Treatment and Palliation of Symptoms in Patients With Advanced Pulmonary Arterial Hypertension

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Pulmonary arterial hypertension (PAH) is a complex disease in which the illness as well as the associated treatment can be particularly burdensome. Previously considered to be uniformly fatal, PAH treatment and management has improved with an extended survival. However, this can come with symptom burden. Burden can be associated with the disease itself in addition to the treatment aimed at ameliorating these symptoms. This article explores both the use of PAH-directed therapy as well as traditionally supportive treatment strategies for palliation of symptoms in those with PAH. As highlighted in the patient case described throughout this issue, patients are constantly weighing the benefits and burdens of treatment during each step of their journey.

BACKGROUND

Maximizing therapeutic benefit in the pulmonary arterial hypertension (PAH) patient means minimizing symptoms and improving right ventricular (RV) function, as patients with end-stage PAH generally die of RV failure. Based on major advances in the field, survival has improved over the past several decades. Data from the REVEAL registry have reported 1-year survival rates of 85%, 3-year survival of 68%, 5-year survival of 57%, and 7-year survival of 49%.[1] Still, the course of PAH patients is variable. Patients may present with what appears to be end-stage disease but are often successfully rescued with aggressive therapy and do well for years.[2,3] Thus, it is crucial for the care team to be aware of the substantial efficacy of currently available therapy while recognizing the burden of treatment and shifting focus toward primarily alleviating symptoms when is concordant with the patient's established goals of care.

When PAH is advanced there are several predominant symptoms that patients experience. The predominant symptom affecting most PAH patients is dyspnea. When the RV fails, edema, fatigue, and ultimately anorexia, abdominal swelling, and even anasarca may develop. Severe RV failure may cause dizziness, lightheadedness, near syncope, and syncope. Anxiety and depression are variable but eventually occur to some degree in nearly all patients. It is unusual for chest pain to be a major factor, but it can occur. Complex therapeutic regimens that are beneficial in various disease processes may be associated with adverse effects that can be intolerable to patients.[4] The PAH patient described in this case has other comorbidities making her regimen even more complex that merited additional considerations in the realm of balanced benefit with burden associated with therapy.

PAH PHARMACOLOGIC THERAPY: BALANCING BENEFIT WITH ADVERSE EFFECTS

Several classes of medications target key vasoactive pathways involved in remodeling the pulmonary vasculature in PAH, including prostacyclin pathway agonists, endothelin receptor antagonists (ERAs), and therapies impacting the nitric oxide pathway. Fourteen medications targeting these pathways are approved by the US Food and Drug Administration for treatment of PAH, 7 of which target the prostacyclin pathway.[5] Other medications are utilized to manage the RV failure associated with PAH including diuretics, inotropes, vasopressors, and oxygen.

Key Words—dyspnea, hypotension, PAH-directed therapy, palliation, prostacyclin
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Disclosure: The authors have nothing to disclose.

 DOI: 10.21693/1933-088X-17.1.20

Parenteral Prostanoid Therapy

When the patient described in this case presented after 3 years with more advanced PAH due to underlying liver disease and chronic hemolytic anemia, she was quite symptomatic. She was placed on intravenous (IV) prostacyclin therapy, the most aggressive and effective form of medical therapy for PAH. Intravenous prostanoids provide significant and clinically meaningful improvements in dyspnea, exercise tolerance, hemodynamics, and quality of life.[2,6-8] The primary target of prostacyclin and its analogs appears to be the IP receptor on pulmonary (and other) vascular smooth-muscle cells. Activation of other vasodilatory prostaglandin receptors, such as EP2 and EP4 (prostaglandin E2 and E4 receptors, respectively), has been observed, although the role and importance of these receptors in clinical benefit and adverse events are not entirely clear.[9,10]

The 3 prostanoid therapies available parenterally are epoprostenol, treprostinil, and iloprost. The latter drug is not available in the United States. Prostacyclin, or prostaglandin I2 (IP), is an endogenous eicosanoid produced by endothelial cells. Epoprostenol is a synthetic equivalent of prostacyclin, and treprostinil and iloprost are both stable synthetic analogs. There are 2 approved formulations of epoprostenol: Flolan (1995), which was the first PAH-targeted therapy after demonstrating improved mortality[2]; then later, Veletri (2008), approved for improved room-temperature stability.[11] Both formulations of epoprostenol have a short half-life of several minutes and a very high pH, which is caustic to skin and soft tissues requiring continuous IV administration with an infusion pump through a central catheter. Treprostinil can be infused subcutaneously (SC) and its long half-life makes interruptions in therapy less problematic.

