Characterization of Pulmonary Hypertension in Heart Failure Using the Diastolic Pressure Gradient

Limitations of a Solitary Measurement*

Neal A. Chatterjee, MD, Gregory D. Lewis, MD

When pulmonary hypertension (PH), defined by mean pulmonary artery pressure (mPAP) $\geq 25$ mm Hg, is associated with an abnormally elevated pulmonary capillary wedge pressure (PCWP) $>15$ mm Hg or left ventricular end-diastolic pressure (LVEDP) $>18$ mm Hg (1), it has been variably termed World Health Organization Group 2 PH (1), pulmonary venous hypertension (2), “post-capillary PH” (3), or “passive PH” (4). This type of PH is distinct from primary pulmonary arterial hypertension where there is no increase in left ventricular filling pressure (i.e., pre-capillary PH).

Patients with left ventricular dysfunction (LVD) may develop a pre-capillary pulmonary arterial contribution to PH, reflected by an increased transpulmonary gradient (TPG), defined as mPAP-PCWP that exceeds 12 to 15 mm Hg, or an elevated pulmonary vascular resistance (PVR), defined as TPG/cardiac output that exceeds 2.5 to 3 Wood units (5,6). This type of PH, which is “out of proportion” to underlying left-sided disease in the setting of normalized volume status, has been termed “mixed PH,” given both pre-capillary and post-capillary contributions to elevated PAP. In patients with LVD, a high pre-capillary contribution to PH has been associated with reduced exercise capacity (5,7), inefficient ventilation (8), and increased mortality in some studies (6,9–11) but not others (12). While a pre-capillary contribution to PH in LVD has historically been defined by an elevated TPG or PVR, there has been a recent shift in focus to pulmonary arterial diastolic pressure gradient (DPG), defined as: diastolic PAP - PCWP (mm Hg) (13). In comparison with TPG and PVR, DPG has been shown to be less sensitive to changes in left atrial pressure or changes in stroke volume (14), and therefore has been proposed to be a higher fidelity marker of pre-capillary pulmonary arterial remodeling and dysfunction in LVD (13,15,16).

At a time when the nomenclature and optimal assessment of PH-LVD continue to evolve (4,13) and the value of PH-LVD as a prognostic marker and therapeutic target remain under debate (17), the study by Tampakakis et al. (18) in this issue of JACC: Heart Failure is both important and timely. The study is a retrospective analysis of the Johns Hopkins Cardiomyopathy Database evaluating the prognostic significance of DPG in comparison to TPG and PVR in patients with LVD. In their primary analysis, the authors demonstrate that in patients with PH, increasing TPG and PVR are associated with a significant increased hazard ratio for all-cause mortality even following adjustment for standard covariates. In contrast, DPG (considered continuously and at multiple cut points) did not demonstrate a significant association with survival. Strengths of this study include: 1) the availability of hemodynamic data and complete follow-up from a center of excellence in...
precise hemodynamic measurements; 2) the thorough investigation of multiple potential cut points for DPG, TPG, and PVR as they relate to prognosis; and 3) the fulfillment of an unmet need to further investigate the prognostic significance of DPG, which was incorporated into recommendations of the 5th World Symposium on Pulmonary Hypertension (13) as the metric of choice for assessing pre-capillary PH in LVD based largely on a single outcomes study (15).

To put the findings by Tampakakis et al. (18) into context, it is important to examine the population studied in detail. The subjects were relatively young (average age 50 years) with a paucity of ischemic etiology of cardiomyopathy (7%). PH prevalence (40%) was lower than that reported in community cohorts of heart failure (79%) (19) as well as prevalence rates in heart failure referral populations (63% to 73%) (5,9). In addition, the prevalence of pre-capillary PH varied by the metric utilized (13% as defined by DPG ≥7 mm Hg; 31% as defined by TPG >12 mm Hg; 38% as defined by PVR ≥3 Wood units) and was similarly less prevalent than rates reported from studies performed in other heart failure populations (36% to 50%) (5,20). Young age and relatively new onset heart failure may explain the relatively low prevalence of PH in this cohort. Although comprehensive data was not available on co-morbidities, it is likely that conditions known to influence DPG (e.g., chronic obstructive pulmonary disease) (21) and/or PAP (e.g., reduced creatinine clearance, atrial fibrillation, anemia) (2,19) were relatively unrepresented in this population compared to the broader heart failure population.

