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The Quest for Biomarker Discovery in Pulmonary Arterial Hypertension: The Right Takes Lessons from the Left

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Pulmonary arterial hypertension (PAH) is a severe form of cardiopulmonary disease that is characterized by plexogenic, hypertrophic, and fibrotic remodeling of distal pulmonary arterioles. Although abnormal pulmonary vasoreactivity and increased vasoconstriction occurs in the setting of these maladaptive changes to blood vessel phenotype, the 5-year mortality rate for PAH remains elevated even in the contemporary era of pulmonary vasodilator therapy.¹ An obvious approach to address this is the development of novel therapeutics that target the pathogenesis of vascular remodeling. However, accumulating clinical trial data also suggests that treatment timing and drug class selection when based on clinical status² and disease subtype,³ respectively, are important factors for optimizing therapeutic efficacy and reducing PAH clinical events. Nonetheless, point-of-care risk stratification methods to guide initiation or escalation of treatment in PAH are limited currently to elaborate scoring systems that require invasive hemodynamic data, or metrics such as changes in 6-minute walk distance and functional class that hinge on subjective assessment or are of controversial utility in clinical practice.⁴

This dilemma illustrates a critical, but incompletely met need in the field of clinical pulmonary vascular disease: the identification of an accessible biomarker that informs pathobiology *and* clinical status in PAH. These qualifications are not met by troponin-T and N-terminal pro-B-type natriuretic peptide (NT-BNP), which are two biomarkers used most commonly in practice currently.⁵ Although troponin-T and NT-BNP correlate with outcome in clinical trials, these are only surrogates for increased circulating plasma volume and right heart pressure, respectively, and do not offer insights into disease mechanism. Providing a non-invasive window by which to assess disease pathobiology is an attractive feature of biomarkers in general, but is of particular relevance to PAH owing to the heterogeneous range of vascular end-phenotypes that are associated with the pathogenesis of this disease

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Conflicts of Interest

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(i.e., vascular proliferation, inflammation, apoptosis resistance, dysregulated metabolism, fibrosis, others). Identifying and quantifying vascular remodeling pattern subtype may, in turn, have important potential ramifications on the development of patient-specific clinical care strategies, although troponin-T and NT-BNP do not permit this degree of interpretation.⁶

Galectin-3 is a β -galactoside-binding lectin expressed in circulating monocytes, myocardial monocytes, endothelial cells, and other cell types relevant to cardiovascular disease. Mineralocorticoid receptor stimulation by the hormone aldosterone induces monocyte release of galectin-3, which, in turn, interacts with fibrillar collagen and key remodeling proteins in the extracellular matrix of heart and systemic blood vessels to promote myocardial and vascular collagen fibrosis. In left heart failure, hyperaldosteronism occurs due to a decline in cardiac output that simulates over-activation of the renin-angiotensin axis. Indeed, aldosterone-galectin-3 signaling increases cardiac and vascular smooth muscle cell collagen deposition *in vitro*, and promotes left ventricular hypertrophy and cardiovascular fibrosis in experimental models of left heart failure *in vivo*.⁷ To this end, galectin-3 has emerged as a *bona fide* biomarker to prognosticate hard clinical end-points in left heart failure,⁸ while pharmacological inhibition of the mineralocorticoid receptor is standard of care to decrease mortality in selected patients with left ventricular systolic heart failure.

In the current edition of *Heart*, Calvier and colleagues⁹ report that among several putative biomarkers tested, including ICAM-1, IL-12, and VCAM-1, only circulating levels of galectin-3 were increased significantly in idiopathic PAH (iPAH) and connective tissue disease-associated PAH, and in these patients correlated with functional class severity. Moreover, galectin-3 associated positively with plasma aldosterone levels in iPAH, lending additional support to previous findings suggesting over-activation of the renin-angiotensin-aldosterone axis in patients with right heart failure due to pulmonary vascular disease.¹⁰ By identifying increased galectin-3 as part of the PAH clinical profile, the authors observations shed important new light on the potential mechanistic relationship between aldosterone and pulmonary vascular fibrosis.¹¹ Perhaps more importantly, however, these observations expose levels of galectin-3, possibly in combination with other signaling partners, as potential biomarker(s) that correspond to both PAH pathobiology and clinical status.

Despite these exciting findings, additional prospective investigations would seem necessary to clarify the relevance and accuracy of galectin-3/aldosterone as biomarkers in PAH clinically. In the current study,⁹ samples were obtained from an ambulatory population of patients for whom cardiopulmonary hemodynamic and dietary statuses were unavailable, despite the fact that cardiac output and salt loading conditions are known to regulate aldosterone levels. In future studies, controlling for a comprehensive range of clinical and demographic patient characteristics, increasing the patient sample size, and including additional clinical end-points beyond only functional class are likely to clarify further the relationship between galectin-3/aldosterone and PAH. In particular, such adjustments may account for interesting but unexplained observations from the current study, such as uncoupling between galectin-3 and aldosterone levels in patients with PAH due to connective tissue disease.

Taken together, Calvier and colleagues provide a key contribution to an underdeveloped area of pulmonary vascular medicine and in doing so identify galectin-3/aldosterone as promising biomarker(s) for informing both disease pathobiology and clinical status in PAH. The rationale of this pursuit in PAH was based, in part, on lessons learned from left heart failure in which the importance of systemically circulating vasoactive factors to clinical trajectory is well established. In this regard, the current work not only develops a novel scientific avenue worthy of further investigation, but also adds to the evolving body of evidence implicating a role for neurohumoral activation in the pathophysiology of PAH.

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