MEDWIN PUBLISHERS
Committed to Create Value for Researchers

Open Access Journal of Cardiology
ISSN: 2578-4633

Pulmonary Vasodilators in LVAD Patients: A Never-Ending Debate

Benedetto M*, Piccone G, Roncarati V and Baiocchi M

Cardiothoracic Anaesthesia and Intensive Care Unit Sant'Orsola University Hospital, Italy

***Corresponding author:** Maria Benedetto, Cardiothoracic Anaesthesia and Intensive Care Unit Sant'Orsola University Hospital, Bologna, Italy, Email: mariabenedettoanestesista@gmail.com

Mini Review

Volume 5 Issue 1

Received Date: November 24, 2021

Published Date: December 15, 2021

DOI: 10.23880/oajc-16000166

Abstract

Left ventricular assist device is a life-saving option in patients with end-stage left heart failure. It leads to a decrease of pulmonary arterial pressure, wedge pressure and pulmonary vascular resistences. However, a post capillary pulmonary hypertension persists in a significant proportion of patients despite adequate LV unloading. A possible explanation is the pulmonary venous congestion and subsequent decrease in the level of nitric oxide. This observation has led to an increased interest for pulmonary vasodilators, especially phosphodiesterase 5 inhibitors (PD-5 I). They enhance the nitric oxide (NO) signaling through the increase of cyclic guanosine monophosphate availability. Sildenafil allows to tritate down the iNO and succesfully extubated the patient; it has been shown to significantly reduce mPAP and PVR 2-4 weeks after LVAD implantation and to wean from inotropic support within the first 72 hours. However, whereas literature seems to support its use in the immediate postoperative period, there are not enough evidences about their long term use.

Keywords: Pulmonary Vasodilators; Patients; Dysfunction

Abbreviations: LVAD: Left Ventricular Assist Device; LV: Left Ventricle; PAP: Pulmonary Arterial Pressure; PCWP: Pulmonary Capillary Wedge Pressure; PVR: Pulmonary Vascular Resistance; PH: Pulmonary Hypertension; CO: Cardiac Output; TPG: Transpulmonary Pressure Gradient.

Introduction

Left ventricular assist device (LVAD) is a life-saving option in patients affected by end-stage left heart disease. It can represent a bridge to recovery, a bridge to heart transplant or a destination therapy. In all these cases, the occurrence of right ventricular failure (RVF) may dramatically affect the clinical outcomes and patient's candidacy to heart transplant. RVF incidence after continuous-flow LVADs ranges from 20 to 40% [1,2] with a mortality rate of 40 to 50% [3,4]. The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) has provided a definition for RVF following LVAD implantation [5]. This includes signs and symptoms of right ventricle (RV) dysfunction: central venous pressure (CVP) > 18 mm Hg and cardiac index (CI) < 2.0 L/min/m2), with a pulmonary capillary wedge pressure (PCWP) >18 mm Hg, requirement of a RV assist device (RVAD), or requirement of inhaled nitric oxide (iNO), or prolonged-duration inotropic support. Possible mechanisms of RVF after LVAD implantation may include the acutely increased venous return to the RV, the leftward shift of the interventricular septum, atrial and ventricular arrhythmias which may occur in approximately 20% of patients. Furthermore, an excessive perioperative fluid challenge may exacerbate RV dilation [6].

Pulmonary Hypertension in LVAD Patients

Mechanical unloading of the left ventricle (LV) leads to a decrease of Pulmonary Arterial Pressure (PAP), Pulmonary

Capillary Wedge Pressure (PCWP) and Pulmonary Vascular Resistance (PVR), due to decongestion of the pulmonary circulation. However, pulmonary hypertension (PH) persists in a significant proportion of patients after LVAD positioning, despite adequate LV unloading. This is a postcapillary PH defined by a mean PAP (mPAP) ≥ 25 mmHg in the presence of an abnormally elevated PCWP > 15 mm Hg and a normal or reduced cardiac output (CO). It is classified as Group 2 PH according to current guidelines [7,8]. This subgroup of patients with PH type 2 exhibits high PVR and transpulmonary pressure gradient (TPG), which are characteristics of Group 1 precapillary PH. A possible explanation is the pulmonary venous congestion and subsequent decrease in the level of nitric oxide, with contemporary increase in the level of endothelin expression that bring to pulmonary vasoconstriction and vascular remodeling [8-10]. This observation led to an increased interest in pulmonary vasodilators, especially phosphodiesterase 5 inhibitors (PD-5 I), in order to target the adverse pulmonary vascular remodeling and prevent post-LVAD RVF.