The retrospective study design, which relied on reported hemodynamic values from multiple physicians, did not lend itself to a uniform core laboratory pre-specified approach to DPG measurements or uniform assessment of hemodynamic tracings. Values of DPG that cluster around 0 mm Hg are particularly sensitive to inherent errors with fluid-filled catheter measurements related to catheter motion artifact, as the authors acknowledge. The common finding of negative DPG values (e.g., ~1/3 of the PH group) that were associated with particularly high PCWPs raises the possibility that V waves from mitral regurgitation might have been variably integrated into PCWP measurements, thus contributing to negative DPG values. However, these limitations reflect real-world conditions in which the measurement has been recommended for deployment by recent guidelines (13), making the study highly clinically relevant.

The relatively rare prevalence of DPG-defined pre-capillary PH compared to TPG- or PVR-defined PH-LVD resulted in limited power to detect a significant association between DPG and mortality (i.e., only 62 patients had PH-LHD and DPG ≥7 mm Hg), though this concern is mitigated by the various DPG cut points examined. The magnitude of increased hazard for DPG as a continuous variable was similar to that of TPG (1.02 per unit increase for both in adjusted continuous variable analysis) yet the associations fell on either side of statistical significance (TPG, p = 0.046; DPG, p = 0.10 in adjusted analyses). In contrast, the relationship between PVR and mortality was highly significant in adjusted analysis (p = 0.002). Given the known relationship between PH and functional capacity in LVD (3,4), the investigation of additional endpoints beyond all-cause mortality (e.g., peak VO2, 6-min walk distance, heart failure hospitalizations) would have been of particular interest. Despite these limitations, the null findings of this study suggest that, in the heart failure community, widespread use of DPG as a prognostic variable may be premature, and that it is necessary to carefully compare this study to the previous landmark study of Gerges et al. (15) that drew opposite conclusions.

**DPG: Weighing Advantages and Disadvantages of Its Measurement**

Recent work has highlighted the important relationship between increasing left atrial pressure (LAP) and increasing pulmonary artery wave reflections due to reduced arterial compliance, with subsequent augmentation of pulmonary artery systolic pressures (22). As a result, mPAP and measurements that incorporate mPAP (TPG and PVR) are influenced by the degree of elevation in LAP/PCWP and therefore lack specificity as indicators of pulmonary vascular remodeling and dysfunction. To that end, DPG is an attractive descriptive metric of pre-capillary PH that is relatively immune to variability in cardiac output as well as the influence of elevated LAP on pulmonary arterial compliance (13,14). However, the findings of Tampakakis et al. (18) reported here challenge the real world use of DPG as both a descriptive and prognostic metric in LVD.

First, the fact that half of the patients in this study with elevated DPG (≥7 mm Hg) did not even have PH (i.e., mPAP <25 mm Hg) raises concern about the specificity of DPG for pulmonary vascular remodeling and dysfunction as an isolated variable. Second, the results of the Tampakakis et al. (18) study are concordant with those from a recent report of nearly 6,000 patients with advanced heart failure listed for heart transplantation that found no difference in survival in patients with elevated DPG (defined at multiple cut points) versus normal DPG, even within the subset of patients with PH-LVD (23).
In contrast to both of these studies, Gerges et al. (15) found that elevated DPG (≥7 vs. <7 mm Hg) was associated with worse median survival in patients with left heart disease (LHD) with PH and TPG >12 mm Hg. The study by Gerges et al. (15) was performed at a PH referral center in more than 1,000 patients selected on the basis of the presence of PH. Within the DPG ≥7 mm Hg group in the Gerges et al. (15) study, the TPG and DPG were approximately 30% higher than in the study by Tampakakis et al. (18). Patients in the Gerges et al. (15) study were older, with a higher burden of ischemic heart disease, and more severe heart failure, all of which may have impacted the prevalence of comorbidities that influence pulmonary vascular disease and survival (23).

