International Journal of Anesthesia and Clinical Medicine
2025, Vol. 13, No. 1, pp. 24-29
https://doi.org/10.11648/j.ijacm.20251301.14

Review Article

Vasopressors Aggravate Passive Pulmonary Hypertension Due to Left Heart Disease, from Basic Pathophysiology to Clinical Management

Xiao Xiao, Yan Xu, Chunling Jiang*

Department of Anesthesiology and Translational Neuroscience Center, West China Hospital, Sichuan University, Chengdu, China

Abstract

Pulmonary hypertension due to left heart disease (PH-LHD) is the most common form of pulmonary hypertension (PH), accounting for 65–80% of cases, and is associated with significant morbidity and mortality. PH-LHD is traditionally considered a passive condition, primarily driven by elevated left heart pressure, which increases pulmonary venous pressure. However, vasopressors, such as phenylephrine, frequently used in critical care to enhance vascular tone, can induce another form of passive PH. This vasopressor-induced PH shares hemodynamic similarities with PH-LHD, characterized by increased pulmonary blood volume and left atrial pressure, and exerts additive effects on pre-existing PH-LHD, exacerbating pulmonary congestion and worsening clinical outcomes. The interaction between vasopressors and PH-LHD is often overlooked, yet it poses significant risks, particularly in patients with heart failure. This review explores the pathophysiology of passive PH-LHD, the mechanisms of vasopressor-induced PH, and their additive effects. We also highlight the challenges in diagnosing passive PH, which is frequently misclassified as pulmonary arterial hypertension (PAH), leading to inappropriate treatment and potential harm. Current therapeutic strategies, such as diuretics and blood volume management, are discussed as potential approaches to mitigate these effects. Improved understanding of these mechanisms is crucial for optimizing treatment and reducing morbidity and mortality. Future research is needed to develop targeted therapies and improve outcomes for patients with PH-LHD and vasopressor-induced PH.

Keywords

Vasopressor Agents, Pulmonary Hypertension, Passive, Left Heart Disease, Pulmonary Circulation, Additive Effects

1. Introduction

Pulmonary hypertension (PH) is defined as a mean pulmonary artery pressure (mPAP)≥ 25 mm Hg at rest, during right heart catheterization and is estimated to affect about 1% of the global population [1-5]. The 2022 ESC/ERS guidelines provide a comprehensive and simplified classification of pulmonary hypertension, dividing it into five subgroups: (1) pulmonary arterial hypertension (PAH), (2) PH associated with left heart disease, (3) PH associated with lung diseases and/or hypoxia, (4) PH associated with pulmonary artery obstructions, and (5) PH with unclear and/or multifactorial

*Corresponding author: Jiangchunling @scu.edu.cn (Chunling Jiang)

Received: 2 March 2025; **Accepted:** 14 March 2025; **Published:** 28 March 2025

mechanisms [3]. Recently, with better understanding of the underlying pathological processes, PH is also classified into pre-capillary (pulmonary arterial wedge pressure, PAWP ≤ 15 mm Hg) and post-capillary PH (PAWP > 15 mm Hg) [3, 6]. Post-capillary PH, caused by downstream elevation in left heart pressure is also considered to be passive [5]. Additionally, both clinical and animal studies showed that administration of vasopressors can induce PH. It has been proposed that the underlying pulmonary hemodynamic pattern of vasopressor-induced PH is similar to the passive PH-LHD [7-10]. Moreover, vasopressor induced passive PH has an additive effects on PH-LHD [11, 12], that may exacerbate cardiac decompensation. However, both vasopressors induced passive PH and its interaction with PH-LHD is often clinically ignored. And there is a lack of sufficient data on the clinical prevalence or status of this passive PH. Consequently, the detrimental impact of this phenomenon may exceed initial expectations. A deeper comprehension of how vasopressors influence pulmonary hypertension associated with left heart disease is crucial for enhancing treatment strategies for left heart disease. Such advancements would ultimately lead to a reduction in both the morbidity and mortality rates among patients suffering from heart failure (HF).

