Renal biomarkers and prognosis in acute pulmonary embolism

Thomas M Berghaus, Martin Schwaiblmair, Wolfgang von Scheidt

Renal dysfunction has become a validated prognostic factor indicating increased morbidity and mortality in different cardiovascular diseases, such as acute coronary syndrome[1] or chronic heart failure.[2] Impaired kidney function may not only reflect chronic renal disease but also deterioration secondary to haemodynamic disturbances, as decreased cardiac output and elevated central venous pressure may contribute to renal insufficiency.[3] Kidney dysfunction has previously been observed in patients with acute pulmonary embolism (APE) and was found to be associated with worse short-term outcomes.[4 5] However, those studies were not able to distinguish between acute kidney injury due to haemodynamic compromise cause by APE or chronic pre-existing renal insufficiency.

Kostrubiec and co-workers[6] investigated markers of acute kidney injury such as cystatin C and serum neutrophil gelatinase-associated lipocalin (N-GAL) and their association with left and right heart function, disease severity, and prognosis in patients with APE. Cystatin C is a 13 kDa endogenous cysteine proteinase inhibitor and is produced by nucleated cells at a constant rate. It is freely filtered by the glomerulus, reabsorbed and catabolised, but it is not secreted by the tubules. Earlier studies demonstrated the superiority of serum cystatin C compared with creatinine, especially to detect minor changes in glomerular filtration rate (GFR).[7] In addition, it was suggested that serum cystatin C performed better than creatinine as a marker to detect acute GFR reductions.[8] The release of N-GAL represents an intrinsic response of the proximal renal tubule cells to ischaemic injury of the kidney. In the animal model, the response is extremely rapid, with N-GAL appearing in the first urine portion after the acute kidney injury.[9] Serum N-GAL elevation was found to indicate acute GFR reductions much faster than creatinine measurements in different clinical conditions, for example, in patients undergoing cardiac surgery[10] or percutaneous coronary interventions.[11] The determination of cystatin C and serum N-GAL might thus be appropriate tools for detecting acute kidney injury secondary to haemodynamic compromise or hypoxaemia resulting from APE.

The authors investigated 142 consecutive patients with APE. The all-cause mortality rate up to 30 days after the diagnosis of APE was 10%, nine deaths (6%) were found to be pulmonary embolism related. The estimated glomerular filtration rate (eGFR) was noted to be 60 ml/min per 1.73 m^2 or less in 48% of the study population. Both, N-GAL and cystatin C levels significantly correlated with the eGFR. In contrast to cystatin C, serum N-GAL concentrations were significantly higher in patients who died from APE. Decrease in eGFR as well as elevations of cystatin C and serum N-GAL were significant predictors of all-cause and pulmonary embolism-related 30-day mortality in univariate analysis. However, only cystatin C levels independently predicted 30-day all-cause mortality but not PE-related deaths in the multivariate analysis. Both cystatin C and N-GAL elevations were associated with less favourable clinical outcomes in the Kaplan–Meier analysis. Left ventricular ejection fractions correlated with both eGFR and cystatin C levels, while plasma N-GAL concentrations were found to correlate with right ventricular function parameters assessed by echocardiography. Other risk stratification models such as the simplified pulmonary embolism severity index significantly correlated with eGFR, cystatin C levels and serum N-GAL concentrations.

In contrast to previous studies[4 5] the authors were able to demonstrate that haemodynamic compromise during APE might have contributed to renal dysfunction, as markers of acute kidney injury were associated with signs of acute right ventricular dysfunction or increased central venous pressure. Sudden pressure overload in the pulmonary circulation due to APE may lead to acute right ventricular dysfunction along with tricuspid regurgitation. As a consequence, central venous pressure rises and may lead to renal dysfunction by a stagnation of venous blood flow in the kidneys.[12] The findings of the study are new and possibly represent an important step forward in the understanding of the interactions between the cardiopulmonary and renal systems during APE. On the other hand, the study included many patients with relevant comorbidities, such as diabetes mellitus and congestive heart failure, which are well known to affect kidney function themselves. As a consequence, the eGFR was found to be reduced in nearly one out of two study participants. Therefore, both cystatin C and N-GAL elevations might have been aggravated by chronic pre-existing renal insufficiency.

The results of the present study underline the notion that renal dysfunction may be associated with a worse prognosis of patients with APE and, therefore, might represent an additional aspect in risk stratification. A number of clinical and instrumental findings such as haemodynamic instability, right ventricular dysfunction or myocardial injury have been associated with a high risk of adverse short-term clinical outcomes in patients with APE and are the basis of risk stratification according to current guidelines.[13] Therefore, particularly in haemodynamically stable patients who are believed to be at low risk of death, markers of acute kidney injury might be additionally helpful in risk stratification, as signs of right ventricular dysfunction or myocardial injury are missing and both cystatin C and N-GAL elevations showed very high negative predictive values in the estimation of the all-cause mortality in this subgroup of patients. However, the results of this single-centre trial have to be interpreted with caution, as the statistical analysis is limited by the relatively small numbers of study participants and the low death rates. For example, the evaluation for pulmonary embolism-related 30-day mortality is based on the outcome analysis of only nine patients. The small study size might explain the partially inconsistent findings of the study, as the results might have been biased by concomitant factors such as age or comorbidity even after forward stepwise multivariate analysis.

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Is the evaluation of renal function a new aspect in the risk stratification of patients with APE? The study of Kostrubiec and colleagues[6] is promising, but it is too early to answer the question. Larger multicentre studies need to follow, and markers of acute kidney injury have to be validated against other biomarkers such as brain-type natriuretic peptide or troponin, which are already accepted components in risk stratifications models of patients with APE.[14]

Competing interests None.

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