Intraoperative Management of Patients with Pulmonary Hypertension

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Patients with pulmonary hypertension are some of the most challenging for an anesthesiologist to manage. Pulmonary hypertension in patients undergoing surgical procedures is associated with high morbidity and mortality due to right ventricular failure, arrhythmias and ischemia leading to hemodynamic instability, and intra- and postoperative hypoxia. Considering the challenges that these patients pose in the perioperative period, it is critical for anesthesiologists, surgeons, and other physicians who care for these patients to be well versed in managing pulmonary hypertension. The purpose of this article is to review the anesthetic considerations that pertain to patients with pulmonary hypertension in the perioperative period, with particular emphasis on the choice of anesthesia, the relative risks of moderate sedation and general anesthesia, and the most recent intraoperative monitoring recommendations.

Until relatively recently, most patients with idiopathic pulmonary arterial hypertension (IPAH) were not expected to survive more than a few years beyond the initial diagnosis. Pulmonary hypertension was a difficult condition to manage, and a relative contraindication to anesthesia. However, with the advent of innovative treatments, the functional status and life expectancy of patients with this condition has increased significantly. Thus, today, anesthesiologists are more likely to encounter patients with pulmonary hypertension presenting for elective surgical procedures.

The anesthetic management of patients with pulmonary hypertension requires a concerted approach guided by the etiology of the disease and the nature of the surgical procedure. Understanding the cause, type, and severity of pulmonary hypertension allows the clinician to formulate a management plan that balances the risks and benefits of the various anesthetic and surgical alternatives.

DEFINITION AND CLASSIFICATION OF PULMONARY HYPERTENSION

Properly defining pulmonary hypertension requires invasive measurement of the pulmonary artery pressures via right heart catheterization. According to the 4th World Symposium, pulmonary hypertension is defined as "a mean pulmonary artery pressure (mPAP) greater than 25 mm Hg at rest, based on a review demonstrating that the normal mPAP is 14.0±3.3 mm Hg."[1]

The disease of pulmonary hypertension arises from several etiologies; the elevations in pulmonary artery pressure may result from increased pulmonary artery resistance, increased pulmonary venous pressures, increased blood flow, or a combination of these factors.[2] The evolution of pulmonary hypertension can be insidious. Many patients present with vague complaints such as fatigue and shortness of breath. Unless there is a high index of suspicion, selecting the appropriate workup to identify the disease can present a diagnostic challenge.

The World Health Organization (WHO) classifies pulmonary hypertension into 5 groups on the basis of the mechanisms causing the disease. These are:

1. Pulmonary arterial hypertension (PAH)
2. Pulmonary hypertension owing to left heart disease
3. Pulmonary hypertension owing to lung diseases and/or hypoxia
4. Chronic thromboembolic pulmonary hypertension
5. Pulmonary hypertension related to disorders affecting the pulmonary vasculature with unclear multifactorial mechanisms

These categories in turn encompass multiple etiologies, such as heritable factors, connective tissues diseases, valvular heart disease, hypoxia, and other yet to be elucidated mechanisms. This classification reveals the extraordinarily varied clinical situations that can lead to this condition.[3] However, the anesthetic management of pulmonary hypertension is so dynamic in nature that the underlying WHO classification, while important for the patient's overall management, does not necessarily dictate the choice of anesthetic technique or monitoring. Rather, these choices are constrained by the overall condition of the patient and the severity of the disease, coupled with the nature of the surgical procedure.

PREOPERATIVE EVALUATION OF PATIENTS WITH PULMONARY HYPERTENSION

The signs of pulmonary hypertension (Table 1) include dyspnea, fatigue, angina, and syncope. Syncope is an ominous sign, associated with a poor prognosis.[2] Echocardiography can be used to estimate pulmonary artery pressures, right and left ventricular size and function, valvular abnormalities, and

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Table 1: Clinical Signs of Advanced Pulmonary Hypertension

Dyspnea at rest
Low cardiac output with metabolic acidosis
Hypoxemia
Third and fourth heart sound of right ventricular origin
Large "a" wave in jugular pulse
Prominent "v" waves in jugular pulse with holosystolic murmur, indicating tricuspid regurgitation
Diastolic murmur of pulmonary regurgitation
Right-heart failure (hepatomegaly, peripheral edema, and ascites)
Syncope

Adapted from Blaise G, Langleben D, Hubert B. Pulmonary arterial hypertension: pathophysiology and anesthetic approach. *Anesthesiology*. 2003;99(6):1415-1432; and Subramaniam K, Yared JP. Management of pulmonary hypertension in the operating room. *Semin Cardiothorac Vasc Anesth*. 2007;11(2):119-136.

intracardiac shunts. While right heart catheterization is necessary to confirm the diagnosis of PAH, left heart catheterization can be necessary to measure the left ventricular end diastolic pressure due to difficulty in obtaining reliable and accurate pulmonary artery wedge pressure. It is crucial for treatment planning to differentiate left-sided causes of pulmonary hypertension. Prior to anesthesia and surgery, all potentially underlying causes of pulmonary hypertension should be identified and optimized, including sleep apnea, chronic obstructive pulmonary disease, recurrent thromboembolism, fluid overload, cardiomyopathy, and valvular heart disease.