In this study, our primary objective is to highlight the significance and mechanism of vasopressor-induced PH, and its interaction with PH-LHD. We also provide insights into the limitation of current diagnosis, and discuss therapeutic options in this context.

2. Pathophysiology of Passive PH-LHD

PH-LHD, the most common cause of PH, accounts for 65~80% of cases. PH-LHD is associated with high morbidity and mortality [4]. PH-LHD is believed to be caused by passive downstream elevation in left heart pressure or by a combination of the passive elevation in left heart pressure with pulmonary arteriolar pathologies at late stage [4]. Therefore, the hemodynamic patterns of passive PH is an elevation of left-side filling pressure, caused by systolic or diastolic left ventricular dysfunction [13].

However, the pathophysiology of passive PH-LHD is more complex and remains inadequately defined. It is reported that in the systemic circulation, downstream filling pressure of right atrium contributes little (5%) to systemic arterial pressure; whereas, in the pulmonary circulation, downstream filling pressure of left atrium contributes substantially to (mPAP) (50%) [14], which will be even greater in HF. Therefore, in the early stages of PH-LHD, with normal transpulmonary gradient (TPG) and pulmonary vascular resistance (PVR), increase of PAP related to elevation in left atrial pressure (LAP) may be purely passive, as a result of systolic or diastolic left ventricular (LV) dysfunction [12, 13]. A sudden rise in LAP can lead to 'alveolar-capillary stress failure,' resulting in reversible barotrauma. This trauma alters endothelial permeability, compromises cellular integrity, and allows erythrocytes and proteins to leak into the alveolar lumen, ultimately leading to interstitial and alveolar edema [5]. Nevertheless, the pulmonary–capillary interface exhibits remarkable elasticity, being able to restore its integrity after normalization of LAP at this stage [15]. However, a prolonged elevation in left-side filling pressure and pulmonary venous pressure can result in excessive vasoconstriction with or without vascular remodeling in the alveolar–capillary membrane interface and at the arteriolar and pulmonary artery levels [5]. Structural and functional alterations within the pulmonary vasculature, such as reduced nitric oxide bioavailability, elevated endothelin-1 levels, diminished responsiveness to natriuretic peptide-mediated vasodilation, inflammatory cell infiltration, and the influence of neurogenic or metabolic mediators, may collectively drive the process of microvascular remodeling [16, 17]. The remodeling reduces membrane conductance and gas exchange [18]. Additionally, hypoxia promotes vasoconstriction [19]. These factors collectively have the potential to induce vasoconstriction in the pulmonary arteries, ultimately leading to the progressive structural remodeling of pulmonary resistance vessels over time [5]. At this stage, mPAP increases further, in excess of the elevation of PAWP [20, 21]. Therefore, these stages of PH are defined as reactive, when structural and functional abnormalities of the pulmonary vasculature cause elevation in PVR and TPG. Microscopic alterations involve the thickening of the alveolar-capillary barrier, hypertrophy of the medial layer, intimal and adventitial fibrosis, and luminal occlusion in small pulmonary arterioles, whereas ‘plexiform lesions’ pathognomonic of PAH are not usually found [22, 23]. These changes may be either reversible or fixed. The duration of the transition from passive to reactive PH stage is highly variable among individuals and is not consistently related to severity of elevation in LAP [12].

3. Pathophysiology of Vasopressor-induced Passive PH

Vasopressors (phenylephrine, vasopressin) and vasoactive catecholamine inotropes (dopamine, epinephrine, norepinephrine) are frequently used in patients with severe left heart diseases, HF, cardiogenic shock, post cardiac surgery vasoplegia, post cardiac surgery hypotensive states, or resuscitation, in order to increase myocardial contractility and vascular tone [7, 24-26]. However, administration of vasopressors may induce passive PH, characterized by elevation of pulmonary blood volume, left atrial pressure and pulmonary capillary wedge pressure (PCWP), which is similar to left heart diseases.

