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EDITORIAL

Heart biomarkers as prognostic tools for chronic thromboembolic pulmonary hypertension: a step forward by the fatty acid-binding protein

S.E. Orfanos* and S. Zakynthinos#

During the last 20 yrs, a tremendous amount of scientific discoveries have greatly improved our knowledge on the pathophysiology of pulmonary hypertension, and expanded our armamentarium of important novel medications that have substantially improved survival and the quality of life of patients suffering from this devastating disorder. Although most investigations have focused on pulmonary arterial hypertension (PAH), chronic thromboembolic pulmonary hypertension (CTEPH) has also gained increasing attention [1]. CTEPH could be viewed as an extension of the natural history of acute pulmonary embolism (PE). However, its pathophysiology is not entirely understood; only a minority of patients who have undergone acute PE will develop chronic thromboembolic disease, while disorders associated with abnormal fibrinolysis and/or a pro-thrombotic lung vascular phenotype appear to be predisposing factors for CTEPH development [2].

Chronic thromboembolic pulmonary arterial obstruction will increase pulmonary vascular resistance, subsequently leading to right heart failure and, if untreated, to death [1, 3]. It has been suggested that in addition to organised thromboemboli, structural remodelling of the pre-capillary vessels, such as in PAH, may also occur in CTEPH further contributing to the haemodynamic compromise of the patient [4]. Organised thrombi located in central proximal vessels can be removed by means of pulmonary thrombo-endarterectomy (PEA) and might lead to phenomena of patients who had been in World Health Organization functional class IV pre-operatively, and who improve to functional class II, or even I, post-operatively. Patients with either distal or inoperable disease, or persistent pulmonary hypertension post-PEA are candidates for treatment with agents used in PAH [3, 5]. PEA is usually performed in specialised centres, is relatively expensive and carries a perioperative mortality that could still be >10%, depending on the operative centre [6]. Thus, it is apparent that markers that identify patients who would benefit the most from surgery, as well as allowing monitoring of the effect of medical treatment on disease progress, are of great value.

Optimal biomarkers should be sensitive, specific and provide quantification of the underlying pulmonary vascular disease and/or right heart dysfunction [7]. In addition, they should be noninvasive, inexpensive and able to offer predictive information on the best possible treatment for patients (*i.e.* medical or surgical) and outcome. Despite the fact that several compounds, such as the best studied natriuretic peptides in plasma, have already been used along with parameters related to pulmonary haemodynamics and patients' functional performance [7], the need for optimal biomarkers is always present.

In this issue of the *European Respiratory Journal*, LANKEIT *et al*. [8] have validated the prognostic value of heart-type fatty acid-binding protein (H-FABP) in CTEPH. Fatty acid-binding proteins (FABPs) are relatively small (15 kDa) cytosolic proteins that are widely distributed and highly expressed in tissues undergoing active fatty-acid metabolism, such as the heart and the liver [9]. FABPs exhibit a high affinity for the noncovalent binding of fatty acids and are named after the tissue from which they are initially identified. The H-FABP isoform is one of the most abundant proteins in the heart, representing 5–15% of the whole aqueous cytosolic protein pool. H-FABPs are truly cytosolic and cannot been found outside the cell under normal conditions [10]. The fact that H-FABP is a small protein, allows for rapid diffusion outside the injured myocardium and subsequently rapid detection on plasma post-myocardial injury [9]. All the aforementioned properties suggest strong theoretical and practical advantages for the use of H-FABP in detecting myocardial injury.

Several recent studies have provided evidence on the validity of H-FABP for the diagnosis and risk stratification in acute coronary syndromes, as well as the advantage of this novel biomarker over compounds such as troponin and brain natriuretic peptide (BNP) [11–13]. Besides its use in acute coronary syndromes, the validity of this novel biomarker has been additionally demonstrated in chronic heart decompensation. Patients with advanced chronic heart failure have increased serum levels of H-FABP that persist over time in subjects at high risk for adverse clinical outcomes, in contrast to the concomitant BNP decrease [14].

In addition to the study by LANKEIT *et al.* [8] on the use of H-FABP in CTEPH [8], PULS *et al*. [15] have validated the use of

*Second Dept of Critical Care, University of Athens Medical School and Pulmonary Hypertension Clinic, Attikon Hospital, and #First Dept of Critical Care and Pulmonary Services, Evangelismos Hospital, University of Athens Medical School, Athens, Greece.