Additionally, it is important to note that hemodynamic measurements in the study by Gerges et al. (15) were required to be over 8 cardiac cycles with standardized interpretation of data inclusive of handling of prominent ventricular waves in the setting of mitral regurgitation. Finally, in an exploratory analysis within the Gerges et al. (15) study, patients with TPG >12 mm Hg/elevated DPG (n = 9) demonstrated greater pathological pulmonary vascular remodeling compared to patients with TPG >12 mm Hg/normal DPG (n = 9), suggesting that elevated DPG (and not elevated TPG alone) identifies “true” pathological remodeling.

### OPTIMAL APPROACH TO PROGNOSTICATION IN PH-LVD: CONSIDERATION OF THE RIGHT VENTRICULAR-PULMONARY VASCULAR UNIT

Given the integrated nature of the right ventricular-pulmonary vascular (RV-PV) unit (17,23), we would propose that metrics that relate to pulmonary vascular pathophysiology (e.g., TPG, PVR, DPG) are most likely to translate to prognostic significance in LVD in the context of their relationship to RV-PV function. Integrated measures of RV-PV function clearly outperform more isolated measurements such as DPG in predicting clinical outcome in LVD (Table 1).

While proponents of DPG highlight the “load” and “flow” independence of the parameter, the superior performance of PVR (compared to TPG and DPG) in predicting survival in this study suggests that rather than viewing cardiac output as a source of error, it should be accounted for in performing assessment of PAP measurements. It is also important to emphasize that DPG accounts for a relatively modest percentage of the hemodynamic load faced by the RV (24). In addition to accounting for ramifications of pressure measurements on RV performance, serial measurements before and after provocation are likely to provide refinement of hemodynamic prognostication. Whether it is use of pre- and post-therapy hemodynamics (25), exercise provocation (8,26), acute vasoreactivity testing with selective pulmonary vasodilators (11), or continuous PAP measurement with implantable device therapy (27), there is mounting evidence that serial measurements of PAPs potentially predict functional capacity and outcomes in patients with heart failure.

### OPPORTUNITIES FOR REFINEMENT IN DEFINING PRE-CAPILLARY PH IN HEART FAILURE

This study raises many important questions regarding the use of contemporary measures of pre-capillary

#### TABLE 1 Prognostic Significance of Pulmonary Vascular Function Metrics in Patients With Left Ventricular Systolic Dysfunction

