Biomarkers in Pulmonary Arterial Hypertension

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Pulmonary arterial hypertension (PAH) is a severe medical condition characterized by elevated pulmonary vascular resistance (PVR), right ventricular (RV) failure, and death in the absence of appropriate treatment. The progression and prognosis are strictly related to the etiology, biochemical parameters, and treatment response. The gold-standard test remains right-sided heart catheterization, but dynamic monitoring of systolic pressure in the pulmonary artery is performed using echocardiography.

pulmonary arterial hypertension biomarkers right-sided heart failure

1. Biomarkers Related to Heart Failure, Myocardial Stress and Injury, and Remodeling

Natriuretic peptides are molecules released by cardiac myocytes in response to increased heart pressure, volume overload [1], and wall stretching. Atrial natriuretic peptide (ANP) is released from storage granules, and its secretion is stimulated by atrial volume overload and atrial stretching. Brain (B-type) natriuretic peptide (BNP) is a 32-amino-acid polypeptide secreted by ventricular tissue in response to ventricular stretching of cardiomyocytes and is more stable than ANP [2]. ANP and BNP are released as prehormones and act at the renal level by stimulating diuresis and natriuresis, and by relaxing the smooth vascular musculature with veno- and arteriodilatory effects [3]. In recent years, attention has focused on the N-terminal fragment of BNP (NT-proBNP) as an alternative biomarker of BNP, which provides the same information and is still preferred in clinical practice as it has a longer half-life, greater stability, and higher assay accuracy compared to BNP [4]. BNP and NT-proBNP correlate with hemodynamic parameters and the New York Heart Association (NYHA) functional class, being independent predictors for the stratification of mortality risk [5]. They are released in response to myocardial ischemia, hypoxia, and ventricular wall stress. Both BNP and NT-proBNP are markers for screening, diagnosis, and prognosis, and they are also used to monitor the state of patients with acute and chronic heart failure [6]. Regarding PAH patients, clinical studies have shown that ANP levels change in response to pulmonary vasodilator therapy [7]. Nagaya et al. [8] were the first to show that BNP plasma levels have prognostic value in IPAH. Over time, it has been demonstrated that the natriuretic peptides BNP and NT-proBNP remain the only markers recommended by the latest guidelines of the European Society of Cardiology [5] for diagnostic algorithms, as well as for risk stratification, providing prognostic information [9][10], and playing a significant role in monitoring the efficacy of specific treatments [10][11]. They are routinely used in all centers specializing in pulmonary hypertension for monitoring RV myocardial stress and progression to RV failure. NT-proBNP is correlated with hemodynamic parameters obtained in cardiac

catheterization, echocardiographic parameters of RV overload, and the 6-min walk test (6MWT) [9]. Over time, several cutoff values have been proposed for BNP and NT-proBNP. The latest recommendations of the REVEAL registry include stratification into four risk-assessment strategies [9][12] (a method also accepted by the ESC guidelines [5]): BNP < 50 ng/L and NT-proBNP < 300 ng/L for low risk (<5% mortality risk after 1 year), BNP 50–199 ng/L and NT-proBNP 300–649 ng/L for intermediate–low risk (5–10%), BNP 200–800 ng/L and NT-proBNP 650–1100 ng/L for intermediate–high risk (10–20%), and BNP > 800 ng/L and NT–proBNP >1100 ng/L for high risk (>20% mortality risk after 1 year). Moreover, in the DETECT study (Detection of Pulmonary Hypertension in Systemic Sclerosis), NT-proBNP was used to stratify the risk of PAH in patients with systemic sclerosis [13], and it was also found to be correlated with hemodynamic parameters.

Serum cardiac troponins (cTn) are regulatory proteins of thin actin filaments of the cardiac muscle [9]. The disruption of the myocyte membrane determines their release into the bloodstream, and they can be detected with high sensitivity [14]. cTnI and cTnT are the main biomarkers used in the diagnosis and prognosis of acute myocardial infarction [15]. The development of high-sensitivity cTn assays has further increased the accuracy of detection in various chronic pathologies, such as ischemic heart disease, left-sided heart failure (HF), and renal failure; cTn can therefore be interpreted as an increased risk marker for morbidity and mortality [16]. Various studies have assessed two mechanisms by which cardiac troponins are released during RV failure and PAH: microcirculation impairment, and demand–perfusion mismatch. Clinical studies have highlighted a direct correlation between plasmatic troponin levels and increased pulmonary vascular resistance (PVR), lower RV ejection fraction, lower mixed venous oxygen saturation ($mvSatO_2$), and shorter 6MWT [14][17][18]. The presence of both cTnI and cTnT is associated with an increased mortality risk among patients with PAH [14][19]. Elevated levels of cTnI indicate patients with more advanced disease, constituting an independent prognostic role [18]. cTnT shows increased values only among patients with a reserved prognosis [19]. For this reason, the ESC guidelines recommend that troponin levels be measured both at the time of diagnosis and at least once per year or every time there is a clinical aggravation [5]. Therefore, it is not a marker of early disease, and the limitations regarding the interpretation of troponin levels in PAH are influenced by their association with renal failure or left-sided heart failure.