Parenteral prostanoids can offer substantial improvement in severe dyspnea as well as edema, dizziness, lightheadedness, and syncope associated with an inadequate cardiac output. Early after the initiation of parenteral prostacyclin therapy, jaw pain, headache, musculoskeletal pain, flushing, hypotension, nausea, vomiting, and diarrhea may occur. Having an informed, patient-centered discussion of the pros and cons of these medications with anticipated benefits as well as these nearly universal side effects becomes essential. Therefore, prostacyclin pathway therapies are initiated at low doses and titrated up slowly, as tolerated, until a maintenance dose is achieved. Importantly, side effects are more common during the dose titration phase than in the maintenance phase. We learned very early that large dose increases (eg, 1 ng/kg/min) in epoprostenol could precipitate side effects and be difficult to tolerate. By titrating the drug in smaller increments but more frequently (eg, 0.25 ng/kg/min every 6 hours), patient comfort can be improved. Alternatively, by delaying dose increases for 12 to 24 hours when side effects are intolerable or excessive, more effective titration can be accomplished. Symptomatic improvement often takes weeks, however, during which time adverse effects are quite common.

Prostacyclins are known to be endogenous pain mediators and therefore can cause some unusual forms of pain, particularly in the first few weeks after initiation. Jaw pain is a side effect unique to parenteral prostanoid therapies and often occurs with the first bite of a meal. Our patient would likely learn that with nonpharmacologic strategies around chewing and food consumption, including eating softer-consistency foods, taking smaller bites, and chewing slowly, the pain would likely dissipate.

Headache is common and can often be controlled with nonpharmacologic therapy or nonopioid analgesics such as acetaminophen. Counseling our patient on disconcerting myalgias or bone pain prior to therapy can be helpful. Many patients experience pain in their legs (often the shins) and/or feet. This leg pain has not been well characterized and could be due to a small-fiber neuropathy.[12] Counseling should be provided as simply understanding this can sometimes be reassuring. Nonpharmacologic measures include use of a heating pad, massage, and acupuncture. Pharmacologic therapy can include acetaminophen, gabapentin, pregabalin, or tramadol. Gabapentin is often successful for leg pain.[13] Naturally, opioids are avoided when possible but should be utilized on a case-by-case basis and certainly considered when aforementioned strategies do not achieve adequate pain control. In cases of refractory pain, potential metabolic contributors such as vitamin B_{12} deficiency or thyroid dysfunction should be considered, and a referral to a pain management or palliative care specialist can be an option.

It is beneficial to include flushing as an erythematous rash as an anticipated side effect during the medication counseling before initiation, as this is common. Cold packs can help when there is associated discomfort. As with other adverse effects, careful dose titration can help limit flushing. Severe flushing that evolves into a skin rash may herald leukocytoclastic vasculitis, necessitating dose reduction.[14] Hypotension from parenteral prostanoids rarely requires intervention; however, cautious administration of fluids and vasopressors has been utilized in refractory cases. Antiemetics are recommended for nausea, and this may prevent vomiting; targeting the serotonin and/or dopamine pathways may be helpful. Loose stools are expected and can be controlled with antidiarrheal agents such as loperamide or diphenoxylate/atropine.[13] If diarrhea becomes severe, other pathology including Clostridium difficile should be excluded and diuretics may need to be limited to avoid hypovolemia.

If our patient were transitioned to SC treprostinil for convenience of a smaller pump and SC delivery, she might note site pain. Infusion site pain has been the most common side effect attributed to treprostinil. The mechanism remains unclear: it does not appear to be dose-related but correlated to the rate of dose increase as well as the specific site used. The pain can be associated with erythema, induration, inflammation, site pain, bleeding, and occasionally cellulitis and abscess formation.[13] The site can vary depending on what a patient finds comfortable, including the abdomen, upper buttocks, lower flanks, outer thighs, and even the back of the upper arm. From patient reports, leaving the infusion at a "good" site could minimize site pain. In fact, we now teach patients with uncom-

fortable site pain to maintain their sites as long as possible, while closely observing for signs of early infection.[14] Both nonpharmacologic therapies including ice as well as various pharmacologic topical therapies are recommended. If site pain is particularly severe, systemic therapies such as gabapentin, tramadol, or tricyclic antidepressants can be administered within the first week of a site change.[13,16,17]

Overall, the benefits of these medications in alleviating the troublesome and often very severe symptoms of PAH must be balanced with the common side effects. Despite the potential considerable side effects, patients receiving prostacyclin pathway therapies have improvement in their quality of life.

