should be performed in patients in certain subsets of PAH, including IPAH.[5] A near

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* Address reprint requests to Abhishek Sharma, MD, 125 96th Street, Apt 5B, Brooklyn, NY, 11209.
E-mail address: abhisheksharma4mamc@gmail.com (A. Sharma).

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Abbreviations and Acronyms

CCB = calcium channel blockers

CO = cardiac output

HF = heart failure

IPAH = idiopathic pulmonary arterial hypertension

i NO = inhaled nitric oxide

LSHD = left sided heart disease

LV = left ventricular

MRI = magnetic resonance imaging

NO = nitric oxide

PA = pulmonary artery

PAH = pulmonary arterial hypertension

PAP = pulmonary artery pressure

PAWP = pulmonary artery wedge pressure

PGI2 = prostacyclin

PH = pulmonary hypertension

PVR = pulmonary vascular resistance

PVH = pulmonary venous hypertension

RHC = right heart catheterization

RV = right ventricle

RVF = right ventricle failure

normalization of pulmonary hemodynamics is needed before patients can be considered for therapy with CCBs. Intravenous adenosine, intravenous epoprostenol, inhaled nitric oxide (iNO), or inhaled iloprost are the standard agents used for vasoreactivity testing in patients with idiopathic PAH.[1,5,6] This review will explore the various aspects of vasodilator testing including the rationale, pathophysiology and agents used in the procedure.

Vasodilator testing in pulmonary hypertension

Our understanding of the pathophysiology of PAH has drastically shifted from simple PA vasoconstriction to the increasingly recognized role of endothelial dysfunction. PAH involves small arteries, and varying degrees of vascular proliferation including intimal hyperplasia, medial hypertrophy and inflammation, are seen.[1,6,7]

While transthoracic echocardiography remains the most important initial screening tool for assessing PH,[8] RHC is the gold standard for diagnosis of PH, and is mandatory whenever PAH is suspected.[6] The risks of vasodilator testing are similar to the risks of RHC as testing is done during the latter procedure and this procedure has a low morbidity and mortality of 1.1% and 0.055% respectively.[9] The European guidelines recommend that testing should be done at the time of RHC in an experienced referral testing center which attends to at least fifty patients and at least two new patients a month.[1]

Indications for vasodilatory testing

The American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) published an expert consensus document in 2009 that recommended that all patients with IPAH (a subset of PAH) undergo vasodilator testing.[6] This position is also supported by the European guidelines, which also recommends testing in patients with heritable PAH and drug induced PAH (other subsets of PAH) in addition to IPAH patients.[1] Most of the data supporting testing recommendations comes from studies on patients with IPAH (Table 2).[6]

Both guidelines do not recommend vasodilator testing in other groups of PH (i.e., Groups 2, 3, 4 and 5).[1,6,10] This is particularly important in patients with elevated left heart filling pressures/PAWP (Group 2) where CCBs have a deleterious effect. Montani et al. provided evidence where 663 consecutive non-idiopathic PAH (non-IPAH Group 1) patients were studied for vasodilator testing and CCB response between 1984 and 2003.[11] It has been shown that in anorexigen-induced PAH, an acute response predicted a sustained response to CCBs.[11] However, an acute response is not predictive of long term response in patients with PAH secondary to majority of connective tissue disease (CTD), pulmonary veno-occlusive disease, pulmonary capillary hemangiomatosis (PCH) and congenital heart disease, and initiation of CCB therapy may lead to clinical deterioration.[11]

Further indications for testing include (a) complicated congenital heart disease with severe pulmonary arterial hypertension (PAH) to determine the next best step in management, (b) prior to Fontan (atriopulmonary connection) surgery or one of its modifications, with elevated PVR, (c) in heart transplantation candidates to assess the need for concomitant lung transplantation.[10,12]

The rationale of cost

An important consideration in the management of PH is cost. Drugs used for PH are very expensive, for example, the lowest dose of oral sildenafil (20 mg thrice daily) costs approximately $12,000 annually.[13] CCBs are an inexpensive therapeutic strategy that can be effective in patients found to be responsive to vasodilator testing. IPAH patients with overt RVF or hemodynamic instability should not undergo acute vasodilator testing.[6] However, empiric treatment with CCBs in PAH can cause systemic hypotension, worsening RVF and death and should never be done.[14,15]

Interpretation of vasodilator test findings

A positive vasodilator test is defined as a decrease in PAP of at least 10 mm Hg to a mean PAP of less than or equal to 40 mm Hg, and a preserved or increased cardiac output (CO). A positive test is not synonymous with benefit from CCB therapy, but is required before starting treatment.[1,6] Less than 10% of IPAH patients have an acute response and only half of these patients go on to have a long-term response to CCBs.[1,16] These recommendations were retrospectively based on data from the Sitbon et al. study which showed that the sensitivity, specificity, positive and negative predictive values of pulmonary vasodilator testing using the above criteria, are 69%, 87%, 78% and 81%, respectively.[16]