Protein ST2 is part of the toll interleukin 1 superfamily receptor and is found in two forms: the transmembrane ST2 ligand (ST2L) is expressed in inflammatory cells, cardiomyocytes, and the endothelium [20], along with the blood-soluble suppression of tumorigenicity from sST2. The ligand for ST2 is interleukin 33 (IL-33), and this paracrine system (IL-33/ST2) plays an antifibrotic protective role [21]. However, the sST2 protein prevents IL-33 from binding to ST2L, thereby disrupting this cardioprotective effect. Over time, increased sST2 plasma levels have proven to be associated with acute or chronic HF as well as cardiac pathological remodeling [22][23]. Consequently, sST2 may be considered as an additional biomarker for adverse outcomes in this category of patients [24]. Levels above 35 ng/mL in patients with HF are associated with a high risk of hospitalization and death at 1 year.

In PAH, elevated levels of sST2 are correlated with inflammation, fibrosis, and/or pathological RV remodeling [25]. Clinical studies published in the past few years have highlighted that sST2 levels are statistically significantly correlated with cardiac index, PVR, RV dysfunction, and higher mean pulmonary arterial pressure (PAP) [26]. In addition, they could reflect PAH severity with a sensitivity and specificity of 83.3% and 78.6%, respectively [27][28].

Therefore, sST2 can be considered an independent predictor of clinical worsening, it can be correlated with disease severity or therapeutic efficiency, and it plays a prognostic role, independent of age or renal function [29].

There are statistically significant correlations between sST2 and mean PAP, NT-proBNP, and 6MWT in patients with PAH or chronic thromboembolic pulmonary hypertension (CTEPH) [28][30]. Moreover, it has been shown that sST2 can be considered to be a marker for therapeutic response in CTEPH patients treated with balloon angioplasty [28]. As such, sST2 is a complex marker reflecting diseases of the pulmonary vascular system and heart. Increasing evidence suggests that sST2 is a candidate biomarker in the context of PAH [27], as well as for risk stratification in patients with RV failure due to PAH [26].

Cystatin C (CysC) is a highly sensitive endogenous marker of renal filtration, with an important role in myocardial remodeling, and is able to predict acute left HF and cardiovascular mortality [31]. Compared to BNP and NT-proBNP, CysC serum levels are independent of muscle mass, gender, and age [32]. Clinical studies have shown a significant correlation with RV ejection fraction in HF populations [33]. As for PAH, Fenster et al. [34] studied the correlation between RV failure and plasmatic cystatin C concentration in a small group of subjects with preserved renal function. CysC showed a statistically significant correlation with function, morphology, and RV systolic pressure, all of which supported its role as a potential biomarker of PAH. Furthermore, CysC predicts long-term mortality and clinical events in patients with PAH–CHD, and it may also contribute to clinical decision-making regarding treatment intensity [35] Because CysC is an indicator of glomerular filtration, there are currently no data related to the association of PAH with advanced renal failure. Further information is required in this regard.

Regarding **homocysteine** levels, there is little information in the specialized literature. Small studies have highlighted homocysteinemia among patients with PAH and CHD, but without a statistically significant correlation [36][37]. Total homocysteine levels in plasma may be an important factor in the pathogenesis of PAH [38], but large-scale clinical trials are necessary for homocysteine to be recommended as a diagnostic or prognostic marker.

2. Inflammation Markers

The inflammatory process is an important mechanism in PAH, induced by sympathetic hyperreactivity due to decreases in cardiac output in the RV. Moreover, it reflects the degree of pulmonary arterial remodeling. A variety of pro- and anti-inflammatory markers have been studied over time in PAH patients.

C-reactive protein (CRP) elevation is broadly established as a predictor of numerous cardiovascular diseases and different types of PAH [29]. In PAH, a direct correlation between CRP and NYHA class, 6MWT, and right atrial pressure has been highlighted [39]. In PAH–CHD, an increase of over 10 mg/mL has been associated with an increased risk of death, so CRP is a simple but powerful marker of mortality in CHD–PAH patients. It should therefore be integrated in risk stratification and routine evaluation of these patients [40]. In CTEPH patients, a decrease in CRP was observed 12 months after endarterectomy [39]. Accordingly, this anti-inflammatory marker could be used for prognosis as well as for guiding therapeutic response in PAH.