Phosphodiesterase-5 Inhibitors (Pde5i) and LVAD

PDE5i are pulmonary vasodilators most frequently used to unload the RV in LVAD patients. However, supporting literature with big sample size studies is still lacking. The oral PDE5i (sildenafil and tadalafil) are already recognized as a treatment option in Group 1 PH either as a monotherapy or in combination with other pulmonary vasodilators (endothelin receptor antagonists, PDE3i, and prostanoids). They act enhancing the nitric oxide (NO) signaling through the increase of cyclic guanosine monophosphate (cGMP) levels [11-13]. INO is the first step in preventing and treating RVF after LVAD surgery [14-16]. However, the need of mechanical ventilation may itself affect RV function. Furthermore, there can be a rebound effect on PAPs after its discontinuation. Sildenafil allows titrating down the iNO and successfully extubate the patient, with less rebound effect on PVR and less risk of metahemoglobinemia [18]. Sildenafil has been shown to significantly reduce mPAP and PVR 2-4 weeks after LVAD implantation and to wean from inotropic support within the first 72 hours [17]. However, no significant differences between sildenafil and control groups have been found for either PCWP or CO [18]. Despite the possible side effects of dizziness, nausea, systemic hypotension, no significant increase in gastrointestinal bleeding and stroke have been found. This is noteworthy given the potential for platelet inhibition with PDE5i [19].

Discussion and Conclusion

Promising effects of sildenafil therapy are well accepted in critically ill patients with RV disfunction (INTERMACS CLASS 2.3) [20]. However, literature is made mainly by observational small sample size studies that limit the power to achieve statistically significant results. Furthermore, there is no a predefined algorithm to guide sildenafil use after LVAD placement. Patients with combined pre and postcapillary PH or significant RV dysfunction would be the ideal target subgroups for this treatment. Similarly, there are ongoing studies about indications and efficacy of other pulmonary vasodilators. Currently, the prospective, randomized clinical trial SOPRANO (about the role of Macitentan in patients with PH after LVAD implantation) may be a further step in understanding the role of pulmonary vasodilators in LVAD patients. The International Society for Heart and Lung Transplantation guidelines for mechanical circulatory support recommend the use of pulmonary vasodilators additional to diuretics and inotropes for the treatment of RVF after LVAD. The recommended agents include iNO or inhaled prostacyclin (Class I, Level of evidence C) as well as PDE5I (Class IIb, Level of evidence C). However, they largely represent expert opinions and are based on several small studies [21].

In conclusion, whereas literature seems to support the use of pulmonary vasodilators in the immediate postoperative period of LVAD surgery, we still do not know enough about their long-term use in order to prevent late RVF. Promising results come from the evidence that sildenafil profoundly reduces RV afterload and volumes, predominantly through relief of pericardial constraint, without effects on RV contractility [22]. These findings may potentially support further studies on the role of PDE5i in protecting RV function in advanced heart failure or in patients at high risk of developing RVF.

References

1. Grant AD, Smedira NG, Starling RC, Marwick TH (2012) Independent and incremental role of quantitative right ventricular evaluation for the prediction of right ventricular failure after left ventricular assist device implantation. J Am Coll Cardiol 60(6): 521-528.

2. Kormos RL, Teuteberg JJ, Pagani FD, Russell SD, John R, et al. (2010) Right ventricular failure in patients with the HeartMate II continuous-flow left ventricular assist device: incidence, risk factors, and effect on outcomes. J Thorac Cardiovasc Surg 139(5): 1316-1324.

3. Baumwol J, Macdonald PS, Keogh AM, Kotlyar E, Spratt P, et al. (2011) Right heart failure and "failure to thrive" after left ventricular assist device: clinical predictors and outcomes. J Heart Lung Transplant 30(8): 888-895.

4. Neragi-Miandoab S, Goldstein D, Bellow R, Michler R, et al. (2012) Right ventricular dysfunction following

continuous flow left ventricular assist device placement in 51 patients: predictors and outcomes. J Cardiothorac Surg 7: 60.