<table>
<thead>
<tr>
<th>First Author (N) (Ref. #)</th>
<th>Study Population</th>
<th>Measurement(s)</th>
<th>Comparison</th>
<th>Pulmonary Vascular Specificity</th>
<th>Degree of RV-PV Integration</th>
<th>Prognostic Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewis et al. (N = 60) (3)</td>
<td>HF, NYHA functional class II-IV</td>
<td>ΔPAP/ΔWork (rest + exercise)</td>
<td>Plateau pattern versus linear increment, RV uncoupling</td>
<td>+</td>
<td>+++</td>
<td>HR death 8.1</td>
</tr>
<tr>
<td>Ghi et al. (N = 377) (9)</td>
<td>HF, NYHA functional class II-IV</td>
<td>mPAP &gt;20 + RVEF &lt;35%</td>
<td>PH/reduced RVEF versus no PH/normal RVEF</td>
<td>+</td>
<td>+++</td>
<td>HR death 7.0</td>
</tr>
<tr>
<td>Cappola et al. (N = 1,134) (6)</td>
<td>PVR &gt;3 WU</td>
<td>PVR &gt;3 WU versus PVR &lt;2.5 WU</td>
<td>HR death 2.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tampakakis (N = 469) (18)</td>
<td>HF + HFrEF</td>
<td>PVR &gt;3 WU</td>
<td>PVR &gt;3 WU versus PVR &lt;3 WU</td>
<td>+</td>
<td>++</td>
<td>HR death 1.8</td>
</tr>
<tr>
<td>Chatterjee et al. (N = 101) (29)</td>
<td>HF, NYHA functional class II-III</td>
<td>TPG ≥12</td>
<td>TPG ≥12 versus &lt;12</td>
<td>++</td>
<td>++</td>
<td>HR death 3.2</td>
</tr>
<tr>
<td>Gerges et al. (N = 490) (15)</td>
<td>PH, PVR &gt;12</td>
<td>DPG ≥7</td>
<td>DPG ≥7 versus &lt;7</td>
<td>++++</td>
<td>+</td>
<td>Survival 78 versus 101 months</td>
</tr>
<tr>
<td>Tampakakis (N = 469) (18)</td>
<td>HFrEF + HFrEF</td>
<td>DPG ≥7</td>
<td>DPG ≥7 versus &lt;7</td>
<td>++++</td>
<td>+</td>
<td>HR death 0.91</td>
</tr>
</tbody>
</table>

All hazard ratios (HRs) and survival comparisons were significant with p < 0.05 with the exception of the bottom row. If not explicitly indicated, units for pressure measurement (e.g., mPAP, TPG, DPG) are mm Hg. DPG = diastolic pressure gradient; HFrEF = heart failure with preserved ejection fraction; HFrEF PVR = heart failure with reduced ejection fraction; mPAP = mean pulmonary artery pressure; NYHA = New York Heart Association; PVR = pulmonary vascular resistance; RV-PV = right ventricular-pulmonary vascular; RVEF = right ventricular ejection fraction; TPG = transpulmonary gradient; WU = Wood units.
PH in LVD. The fact that DPG can be readily calculated from right heart catheterization data with no added time, risk, or expense highlights the importance of continuing to understand how best to utilize the measurement. DPG— in contrast to TPG and PVR— may uniquely isolate pulmonary vascular pathological dysfunction (15). Going forward, we would propose that there is a need to evaluate: 1) a highly standardized approach to measuring DPG, including the contribution of V waves and a minimum number of cardiac cycles (e.g., 8), as implemented by Gerges et al. (15), with comparison of such an approach to that from routine catheterization reports within a single study to understand the effect of standardization on reclassification of PH subtype and prognostication; 2) further histopathologic and physiological studies to assess the degree to which DPG reflects abnormal pulmonary vascular remodeling and function as well as responses to interventions; 3) further assessment of the influence of heart failure comorbidities on DPG; and 4) reconsideration of the use of t-time resting hemodynamic measurements, as opposed to serial measurements with provocative testing, for PH classification and prognostication in patients with and without heart failure.

In summary, the study from Tampakakis et al. (18) highlights the descriptive and prognostic limitations of using resting DPG as an isolated measure of pre-capillary PH in a “real-world” heart failure referral population. Given the significant clinical implications of determining pre-capillary PH burden in patients with LVD (28), these data underscore the continued need to refine the definition of abnormal pulmonary vascular function in LVD. Different metrics of pre-capillary pulmonary hypertension may be better suited to identify pathological changes versus prognosis in heart failure, with more integrative measurements of RV-PV function providing superior prognostication but less specificity for the pulmonary vasculature. Because invasive hemodynamic evaluation continues to be considered the “gold standard” measure of PH in heart failure, studies such as this are critical to refine our knowledge of the utility, limitations, and applicability of these measurements in specific populations.

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REPRINT REQUESTS AND CORRESPONDENCE: Dr. Gregory D. Lewis, Heart Failure and Cardiac Transplantation Unit, Massachusetts General Hospital, Bigelow 800, Fruit Street, Boston, Massachusetts 02114. E-mail: glewis@partners.org.
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