Diastolic Pulmonary Artery to Pulmonary Capillary Wedge Pressure Difference: A Predictor of Outcome After Left Ventricular Assist Device Implantation

Irene M. Lang, MD

At present, implantable left ventricular assist devices (LVADs) represent the only available and effective alternative to heart transplantation for end-stage heart failure, and may be utilized within a broad spectrum of indications, including bridge to heart transplantation or recovery, or destination therapy. Right ventricular (RV) function is an independent prognostic factor in patients with chronic heart failure.[1] RV failure after LVAD implantation for chronic heart failure treatment portends a particularly poor prognosis. However, many aspects of RV failure following LVAD implantation are still uncertain. What has been observed is that immediately after device implantation, the left ventricle is decompressed, causing a leftward shift of the interventricular septum, which reduces its mechanical contractile properties. In addition, RV output must match the flow generated by the device. In this setting, the RV is sensitive to its afterload, which is driven by elevated left atrial pressure and is further increased by elevated small vessel resistance in the setting of preexisting heart failure, operative stress, inflammation, and shear stress. Several hemodynamic parameters have been examined to reflect RV afterload in pulmonary hypertension caused by left heart disease, including the diastolic pulmonary artery to pulmonary capillary wedge pressure difference or gradient (DPG).[2]

In this issue of the *Journal of the American Heart Association* (*JAHA*), Imamura and colleagues[3] investigated the impact of a DPG >5 mm Hg on outcomes of LVAD assessed by right heart function measurements with echocardiography and hemocompatibility-related adverse events. While this is a small study (92 patients, with few data on the pre-LVAD hemodynamics), and even fewer data (≈69 patients undergoing complete RV functional measurements), it presents novel, clinically meaningful data.

Research in the area of precapillary pulmonary hypertension has seen major advances over the past years in terms of genetics, vascular biology, and treatments, but PH-LHD has generally remained poorly understood. In the current work, Imamura and colleagues[3] have utilized a DPG of >5 mm Hg in a prospective study setting to predict outcomes after LVAD implantation. A threshold of 5 has been described in early work[4] to discriminate cardiac from pulmonary causes of increased vascular resistance. Imamura and colleagues[3] found that almost half of the patients (48%) had a DPG >5 mm Hg, suggesting a pulmonary vascular disturbance. Of 71 patients who had pre-LVAD hemodynamic data, 33 had post-LVAD DPG >5 mm Hg, with 13 of 33 who had persistent DPG >5 mm Hg before and after LVAD implantation, and 20 of 33 who experienced a de novo elevation of DPG >5 mm Hg. The authors' main finding was a DPG >5 mm Hg irrespective of pulmonary artery wedge pressure in almost 50% of clinically stable LVAD patients. A DPG >5 mm Hg was associated with worsening RV function and a higher incidence of RV failure within 10 months after LVAD implantation, and significantly higher rates of hemocompatibility-related adverse events, which defines any nonsurgical bleeding, thromboembolic event, pump thrombosis, or neurological events.

While, for example, the elevation in the right atrial to pulmonary artery wedge pressure (RA/pulmonary artery wedge pressure) ratio may be a hemodynamic marker for poor postoperative outcomes including length of stay and RV function in patients undergoing LVAD implantation,[5] DPG is a novel hemodynamic biomarker for LVAD outcomes. In the past, DPG has mainly been used to diagnose pulmonary causes of heart failure,[4] or to prognosticate pulmonary hypertension caused by left heart disease. RV afterload is driven by elevated left atrial pressure in isolated postcapillary PH. When mean pulmonary artery pressure is

From the Division of Cardiology, Department of Internal Medicine II, Vienna General Hospital, Vienna, Austria.

Correspondence to: Irene M. Lang, MD, Division of Cardiology, Department of Internal Medicine II, Medical University of Vienna, Währinger Gürtel 18-20, 1090 Vienna, Austria. E-mail: irene.lang@meduniwien.ac.at

J Am Heart Assoc. 2020;9:e016110. DOI: 10.1161/JAHA.120.016110.

