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EDITORIAL

Right Ventricular/Pulmonary Artery Coupling in Patients With Heart Failure With Preserved Ejection Fraction: A Clue for Pulmonary Hypertension?

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Pulmonary hypertension (PH) in left heart disease is a common condition, primarily caused by backward transmission of an elevated left atrial pressure (this hemodynamic picture is defined as isolated postcapillary PH). Through poorly understood mechanisms, the increase in pulmonary venous pressure may cause a remodeling of the small pulmonary arteries with the development of a precapillary component that identifies a combined pre-post capillary PH.[1] As pulmonary vascular resistance increases, right ventricular (RV) adaptation to the increased afterload may fail, and abnormal RV systolic function develops during exercise and at rest. The development of PH in patients affected by heart failure has a relevant prognostic impact, increasing morbidity and mortality; and, in particular, when associated with RV dysfunction, it represents an adverse clinical turning point in the history of the disease.

See Article by Chen et al.

RV to pulmonary artery uncoupling has in fact been shown to be a powerful predictor of poor prognosis in all forms of heart failure, whether associated with reduced ejection fraction, mildly reduced ejection fraction, or preserved ejection fraction of the left ventricle (heart failure with preserved ejection fraction [HFpEF]). This occurs despite the fact that the determinants of a dysfunctioning right ventricle differ in all these conditions.[2] In particular, PH is by far the strongest correlate of RV dysfunction in patients with HFpEF and heart failure with mildly reduced ejection fraction, whereas in patients with heart failure with reduced ejection fraction, other conditions, such as atrial fibrillation and myocardial ischemia, are associated with RV dysfunction.[3] This is not completely unexpected, because heart failure with reduced ejection fraction and HFpEF may exhibit a similar pulmonary hemodynamic profile (and similar outcomes) but are characterized by important differences in the underlying clinical causes, in comorbidities, in triggers, and in molecular pathways for pulmonary vascular injury and, finally, in type and extent of remodeling of the left ventricular and the RV chambers.[4,5] In clinical practice, PH in advanced heart failure is a contraindication for heart transplantation as the RV of the new heart could not be able to adapt toward the high afterload of the native pulmonary circulation.[6]

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A different pathophysiological setting is present in patients who need a left ventricular assist device: the implant of the device causes an unload of the left ventricle, a decrease in left atrial pressure, an increase in systemic cardiac output, and an increase of the RV venous return. Despite the positive changes provided by left ventricular assist device support, RV function may acutely worsen and RV failure may occur. Indeed, if the pulmonary vascular resistance does not decrease because of pulmonary vascular remodeling, the RV may not be able to cope with the increased preload and may enlarge, developing severe tricuspid regurgitation and systolic dysfunction.[7] On the other hand, the long-term reduction in left atrial pressure guaranteed by left ventricular assist device could cause a significant reduction of pulmonary vascular resistance even in combined pre-post capillary PH, with a recovery of RV systolic function.[8]

As widely demonstrated, PH can also have a negative impact on the clinical course of patients with HFpEF. In this case, PH can be misdiagnosed as idiopathic pulmonary arterial hypertension if a hemodynamic evaluation is not performed or if the right heart catheterization is assessed under optimal diuretic therapy, resulting in normalization of wedge pressure.[6] The correct identification of such patients has an important therapeutic implication as the treatment with specific pulmonary arterial hypertension drugs in this population is not effective and probably harmful for the risk of systemic and pulmonary congestion. Thus, an accurate echocardiographic evaluation and a fluid challenge during the hemodynamic assessment are critical for the definitive diagnosis of PH-Left heart disease.