Red blood cell distribution width (RDW) is a constantly measured laboratory marker. Increased levels are associated with anisocytosis, underlinked to a non-specific inflammatory process [41]. Over time, it has been studied in patients with various cardiovascular diseases (e.g., coronary arterial disease [42], pulmonary embolism [43], HF [44]). As for PAH, RDW can be considered a prognostic marker in patients with IPAH, along with GDF-15, IL-6, creatinine, and NT-proBNP levels [45], since its plasma concentration is correlated with disease severity. Another study, which included 77 patients with PAH and CTEPH, revealed that RDW meets all of the criteria to be used as a potential prognostic biomarker, also showing a significant decrease after the escalation of targeted drugs for PAH and CTEPH [46]. Decreased RDW levels are associated with good treatment response and better prognosis, but further prospective studies are still necessary in order to better understand the value of RDW in precapillary PAH.

Growth differentiation factor-15 (GDF-15) is a stress-responsive murine transforming growth factor-β-related cytokine that is highly expressed in the adult liver. It has recently been described as a non-specific inflammatory marker for various cardiovascular pathologies, as well as an independent prognostic marker in patients with acute pulmonary embolism and chronic left-sided HF. It is secreted in response to oxidative stress, inflammation, hypoxia, telomere erosion, and oncogene activation [47]. Moreover, it has been shown to be elevated in the sera of patients with IPAH. Nickel el al. [48] demonstrated that GDF-15 was abundantly expressed in the plexiform lesions of the pulmonary vascular endothelial cells, involved in both the apoptosis and the proliferation of the vascular pulmonary endothelium. In a group of 76 patients with IPAH, it was shown that GDF-15 can be considered an independent predictive marker of survival [48]. GDF-15 levels were correlated with biological (i.e., creatinine, uric acid, and NT-proBNP levels), clinical (i.e., NYHA class), functional (i.e., lower 6MWT), and hemodynamic parameters (i.e., mean right atrial and pulmonary capillary wedge pressures). High levels of GDF-15 are associated with an increased risk of mortality, independent of age or NT-proBNP; it is therefore a promising prognostic marker whose prognostic value should be detailed in future studies. Increased values have also been identified in the sera of patients with SSC–PAH, with GDF-15 levels positively correlated with PVR and plasma NT-proBNP levels [49].

Galectin-3 (GAL3), a beta-galactoside-binding lectin, is a mediator for inflammation and fibrosis that is expressed in macrophages, neutrophils, eosinophils, and endothelial cells in response to tissue damage [29]; its involvement in cardiac remodeling and fibrosis is well known, and it plays a prognostic and diagnostic role in chronic HF [50][51]. GAL3 is approved by the American Heart Association as a marker for risk stratification in class IIb HF [52]. There are few studies focusing on the relationship between GAL3 and PAH; however, small-group studies have highlighted that RV failure in patients with PAH is statistically significantly correlated with functional and morphological RV changes [53] and high GAL3 concentrations [54]. The data in this regard are still scarce, and further studies are required.

Cytokines are considered to be prognostic inflammatory markers in numerous pathologies. Circulating levels of cytokines have been reported in PAH, with an important role in its progression. Soon et al. [55] showed increased levels of pro-inflammatory serum cytokines (e.g., interferon-gamma; interleukin (IL)-1beta, -2, -4, -5, -6, -8, -10, -12p70, and -13; tumor necrosis factor-alpha (TNF–α)) in patients with IPAH and HPAH compared to the control

group. Moreover, in the same study, IL-6, -8, -10, and -12p70 were prognostic markers associated with low survival rates in IPAH and HPAH [55]. This information is supported by another study that showed increased levels of IL-6, vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF)-BB in patients with PAH [56].

Osteopontin (OPN) is a pleiotropic cytokine that, over time, has proven to be potentially related to mortality in PAH [57]. OPN levels were found to be correlated with age, 6MWT, NYHA class, mean right atrial pressure, and NT-proBNP in a study published by Lorenzen et al. in 2011 on patients with IPAH [57]. The data were also confirmed by Rosenberg et al. [58], who demonstrated that OPN is an independent prognostic marker of RV failure and pathological remodeling, most likely through its autocrine effect. Circulating OPN could be useful as a prognostic marker, in monitoring therapeutic response, and for improving risk stratification. Further studies on larger groups still need to be validated for use in clinical guidelines. Akin et al. emphasized another prognostic inflammatory marker, serum B-cell lymphoma 2 (sBCL2), found in high concentrations in children with PAH [59].