Vasopressor-induced PH is another subcategory of passive PH [11]. Research involving both human subjects and animal models has demonstrated that vasopressor agents are capable of triggering PH [8, 27, 28]. It has been proposed that vasopressors induce PH via direct drug-induced pulmonary vasoconstriction [8, 10, 29]. However, our recently published

work showed that the hemodynamic pattern of vasopressors-induced PH is similar to that of passive PH-LHD. This pattern is marked by increased pulmonary blood volume, elevated left atrial pressure, and higher PCWP, while showing minimal impact on pulmonary vascular resistance and right atrial pressure [11].

In our study, phenylephrine from 1 to 2 mcg/kg/min dose-dependently increased both LAP and PAP, while TPG, PVR and RAP (right atrial pressure) remained unchanged [11]. Additionally, we measured the pulmonary blood volume using Sono Vue contrast agent, and found that the elevated PH induced by vasopressor is accompanied by increased pulmonary blood volume. Since vasopressors strongly constrict systemic vasculature, and lead to blood volume redistribution from systemic to pulmonary circulation, including a decrease in the capacity of the systemic vascular system and an increase in steady-state venous return to right atrium. And this in turn affects the output of the right ventricle, leading to pulmonary congestion and pulmonary hypertension [30]. On the other hand, the elevation in left ventricular afterload related to increasing systemic blood pressure may impair left ventricular function (Figure 1). Therefore, vasopressor-induced PH is caused by blood volume redistribution from systemic to pulmonary circulation, and increased pulmonary blood volume, but not by pulmonary vasoconstriction. Thus, vasopressor-induced PH should be classified as passive PH [11]. This type of PH may give rise to functional lesion of lungs, left and right ventricles (Figure 1).