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CORRESPONDENCE: S.E. Orfanos, Second Dept of Critical Care, Attikon Hospital, 1, Rimini St, 124 62, Haidari-Athens, Greece. Fax: 30 2105326414. E-mail: sorfanos@med.uoa.gr

this novel biomarker in risk stratification of patients with acute PE. PULS *et al.* [15] prospectively studied 107 patients for PE-related death or major complications and overall 30-day mortality. Serum H-FABP on admission, along with N-terminal pro-BNP (NT-proBNP) and cardiac troponin, were compared by means of multivariate logistic regression analysis. H-FABP was identified as a strong independent predictor of the aforementioned study end-points, in contrast with the N-terminal pro-BNP (NT-proBNP) and cardiac troponin, which revealed no significant predictivity. H-FABP remained a superior prognostic indicator even when compared with the maximal NT-proBNP and troponin levels over the first 24 h post-patient admission [15]. The superiority of H-FABP over troponin and myoglobin for risk stratification in acute PE has also been shown by KACZYNSKA *et al.* [16]. The fact that H-FABP appears to be an early and promising indicator of right ventricular dysfunction and injury, following acute lung vascular decompensation, has provided a strong rationale for investigating its potential usefulness in CTEPH.

LANKEIT *et al.* [8] studied 93 consecutive patients with CTEPH and investigated the value of H-FABP as a predictor of adverse outcome, defined as CTEPH-related death, lung transplantation or persistent pulmonary hypertension after PEA. Baseline H-FABP levels in plasma ranged 0.69–24.3 $ng \cdot mL^{-1}$ and were weakly correlated with cardiac output, mean right atrial pressure, pulmonary capillary wedge pressure and 6-min walking distance. Levels were significantly higher in patients with an adverse outcome, while a univariable Cox regression analysis revealed a hazard ratio of 1.10 for each increase of H-FABP by 1 $ng \cdot mL^{-1}$. Additional multivariate analysis revealed that H-FABP was an independent predictor of adverse outcome, along with mean right atrial pressure and PEA (with PEA being associated with a lower risk of adverse outcome). It is noteworthy that all other pulmonary haemodynamic parameters, including cardiac output, did not exhibit significant predictivity at multivariate analysis, further supporting the greater prognostic value of this new biomarker. Cardiac troponin T was additionally measured but, in contrast with a previous report on patients with pre-capillary pulmonary hypertension of diverse aetiologies [17], it was detected in only four patients, indicating a superiority of H-FABP in relation to cardiac troponin T in stratifying risk in CTEPH. However, it should be mentioned that all four patients had an adverse outcome, suggesting that cardiac troponin T elevation appears, when present, to be an ominous prognostic indicator in CTEPH.

Although the findings mentioned previously already add substantial novel information to our knowledge of CTEPH, perhaps the major finding of the study by LANKEIT *et al.* [8] is related to the identified value of H-FABP as an outcome predictor in patients who underwent PEA. Indeed, LANKEIT *et al.* [8] further analysed the data obtained from the 52-patient subgroup that underwent surgery. They showed that subjects with an adverse long-term outcome had significantly higher baseline levels of H-FABP than patients carrying a favourable outcome. This finding was further supported by Kaplan–Meier analysis showing that surgically treated patients with H-FABP plasma values >2.7 $ng \cdot mL^{-1}$ (*i.e.* the median value in the surgically treated cohort) at diagnosis had a lower probability of event-free survival post-PEA. Therefore, it is probable that H-FABP estimations may help identify CTEPH patients who will benefit the most from surgical treatment. Future large prospective studies should be performed to further validate this finding. Studies that will include sequential measurements of H-FABP could additionally validate its use as a marker for monitoring and probable quantification of patients' responses to medical and/or surgical treatment.

As already acknowledged by the authors, two issues were not addressed in the study by LANKEIT *et al.* [8]. First, the prognostic value of H-FABP was not compared with that of the natriuretic peptides BNP and NT-proBNP, which are commonly used as biomarkers in pulmonary hypertension assessment [7]. In this respect, REESINK *et al.* [18] have recently shown that plasma BNP levels in CTEPH patients correlated with right ventricular remodelling, as revealed by cardiac magnetic resonance imaging, and could identify right ventricular dysfunction. Studies combining and comparing measurements of H-FABP with those of additional biomarkers in use are needed.

The second issue is related to the fact that patients receiving treatment with novel agents originally reserved for pulmonary arterial hypertension were not included in the study by LANKEIT *et al.* [8]. Epoprostenol and prostacyclin analogues, the dual endothelin-1 receptor antagonist bosentan, and the phosphodiesterase-5 inhibitor sildenafil have been shown to be efficacious in chronic thromboembolic pulmonary hypertension patients [5, 6]. Such pharmacotherapy is now part of the current paradigm of chronic thromboembolic pulmonary hypertension management as a ''therapeutic bridge'' to pulmonary thrombo-endarterectomy, in inoperable patients, or in persistent pulmonary hypertension post-pulmonary thrombo-endarterectomy. It is likely that future studies will prove that heart-type fatty acid-binding protein is useful in choosing, monitoring or modifying chronic thromboembolic pulmonary hypertension pharmacotherapy.

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