Table. DPG as Predictor of Survival in PH-LHD

Study	N	Model	Predictive Role of DPG
Gerges C et al *Chest* 2013[2]	1094	Multivariable	+
Tedford RJ et al *J Heart Lung Transplant* 2014[19]	16 811	Univariable	–
Tampakakis et al *JACC Heart Fail* 2015[20]	469	Multivariable	–
Dragu R et al *Eur J Heart Fail* 2015[9]	164	Univariable	+
Zotter-Tufaro C et al *JACC Heart Fail* 2015[10]	148	Multivariable	+
Al-Naamani N et al *JACC Heart Fail* 2015[21]	73	Univariable	–
Gerges M et al *AJRCCM* 2015[8]	1454	Multivariable	+
O'Sullivan CJ, et al *Circ Cardiovasc Intervent* 2015[11]	325	Multivariable	+
Mazimba S et al *Respir Med* 2016[12]	225	Multivariable	+
Rezaee ME et al *Clin Cardiol* 2016[13]	510	Univariable	+
Yamabe S et al *Circ J* 2016[14]	243	Univariable	+
Ibe T et al *J Cardiol* 2016[15]	164	Univariable	+
Naeije R et al *Circ Heart Fail* 2017[16]	636	Multivariable	+
Brunner NW et al *Catheter Cardiovasc Interv* 2017[22]	133	Multivariable	–
Palazzini M et al *Eur J Heart Fail* 2018[23]	276	Univariable	–
Vanderpool R et al *JAMA Cardiol* 2018[17]	10 023	Multivariable	+
Albers EL et al *Pediatr Transplant* 2018[18]	1468	Multivariable	+
Alnsasra A et al *JAHA* 2019[25]	268	Multivariable	+

DPG indicates diastolic pulmonary artery to pulmonary capillary wedge pressure difference or gradient; and PH-LHD, pulmonary hypertension caused by left heart disease.

disproportional to left atrial pressure because of a contribution of arterial and venous pulmonary vascular disease,[6] combined post- and precapillary PH is present.[7] According to a large hemodynamic database,[7] combined post- and precapillary PH is predicted by a DPG ≥7 mm Hg, and associated with decreased right ventricular-pulmonary vascular coupling and increased mortality.[8] The prognostic relevance of DPG has been confirmed in some reports,[2,8–18] but has also been refuted by others[19–23] (Table). Because of discordant data sets that are mainly based on discordant populations of patients, the 2018 World Meeting on Pulmonary hypertension groups have redefined postcapillary PH as mean pulmonary artery pressure >20 mm Hg and PAWP >15 mm Hg; and if these criteria apply, then isolated postcapillary-PH is defined by a PVR ≤3 (Wood Units); and combined post- and precapillary PH is defined when PVR >3 WU, thus eliminating DPG from the definition.[24]

While the data of Imamura and colleagues[3] lend further support to the meaningfulness of DPG, their study is limited by a lack of follow-up data and information on medical therapy changes. A further limitation is the authors' use of the term diastolic pulmonary artery pressure to pulmonary artery wedge pressure (*PADP-PCWP*) *decoupling* for the description of a DPG of >5 mm Hg. In pulmonary hypertension, the RV adapts to the increasing vascular load by enhancing contractility to maintain flow, which is termed "coupling." "Coupling" is a measure of energy transfer from the RV to the pulmonary circulation and can be assessed from the ratio between end-systolic elastance and arterial elastance. While DPG may serve as a surrogate for pulmonary small vessel resistance that is a strong determinant of ventriculoarterial coupling, the authors' use of the term *decoupling* must be carefully separated from the term *uncoupling*, which describes RV failure from a conductance catheterization standpoint.

Taken together, Imamura and colleagues[3] provide new support for the role of pulmonary resistance vessels determining RV afterload and outcomes after LVAD implantation, and for the concept that DPG may serve as a "hemodynamic lung biopsy."