AN OVERVIEW OF THE MODES OF ANESTHESIA

The practice of anesthesia involves the pharmacological manipulation of patient physiology such that the noxious stimulation of surgery is not perceived by the patient. Two broad strategies exist, and may be applied in combination.

1. Suppression of neuronal transmission of pain within the peripheral nervous system or spinal cord (permitting anesthesia with full maintenance of consciousness and spontaneous ventilation)
2. Suppression of the central nervous system processing or conscious perception of pain (usually accompanied by diminished or abolished consciousness, and diminished or abolished spontaneous ventilation)

The first strategy comprises local anesthesia, regional anesthesia, and neuraxial anesthesia. For the simplest of surgical procedures, provided that anxiety is not an important factor, local anesthesia alone applied in a field block around the surgical site can be the safest approach. For surgery on the extremities within well-defined anatomical boundaries, it may be possible to place local anesthetic under ultrasound guidance around more proximal nerve trunks, providing regional anesthesia across that anatomical territory. Examples of this are the approaches to the brachial plexus, capable of providing surgical levels of anesthesia within various regions of the upper extremities. Neuraxial anesthesia includes both spinal and epidural anesthetic techniques, in which local anesthetics are placed within either the intrathecal space or the epidural space, capable of providing surgical anesthesia in the lower extremities and abdomen. Epidural anesthesia is slow in onset, about 15 to 20 minutes, but usually allows for hemodynamic stability to be maintained homeostatically. Conversely, the onset of spinal anesthesia is rapid, usually within 1 to 2 minutes, and the sudden associated peripheral vascular dilatation may lead to significant systemic hypotension requiring immediate intervention.

Within the second strategy, a continuum exists between light sedation and general anesthesia, the boundaries of which are often blurred. Conscious sedation may consist of intermittent administration of a short-acting benzodiazepine (such as midazolam) for anxiolysis, and a short-acting opioid (such as fentanyl) to provide increased tolerance of noxious stimuli; the patient may breathe spontaneously, and remain conscious, yet have diminished recollection of the procedure. Much deeper levels of sedation may be obtained by administering, for instance, an infusion of propofol while maintaining spontaneous ventilation. However, some degree of hypercapnea is likely to occur due to respiratory depression. Increasing dosages of these or similar agents will lead to a state of general anesthesia, in which the patient may respond only to the most noxious of stimuli and will be unable to maintain suitable ventilation without instrumentation of the airway. Supraglottic airway devices such as the laryngeal mask airway (LMA) are often appropriate for supporting the airway during moderate surgical procedures of the extremities, of less than 3 hours' duration. Placement of these devices is usually well tolerated shortly after the onset of unconsciousness and apnea, and adequate ventilation via the LMA may often be maintained with support once residual spontaneous respiratory activity returns. General anesthesia for major procedures will usually require endotracheal intubation, for which more profound levels of unconsciousness are achieved, accompanied by the induction of paralysis with neuromuscular blockers. Even in the unconscious, paralyzed patient, endotracheal intubation can be a highly stimulating procedure triggering significant sympathetic outflow, tachycardia, and hypertension. Paralyzed patients require controlled ventilation. Ultimately, for major surgeries performed on the heart, lungs, or major proximal blood vessels such as the aorta, cardiopulmonary bypass and even intentional hypothermic cardiac arrest may be indicated.

Within this second strategy, monitored anesthesia care (MAC) is sometimes used to denote the practice of moderate sedation with propofol. However, this nomenclature is incorrect. MAC is the process of continual reassessment of the patient's clinical state and dynamic titration of sedation. While performing MAC, an anesthesiologist may appropriately provide no sedation at all, or conversely may decide to transition to general anesthesia. Inherent in

MAC is the ability of the anesthesiologist to transition the patient between all appropriate levels of sedation and unconsciousness.