Nonparenteral Prostanoid Therapy

Inhaled (iloprost and treprostinil) and oral (selexipag and treprostinil) prostanoid formulations have clearly proven effective and share similar side effect profiles. Inhaled iloprost and treprostinil have a more localized effect within the pulmonary vasculature and have been shown to improve functional class, hemodynamics, dyspnea, and quality of life.[18] Inhaled iloprost is inconvenient, requiring administration 6 to 9 times per day. This can be intolerable, particularly in end-stage patients where physical administration of medication may be difficult. Inhaled treprostinil can be delivered every 6 hours. Side effects with inhaled therapies include typical prostanoid side effects but with the addition of increased cough and bronchospasm, which occasionally mandates drug discontinuation. Counseling, monitoring, and potentially bronchodilator therapy may be required for bronchospasm, particularly in patients with concomitant reactive airway disease.

Oral treprostinil is dosed 2 or 3 times daily. Slow and cautious dose titration is crucial in avoiding nausea and other symptoms. It is often necessary to start as low as 0.125 mg 3 times daily with food. The dose should be increased at increments of 0.125 or 0.25 twice or 3 times daily every 3 to 4 days to the highest tolerated dose. Not surprisingly, common side effects include headache, diarrhea, nausea, flushing, jaw pain, and leg pain.

Selexipag is an oral nonprostanoid prostacyclin pathway agonist and has been shown to improve functional class, decrease hospitalizations, and increase time to clinical worsening.[19] Due to a unique long-acting metabolite, it can be administered twice a day, thereby greatly decreasing the burden of administration compared with other prostacyclin pathway agonists. Common side effects are those described above for other prostanoids. Importantly, the most advanced patients such as the one described in this case still require parenteral prostanoid therapy.

Endothelin Receptor Antagonists

Endothelin receptor antagonists (ERAs) have served as critical components of the PAH treatment armamentarium. During the acute management and stabilization of this patient, an ERA was started as part of her combination therapy. Bosentan, ambrisentan, and macitentan are the available ERAs and have been shown to improve dyspnea, exercise tolerance, and hemodynamics as well as to prevent clinical worsening.[20,21] ERAs block the potent vasoconstriction pathway in vascular smooth muscle and endothelium, resulting in vessel relaxation and remodeling.

ERAs can cause fluid retention, peripheral edema, nasal congestion, and anemia. Fluid retention and peripheral edema can usually be effectively managed using diuretics, discussed below. If a patient has refractory edema, switching to macitentan may provide symptom relief.[20] Nasal congestion can also be managed with relatively low burden interventions such as saline spray or in severe cases intranasal glucocorticoids. Although rarely requiring intervention, bosentan and macitentan showed a significantly higher risk of anemia compared with placebo, whereas ambrisentan did not.[22] Bosentan causes transaminitis in about 7% of patients requiring monthly liver function testing. This hepatotoxicity appears to be rare with macitentan and ambrisentan, and naturally, very advanced pulmonary hypertension (PH) is associated with abnormal liver function. Bosentan would not be an acceptable form of therapy for our patient based on the potential for hepatotoxicity. In our patient, with her symptomatic PAH, cirrhosis, hemolytic anemia, and frequent need for transfusion, the risks of adverse effects have to be weighed against the severity of PAH symptoms in order to balance effective treatment and quality of life.

THE NITRIC OXIDE PATHWAY

Phosphodiesterase Type 5 Inhibitors

Phosphodiesterase type 5 (PDE-5) inhibitors are commonly used early in the course of PAH. These drugs have been shown to improve dyspnea, exercise tolerance, and hemodynamics and increase time to clinical worsening.[5] Common side effects include headache, flushing, nasal congestion, epistaxis, and acid reflux. Less commonly, nausea, myalgias, insomnia, and visual disturbance may occur. The potential side effects are variable among patients and can often be alleviated with supportive treatment. As with all PAH medications, dose adjustment may relieve symptoms and sometimes discontinuation is necessary. Hypotension caused by nitrates or other drugs that lower blood pressure may be magnified by PDE-5 inhibitors. This hypotension may be confused with that caused by the PAH itself.