Disclosures

Lang has relationships with drug companies including AOPOrphan Pharmaceuticals AG, Actelion-Janssen, MSD, Medtronic, and Ferrer. In addition to being investigator in trials involving these companies, relationships include consultancy service, research grants, and membership of scientific advisory boards.

References

1. Ghio S, Gavazzi A, Campana C, Inserra C, Klersy C, Sebastiani R, Arbustini E, Recusani F, Tavazzi L. Independent and additive prognostic value of right ventricular systolic function and pulmonary artery pressure in patients with chronic heart failure. *J Am Coll Cardiol*. 2001;37:183–188.
2. Gerges C, Gerges M, Lang MB, Zhang Y, Jakowitsch J, Probst P, Maurer G, Lang IM. Diastolic pulmonary vascular pressure gradient: a predictor of prognosis in "out-of-proportion" pulmonary hypertension. *Chest*. 2013;143:758–766.
3. Imamura T, Narang N, Kim G, Raikhelar J, Chung B, Nguyen A, Holzhauser L, Rodgers D, Kalantari S, Smith B, et al. Decoupling between diastolic pulmonary artery and pulmonary capillary wedge pressures is associated with right ventricular dysfunction and hemocompatibility-related adverse events in patients with left ventricular assist devices. *J Am Heart Assoc*. 2020;9: e014801. DOI: 10.1161/JAHA.119.014801.
4. Buchbinder N, Ganz W. Hemodynamic monitoring: invasive techniques. *Anesthesiology*. 1976;45:146–155.
5. Bhat G, Ali A, Yost G, Tatooles G. Right atrial to pulmonary capillary wedge pressure ratio as predictor for postoperative outcomes in left ventricular assist device implantation. *J Heart Lung Transplant*. 2017;36:S341.
6. Fayyaz AU, Edwards WD, Maleszewski JJ, Konik EA, DuBrock HM, Borlaug BA, Frantz RP, Jenkins SM, Redfield MM. Global pulmonary vascular remodeling in pulmonary hypertension associated with heart failure and preserved or reduced ejection fraction. *Circulation*. 2018;137:1796–1810.
7. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, et al. 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;37:67–119.
8. Gerges M, Gerges C, Pistritto AM, Lang MB, Trip P, Jakowitsch J, Binder T, Lang IM. Pulmonary hypertension in heart failure. Epidemiology, right ventricular function, and survival. *Am J Respir Crit Care Med*. 2015;192:1234–1246.
9. Dragu R, Rispler S, Habib M, Sholy H, Hammerman H, Galie N, Aronson D. Pulmonary arterial capacitance in patients with heart failure and reactive pulmonary hypertension. *Eur J Heart Fail*. 2015;17:74–80.
10. Zotter-Tufaro C, Duca F, Kammerlander AA, Koell B, Aschauer S, Dalos D, Mascherbauer J, Bonderman D. Diastolic pressure gradient predicts outcome in patients with heart failure and preserved ejection fraction. *J Am Coll Cardiol*. 2015;66:1308–1310.
11. O'Sullivan CJ, Wenaweser P, Ceylan O, Rat-Wirtzler J, Stortecky S, Heg D, Spitzer E, Zanchin T, Praz F, Tuller D, et al. Effect of pulmonary hypertension hemodynamic presentation on clinical outcomes in patients with severe symptomatic aortic valve stenosis undergoing transcatheter aortic valve implantation: insights from the new proposed pulmonary hypertension classification. *Circ Cardiovasc Interv*. 2015;8:e002358.
12. Mazimba S, Mejia-Lopez E, Black G, Kennedy JL, Bergin J, Tallaj JA, Abuannadi M, Mihalek AD, Bilchick KC. Diastolic pulmonary gradient predicts outcomes in group 1 pulmonary hypertension (analysis of the NIH primary pulmonary hypertension registry). *Respir Med*. 2016;119:81–86.