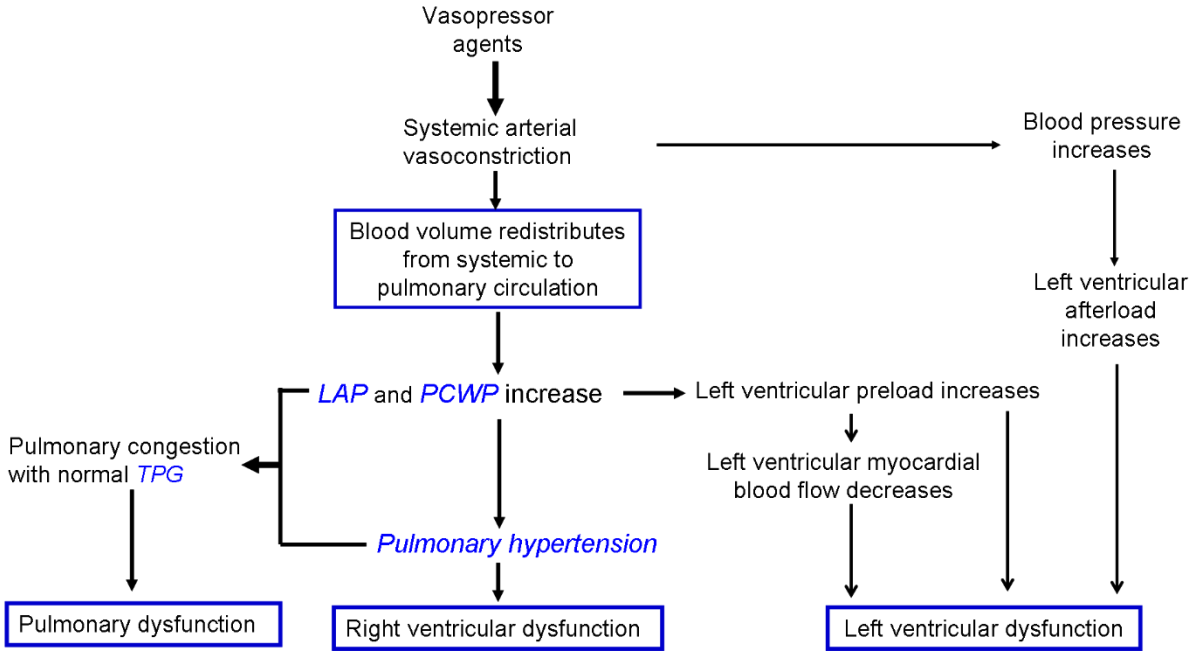

Figure 1. *Vasopressor agent-induced passive pulmonary hypertension and its adverse effects. This type of pulmonary hypertension is characterized by increased LAP, PCWP and pulmonary arterial pressure, as well as normal TPG and central venous pressure (CVP). This type of pulmonary hypertension may cause functional lesion of lungs and both ventricles. Administration of vasopressor agents may induce systemic arterial constriction, and even venous constriction if the dosage is excessive Systemic vascular constriction pushes blood volume from systemic to pulmonary circulation. The resulting pulmonary congestion increases LAP, followed by an increase in PCWP, ultimately inducing pulmonary hypertension. The TPG remains normal. Pulmonary congestion may reduce pulmonary function, and passive pulmonary hypertension may reduce right heart function. In the event of right heart compensation, CVP remains normal. Increased left ventricle preload compromises myocardial perfusion by raising LV filling pressures, reducing the coronary perfusion gradient and increasing myocardial oxygen requirements. Decrease in coronary perfusion, together with an increase in both pre- and afterload, may induce left ventricle dysfunction.*

4. Additive Effects of Vasopressors on PH During Cardiac Dysfunction

Since both vasopressor-induced PH and PH-LHD are passive characterized with increases in pulmonary blood volume, PCWP and LAP, vasopressor therapy may aggravate PH-LHD. Indeed, according to our previous study, left ventricle dysfunction increased both LAP (from 11 ±4 to 23 ±5 mmHg) and PAP (from 20 ±4 to 31 ±5 mmHg) [11]. The infusion of phenylephrine (1 mcg/kg/min) led to a further rise in PAP by 31% and left atrial pressure by 43%, while having minimal impact on pulmonary vascular resistance (4%) and the trans-pulmonary gradient (2%). Therefore, there is an additive interaction between phenylephrine and left myocardial dysfunction in PH patients. More importantly, vasopressors, like phenylephrine, can exacerbate PH in individuals with cardiac dysfunction via the additive effects of these

agents on PH in the context of impaired cardiac function, potentially worsening clinical symptoms and overall outcomes [11]. This may explain why adverse reactions are greater than anticipated when vasopressin is given to patients with septic shock, who have coexisting heart diseases [31].

Interestingly, a predominant feature of passive PH is its dependence on volume status. Consequently, in clinical practice, PH-LHD can be alleviated by diuretics [11]. Similarly, patients with vasopressor-induced PH may likewise benefit from diuretics therapy as part of their treatment regimen [32]. Accordingly, reducing blood volume through therapeutic interventions may prove beneficial in prevention and treatment for both PH-LDH and vasopressor-induced PH, and in alleviation of their additive effects.

5. Clinical Relevance

Since PH-LHD constitutes the predominant etiology of PH, coupled with the widespread utilization of vasopressors in intensive care environments, the passive PH is likely to exhibit higher prevalence rates and pose a more significant influence on clinical outcomes, including disease advancement, complication rates, and patient survival. The occult nature of vasopressor-induced passive PH and PH-LHD may result in underestimation of the occurrence. It has been noticed that right atrial pressure, typically assessed through central venous pressure monitoring in clinical practice, maintains stability regardless of whether patients are receiving high-dose vasopressors therapy or experiencing left cardiac dysfunction [11]. Therefore, its harmfulness may be greater than anticipated, and this tends to be underestimated in the left heart disease patients. On the other hand, targeted therapies available for passive PH have not been adequately evaluated and current treatment for PAH may even aggravate passive PH [5]. Patients with passive PH are often erroneously categorized as having PAH, leading to inappropriate administration of PAH-targeted pharmacological therapies. Such therapeutic misdirection could potentially exacerbate pulmonary vascular dilation and augment pulmonary circulation volume, particularly in cases where elevated left ventricular filling pressures are present. Thus, this therapy in turn exacerbates pulmonary edema and cardiac decompensation. Consequently, accurate diagnostic evaluation and proper classification of PH must be established prior to initiating any therapeutic interventions.