An anesthetic plan may include any of the previous modes of anesthesia as required by the surgical procedure, and as constrained by the comorbidities of the patient. For instance, a routine planned cesarean section is commonly performed solely with neuraxial anesthesia. Anesthesia for the replacement of the knee joint may be performed in many ways, such as combining a femoral nerve block (regional) and general anesthesia (either a supraglottic device or an endotracheal tube), or combining an epidural (neuraxial) with light to moderate sedation (MAC). The chosen anesthetic plan should not inappropriately exceed the requirements of the expected surgical procedure, but should also be sufficient to meet the needs of any reasonably foreseeable contingencies or complications that may arise from that procedure. This point is of particular concern in patients with pulmonary hypertension, whose stability under anesthesia can be very brittle. A less invasive anesthetic plan may be better tolerated, in terms of allowing the ultimate return of consciousness and adequate spontaneous ventilation. However, if the anesthetic limits of that less invasive plan are exceeded during the surgical procedure, the patient may rapidly enter a vicious cycle of decompensation. Consequently, an anesthesiologist might instead select a more invasive anesthetic plan with the intent to overcome the challenges of induction, intubation, and extubation in exchange for greater physiological control during the surgical procedure itself.

OPERATIVE, ANESTHETIC MANAGEMENT OF PULMONARY HYPERTENSION

It is well known that pulmonary hypertension is associated with increased morbidity and mortality in the perioperative period, particularly if the surgical procedure is major and performed under emergency circumstances. The practice of anesthesiology may involve the induction of transient but significant physiological derangements in order to provide the clinical conditions necessary for the surgeon to perform surgery and for the patient to be able to bear the pain and physical and emotional stress of the procedure. It is a testimony to the progress that has been achieved in this field that we are able to administer anesthesia with our current degree of safety and efficacy; in experienced hands, these derangements are generally well tolerated and ultimately reversible without prolonged adverse consequences. Nevertheless, when administering anesthesia, including induction, maintenance, and emergence, patients may be exposed to physiological insults such as: periods of apnea and hypoventilation, periods of hypoxemia, fluctuations in body temperature, episodes of systemic hypotension, bursts of intense sympathetic stimulation arising from the unconscious experience of somatic pain, rapid fluid shifts and changes in cardiac preload, and mechanical ventilation.[4,5] The nature of the pathophysiology of pulmonary hypertension is such that any of the abovementioned conditions may be poorly tolerated, leading to rapid and potentially irreversible clinical deterioration. The acuity with which this deterioration can occur makes the intraoperative management of patients with pulmonary hypertension challenging and demands particular attentiveness.[6] The goals of the anesthetic management of pulmonary hypertension therefore include maintaining an adequate balance between the preload and ventricular contractility, and maintaining the cardiac output by exercising control of the pulmonary vascular resistance (PVR) and right ventricular afterload. Hypoxia, hypercarbia, hypothermia, and inadequately controlled pain must be avoided.

Hemodynamic changes can occur rapidly in these patients, and therefore invasive arterial blood pressure monitoring is almost always indicated as part of the anesthetic plan. In patients with significant pulmonary hypertension, either pulmonary artery catheterization or transesophageal echocardiography can be very helpful in guiding anesthetic management, particularly in high-risk procedures. However, pulmonary artery rupture caused by a pulmonary artery catheter[7,8]—a disastrous complication—is more likely to occur in patients with pulmonary hypertension and the risks and benefits of this monitoring tool must be carefully weighed. The placement of a pulmonary artery catheter may also result in transient atrial and ventricular arrhythmias that can compromise right ventricular filling. While a small risk of esophageal injury attends to the use of transesophageal echocardiography, this technique provides valuable and direct information on ventricular filling and monitoring of wall motion abnormalities and allows the onset of ventricular ischemia to be detected with high sensitivity.

The assessment of perioperative risk depends on the type of surgery, the severity of pulmonary hypertension, and the functional status of the patient. The outcomes of major noncardiac surgeries showed mortality and short-term morbidity rates of 7% and 42% respectively.[9] However, for patients with portopulmonary hypertension undergoing liver transplantation presenting with mPAP of greater than 50 mm Hg, mortality was found to be 100%.[10] Thoracic surgery can lead to significant changes in intrathoracic pressures and oxygenation, which in turn can worsen pulmonary hypertension and precipitate right ventricular dysfunction. Laparoscopic operations require a carbon dioxide pneumoperitoneum, often resulting in hypercapnea and increased intra-abdominal pressures that are transmitted across the diaphragm to the thorax. These increases in intrathoracic pressures decrease preload and increase afterload that can trigger hemodynamic instability. Therefore, although laparoscopic procedures are commonly considered to be more tolerable than the comparable open approach, they may be less well tolerated by patients with pulmonary hypertension.

