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Cardiovascular biomarkers in pulmonary hypertension- current applications and future directions

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Abstract

Biomarkers are non-invasive tools, which can be very useful in diagnosis and prognosis of a specific disease. Pulmonary hypertension (PH) is a serious health condition, characterized by increased pulmonary arterial pressure, elevated pulmonary vascular resistance often leading to right heart failure. If not treated properly, it can significantly reduce patients' quality of life and even lead to death. Nowadays, there is an increasing interest on PH markers and more specifically how they can contribute to the diagnosis, prognosis, and monitoring of the development of this disease. Recent studies on biomarkers in PH suggest several novel and promising molecules, which can be potentially useful in PH work-up and follow-up strategies. This review focuses on biomarkers for diagnosis and prognosis of PH via well-known and some novel cardiovascular disease (CVD) indicators associated with heart failure, myocardial remodelling, and injury. Current thinking holds that CVD biomarkers can detect not only heart abnormalities but also pulmonary vascular system damage.

Keywords: pulmonary hypertension, biomarkers, heart, lung, pulmonary arterial hypertension

1. Introduction

1.1. Pulmonary hypertension- overview

Pulmonary hypertension (PH) is a progressive disease caused by different etiological factors and classified into many subtypes according to the specific cause which can lead to irreversible complications and a lethal outcome if not treated properly (1). Based on the current approach towards PH pathogenic mechanisms, increased pulmonary arterial pressure (PAP) and elevated pulmonary vascular resistance (PVR) have been considered as PH's cardinal features. They often lead to right ventricular (RV) overload and right heart failure (HF) (2). According to the latest ESC and ERS guidelines, right heart catheterization has been highlighted as the definitive and confirmatory gold standard for diagnosis, prognosis, and defining the etiology of PH (3). The disease's course can be monitored by image tests such as pulmonary artery systolic pressure measurement via transthoracic echocardiography. Functional measures, such as estimation of functional class and the 6-min walk test can also be evaluated (4).

Biomarkers are non-invasive indicators which can be related to structural and/or functional changes in various organs and systems in human body. These parameters can be associated with specific diseases and have been proposed for assessing diagnosis, prognosis and response to therapy. Nowadays, significant advances have been made in the investigation of PH circulating biomarkers. Different blood indicators have been identified and the large majority of them have the potential to be implemented in the routine clinical practice in the future.

2. Heart structure/function related biomarkers in pulmonary hypertension

Researchers are intensively studying various molecules, which are candidates for potential PH biomarkers. Noteworthy, cardiovascular biomarkers are promising indicators for that role, because they can reveal not only heart abnormalities, but also pulmonary vascular system injury. Despite the overlap in some features of cardiovascular biomarkers, they can be classified into the following basic categories:

2.1. Markers Related to Myocardial Remodeling

Galectin-3 (Gal-3) is a protein, member of lectins family known to be secreted by macrophages as a result of mechanical and neurohumoral stimulation (5). It is presumed to have an interaction with extracellular matrix (ECM) proteins and cell surface glycoproteins. Gal-3 has abilities to interact with ECM proteins and cell surface glycoproteins in physiological and pathological conditions (6). Moreover, Gal-

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3 can also activate other macrophages, fibroblasts and inflammatory cells. Galectin-3 has been associated with myocardial remodeling and fibrosis in patients with heart failure (7,8,9). In terms of pulmonary hypertension, Fensteret et al. (10) examined Gal-3 in patients with RV dysfunction and pulmonary arterial hypertension (PAH) and found a significant correlation between abnormal changes in RV structure and Gal-3 concentrations. Of note, Gal-3 levels were increased in all patients with PAH (11). In another investigation, Calvier et al. found increased Gal-3 concentrations in patients with PAH. The authors also described correlations between Gal-3 and functional parameters (12). Mazurek et al. conducted a research involving both PAH and PH patients due to left-sided HF. Authors reported that increased Gal-3 levels were associated with mortality in PH patients (13). In the study of Geenen et al. including 164 patients with PAH, chronic thromboembolic pulmonary hypertension (CTEPH) or PH caused by lung disease, there were no significant differences in the Gal-3 levels between subgroups (14).

