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Preoperative serum h-FABP concentration is associated with postoperative incidence of acute kidney injury in patients undergoing cardiac surgery

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Abstract

Background: Fatty acid binding protein (FABP) is an intracellular transport protein associated with myocardial damage size in patients undergoing cardiac surgery. Furthermore, elevated FABP serum concentrations are related to a number of common comorbidities, such as heart failure, chronic kidney disease, diabetes mellitus, and metabolic syndrome, which represent important risk factors for postoperative acute kidney injury (AKI). Data are lacking on the association between preoperative FABP serum level and postoperative incidence of AKI.

Methods: This prospective cohort study investigated the association between preoperative h-FABP serum concentrations and postoperative incidence of AKI, hospitalization time and length of ICU treatment. Blood samples were collected according to a predefined schedule. The AKI Network definition of AKI was used as primary endpoint. All associations were analysed using descriptive and univariate analyses.

Results: Between 05/2009 and 09/2009, 70 patients undergoing cardiac surgery were investigated. AKI was observed in 45 patients (64%). Preoperative median (IQR) h-FABP differed between the AKI group (2.9 [1.7–4.1] ng/ml) and patients without AKI (1.7 [1.1–3.3] ng/ml; $p = 0.04$), respectively. Patients with AKI were significantly older. No statistically significant differences were found for gender, type of surgery, operation duration, CPB-, or X-Clamp time, preoperative cardiac enzymes, HbA1c, or CRP between the two groups. Preoperative h-FABP was also correlated with the length of ICU stay ($r_s = 0.32$, $p = 0.007$).

Conclusions: We found a correlation between preoperative serum h-FABP and the postoperative incidence of AKI. Our results suggest a potential role for h-FABP as a biomarker for AKI in cardiac surgery.

Background

Fatty Acid Binding Protein (FABP) is an intracellular transport protein responsible for transporting long chained fatty acids to their destination and has organ specific subtypes (e.g. heart-type, liver-type and brain-type FABP) [1,2]. Heart-type FABP (h-FABP) is a marker for myocardial ischemia and is associated with ECG changes, arrhythmia and mortality after cardiac surgery [3-8]. Furthermore, h-FABP is elevated in patients with heart insufficiency,

diabetes mellitus, chronic kidney disease, metabolic syndrome and is positively correlated with age [1,4,9-11]. These entities also represent important risk factors for postoperative acute kidney injury (AKI), which is a common postoperative complication with an incidence of 20 to 40% after cardiac surgery with high impact on postoperative mortality [12-20].

Utilizing h-FABP as a single marker for the described variety of risk factors of AKI seems to be possible. But studies regarding the association of h-FABP's pre-operative serum concentration and post-operative outcomes for patients undergoing operations with cardiopulmonary bypass (CPB) are lacking. Although postoperative I-FABP has been

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described as a marker for AKI, pre-operative h-FABP has not been investigated as an AKI marker in a cohort of cardiac surgical patients [14,15,17,21-24].

In the current study, we aimed to explore the association between preoperative h-FABP levels and the occurrence of AKI in patients undergoing cardiac surgery within the setting of a prospective mono-center cohort study.

Methods

The study protocol was approved by the Ethics Committee at the University Hospital of Würzburg. Adult (>18 years) patients scheduled for elective CABG surgery or single valve repair/replacement in the Department of Cardio-Thoracic Surgery at the University Hospital Würzburg, Germany were eligible if they provided written informed consent. Exclusion criteria comprised chronic kidney disease stage 3 or greater (i.e. $eGFR_{CKD-EPI} < 30$ ml/min/1.73 m²), off pump surgery, acute inflammation (defined by C-reactive protein (CRP) > 4 mg/dl, and procalcitonin (PCT) > 1.0 µg/l), history of immunological or musculoskeletal disorders, stroke within 30 day prior to admission, preoperative resuscitation, preoperative electrical cardioversion, salvage or urgent operations (defined as preoperative beginning of cardiopulmonary support). All patients were operated with blood cardioplegia at 4°C applied every 20 minutes and in mild hypothermic perfusion (32°C).

Primary endpoint was defined as incidence of AKI according to acute kidney injury network (AKIN) (increase of serum creatinine by ≥ 0.3 within 48 hours), while baseline was set at admission to hospital, which was usually the day before operation; secondary endpoints were mechanical ventilation time, length of ICU stay, and hospitalization time [16].