Enhancing our comprehension of the underlying pathophysiological mechanisms in passive PH is crucial for developing standardized, evidence-driven therapeutic strategies for affected patients. Of particular clinical significance is the substantial influence of increased PAWP in individuals with passive PH, which necessitates focused clinical consideration. Effective management of the causative LHD, encompassing both pharmacological interventions and procedural approaches, serves to reduce both left ventricular filling pressures and PAP [5]. However, therapeutic volume reduction typically correlates with significant decreases in both PAWP and PAP [5]. Consequently, in the CHAMPION trial, strategic management of HF through optimized therapeutic approaches, particularly diuretic titration for volume control, resulted in substantial PAP reduction and a marked decrease in HF-related hospital admission rates [33]. Taken together, blood volume management should be an important method in prevention and treatment for passive PH to a certain extent. Furthermore, the utilization of LV assist devices can effectively reduce pulmonary vascular pressures by facilitating ventricular decompression, while simultaneously maintaining a favorable safety profile regarding RV dysfunction following implantation [34, 35].

6. Prospective

Notwithstanding significant progress in elucidating the pathophysiological mechanisms underlying passive PH and enhanced clinical management approaches, patient outcomes remain suboptimal. Identifying passive PH and comprehending its fundamental pathophysiological processes could enhance clinical management strategies for critically ill individuals requiring vasopressor therapy, especially for those with coexisting heart diseases. However, targeted therapies have never been investigated properly in this condition. Thus, a multi-center clinical study exploring the effect of vasopressors on passive PH-LHD is in urgent needed.

Abbreviations

PH-LHD	Pulmonary Hypertension Due to Left Heart Disease
PH	pulmonary Hypertension
PAH	pulmonary Arterial Hypertension
mPAP	Mean Pulmonary Artery Pressure
PAWP	Pulmonary Arterial Wedge Pressure
HF	Heart Failure
TPG	Transpulmonary Gradient
PVR	Pulmonary Vascular Resistance
LAP	Left Atrial Pressure
PCWP	Pulmonary Capillary Wedge Pressure
RAP	Right Atrial Pressure
CVP	Central Venous Pressure
LV	Left Ventricular

Conflicts of Interest

The author of this article declares no conflicts of interest.

References

[1] Sommer N, Richter MJ, Tello K, et al. Update pulmonalarterielle Hypertonie: Definitionen, Diagnose, Therapie [Update pulmonary arterial hypertension: Definitions, diagnosis, therapy]. Internist (Berl). 2017; 58(9): 937-957. https://doi.org/10.1007/s00108-017-0301-5

[2] Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 2023; 61: 2200879. https://doi.org/10.1183/13993003.00879-2022

[3] Kovacs G, Bartolome S, Denton CP, Gatzoulis MA, Gu S, Khanna D, Badesch D, Montani D. Definition, classification and diagnosis of pulmonary hypertension. Eur Respir J. 2024 Oct 31; 64(4): 2401324. https://doi.org/10.1183/13993003.01324-2024

[4] Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019; 53(1). https://doi.org/10.1183/13993003.01913-2018

[5] Rosenkranz S, Gibbs JSR, Wachter R, et al. Left ventricular heart failure and pulmonary hypertension†. Eur Heart J 2016; 37(12): 942-954. https://doi.org/10.1093/eurheartj/ehv512