Soluble ST2 (sST2) ST2 protein is part of Toll inteurleukin-1 receptor superfamily and has two isoforms: transmembrane ST2 ligand (ST2L) and soluble ST2 (sST2), which circulates in the blood (15). It has been postulated that the transmembrane form is expressed predominantly on inflammatory cells and plays an important role in the acceleration of the immune response of Th2-lymphocytes. An intriguing fact is that ST2 has also been detected in cardiomyocytes and endothelium. Interleukin-33 has been recognized as a ligand for ST2. In that way, IL-3/ST2L system plays a protective role and has anti-fibrotic and anti-hypertrophic functions. Increased ST2 serum levels have been recognized to be related with cardiac remodeling (16). Studies have shown that the ST2 gene is induced during abnormal cardiomyocyte stretch or cardiac fibrosis. ST2 has been reported to be involved in left ventricular (LV) hypertrophy, fibrosis and remodeling via interaction with interleukin-33 (IL-33).

Recently, sST2 levels have been found to correlate with RV remodeling in various PAH types. The higher sST2 levels have been suggested to be linked with RV remodeling in different types of PH (17). In 2020, Banaszkiewicz et al. studied patients diagnosed with PAH or CTEPH. Researchers found correlations between sST2 and cardiac index (CI), mean right atrial pressure (mRAP), PVR, mixed venous oxygen saturation, N-terminal pro b-type natriuretic peptide concentration and 6 min walking distance (6MWD) (18). These observations are consistent with those from other studies conducted in smaller populations of patients with precapillary PH (19,20). Contrary to that, no analogous changes in N-terminal pro b-type natriuretic peptide levels were noticed, which may be suggestive of an additional noncardiac source of sST2 in CTEPH patients. Therefore, in PH, sST2 may reflect not only heart condition, but also pulmonary vascular system and lung tissue (21). These findings support the theory that sST2 could be used as a marker for risk stratification of patients with RHF.

2.2. Indicators of Neurohumoral Activation

Mid-regional proadrenomedullin (MR-proADM) is a novel cardiovascular biomarker, which has been investigated in recent years. It is known that one of the first evidences of cardiac dysfunction is the activation of the sympatic nerve system. MR-proADM has been described as a precursor of the powerful vasodilator with inotropic properties-adrenomedullin, initially isolated from pheochromocytomic cells. MR-proADM has been shown to be increased in patients with acute and chronic heart failure (22,23,24). MR-proADM has been demonstrated as a strong predictor of clinical events such as mortality and hospitalization, even in addition of natriuretic peptides.

MR-proADM has been suggested as a promising indicator to predict prognosis and a helpful tool in the evaluation of different cardiopulmonary diseases (25,26,27). As for functional parameters, it was found that MR-proADM strongly correlates with exercise capacity in PAH patients (28).

Copeptin is also known as CT-proAVP. COP is a peptide involving 39 amino acid chains, derived by C-terminal of pre-pro-hormone of arginine vasopressin, neurophisin II and copeptin. Arginine vasopressin (AVP), known also as antidiuretic hormone (ADH) plays a key role in many cardiovascular and renal conditions. Its abnormal levels have been associated with different pathologies. Unfortunately, AVP measurement has not been incorporated in the routine clinical practice, because of its short half-life. Contrary to that, copeptin can be easily detected by immunoassays and is also used as a vasopressin secretion surrogate indicator. Copeptin has been reported as a valuable tool in the monitoring of cardiovascular pathologies such as myocardial infarction, left ventricular hypertrophy, cardiogenic shock and heart failure. Its expression correlated with survival, severity and disease prognosis (29). Copeptin also significantly correlates with 6MWD and New York Heart Association (NYHA) class as well as with kidney function in PAH patients (30,31,32). Moreover, in a study performed by Nickel et al., elevated copeptin concentration was related to a higher risk of death and it was an independent predictive factor of adverse outcomes in PAH patients (33).

2.3. Biomarkers Related to Myocardial stress/injury

Natriuretic peptides- brain natriuretic peptide (BNP) and N-terminal pro b-type natriuretic peptide (NT-pro-BNP). BNP is initially secreted as a pro-hormone (pro-BNP) by the heart ventricles in response to increased ventricular wall stress and myocardial hypoxia or ischemia. BNP and NT-proBNP are produced from pro-BNP via several enzyme-controlled reactions. BNP and NT-pro-BNP have predictive value for cardiovascular death and congestive heart failure (34).

