Pulmonary Vasodilators and Anesthesia Considerations

Jeremy B. Green, MD[a], Brendon M. Hart, MD[b], Elyse M. Cornett, PhD[b], Alan D. Kaye, MD, PhD, DABA, DABPM, DABIPP[c,*], Ali Salehi, MD[d], Charles J. Fox, MD[b]

KEYWORDS

• Pulmonary hypertension • Anesthesia • Inhaled nitric oxide • Endothelin antagonists • Calcium channel blockers • Prostacyclin

KEY POINTS

- The normal adult pulmonary circulation is a low-pressure, low-resistance circuit that accommodates the whole output of the right ventricle to the gas exchanging surface at less than one-fifth of systemic pressure.
- Vasodilators normally have little if any effect on pulmonary vascular pressures, indicating that there is little or no resting tone under healthy conditions.
- Factors including the autonomic nervous system, humoral agents, and atmospheric gases, have the ability to alter pulmonary vascular resistance by inducing contraction or relaxation of vascular smooth muscle in resistance vessels elements in the lung.
- There are three major underlying components involved in the pathogenesis of pulmonary arterial hypertension: endothelial dysfunction leading to vasoconstriction, vascular remodeling with in situ thrombosis, and the formation of plexiform lesions.
- Numerous pulmonary vasodilators are currently being evaluated and being used in the treatment of pulmonary hypertension, including calcium channel blockers, inhaled nitric oxide, prostacyclin derivatives, endothelin antagonists, phosphodiesterase (PDE)-5 inhibitors, and diuretics.

INTRODUCTION

Pulmonary hypertension (PH) is a complex disease process of the pulmonary vasculature system characterized by elevated pulmonary arterial pressures (PAP). Despite being a rare disease, patients with PH represent a distinct challenge in the operating

[a] Department of Anesthesiology, Louisiana State University Health Science Center-New Orleans, New Orleans, LA, USA; [b] Department of Anesthesiology, Louisiana State University Health Science Center-Shreveport, Shreveport, LA, USA; [c] Department of Anesthesiology, Louisiana State University Health Science Center-New Orleans, 1542 Tulane Avenue, New Orleans, LA 70112, USA; [d] Department of Anesthesiology, Ronald Regan UCLA Medical Center, Los Angeles, CA, USA
* Corresponding author.
E-mail address: alankaye44@hotmail.com

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room given their increased risks for morbidity and mortality, even in the setting of noncardiac surgeries. Studies suggest that the postoperative mortality rate for patients with PH ranges from 1% to 18%,[1] whereas perioperative morbidity rates may be 42% and include complications, such as respiratory failure, dysrhythmias, congestive heart failure, renal insufficiency, hemodynamic instability, hepatic dysfunction, myocardial infarction, and even stroke.[2]

Over the past two decades, the classification system for PH has undergone several changes, with the most recent update coming in 2013 following the 5th World Symposium on Pulmonary Hypertension. Previously divided into primary pulmonary hypertension (no identifiable cause) and secondary pulmonary hypertension (identifiable cause), it is now divided into five different groups based on several specific etiologies (**Box 1**):

- Group 1: Pulmonary arterial hypertension
- Group 2: PH caused by left heart disease
- Group 3: PH caused by chronic lung disease and/or hypoxemia
- Group 4: Chronic thromboembolic PH
- Group 5: PH caused by unclear multifactorial mechanisms

PH is defined by a mean PAP greater than or equal to 25 mm Hg at rest via right heart catheterization, whereas the category 1 (pulmonary arterial hypertension [PAH]) also requires a pulmonary artery wedge pressure equal to less than 15 and a pulmonary vascular resistance (PVR) greater than 3 woods units.

Related to a multitude of causes, and the insidious onset of PH, prevalence data in the general population are unclear. One individual study used national registries to examine mortality rates for patients with all types of PH and found that African Americans were most affected (7.3 per 100,000), followed by females (5.5 per 100,000), males (5.4 per 100,000), and white persons (5.3 per 100,000).[3]

Further studies have focused on data for PAH, which includes idiopathic and heritable causes of PH. Research using national registries from the United Kingdom and Ireland showed an incidence of 1.1 cases per million each year with and overall prevalence of 6.6 cases per million.[4] Similar studies from France showed an incidence and prevalence of 2.4 cases per million annually and 15 cases per million, respectively.[5]

Traditionally, PAH was thought to be a disease of middle-aged women. More recent registries, however, have shown an increase in the mean age at diagnosis up from 36 $\pm$ 15 years (1981[6]) to between 50 $\pm$ 14 and 65 $\pm$ 15 years[7] and a female-to-male ratio of 1.2:1 among the elderly.[8]

Although there is no cure for PAH, multiple meta-analyses have shown decreases in morbidity and mortality thanks to the development of prostacyclins, endothelin antagonists, and phosphodiesterase (PDE)-5 inhibitors.[9,10] Still, 1-year mortality rate remains high at 15%.[11]

STRUCTURE OF PULMONARY VESSELS AND THE ROLE OF ENDOTHELIUM AND NEURAL MECHANISMS

Pulmonary arteries, in contrast to systemic arteries, have a much thinner smooth muscle layer under normal physiologic states. Small pulmonary arteries of several hundred micrometers internal diameter are the major site of vascular resistance and are the site of hypoxic pulmonary vasoconstriction.[12] The pulmonary capillary bed is the major site of action and metabolism of several vasoactive agents. Pulmonary veins are similar in structure to pulmonary arteries but have less smooth muscle