CHEST Recent Advances in Chest Medicine

Biomarkers in Pulmonary Hypertension

What Do We Know?

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Pulmonary hypertension (PH) is a hemodynamic condition that has a poor prognosis and can lead to right-sided heart failure. It may result from common diseases such as left-sided heart or lung disease or may present as the rare entity of idiopathic pulmonary arterial hypertension. Biomarkers that specifically indicate the pathologic mechanism, the severity of the disease, and the treatment response would be ideal tools for the management of PH. In this review, markers related to heart failure, inflammation, hemostasis, remodeling, and endothelial cell-smooth muscle cell interaction are discussed, and their limitations are emphasized. Anemia, hypocarbia, elevated uric acid, and C-reactive protein levels are unspecific markers of disease severity. Brain natriuretic peptide and N-terminal fragment of pro-brain natriuretic peptide have been recommended in current guidelines, whereas other prognostic markers, such as growth differentiation factor-15, osteopontin, and red cell distribution width, are emerging. Chemokines of the CC family and matrix metalloproteases have been linked to the vascular pathologic mechanisms, and new markers such as apelin have been described. Circulating endothelial and progenitor cells have received much attention as markers of disease activity, but with controversial findings. A lack of standards for cell isolation and characterization methods and differences in the pathologic mechanisms of the investigated patients may have contributed to the discrepancies. In conclusion, although several promising markers have been identified over the past few years, the development of more specific markers, standardization, and prospective validation are warranted. ***CHEST 2013; 144(1):274–283***

Abbreviations: ADMA = asymmetric dimethylarginine; ANP = atrial natriuretic peptide; BNP = brain natriuretic peptide; CEC = circulating endothelial cell; CRP = C-reactive protein; CTEPH = chronic thromboembolic pulmonary hypertension; EPC = endothelial progenitor cell; ET_B = endothelin B receptor; GDF-15 = growth differentiation factor-15; IPAH = idiopathic pulmonary arterial hypertension; LIGHT = lymphotoxin-like inducible protein that competes with glycoprotein D for herpesvirus entry mediator on T lymphocytes; MP = microparticle; NO = nitric oxide; NT-proBNP = N-terminal fragment of pro-brain natriuretic peptide; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PDGF = platelet-derived growth factor; PH = pulmonary hypertension; PIC = plasmin-α_2-plasmin inhibitor complex; RDW = red cell distribution width; sCD40L = soluble CD40 ligand; SSc-PAH = systemic sclerosis-associated pulmonary arterial hypertension; TGF = transforming growth factor; VEGF = vascular endothelial growth factor

Pulmonary arterial hypertension (PAH) is a rare hemodynamic and pathologic condition that has a poor prognosis and may lead to right-sided heart failure. Patients with idiopathic pulmonary arterial hypertension (IPAH) are particularly likely to be diagnosed at a late stage of disease because their symptoms are unspecific and diagnosis requires complicated or even invasive tests. When patients have the more common forms of pulmonary hypertension (PH) caused by left-sided heart or lung disease, PH is an important prognostic factor. This emphasizes a need for better recognition tools.

At present, there are no specific, inexpensive, and noninvasive screening tools. Elevation of pulmonary arterial pressure can be estimated by transthoracic echocardiography. This is currently used for screening but frequently over- or underestimates pulmonary arterial pressure and cardiac output in patients with PH.[1] Nonetheless, echocardiography is the noninvasive modality of choice for PH screening.[2] Right-sided heart catheterization is the gold standard for diagnosis but as an invasive procedure it is not suitable for screening. With this in mind, early recognition of the disease is a high priority, and additional

diagnostic and noninvasive screening tools need to be developed.

Although there are targeted therapies for PAH that prolong survival and improve quality of life, treatment response is generally unpredictable. The only established predictor of an excellent prognosis with therapy is a strong acute vasodilative response to inhaled nitric oxide (NO) or prostacyclin. These patients ("responders") can be treated successfully with high-dose calcium channel blockers. For the other therapies, there are no reliable predictors of the long-term response.

Biomarkers that specifically indicate the disease, the disease stage, and the treatment response to specific therapies would be ideal tools for the optimization of PH management. Current guidelines recommend the use of either brain natriuretic peptide (BNP) or the N-terminal fragment of pro-BNP (NT-proBNP) as biomarkers for mortality risk stratification.[3] In this article, we review the most important biomarkers related to PH and their role in the pathophysiology of the disease, emphasizing some limitations of their use and the need for further development.

Markers Related to Heart Failure

Myocardial strain, excessive stretching of the heart, and increased heart rate result in the release of molecular mediators from the heart that have been shown to be indicative of several cardiovascular diseases and have prognostic relevance in PH. Several studies have investigated the natriuretic peptide family, troponin T, and heart-type fatty acid-binding protein, and further markers are associated with the prognosis of PH although the pathologic mechanism remains speculative.

Natriuretic peptides were the first blood-derived markers of PH. In small cohorts of patients with PH, elevated levels of atrial natriuretic peptide (ANP) were found, in comparison with levels in healthy subjects.[4,5] Additionally, it was shown that ANP levels change acutely in response to pulmonary vasodilators.[6] For practical analytical reasons, interest has focused primarily on BNP. BNP is a 32-amino acid polypeptide secreted by the ventricles of the heart in response to excessive stretching of cardiomyocytes. BNP is much more stable than ANP and does not need immediate cooling and enzyme inhibition after blood is drawn. Nagaya et al[7] were the first to show that plasma levels of BNP have a prognostic significance in PH. In their cohort, plasma levels of BNP >150 pg/mL at baseline and >180 pg/mL after therapy were associated with worse prognosis. In the French reference center for PH in Paris, BNP, among other markers, was a predictor of survival.[8] ANP and BNP levels predicted mortality in adult patients with symptomatic congenital heart disease,[9] and BNP was also an independent predictor of therapy response. BNP decreased substantially 1 month after pulmonary endarterectomy in patients with chronic thromboembolic pulmonary hypertension (CTEPH).[10] Twelve weeks of therapy with the endothelin receptor antagonist ambrisentan were associated with decreasing BNP plasma levels from baseline.[11]

NT-proBNP, the byproduct of BNP synthesis, also has prognostic significance for response to targeted PAH treatment and mortality. Although the sample can be shipped on ice overnight to the laboratory for both BNP and NT-proBNP determination, NT-proBNP[12,13] has the advantage in that the metabolic clearance is slower, which allows overnight shipping without ice. In a restrospective study in patients with PAH, serial measurements of NT-proBNP were associated with survival.[14] Log-transformation of NT-proBNP values identified patients with PAH who were at risk of adverse events with a specificity of 98% and a sensitivity of 60%.[15]

In a prospective randomized controlled clinical trial with inhaled treprostinil, NT-proBNP level changes were associated with therapy, serving as an ancillary end point.[16] Calcium channel blockers have been shown to inhibit ANP secretion in isolated cardiomyocytes[17]; however, other PAH medications have not been investigated for direct pharmacologic effects on BNP release. In conclusion, although natriuretic peptides were associated with prognosis in retrospective studies and with PAH therapy in prospective studies, there is no established threshold for a good or poor prognosis in individual patients. A threshold for a clinically meaningful change has not been defined.

In patients with PAH, multivariate analysis revealed that serum cardiac troponin T was an independent marker of mortality.[18] The same was shown for high-sensitive troponin T,[19] but only patients with a very poor prognosis showed elevated levels, limiting the clinical value of this marker.

Manuscript received May 16, 2012; revision accepted December 31, 2012.

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DOI: 10.1378/chest.12-1246