Measurement of NT-pro-BNP increases prognostic assessment for cardiovascular death and exacerbation of HF. BNP is a powerful predictor for cardiovascular death and strongly correlates with LV-systolic stress and LV-dysfunction. Therefore, BNP and NT-pro-BNP are independent predictors for CVD morbidity and mortality in patients with HF. The American College of Cardiology (ACC) and American Heart Association (AHA) recommend BNP и NT-pro-BNP assessment in diagnosis and prognosis of HF. The European Society of Cardiology (ESC) also recommends BNP and NT-pro-BNP for evaluation of HF severity and evaluation of therapeutic response (35).

As mentioned above, BNP is produced as an inactive precursor (pro-BNP), then converted into the active form NT-pro-BNP and released from cardiomyocytes. Due to the longer half-life of NT-pro-BNP compared to BNP, NT-pro-BNP is preferred in clinical practice as a marker of heart overload and myocardial dysfunction. NT-pro-BNP remains a well-established and widely used biomarker in numerous cardiovascular diseases. NT-pro-BNP is mostly used in the diagnostic process of patients with acute or chronic HF as well as in prognostic strategies. ESC/ERS guidelines classify the risk of 1-year mortality according to NT-pro-BNP concentrations as low (<5%), intermediate (5–10%), or high (>10%), by using specific thresholds of 300 and 1400 ng/L (36). Similarly, data from the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) registry show that a baseline NT-pro-BNP level of 340 ng/L is a strong predictor of improved survival in PAH patients for up to 5 years (37). Studies by Galie et al. in 2017 and Chin et al. in 2019 demonstrated that a significant decrease in NT-pro-BNP levels among patients with PAH is associated with the response to targeted medical therapy (38,39). There is evidence that in PH patients, NT-pro-BNP concentrations correlate with right heart dysfunction. Measurement of this indicator can provide prognostic information at diagnosis and during follow-up assessment (40,41,42). In 2017, Berghaus et al. described a high variability of NT-pro-BNP levels and proposed a possible inadequate correlation with hemodynamic parameters and exercise capacity. That is why, it should only be interpreted in the clinical context (40). Currently, NT-pro-BNP is an important component in the PAH risk stratification strategy proposed by ESC/ERS guidelines (39) and is addressed in both the risk score method developed from the REVEAL registry (37,43). An important conclusion has been provided from the analysis of patients' data with CTEPH: BNP seemed to be related with both: (1) the degree of RV dysfunction and hemodynamic severity of the disease, and (2) BNP may contribute to the assessment of pulmonary endarterectomy effect with estimated BNP baseline cut-off values predictive of worse postoperative survival (44,45). In another study, Kriechbaum et al. reported two intriguing findings: (1) balloon pulmonary angioplasty (BPA) as well as pharmacological treatment result in a decrease of NT-pro-BNP concentration and (2) the procedural success of BPA in patients treated with BPA could be indicated by a reduction in NT-pro-BNP concentration (46).

Cardiac Troponins

The 2020 ESC Guidelines for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation pointed-out both cardiac troponin I (cTnI) and T (cTnT) as one of the key laboratory parameters from all ACS diagnostic methods (47). Furthermore, the development of high-sensitivity assays has made it possible to detect troponin concentrations and their association with morbidity and mortality in many chronic diseases, such as heart failure, coronary artery disease, or chronic kidney disease (48–51). Literature data describes that in most cases troponin levels correlate with left heart structural and functional parameters and some other indicators related to left HF. There is increasing evidence that the mechanism of troponins release in patients with PH seems to be associated with RV pathology. It has been theorized that RV alteration is caused by misbalance of demand/perfusion processes or microcirculatory injury. Researches by Velez-Martinez et al. and Torbicki et al. have found significant correlations between troponins' concentration and some hemodynamic parameters as mean PAP, mixed venous oxygen saturation and RV ejection fraction (52,53). Moreover, both cTnT and cTnI concentrations were associated with worse outcomes in mixed cohorts of PH patients (54,55). In order to perform accurate prognostic assessment and risk stratification of patients, ESC guidelines recommend troponin levels to be measured at the diagnosis of PAH, then at least once a year or whenever the patient presents with clinical worsening (36). In 2018, Kriechbaumet al. analysed a group of CTEPH patients undergoing interventional treatment with BPA. The authors found that high-sensitivity cTnT concentration decreases stepwise under therapy. This finding indicates a reduction of ongoing myocardial damage due to decreased right ventricular afterload following BPA therapy (56). Consequently, troponins can be useful markers in monitoring the treatment results of CTEPH patients.