5. LaRue SJ, Raymer DS, Pierce BR, Nassif ME, Christopher TS, et al. (2017) Clinical outcomes associated with INTERMACS-defined right heart failure after left ventricular assist device implantation. J Heart Lung Transplant 36(4): 475-477.

6. Brisco MA, Sundareswaran KS, Milano CA, Feldman D, Testani JM, et al. (2014) Incidence, risk, and consequences of atrial arrhythmias in patients with continuous-flow left ventricular assist devices. J Card Surg 29(4): 572-580.

7. Papathanasiou M, Ruhparwar A, Kamler M, Rassaf T, Luedike P (2020) Off-label use of pulmonary vasodilators after left ventricular assist device implantation: Calling in the evidence. Pharmacol Ther 214: 107619.

8. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, et al. (2015) ESC/ERS Guidelines 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 Respir J 46(4): 903-975.

9. Delgado JF, Conde E, Sanchez V, Lopez-Rios F, Gomez-Sanchez MA, et al. (2005) Pulmonary vascular remodelling in pulmonary hypertension due to chronic heart failure. Eur J Heart Fail 7(6):1011-1016.

10. Vachiery JL, Adir Y, Barbera JA, Champion H, Coghlan JG, et al. (2013) Pulmonary hypertension due to left heart diseases. J Am Coll Cardiol 62(25 Suppl): D100-108.

11. Prasad S, Wilkinson J, Gatzoulis MA (2000) Sildenafil in primary pulmonary hypertension. N Engl J Med 343(18): 1342.

12. Galie N, Corris PA, Frost A, Girgis RE, Granton J, et al. (2013) Updated treatment algorithm of pulmonary arterial hypertension. J Am Coll Cardiol 62(25 Suppl): 60-72.

13. Vachiery JL, Delcroix M, Al-Hiti H, Efficace M, Hutyra M, et al. (2018) Macitentan in pulmonary hypertension due to left ventricular dysfunction. Eur Respir J 51(2): 1701886.

14. Potapov E, Meyer D, Swaminathan, M, Ramsay M, Banayosy AE, et al. (2011) Inhaled nitric oxide after left ventricular assist device implantation: A prospective, randomized, double-blind, multicenter, placebo-controlled trial. J Heart Lung Transplant 30(8): 870-878.

15. Argenziano M, Choudhri AF, Moazami N, Rose EA, Smith CR, et al. (1998) Randomized, double-blind trial of inhaled nitric oxide in LVAD recipients with pulmonary hypertension. Ann Thorac Surg 65(2): 340-345.

16. Benedetto M, Romano R, Baca G, Sarridou D, Fischer A, et al. (2015) Inhaled nitric oxide in cardiac surgery: Evidence or tradition? Nitric Oxide 49: 67-79.

17. Klodell CT, Morey TE, Lobato EB, Aranda JM et al. (2007) Effect of sildenafil on pulmonary artery pressure, systemic pressure, and nitric oxide utilization in patients with left ventricular assist devices. Ann Thorac Surg 83(1): 68-71.

18. Tedford RJ, Hemnes AR, Russell SD, Wittstein IS, Mahmud M, et al. (2008) PDE5A inhibitor treatment of persistent pulmonary hypertension after mechanical circulatory support. Circ Heart Fail 1(4): 213-219.

19. Ravichandran AK, LaRue SJ, Novak E, Joseph SA, Schilling JD (2018) Sildenafil in Left Ventricular Assist Device is safe and well-tolerated. ASAIO 64(2): 280-281.

20. Hamdan R, Mansour H, Nassar P, Saab M (2014) Prevention of right heart failure after left ventricular assist device implantation by phosphodiesterase 5 inhibitor. Artif Organs 38(11): 963-967.

21. Felman D, Pamboukian SV, Teuteberg JJ, Birks E, Lietz K, et al. (2013) The 2013 International Society for Heart and Lung Transplantation Guidelines for mechanical circulatory support: executive summary. J Heart Lung Transplant 32(2): 157-187.

22. Monzo L, Reichenbach A, Al-Hiti H , Borlaug BA, Havlenova T, et al. (2021) Acute Unloading Effects of Sildenafil Enhance Right Ventricular-Pulmonary Artery Coupling in Heart Failure. J Card Fail 27(2): 224-232.