Soluble Guanylate Cyclase Stimulators

Riociguat is the only approved medication in its class. It has been shown to improve functional class, hemodynamics, and increase time to clinical worsening.[23] Side effects include headache, nausea, vomiting, indigestion, acid reflux, gastritis, hypotension, and diarrhea. Management of these side effects are as aforementioned. Antacids can be used for indigestion, acid reflux, or gastritis but should be spaced at least an hour before or after administration to not adversely affect absorption. A proton-pump inhibitor may be prudent in moderate to severe cases.

COMBINATION THERAPY FOR PAH

PAH therapy is nearly always used in combination, so it must be realized that the adverse effects may overlap and magnify symptoms. Examples include

the hypotension or headache caused by prostanoids, PDE-5 inhibitors, riociguat, and diuretics, or the nasal congestion caused by ERAs in combination with PDE-5 inhibitors. The drugs must be administered and titrated cautiously to minimize these overlapping effects.

DIURETICS AND VASOACTIVE THERAPY

During the acute phase of our patient's course, she required multiple PAH therapies as well as supportive therapy, including diuretics, inotropes, and vasopressors. Loop diuretics are commonly used for edema, ascites, and anasarca and are beneficial, but hypotension and preservation of renal function must be considered.[24] Spironolactone may be particularly beneficial in the setting of portopulmonary hypertension as hypokalemia may cause unwanted adverse effects. When spironolactone causes painful gynecomastia, amiloride can be substituted although it has less natriuretic effect. Eplerenone has not been extensively studied for ascites in PAH.

Inotropes including milrinone, dobutamine, and dopamine have not been studied extensively in PAH but may reduce pulmonary vascular resistance and improve RV function. Adverse effects can be serious including hypotension and potentially life-threatening arrhythmias. Therapy with these medications is empiric and should be done cautiously. No clear recommendations can be given.

OTHER NONSPECIFIC SUPPORTIVE THERAPY

Oxygen can be therapeutic and palliative. In PAH, it is crucial to guarantee an adequate oxygen saturation at rest, during activity, and hypoxic vasoconstriction is particularly deleterious in PAH during sleep. Our patient ultimately needed oxygen, and her severe anemia made it vital to optimize her oxygen carrying capacity. When PAH advances and the oxygen requirement increases, caution is needed to guarantee balanced risk and benefit. Our patient had hepatopulmonary syndrome and her hypoxemia was beyond that typically seen in PAH. While a detailed discussion of hypoxemia and hyperoxia is beyond our scope, it should be noted that even modest hypoxemia is associated with clinically significant cognitive sequelae. With a partial pressure of arterial oxygen less than 60 mm Hg, hypoxic vasodilation occurs as a part of cerebral autoregulation.[25] Hyperoxia, on the other hand, is associated with vasoconstriction and therefore reduces cerebral perfusion[26] so unnecessarily high fraction of inspired oxygen levels should be avoided. In very advanced patients with PAH on comfort measures, oxygen toxicity is less relevant. When a high fraction of inspired oxygen is required to adequately oxygenate a patient and relieve dyspnea, a high-flow nasal cannula may be more comfortable than a mask and may optimize patient-caretaker interactions. For those dependent on continuous bilevel positive airway pressure (BiPAP), alternating BiPAP with high-flow oxygen by cannula may facilitate communication, eating, and facial care. A current trial is evaluating the palliative use of high-flow oxygen by nasal cannula compared with conventional oxygen in end-of-life lung disease patients.[27]

Ascites can cause tremendous discomfort and impact on breathing. Aggressive paracentesis may alleviate symptoms but must be balanced with protein loss, hypotension, and renal dysfunction. Catheter drainage was considered in our patient. A simple drainage catheter, tunneled catheters, percutaneously placed peritoneal ports, modified venous access ports, and the PleurX catheter have been used but again risk infection, protein loss, and intravascular volume depletion. The benefit of delaying and reducing hospitalization for paracentesis must be weighed against the risk of these complications.

