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Heparin-binding protein and organ failure in critical illness

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Abstract

Background For patients severely ill enough to require care in an intensive care unit (ICU), both the disease itself (e.g. bacteria in the blood in sepsis or fractures after trauma) and effects of the immune system can cause circulatory, pulmonary, or renal dysfunction. Leukocytes play a dominant role in the immune system. When activated they release a range of small proteins with different properties Heparin-binding protein (HBP) being one of these proteins, has many functions, including to increase vascular permeability. Heparin-binding protein causes plasma leakage from blood vessels into surrounding tissue (oedema), which can lead to organ dysfunction depending on the site and degree of oedema formation. Increased concentration of HBP in plasma is associated with failing circulation and lung function in subgroups of critically ill patients.

Aims We investigated the possibility of using concentration of HBP in plasma for predicting circulatory, respiratory or renal failure in an ICU population with mixed diagnosis. We assessed concentration of HBP in alveoli in ventilator induced lung injury (VILI), and finally assessed elimination of HBP in urine and effluent fluid from continuous dialysis.

Methods In Papers I and II, HBP concentration in plasma was measured in 278 patients on admission to ICU. Sequential organ failure assessment (SOFA) scores and acute kidney injury (AKI) stage were recorded daily. In Paper III HBP concentration in bronco-alveolar fluid was measured in a pig model of ventilatory induced lung injury, in 16 healthy volunteers and in 10 intubated ICU patients. In Paper IV plasma and urine concentration of HBP was measured in 8 healthy volunteers and 20 burn ICU patients. In addition, HBP was sampled in plasma and effluent fluid in 32 ICU patients on continuous renal replacement therapy (CRRT).

Results In Paper I, patients developing circulatory failure (circulatory sub-score of SOFA = 4) had higher plasma concentration of HBP compared to those who did not (median(IQR)ng/ml) (63.5(32–105) vs 36.4(24–59)) p<0.01), and patients developing respiratory failure (P:F ratio < 27) had higher HBP concentration than those who did not (44.4(30-109) vs 35.2(23-57) p<0.01). Discriminatory capacity was (ROC AUC (95%CI)) (0.65 (0.54–0.76)) for circulatory failure and (0.61(0.54–0.69)) for respiratory failure. In Paper II, patients developing renal failure (AKI stage 2-3) had higher plasma concentration of HBP compared to those who did not (72.1 (13.0–131.2) vs 34.5 (19.7–49.3) p<0.01). Discriminatory capacity for AKI stage 3 was 0.68(0.54-0.83) (ROC AUC (95%CI)). In the subgroup with severe sepsis, it was 0.93 (0.85–1.00). In Paper III, HBP concentration in bronchoalveolar lavage was higher in pigs subjected to injurious ventilation over 6 hours ventilation compared to controls (1144(359–1636) vs 89(33–191) p=0.02) (median(IQR)ng/ml). The median HBP concentration in bronchoalveolar lavage from healthy volunteers was 0.90(0.79– 1.01) compared to 1959(612–3306) from intubated ICU patients (p < 0.01). In Paper IV, renal clearance of HBP was 0.19 (0.08-0.33) in healthy individuals and 0.30 (0.01-1.04) (median, IQR, ml/min) in burn ICU patients. Clearance of HBP was higher in burn patients with increased cystatin C (0.45(0.15-2.81) vs. 0.28(0.14-0.55) p=0.04). Starting CRRT did not alter plasma concentration of HBP (p=0.14). Median HBP concentration in effluent fluid on CRRT was 9.1 ng/ml (7.8-14.4).

Conclusions Papers I and II*:* There is an association between high concentration of HBP in plasma on ICU admission and circulatory, respiratory and renal failure. For the individual patient, the predictive value of a high HBP concentration is low, with the possible exception of renal failure in septic patients. Paper III*:* HBP concentration in alveoli increases in pigs subjected to injurious ventilation. HBP concentration in alveoli of intubated ICU patients ventilated protectively is elevated to similar levels, a factor of approximately 1000 times higher than the concentration seen in healthy controls. Paper IV*:* In healthy study participants, renal clearance of HBP is low. In critically ill burn patients with impaired renal function, clearance of HBP is increased. Starting CRRT in critically ill patients does not alter plasma concentration of HBP. Still, HBP is found in the CRRT effluent fluid, and concentration does not appear to be dependent on plasma concentration.

Keywords
Heparin-binding protein, Critical care, Shock, Acute respiratory distress syndrome, Acute kidney injury, Ventilator induced lung injury, Renal clearance.

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