There is not as much information on the **neutrophil-to-lymphocyte ratio (NLR)** thus far. The first data related to the association between PAH and NLR appeared as early as 2013 [60]. Another study from that time highlighted that NLR could be correlated with the NYHA functional class and BNP in a small group of patients with PAH [61]. NLR ≥ 2.62 G/μL was associated with reduced five-year survival rates in PAH patients, with 69% sensitivity and 56% specificity [62]. Another recent study noted that high-NLR patients had lower 5-year transplant-free survival compared to the control group. Thus, NLR may be considered to be an independent predictor of survival, especially in women with PAH [63]. This simple marker could have prognostic value in PAH, but further studies are required in this direction.

Macrophage migration inhibitory factor (MIF) and its receptor CD74 are overexpressed in muscular pulmonary arterioles of patients with IPAH and contribute to the abnormal pro-inflammatory phenotype [64]. Treatment with the MIF antagonist ISO-1 or anti-CD74 neutralizing antibodies reduced inflammatory cell infiltration and, in addition, reversed the development of pulmonary hypertension in rats [64]. In patients with PAH secondary to systemic sclerosis, high concentrations of MIF have also been found [65]; therefore, in the future, MIF could be considered as a possible prognostic marker for this pathology.

Neopterin (NP) belongs to the pteridines class; it is an inflammatory marker released by dendritic cells and macrophages that interacts with reactive oxygen species (ROS) in response to oxidative stress [66]. Over time, increased values of NP have been highlighted in various cardiovascular diseases, including HF and coronary heart disease. NP is considered to be a prognostic marker for these pathologies [67]. Thus far, the data related to the involvement of NP in PAH are very limited, but it seems to amplify PAH through its effects on ROS. The plasma concentrations of NP were elevated in patients with PAH and inoperable CTEPH, which are associated with various clinical outcomes.

Adrenomedullin (ADM) is a potent hypotensive and vasorelaxant peptide that can reduce blood pressure and PVR and increase pulmonary blood flow [68]. The concentration of ADM increases in direct proportion to the severity of PAH, and circulating ADM is metabolized in the lungs. These data suggest that ADM plays an important

role in pulmonary vascular tone [69]. A recent study showed that intravenous administration of ADM reduced precapillary pulmonary hypertension by decreasing plasma aldosterone concentrations [70]. As a result, ADM could be considered to be a promising endogenic peptide in PAH treatment, as well as a vasoprotective factor [69].

3. Endothelial Cell Dysfunction and Pulmonary Arterial Smooth Muscle Cell (PASMC) Proliferation

Asymmetric dimethylarginine (ADMA) is a natural amino acid and an endogenous competitive inhibitor of nitric oxide (NO) synthase. Endothelial injury can increase its plasma concentration, resulting in decreased NO production, creating an inhibition of the NO/CGMP pathway with an increase in vascular tone. Reduced bioavailability of NO underlies the pathogenesis of pulmonary hypertension [71]. Over the years, clinical studies have highlighted the presence of ADMA in various cardiovascular pathologies, including myocardial infarction [72], CTEPH, and IPAH [71]. Several reports have shown high ADMA values in patients with IPAH, correlated with unfavorable pulmonary hemodynamics (e.g., PVR and CI) [73], but also in studies on patients with CTEPH [71] or CHD–PAH [36]. Increased serum ADMA levels could be used as an important prognostic marker, and in the mortality risk stratification and severity assessment of PAH.

Circulating angiogenic modulatory factors: Vascular endothelial growth factor (VEGF) signaling is involved in vascular remodeling and, implicitly, in the pathogenesis of PAH [74]. Plasma levels are increased in patients with IPAH [75], and the VEGF receptor 2 (VEGFR2) is overexpressed in plexiform vascular lesions. Soluble vascular endothelial growth factor (VEGF) receptor 1 (sVEGFR1) was also studied for its role in PAH. The soluble form of VEGF receptor 1 (also called soluble FMS-like tyrosine kinase 1 (sFlt-1)) was statistically significantly increased in patients with IPAH and CHD–PAH, being associated with the NYHA functional class [76]. The combination of sFlt-1 and PIGF has 83.7% sensitivity and 100% specificity for PAH [77]. In recent years, there has been an increased interest in connective tissue diseases (CTDs)—especially in the association between systemic sclerosis (SSc) and PAH. The potential role of these angiogenic circulating and inflammatory biomarkers in SSc screening is supported by numerous clinical studies, which have shown high levels of soluble vascular endothelial growth factor (VEGF) receptor 1 (sVEGFR1) [76][77] in patients predisposed to the development of PAH [78]. A significant decrease under prostanoid therapy has also been described and is considered to be a biomarker of treatment response [79]. Kylhammar et al. [80] also highlighted that the plasma levels of sVEGFR1 were correlated with both disease progression and worse outcomes. The value of other angiogenic and inflammatory biomarkers, such as placental growth factor (PlGF) [78], VEGF-A, IL-6 [56], IL-12 [78], and tumor necrosis factor-α (TNF-α) [56], seemed to best discriminate SSc patients who were on the verge of developing PAH.

