Copeptin as a non-invasive biomarker in chronic thromboembolic pulmonary hypertension

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Introduction: Copeptin is the C-terminal fragment of the precursor protein of vasopressin. In acute pulmonary embolism, copeptin has been suggested to be a strong predictor of outcome and to provide additional predictive value to the established cardiac biomarkers high-sensitivity cardiac troponin and N-terminal pro-brain natriuretic peptide (NT-proBNP). Chronic thromboembolic pulmonary hypertension (CTEPH) is diagnosed in about 5% of patients who survive acute pulmonary embolism. Individualized risk stratification remains a challenge in the work-up of CTEPH patients.

Purpose: The current study investigated whether copeptin has the potential to aid the stratification of patients who have experienced pulmonary embolism and CTEPH patients. We examined the baseline (BL) levels and dynamics of copeptin during therapy in CTEPH patients who underwent balloon pulmonary angioplasty (BPA) or pulmonary endarterectomy (PEA). Moreover, the study compared copeptin levels between patients with or without therapy response.

Methods: The study included a total of 125 CTEPH patients scheduled for treatment. A total of 78 underwent staged BPA and 64 underwent PEA. In accordance with recent studies from our group, therapy success was defined as a decrease in meanPAP $\geq$25% and PVR $\geq$35% or a normalization below the thresholds defining pulmonary hypertension. Blood samples were collected at BL, prior to each BPA session in the BPA cohort, and at follow-up (FU) 6 months after BPA or 12 months after PEA. Copeptin was measured in thawed serum aliquots by an immunochemical method.

Results: The 78 patients in the BPA cohort underwent a mean of 6 BPA procedures each; there were a total of 413 interventions. The hemodynamic clinical and functional status the CTEPH patients improved after BPA and PEA therapy: meanPAP (BL: 43±9 mmHg vs. FU: 27±9 mmHg; $p<0.001$); PVR (BL: 7.6±3.4 WU vs. FU: 3.8±2.0 WU; $p<0.001$); RAP (BL: 7.9±5.8 mmHg vs. FU: 5.4±2.7 mmHg; $p<0.001$); WHO functional class [BL: I:0 / II:25 / III:80 / IV:20 vs. FU: I:56 / II:57 / III:10 / IV:2]; 6-minute-walk distance (BL: 405±99 m vs. FU: 456±112 m; $p<0.001$).

The median serum levels of copeptin [BL 7.7 (4.6–14.2) pmol/L vs. FU 6.3 (3.9–12.5); p=0.009] and NT-proBNP [BL: 811 (157–1857) ng/L vs. FU: 142 (72–335) ng/L $p<0.001$] decreased significantly after therapy. The copeptin levels did not correlate with hemodynamics at BL: PVR (rrs=0.02; p=0.79) and meanPAP (rrs=0.03; p=0.75). The copeptin levels at BL (AUC=0.61) and the relative change (AUC=0.53) did not predict the endpoint of therapy response.

Conclusions: Copeptin levels are elevated in CTEPH patients compared with normal values in the literature. Although copeptin is known to provide additional value in the context of risk stratification in acute pulmonary embolism, it failed to provide additional diagnostic benefit in CTEPH in the current study.