[6] Hoeper MM, Humbert M, Souza R, et al. A global view of pulmonary hypertension. Lancet Respir Med 2016; 4(4): 306-322. https://doi.org/10.1016/S2213-2600(15)00543-3

[7] Sabry O, Ahmed Z, Kenneth N. Cardiac vasoplegia syndrome: pathophysiology, risk factors and treatment. American Journal of the Medical Sciences 2015; 349(1): 80-88. https://doi.org/10.1097/MAJ.0000000000000341

[8] Rieg AD, Rossaint R, Uhlig S, et al. Cardiovascular Agents Affect the Tone of Pulmonary Arteries and Veins in Precision-Cut Lung Slices. Plos One 2011; 6(12): e29698. https://doi.org/10.1371/journal.pone.0029698

[9] Werner F, Kojonazarov B, Ga ßner B, et al. Endothelial actions of atrial natriuretic peptide prevent pulmonary hypertension in mice. 2016; 111(2): 22. https://doi.org/10.1007/s00395-016-0541-x

[10] Morimatsu H, Ishikawa K, May CN, et al. The systemic and regional hemodynamic effects of phenylephrine in sheep under normal conditions and during early hyperdynamic sepsis. 2012; 115(2): 330-342. https://doi.org/10.1213/ANE.0b013e31825681ab

[11] Jiang C, Qian H, Luo S, et al. Vasopressors induce passive pulmonary hypertension by blood redistribution from systemic to pulmonary circulation. Basic Research in Cardiology 2017; 112(3): 21. https://doi.org/10.1007/s00395-017-0611-8

[12] Vachiery JL, Tedford RJ, Rosenkranz S, et al. Pulmonary hypertension due to left heart disease. Eur Respir J 2019; 53(1). https://doi.org/10.1183/13993003.01897-2018

[13] Vachi éry JL, Al E. Pulmonary hypertension due to left heart diseases. Journal of the American College of Cardiology 2013; 62(25): D100-D108. https://doi.org/10.1016/j.jacc.2013.10.033

[14] Borlaug BA. Discerning pulmonary venous from pulmonary arterial hypertension without the help of a catheter. Circulation Heart Failure 2011; 4(3): 235. https://doi.org/10.1161/CIRCHEARTFAILURE.111.962209

[15] Elliott AR, Fu Z,., Tsukimoto K,., et al. Short-term reversibility of ultrastructural changes in pulmonary capillaries caused by stress failure. Journal of Applied Physiology 1992; 73(3): 1150. https://doi.org/10.1152/jappl.1992.73.3.1150

[16] Guazzi M. Alveolar Gas Diffusion Abnormalities in Heart Failure. J Card Fail 2008; 14(8): 695-702. https://doi.org/10.1016/j.cardfail.2008.06.004

[17] Alexander K, Jun Y, Kaestle SM, et al. Lung endothelial dysfunction in congestive heart failure: role of impaired Ca^{2+} signaling and cytoskeletal reorganization. Circulation Research 2010; 106(6): 1103. https://doi.org/10.1161/CIRCRESAHA.109.210542

[18] Guazzi M,., Pontone G,., Brambilla R,., et al. Alveolar-capillary membrane gas conductance: a novel prognostic indicator in chronic heart failure. Eur Heart J 2002; 23(6): 467-476. https://doi.org/10.1053/euhj.2001.2803

[19] Ten Freyhaus H, Berghausen EM, Janssen W, et al. Genetic Ablation of PDGF-Dependent Signaling Pathways Abolishes Vascular Remodeling and Experimental Pulmonary Hypertension. Arterioscler Thromb Vasc Biol. 2015; 35(5): 1236-1245. https://doi.org/10.1161/ATVBAHA.114.304864

[20] Harvey RM, Enson Y,., Ferrer MI. A reconsideration of the origins of pulmonary hypertension. Chest 1971; 59(1): 82-94. https://doi.org/10.1378/chest.59.1.82