3. Other potential cardiovascular markers in PH

Homocysteine is a sulfhydryl-containing amino acid, known as an intermediate product in the normal biosynthesis of the amino acids methionine and cysteine. Homocysteine is a homologue of the amino acid cysteine. There are only two studies, which have investigated this sulfhydryl-containing amino acid and they revealed increased homocysteine levels in PH. Firstly, Ozerol et al. in 2004 examined patients with congenital heart disease and reported elevated homocysteine concentrations in patients with congenital heart disease and PAH compared to patients with left to right shunt surgery and no PAH (57). Later, a study by Sanliet al. in 2012 focused on patients with congenital heart disease. Authors found an association between homocysteine concentrations and

asymmetric dimethylarginine (ADMA) levels (ADMA is known as a natural amino acid, which plays an important role in the organism via inhibition of nitricoxide production). Researchers reported elevated homocysteine levels in patients with PAH and congenital heart disease. Furthermore, homocysteine concentrations were significantly increased in cyanotic patients compared to those without cyanosis (58).

Heart-Type Fatty Acid-Binding Protein (H-FABP). Fatty Acid-Binding Protein (FABP) plays key role in the regulation of energy metabolism. FABP can be divided into two major types: liver FABP (L-FABP) and heart FABP (H-FABP). The classification is not completely accurate, because these proteins can be found not only in the above mentioned tissues. H-FABP is expressed in the cytosol of cardiomyocytes. It has been estimated that higher levels of H-FAPB are related with increased hospitalizations because of heart failure (59). In patients with chronic heart failure, elevated serum levels of H-FABP have been associated with poor prognosis (60). H-FABP has also been proposed as an additional biomarker for early diagnosis of ACS (61). In terms of PH, Lankeit et al. explored whether H-FABP could contribute in CTEPH risk stratification. They found that H-FABP is an independent marker of adverse outcomes (62). The routine application of markers of PH in clinical practice could provide improved risk stratification and better patient outcomes (63). Fig. 1 represents the basic categories of cardiovascular biomarkers in pulmonary hypertension.

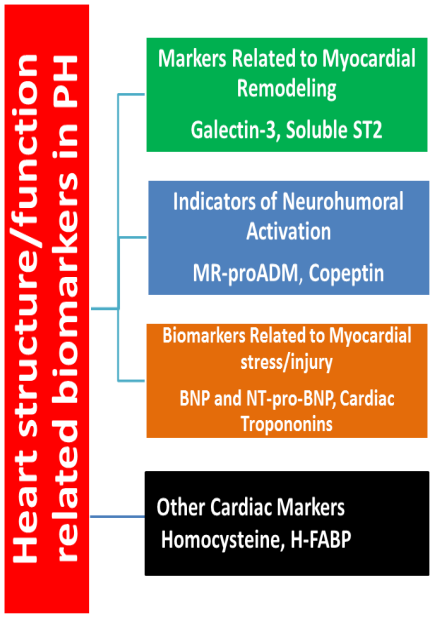

Fig. 1. Schematic presentation of heart structure/function related biomarkers in pulmonary hypertension

4. Conclusions and future directions

Nowadays, there has been an increasing interest in the research field of PH and especially on biomarkers as potential tools for diagnosis and prognosis of this disease. There are a growing number of investigations providing data for novel and promising non-invasive biomolecules, which could be useful in the evaluation of severity, prognosis and monitoring of PH. Given the complexity of PH, because of its different aetiology, hemodynamic, biochemical parameters and response to treatment, it is a great challenge for researchers to point-out only one marker that would be completely informative for clinical assessment of patients with different types of PH. That is why, a combination of different types of biomarkers would probably increase the sensitivity and specificity of the work-up and follow-up algorithms. Unfortunately, the optimal combination of blood indicators has not been discovered yet. Apparently, the use of multimarker strategies would be a more successful method. In conclusion, cardiovascular biomarkers have future potential as PH indicators and might contribute to early diagnosis, prognosis and monitoring of the development of pulmonary hypertension.

Conflicts of Interest

The authors declare no conflict of interest.

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