The cirrhosis that contributed to both the PAH and the ascites in our patient cannot be palliatively approached in precisely the same way as a patient with malignancy or with underlying cirrhosis and no cardiopulmonary disease. For example, the transjugular intrahepatic portosystemic shunt procedure for cirrhotic patients that decompresses the hypertensive portal vein is generally contraindicated in patients with portopulmonary hypertension and known PAH because of the likelihood of worsened RV failure due to the postprocedural increased preload. Restriction of daily dietary sodium must be weighed in the palliative setting. Finally, atrial septostomy may serve as a bridge to lung transplantation in PAH and also offers improvement in RV failure in the palliative setting but significantly increases the oxygen requirement.[28]

CONCURRENT PALLIATIVE CARE

It is a common misconception that treatments that target the underlying disease are somehow separate from symptom management. The PAH disease-targeted treatments that cumulatively have appeared to improve survival in PAH also palliate symptoms. These medications improve functional class and exercise tolerance, which can directly translate into improvement in overall comfort. The balance between improvement in symptoms and side effect burden utilizes a variety of medications that are disease-targeted as well as symptom-supportive.

In the case of our patient, "palliative care was discussed … and [the patient] was happy with her quality of life," alluding to a decisive conversation around burden and benefits associated with therapy. At this point, it was determined that the benefits of increased time to clinical worsening and relief of symptoms from the medical treatment outweighed the burden of hospitalization and adverse effects from her treatment regimen. Her recurrent acute decompensations requiring hospital intervention with subsequent improvement was deemed acceptable by the patient and her family. The highlighted case is a classic example of concurrent disease-directed treatment and palliative care and how collaboration between specialty teams can achieve acceptable symptom relief. The relationship built between the patient, the PAH specialist team, and the palliative care team allowed for flexible and creative management for this patient's journey through her disease trajectory. Although this patient continues to benefit with each hospitalization, each individuals' maximal acceptable burden will be different. Ongoing symptom assessments in parallel with ongoing goals of care conversations are

paramount and may vary throughout the disease course. With each intervention, a separate discussion takes place to assess the continuum of benefit and burden that the patient is constantly weighing. If a disease-focused treatment plan exceeds the acceptable burden of the patient, the types of medications may shift from those with high side effect profile to those that may be more well tolerated. In some cases, the utilization of primarily supportive therapy including diuretics, opioid analgesics, and anxiolytics may be elected over disease-specific therapy due to difficult side effects.

CONCLUSION

PAH therapy has been shown to improve symptoms, quality of life, and mortality. It is also associated with unavoidable side effects that can be controlled to a degree with reassurance, medications, and other ancillary supportive measures, as well as through PAH medication dosing and titration considerations. PAH was previously considered a "uniformly fatal disease." The mortality of this disease has improved substantially, and it is feasible that this phrase no longer applies. However, the disease often advances and as it does, the PH team must keep an appropriate balance between PAH symptom control, adverse effects of this therapy, and patient goals.