[21] Robert N, Jean-Luc V, Patrick Y, et al. The transpulmonary pressure gradient for the diagnosis of pulmonary vascular disease. Eur Respir J 2013; 41(1): 217-223. https://doi.org/10.1183/09031936.00074312

[22] Yingjie C, Haipeng G, Dachun X, et al. Left ventricular failure produces profound lung remodeling and pulmonary hypertension in mice: heart failure causes severe lung disease. Hypertension 2012; 59(6): 1170-1178. https://doi.org/10.1161/HYPERTENSIONAHA.111.186072

[23] Christian G, Mario G, Lang MB, et al. Diastolic pulmonary vascular pressure gradient: a predictor of prognosis in "out-of-proportion" pulmonary hypertension. Chest 2013; 143(3): 758-766. https://doi.org/10.1378/chest.12-1653

[24] Thiele H, Ohman EM, de Waha-Thiele S, et al. Management of cardiogenic shock complicating myocardial infarction: an update 2019. Eur Heart J 2019. https://doi.org/10.1093/eurheartj/ehz363

[25] Holmberg MJ, Issa MS, Moskowitz A, et al. Vasopressors During Adult Cardiac Arrest: A Systematic Review and Meta-Analysis. Resuscitation 2019. https://doi.org/10.1016/j.resuscitation.2019.04.008

[26] Mentz RJ, Metra M, Cotter G, et al. Early vs. late worsening heart failure during acute heart failure hospitalization: insights from the PROTECT trial. Eur J Heart Fail 2015; 17(7): 697-706. https://doi.org/10.1002/ejhf.308

[27] Sarkar J, Golden PJ, Kajiura LN, et al. Vasopressin decreases pulmonary-to-systemic vascular resistance ratio in a porcine model of severe hemorrhagic shock. Shock 2015; 43(5): 475-482. https://doi.org/10.1097/SHK.0000000000000325

[28] Sugawara Y, Mizuno Y, Oku S, et al. Effects of vasopressin during a pulmonary hypertensive crisis induced by acute hypoxia in a rat model of pulmonary hypertension. Br J Anaesth 2019; 122(4): 437-447. https://doi.org/10.1016/j.bja.2019.01.014

[29] Hussain MB, Marshall I,. Characterization of alpha1-adrenoceptor subtypes mediating contractions to phenylephrine in rat thoracic aorta, mesenteric artery and pulmonary artery. British Journal of Pharmacology 2010; 122(5): 849-858.https://doi.org/10.1038/sj.bjp.0701461

[30] Caldini P,., Permutt S,., Waddell JA, et al. Effect of epinephrine on pressure, flow, and volume relationships in the systemic circulation of dogs. Circulation Research 1974; 34(5): 606-23. https://doi.org/10.1161/01.res.34.5.606

[31] Russell JA, Walley KR, Joel S, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. N Engl J Med 2008; 358(9): 877-887. https://doi.org/10.1056/NEJMoa067373

[32] Guazzi M, Borlaug BA. Pulmonary hypertension due to left heart disease. Circulation 2012; 126(8): 975-90. https://doi.org/10.1161/CIRCULATIONAHA.111.085761

[33] Abraham WT, Adamson PB, Bourge RC, et al. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. Lancet 2011; 377(9766): 658-666. https://doi.org/10.1016/S0140-6736(11)60101-3

[34] Salem M, Al-Saffar F, Hall S. Management of Pulmonary Hypertension in Patients on Left Ventricular Assist Device Support. Rev Cardiovasc Med. 2022; 23(9): 308. Published 2022 Sep 13. https://doi.org/10.31083/j.rcm2309308

[35] Torre-Amione G, Southard RE, Loebe MM, et al. Reversal of secondary pulmonary hypertension by axial and pulsatile mechanical circulatory support. The Journal of Heart and Lung Transplantation 2010; 29(2): 195-200. https://doi.org/10.1016/j.healun.2009.05.030