When planning operative management, it is critical to have elucidated the etiology of the disease and to have addressed the underlying causes. For patients receiving warfarin for PAH, it should be discontinued prior to the surgical procedure. The assessment for the need to bridge the patient with heparin must take into consideration the type and length of surgery as well as the patient's underlying comorbidities and

risks for thromboembolic events and risk of bleeding. For patients being treated for pulmonary hypertension, it is important to minimize any interruption and to continue the therapies before, during, and after the operation. This is especially critical for patients receiving continuous systemic prostanoid infusions (epoprostenol, treprostinil), for any rapid change in dose can potentially lead to hemodynamic worsening and decompensation from right ventricular dysfunction. Systemic hypotension should be managed with vasopressors rather than reducing or stopping the pulmonary vasodilator infusion. Patients receiving chronic inhaled treatments (iloprost, treprostinil)[11] should continue these treatments with the fewest possible interruptions. If patients are unable to perform the inhaled treatments, a short-term bridge with inhaled nitric oxide or a low-dose infusion of epoprostenol should be considered.[12] In the event that the patient does not have a pre-established treatment regimen, and if the surgery is not elective and cannot be delayed to establish one, the treatment of choice is inhaled nitric oxide and/or a phosphodiesterase inhibitor (with close monitoring of systemic blood pressure).[13]

Patients can be provided with light and carefully titrated preoperative sedation in order to induce anxiolysis, and to minimize discomfort from procedures such as arterial line placement. It is prudent to ensure that these patients also receive supplemental oxygen to avoid inadvertent oxygen desaturation. Depending on the nature of the surgery, it may be possible to perform either a peripheral nerve block or a neuraxial block to reduce or even eliminate the pain associated with the procedure. Where possible, the use of these regional anesthetic techniques can help to resolve the dilemma of providing too much parenteral pain relief with opioids, thus inducing respiratory depression and hypercapnea, or providing insufficient analgesia resulting in excessive sympathetic stimulation. The use of spinal anesthesia is considered to be relatively contraindicated due to the rapid fluctuations in systemic blood pressure, and hence afterload and preload changes that this technique will generally cause. However, a similar anesthetic effect may be achievable with epidural anesthesia or with an indwelling subarachnoid catheter, allowing the level of neuraxial anesthesia to be increased incrementally, minimizing the same risk of cardiovascular instability. Care must be taken that any anticoagulation regimen is properly held prior to neuraxial anesthesia in order to reduce the risk of an epidural hematoma.[14] Even when an anesthetic based solely on regional or neuraxial anesthesia is planned, placement of invasive hemodynamic monitors must be considered. Although pregnancy is contraindicated in patients with pulmonary hypertension with known association of high morbidity and morbidity, epidural anesthesia is the preferred modality for analgesia for labor and vaginal delivery, or for caesarian section.[15] Although the mortality and morbidity of pregnant patients with pulmonary hypertension, including those undergoing surgical delivery, seems to have decreased in recent times, it still remains relatively high, having been reported from 30% to 70% depending on the study.[2,16]

General anesthesia can be induced in the usual manner with either propofol or etomidate. Propofol may decrease systemic vascular resistance (SVR), venous return, and myocardial contractility. Induction with etomidate maintains hemodynamics without affecting the PVR, but may not be as effective in blunting the hypertensive response to laryngoscopy and intubation. Opioids (eg, fentanyl) can be administered to attenuate the sympathetic response to laryngoscopy and intubation, which can otherwise potentially increase mPAP to super-systemic levels[6] and trigger hemodynamic decompensation. The appropriate administration of these drugs depends on the clinical circumstances and the observed patient response. Muscular relaxation can be achieved with depolarizing (ie, succinylcholine) or nondepolarizing (eg, vecuronium, rocuronium) neuromuscular blocking agents. The use of nondepolarizing agents that can trigger histamine release (eg, atracurium, cisatracurium) should be avoided. The induction of general anesthesia and positive pressure ventilation can be associated with significant hemodynamic changes that may be poorly tolerated by patients with pulmonary hypertension. Even the physical positioning of the patient on the operating room bed must be carefully observed, as some patients are unable to tolerate the supine positioning. Implicit in the intubation of the trachea is the goal of ultimate extubation following surgery; similarly, extubation of the trachea is frequently associated with hemodynamic derangements caused by transient hypoxia, hypercapnea, coughing, and pain.