13. Rezaee ME, Nichols EL, Sidhu M, Brown JR. Combined post- and precapillary pulmonary hypertension in patients with heart failure. *Clin Cardiol*. 2016;39:658–664.
14. Yamabe S, Dohi Y, Fujisaki S, Higashi A, Kinoshita H, Sada Y, Hidaka T, Kurisu S, Yamamoto H, Kihara Y. Prognostic factors for survival in pulmonary hypertension due to left heart disease. *Circ J*. 2016;80:243–249.
15. Ibe T, Wada H, Sakakura K, Ikeda N, Yamada Y, Sugawara Y, Mitsuhashi T, Ako J, Fujita H, Momomura S. Pulmonary hypertension due to left heart disease: the prognostic implications of diastolic pulmonary vascular pressure gradient. *J Cardiol*. 2016;67:555–559.
16. Naeije R, Gerges M, Vachiery JL, Caravita S, Gerges C, Lang IM. Hemodynamic phenotyping of pulmonary hypertension in left heart failure. *Circ Heart Fail*. 2017;10:e004082.
17. Vanderpool RR, Saul M, Nouraie M, Gladwin MT, Simon MA. Association between hemodynamic markers of pulmonary hypertension and outcomes in heart failure with preserved ejection fraction. *JAMA Cardiol*. 2018;3:298–306.
18. Albers EL, Bradford MC, Friedland-Little JM, Hong BJ, Kemna MS, Chen JM, Law YM. Diastolic pressure indices offer a novel approach to predicting risk of graft loss after pediatric heart transplant. *Pediatr Transplant*. 2018;22: 1–10.
19. Tedford RJ, Beaty CA, Mathai SC, Kolb TM, Damico R, Hassoun PM, Leary PJ, Kass DA, Shah AS. Prognostic value of the pre-transplant diastolic pulmonary artery pressure-to-pulmonary capillary wedge pressure gradient in cardiac transplant recipients with pulmonary hypertension. *J Heart Lung Transplant*. 2014;33:289–297.
20. Tampakakis E, Leary PJ, Selby VN, De Marco T, Cappola TP, Felker MG, Russell SD, Kasper EK, Tedford RJ. The diastolic pulmonary gradient does not predict survival in patients with pulmonary hypertension due to left heart disease. *JACC Heart Fail*. 2015;3:9–16.
21. Al-Naamani N, Preston IR, Paulus JK, Hill NS, Roberts KE. Pulmonary arterial capacitance is an important predictor of mortality in heart failure with a preserved ejection fraction. *JACC Heart Fail*. 2015;3:467–474.
22. Brunner NW, Yue SF, Stub D, Ye J, Cheung A, Leipsic J, Lauck S, Dvir D, Perlman G, Htun N, et al. The prognostic importance of the diastolic pulmonary gradient, transpulmonary gradient, and pulmonary vascular resistance in patients undergoing transcatheter aortic valve replacement. *Catheter Cardiovasc Interv*. 2017;90:1185–1191.
23. Palazzini M, Dardi F, Manes A, Bacchi Reggiani ML, Gotti E, Rinaldi A, Albini A, Monti E, Galie N. Pulmonary hypertension due to left heart disease: analysis of survival according to the haemodynamic classification of the 2015 ESC/ ERS guidelines and insights for future changes. *Eur J Heart Fail*. 2018;20:248–255.
24. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, Williams PG, Souza R. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J*. 2019;53: 1801913.
25. Alnsasra H, Asleh R, Schettle SD, Pereira NL, Frantz RP, Edwards BS, Clavell AL, Maltais S, Daly RC, Stulak JM, Rosenbaum AN, Behfar A, Kushwaha SS. Diastolic Pulmonary Gradient as a Predictor of Right Ventricular Failure After Left Ventricular Assist Device Implantation. *J Am Heart Assoc*. 2019; 8:e012073. DOI: 10.1161/JAHA.119.012073. (Epub Aug 14, 2019).

Key Words: Editorials • hemodynamics • pulmonary circulation