Aldosterone is a mineralocorticoid hormone synthesized in the zona glomerulosa of the adrenal gland in response to a decrease in circulating blood volume [79]. Its role in vascular remodeling and fibrosis is well known, with several mechanisms through which it determines its effects, including activation of pathways that decrease NO levels, stimulation of inflammation and cell proliferation, extracellular matrix remodeling, and fibrosis [53]. Its role in vascular remodeling in PAH has been studied both in experimental models [81] and in subgroups of patients, where it was shown that the remodeling of the pulmonary arterioles increases vascular tone, causing irreversible right-

sided HF (cor pulmonale). Perivascular fibrosis is reduced through pharmacological inhibition of aldosterone, along with the improvement of cardiopulmonary hemodynamics. Thus, aldosterone can be considered a partially modifiable marker in pulmonary circulation-right ventricle dysfunction [82]. Other studies consider galectin-3 and aldosterone to be potential tandem biomarkers of idiopathic PAH (IPAH) or PAH associated with PAH–CTD [53].

Endothelin 1 (ET-1) is considered to be a potent vasoconstrictor that stimulates the proliferation and migration of pulmonary artery smooth muscle cells (PASMCs). In the clinical studies published in previous years, statistically significant correlations have been highlighted between increased levels of ET-1 and hemodynamic parameters (e.g., mean PAP, CI, and disease severity) [83]. At the same time, ET-1 could be considered to be an ideal prognostic marker for disease progression, its levels correlating with responses to PAH-specific treatments [84]. According to the latest guidelines, the beneficial effects of endothelin receptor antagonists are well-known in PAH treatment [5]. In contrast, in recent years, it has been shown that COOH-terminal proendothelin 1 (CT-proET-1), a more stable form of ET-1, can provide superior prognostic information regarding ET-1 and death prediction at 12 months [85].

According to studies published in previous years, the **angiopoietin system (ANG)**, consisting of angiopoietin 1 (ANG1) and angiopoietin 2 (ANG2) antagonists, could be involved in both disease staging and treatment response in patients with IPAH [86]. Kumpers et al. showed that ANG2 was statistically significantly correlated with CI, PVR, and mv$SatO_2$, confirming its involvement in the pathogenesis of IPAH [87]. However, additional information has emerged more recently, suggesting that ANG2 is not associated with treatment response in patients with IPAH [88], although it may be used as a diagnostic and prognostic marker in Group 3 patients with PH.

MicroRNAs (miRNAs) are small non-protein-coding genes that function in RNA's post-transcriptional regulation of gene expression. A new opportunity to sensitively detect changes in gene expression is available through RNA sequencing analysis (RNA-Seq) [89]. MicroRNA expression is associated with the progression of different vascular pathologies [38][90]. RNA-Seq was used in PAH patients to evidence changes in the transcriptomes of endothelial cells cultured from lung tissue and blood. Sarrion et al. noted that miR23a expression was correlated with pulmonary function parameters, including patient age, 6MWT, CI, and PVR. Overexpression of miR27a in patients with HPAH was correlated with 6MWT and was also associated with bone morphogenetic protein type 2 receptor (BMPR2) involvement in cell proliferation. The miR199a was correlated with 6MWT and mean PAP, while miR744 was correlated with PVR [90], and miR204 levels were lower in IPAH patients, supporting its importance in the pathogenesis of IPAH [91]. Another important miRNA associated with HPAH and IPAH was miR145, with a role in the pathophysiology of PAH [92]. The miR328 induces apoptosis in smooth muscle cells, inhibits IGFR1, and acts as a protective agent in PAH [93]. A novel relationship between BMPR2 dysfunction and reduced expression of collagen IV and ephrinA1 underlies the vulnerability to injury in PAH [89]. A recent study published by Rodor et al. in *Cardiovascular Research* identified a promising new candidate to target endothelial dysfunction in PAH—specifically, CD74, which is involved in the regulation of endothelial cell (EC) proliferation in vitro and may contribute to the progression of PAH, being considered a new candidate for future therapeutic development [94].

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