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

The Conundrum of High and Low Diastolic Pulmonary Gradient

We read with interest the paper by Tampakakis et al. (1) and accompanying editorial by Chatterjee and Lewis (2) in a recent issue of JACC: Heart Failure refuting the prognostic value of the diastolic pulmonary gradient (DPG) (3). In addition to numerous limitations that are acknowledged both in the original paper and the editorial, it is important to point out details regarding the prognostic relevance of DPG.

Although there seems to be significant disagreement regarding the predictive role of DPG for pulmonary hypertension due to left heart disease, we concur with Tampakakis et al. (1) that very low DPGs predict poor outcome. In our original work (3), we reported flexible hazard ratio survival functions corrected for sex, age, ischemia, and creatinine clearance. In terms of DPG (data not shown in original paper), there was a bowl-shaped significant increase in hazard ratios for death (p < 0.001) (Figure 1), indicating that both high and very low DPGs predict poor outcome. In contrast to our patient population and contemporary heart failure (HF) populations, the cohort of Tampakakis et al. (1) was very young and represented rare HF subtypes, such as infiltrative, peripartum, viral, and drug-induced cardiomyopathies. An increased baseline heart rate of 94 beats/min compared with 78 beats/min in the original article (3) suggests that the data of Tampakakis et al. (1) were derived from a phenotypically more acute patient subset. Recent-onset HF may not have developed the same degree of pulmonary vascular disease, thus making the HF population of Tampakakis et al. (1) particularly unsuited for a prognostic assessment using DPG. The number of patients with pulmonary hypertension due to left heart disease and a DPG ≤7 mm Hg was low, explaining a lack of significance for prognosis (1). To substantiate that DPG is relevant for prognosis, we have recently demonstrated an upward/rightward shift of the pulmonary vascular resistance-compliance relationship with increasing DPGs. HF patients with higher DPGs have longer product of resistance and compliance times (4), which have served as strong prognostic indicators in patients with chronic HF (5).

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Graph depicting diastolic pulmonary gradient at baseline plotted against the log hazard ratio of death. Dashed lines mark confidence intervals of the hazard functions.
Measurement to Predict Survival: The Case of Diastolic Pulmonary Gradient

When I revived the diastolic pressure gradient (DPG), I never thought of introducing a new prognostic marker (1). The purpose was only to improve the diagnosis of pulmonary vascular disease in heart failure (HF). However, a subsequent report by Gerges et al. (2) showed that an increased DPG is associated with a shorter survival in these patients. Thus Gerges et al. (2) comforted the notion that a high DPG phenotypes a subset of patients with HF and severe pulmonary vascular disease evolving much alike pulmonary arterial hypertension.

In a recent issue of JACC: Heart Failure, Tampakakis et al. (3) reported that poor outcome in pulmonary hypertension on HF is related to a low DPG. How is such a contradiction possible? As discussed by the authors and the companion editorial (4), it is likely that right ventricular function adaptation to afterload matters more than just pulmonary hypertension. Furthermore, the DPG is a small number, most often <10 mm Hg (2,3), and thus within the range of errors on the measurement (5). This lack of precision explains reported negative gradients (3). If the “true” DPG is 0 to 2 mm Hg (as in most patients with HF [2,3]), but the measured DPG is randomly much higher or lower, it is easy to predict 30% to 40% negative values, as found by Tampakakis et al. (4). Because pulmonary vascular disease in HF is uncommon (2,3), this causes signals to drown into noise, with the risk of false-positive or false-negative outcome studies. Measurements of pulmonary vascular pressures with fluid-filled catheters are accurate but imprecise (5). Coping with insufficient precision requires careful analysis of pressure tracings (4) and repetition of measurements (5), as was done in the study by Gerges et al. (2) who measured the pressures over 8 cardiac cycles.

Measurements are not qualified according to prognostic capability only. Although depression scores are potent predictors of outcome in HF, they are of trivial diagnostic relevance. Conversely, diagnosing pulmonary hypertension that is not just the passive upstream transmission of increased filling pressures of the left heart may help to select patients who might benefit from therapies targeting the pulmonary circulation. The best is probably to add the DPG to the transpulmonary pressure gradient and pulmonary vascular resistance in defining inclusion criteria for future drug trials exploring this issue.

The report by Tampakakis et al. (3) and companion editorial (4) offer insight into the difficult diagnosis of pulmonary vascular disease in HF. The case of DPG shows that a variable can be diagnostic yet fail as a prognostic biomarker. This also happens the other way around.

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