In this issue of the *Journal of the American Heart Association* (*JAHA*), Zheng-Wei Chen and colleagues report an interesting and pathophysiologically sound study with the aim of identifying echocardiographic parameters predictive of PH in patients affected by HFpEF.[9] In line with previous findings, the authors found that 60.18% of the overall population had PH, defined as mean pulmonary artery pressure (mPAP) ≥20 mm Hg. Among these patients, 60% had isolated postcapillary PH, 13% had combined pre-post capillary PH, and 8% had precapillary PH. The remaining 19% were not classified as pulmonary artery wedge pressure was not measured for a technical reason. Interestingly, the study emphasizes that ≈5% of these patients have precapillary PH with characteristics that make them similar to patients with pulmonary arterial hypertension with cardiovascular risk factors. These data support the hypothesis by Opitz and colleagues on the existence of a continuum between idiopathic pulmonary arterial hypertension, pulmonary arterial hypertension with cardiovascular risk factors, and precapillary PH and HFpEF.[10]

In the group of 45 patients without PH at rest, the authors found that 16 presented exercise-induced PH, defined as mPAP/cardiac output >3 mm Hg/L per minute. This increase could be attributable to an increase in pulmonary artery wedge pressure, a consequence of the left ventricular diastolic dysfunction, or reduced vascular reserve as a result of anatomic vascular remodeling. However, the lack of pulmonary artery wedge pressure values during exercise makes it impossible to differentiate these conditions. Although not the aim of the study, this analysis could have provided added value to the article by highlighting the possible presence of anatomic reduction of the pulmonary vascular reserve even in patients with exercise-induced PH.

To identify the best echocardiographic variable predicting PH in HFpEF, in the multivariate regression analysis, the authors constructed 4 models, 2 including rest parameters and 2 including stress parameters. The tricuspid annular plane systolic excursion (TAPSE)/pulmonary artery systolic pressure (PASP) ratio, a noninvasive surrogate of the RV–pulmonary artery coupling, was a predictor of exercise pulmonary artery wedge pressure and exercise mPAP in all the models. Interestingly, the tricuspid regurgitation peak gradient significantly correlated to PH in the univariate analysis, and part of the TAPSE/PASP ratio formula itself predicted exercise mPAP in only 1 model. The inclusion of other echocardiographic parameters' expression of diastolic dysfunction in the multivariate analysis could justify this unexpected result.

In line with the findings of the multivariate analysis, the receiver operating characteristic curves confirmed the role of TAPSE/PASP ratio as a good predictor of PH (area under the curve, 0.78), together with Tricuspid anular systolic velocity (TAS')/PASP (area under the curve, 0.74). The best cutoff values for the identification of patients with PH were ≤0.62 mm/mm Hg for TAPSE/PASP and ≤0.47 cm/s per mm Hg for TAS'/PASP. The need to combine 2 parameters arises from their different accuracy. Indeed, for these cutoffs, TAPSE/PASP has a high specificity (86.11%), whereas TAS'/PASP has a high sensitivity (82.7%).

The optimal cutoff value of TAPSE/PASP, identified by Chen et al, was close to the highest quartile of the population studied by Guazzi and colleagues:[11] patients with heart failure with TAPSE/PASP >0.64 mm/mm Hg had the most favorable clinical and prognostic profile. This means that even mild TAPSE/PASP impairment is indicative of abnormal pulmonary pressures. For exercise PH, neither TAPSE/PASP nor TAS'/PASP showed a good accuracy for the identification of this condition. The different accuracy of TAPSE/PASP and TAS'/PASP in predicting PH at rest and during exercise needs a plausible mechanism. Being an expression of RV–pulmonary artery coupling, TAPSE/PASP decreases when the RV is no longer able to cope with the increased afterload. In patients with normal mPAP at rest, but stress-induced PH, TAPSE/PASP is not

impaired thanks to the ability of the RV to support the increased afterload during exercise.

We finally found intriguing that the authors used TAPSE/PASP not for prognostic purposes but for diagnostic purposes (ie, for an early detection of PH). This novel use of this noninvasive indicator of RV to pulmonary artery uncoupling in heart failure may rely on the particular sensitivity of the right ventricle to the increased afterload in HFpEF, which may cause earlier occurrence of RV to pulmonary artery uncoupling when PH occurs in HFpEF.

In conclusion, the article of Chen and colleagues reinforces the importance of diagnosing PH in HFpEF and emphasizes the role of mild TAPSE/PASP and TAS'/PASP impairment in the early identification of PH in this subgroup of patients.

ARTICLE INFORMATION

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