References

1. Benza RL, Miller DP, Barst RJ, Badesch DB, Frost AE, McGoon MD. An evaluation of long-term survival from time of diagnosis in pulmonary arterial hypertension from the REVEAL Registry. *Chest*. 2012;142(2):448-456.
2. Barst RJ, Rubin LJ, Long WA, et al; Primary Pulmonary Hypertension Study Group. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. *N Engl J Med*. 1996;334(5):296-301.
3. Salamonsen M, Keating D, Whitford H, et al. IV epoprostenol as salvage therapy in pulmonary arterial hypertension: an Australian perspective. *Intern Med J*. 2011;41(3):245-251.
4. Taichman DB, Shin J, Hud L, et al. Health-related quality of life in patients with pulmonary arterial hypertension. *Respir Res*. 2005;6:92.
5. Galiè N, Humbert M, Vachiery JL, et al; ESC Scientific Document Group. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J*. 2016;37(1):67-119.
6. Sitbon O, Humbert M, Nunes H, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. *J Am Coll Cardiol*. 2002;40(4):780-788.
7. McLaughlin VV, Palevsky HI. Parenteral and inhaled prostanoid therapy in the treatment of pulmonary arterial hypertension. *Clin Chest Med*. 2013;34(4):825-840.
8. Simmonneau G, Barst RJ, Galie N, et al. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension a double-blind, randomized, placebo-controlled trial. *Am J Respir Crit Care Med*. 2002;165(6):800-804.
9. Whittle BJ, Silverstein AM, Mottola DM, Clapp LH. Binding and activity of the prostacyclin receptor (IP) agonists, treprostinil and iloprost, at human prostanoid receptors: treprostinil is a potent DP1 and EP2 agonist. *Biochem Pharmacol*. 2012;84(1):68-75.
10. Lai YJ, Pullamsetti SS, Dony E, et al. Role of the prostanoid EP4 receptor in iloprost-mediated vasodilatation in pulmonary hypertension. *Am J Respir Crit Care Med*. 2008;178(2):188-196.
11. Chin KM, Badesch DB, Robbins IM, et al. Two formulations of epoprostenol sodium in the treatment of pulmonary arterial hypertension: EPITOME-1 (epoprostenol for injection in pulmonary arterial hypertension), a phase IV, open-label, randomized study. *Am Heart J*. 2014;167(2):218-225.
12. Pagani-Estévez GL, Swetz KM, McGoon MD, et al. Characterization of prostacyclin-associated leg pain in patients with pulmonary arterial hypertension. *Ann Am Thorac Soc*. 2017;14(2):206-212.
13. Kingman M, Archer-Chicko C, Bartlett M, Beckmann J, Hohsfield R, Lombardi S. Management of prostacyclin side effects in adult patients with pulmonary arterial hypertension. *Pulm Circ*. 2017;7(3):598-608.
14. Hargett CW, Myers S, Ahearn GS, et al. Epoprostenol-induced leukocytoclastic vasculitis. *Chest*. 2004;126:Suppl:958S.
15. Skoro-Sajer N, Lang IM, Harja E, Kneussl MP, Sing WG, Gibbs SJ. A clinical comparison of slow- and rapid-escalation treprostinil dosing regimens in patients with pulmonary hypertension. *Clin Pharmacokinet*. 2008;47(9):611-618.
16. Mathier MA, McDevitt S, Saggar R. Subcutaneous treprostinil in pulmonary arterial hypertension: Practical considerations. *J Heart Lung Transplant*. 2010;29(11):1210-1217.
17. White RJ, Levin Y, Wessman K, Heininger A, Frutiger K. Subcutaneous treprostinil is well tolerated with infrequent site changes and analgesics. *Pulm Circ*. 2013;3(3):611-621.
18. Olschewski H, Simonneau G, Galiè N, et al; Aerosolized Iloprost Randomized Study Group. Inhaled iloprost for severe pulmonary hypertension. *N Engl J Med*. 2002;347(5):322-329.
19. Sitbon O, Channick R, Chin KM, et al; GRIPHON Investigators. Selexipag for the treatment of pulmonary arterial hypertension. *N Engl J Med*. 2015;373(26):2522-2533.
20. Liu C, Chen J. Endothelin receptor antagonists for pulmonary arterial hypertension. *Cochrane Database Syst Rev*. 2006;(3):CD004434.
21. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med*. 2002;346(12):896-903.
22. Wei A, Gu Z, Li J, et al. Clinical adverse effects of endothelin receptor antagonists: insights from the meta-analysis of 4894 patients from 24 randomized double-blind placebo-controlled clinical trials. *J Am Heart Assoc*. 2016;5(11).
23. Ghofrani HA, Galiè N, Grimminger F, et al. Riociguat for the treatment of pulmonary arterial hypertension. *N Engl J Med*. 2013;369(4):330-340.
24. Pérez-Ayuso RM, Arroyo V, Planas R, et al. Randomized comparative study of efficacy of furosemide versus spironolactone in nonazotemic cirrhosis with ascites. Relationship between the diuretic response and the activity of the renin-aldosterone system. *Gastroenterology*. 1983;84(5 Pt 1):961-968.
25. Bulte DP, Chiarelli PA, Wise RG, Jezzard P. Cerebral perfusion response to hyperoxia. *J Cereb Blood Flow Metab*. 2007;27(1):69-75.
26. Watson NA, Beards SC, Altaf N, Kassner A, Jackson A. The effect of hyperoxia on cerebral blood flow: a study in healthy volunteers using magnetic resonance phase-contrast angiography. *Eur J Anaesthesiol*. 2000;17(3):152-159.
27. Palliative use of high-flow oxygen by nasal cannula compared with conventional oxygen in end-of-life lung disease patients. ClinicalTrials.gov Identifier: NCT02253667.
28. Reichenberger F, Pepke-Zaba J, McNeil K, Parameshwar J, Shapiro LM. Atrial septostomy in the treatment of severe pulmonary arterial hypertension. *Thorax*. 2003;58(9):797-800.