Subsequent to intubation, mechanical ventilation can be initiated. Careful attention must be paid to the ventilator settings to assure adequate oxygenation and a minute ventilation that avoids hypercarbia. Hypoxia and hypercarbia increase PVR, which can worsen pulmonary hypertension and may lead to decompensation. Capnography[17] is useful for titrating ventilator settings, and is mandated during general anesthesia. Hypercapnea worsens pulmonary hypertension, whereas profound hypocapnea leads to cerebral vasoconstriction and impairs myocardial contractility. Patients' end-tidal carbon dioxide levels should be maintained close to baseline. General anesthesia can be maintained with volatile anesthetic agents. These can produce vasodilation in the pulmonary vasculature, lowering mPAP. This effect was initially established with isoflurane,[18] which is the volatile agent most commonly used for cardiac surgery. The effect of sevoflurane, a more modern volatile agent, appears to be greater or at least similar.[19] However, volatile agents will also tend to lower cardiac index and central venous pressure. In contrast, the volatile agent desflurane appears to antagonize the pulmonary vasodilatory effects of other medications and should therefore be avoided.[20] The anesthesia breathing circuit also provides the means to continue administration of vasodilators such as inhaled nitric oxide, or inhaled prostacyclins. These agents are compatible with inhaled anesthetics.

The anesthetic management during the surgical case involves careful

Table 2: Suggested Treatment of Pulmonary Hypertension During Surgery

Inhaled nitric oxide	10-40 ppm
Milrinone (phosphodiesterase 3 inhibitor)	An infusion of 0.25-0.75 μg/kg/min (initial 50 μg/kg bolus optional, see text)
Inhaled epoprostenol (continuous)	10-50 ng/kg/min
Intravenous prostacyclin	4-10 ng/kg/min Treatments must be weaned gradually postoperatively.
Treatments must be weaned gradually postoperatively.	

Modified from Blaise G, Langleben D, Hubert B. Pulmonary arterial hypertension: pathophysiology and anesthetic approach. *Anesthesiology*. 2003;99(6):1415-1432.

replacement of fluids and blood products to replace measured and insensible surgical losses in order to maintain euvolemia and right ventricular preload. Table 2 summarizes agents that can be administered to reduce PVR. These agents may also tend to cause systemic hypotension sufficient to require correction. Milrinone can be used with a bolus, as described in Table 2, to assist in separating patients with pulmonary hypertension from cardiopulmonary bypass when undergoing cardiac surgery. Cardiopulmonary bypass provides some protection against the hypotension that may occur with the initial bolus of milrinone.[21] In circumstances such as off-pump coronary artery bypass surgery, it may be appropriate to omit the bolus in order to reduce the hypotensive effect.[22] In the event of systemic hypotension, inotropic agents should be administered. Dobutamine is the most commonly used agent: a β-agonist that provides chronotropic and inotropic effects along with systemic and pulmonary vasodilation. If hypotension persists, then a vasoconstrictor should also be added in order to restore coronary artery perfusion. Norepinephrine provides both vasoconstriction and inotropic support through α- and β-adrenergic stimulation and decreases PVR/SVR ratio at lower doses (<0.5 mcg/kg/min). However, its metabolism by the pulmonary endothelium can be inhibited in patients with pulmonary hypertension, causing its serum concentration to increase beyond the intended level with increase in PVR/SVR ratio. Used in lower doses, it can improve right ventricle/pulmonary artery coupling and is considered the best first-line agent in patients with pulmonary hypertension and right heart failure and hypotension. Vasopressin is a V_1 receptor agonist and produces systemic vasoconstriction. Dose-related coronary vasoconstriction has been reported at high doses (>0.4 U/min), though higher doses have been used and can be well tolerated. Vasopressin can be less arrhythmogenic than norepinephrine and is effective for treatment of systemic hypotension refractory to norepinephrine or as a first-line agent.

These perioperative challenges persist into the postoperative period. Any treatments that were instituted intraoperatively should be carefully weaned under close monitoring. Patients with pulmonary hypertension remain at higher risk for complications including sudden death in the days after surgery and should be monitored in an intensive-care setting.

CONCLUSION

Today, anesthesiologists are able to manage pulmonary hypertension more effectively because there is a deeper understanding of the disease, a broader range of therapeutic alternatives, and improved monitoring capabilities. The increasing availability of intraoperative transesophageal echocardiography provides instantaneous information about right and left ventricular dimensions and contractility, which can greatly facilitate the administration of anesthesia. Although the anesthetic management of patients with pulmonary hypertension continues to be a challenge, a thorough assessment of the patient, careful planning, and meticulous attention to detail minimizes the possibility of complications and allows for the best possible outcomes.

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