Standard demographic data of patients was collected prospectively including sex, age, weight, height and waist circumference at the time of operation. Intraoperative data such as operation time, paracorporeal bypass time and aortic cross clamping time were noted. Blood samples were taken at hospital admission, after induction of anaesthesia 30 minutes, 6, 24 and 48 hours after aortic cross clamping. Length of mechanical ventilation, length of ICU stay and hospitalization time was listed.

h-FABP was measured by ELISA (HK402 HUMAN H-FABP ELISE KIT, Hycult biotech, Netherlands) in ng/ml in our own laboratory from blood samples taken after introduction of anaesthesia and 30 minutes after aortic clamping. Creatinine was measured in central laboratory unit of the University of Würzburg.

Statistical analysis

Continuous variables are presented as mean and standard deviations or as medians and interquartile ranges. Categorical variables are presented in percentages. Normal distribution testing was performed with a Kolmogorov-

Smirnov-Test. To test for differences across all groups, χ^2 -test, Fisher's exact test, *t*-test, Mann-Whitney-*U*-Test were used. Correlation analyses were performed employing Spearman correlation. In logistic regression analysis modelling we investigated h-FABP, age and eGFR regarding their association with the risk for AKI. To assure normal distribution of h-FABP natural log was used. Two-sided *p*-values of ≤ 0.05 were considered as statistically significant. Analyses were performed with SPSS Version 21.

Results

A total of 238 consecutive patients admitted to the department of cardiovascular surgery of the University of Würzburg between 05/2009 and 09/2009 were screened for participation in the study. Of those, 122 patients met the inclusion criteria and 70 were included in the study. Reasons for exclusion were: urgent surgery (32 patients), chronic kidney disease stage 3 or greater (14 patients), off pump surgery (5 patients), acute inflammation (1 patient).

Patient characteristics at baseline are shown in Table 1. Patients were predominantly male (80%) with a mean age of 67(± 10) yrs. The mean preoperative eGFR was 88 (± 11) ml/min/1.73 m², 69% (*n* = 48) of the cohort received CABG surgery, while 22 (31%) underwent single valve replacement. Preoperative median troponin T was 0.01 [IQR: 0.01–0.01].

A total of 45 patients (64.3%) achieved the primary endpoint of AKI, while only three patients experienced more severe stages of AKI, including the need for dialysis (4.3%).

Postoperative ischemia markers did not differ significantly between the two groups of AKI vs. non-AKI (see Table 2). Patients with AKI had to remain longer on the ICU, however, mechanical ventilation time and overall hospital stay did not differ (Table 3). Preoperative median (IQR) h-FABP differed between the AKI group (2.9 [1.7–4.1] ng/ml) and patients without AKI (1.7 [1.1–3.3] ng/ml; *p* = 0.04), respectively. Preoperative h-FABP was also correlated with the length of ICU stay ($r_s = 0.32$, *p* = 0.007) and with hospitalization time ($r_s = 0.308$; *p* = 0.009). No relation was found for age with the length of ICU stay ($r_s = 0.089$, *p* = 0.47). h-FABP was associated with preoperative creatinine ($r_s = 0.404$, *p* = 0.001), eGFR ($r_s = -0.603$, *p* < 0.001), and myoglobin levels ($r_s = 0.610$, *p* < 0.001).

Although a number of preoperative variables (e.g., age, waist circumference, HbA1c, operation duration, x-clamp time, all *p* < 0.05) differed between CABG and valve patients, there was no statistically significant difference in the incidence of the primary endpoint AKI (*p* = 0.29). In logistic regression analysis, the association of elevated h-FABP levels with an increased risk for AKI diminished after adjustment for age and preoperative kidney function (Table 4). However, in the final elimination model only

Table 1 Preoperative characteristics

Variable	All patients (n = 70)	AKI (n = 45)	No AKI (n = 25)	P-value
h-FABP [ng/dl]	2.9 (1.4–3.9)	2.9 (1.7–4.1)	1.7 (1.1–3.3)	0.039
Age (yr)	67 (±10)	69 (±9)	64 (±11)	0.016
Male	56 (80%)	37 (82%)	19 (76%)	0.76
CABG	48 (69%)	33 (73%)	15 (60%)	0.29
Preoperative creatinine [mg/dl]	1.0 (±0.3)	1.0 (±0.2)	0.9 (±0.1)	0.50
eGFR–CKDEPI preoperative [ml/min/1,73 m ²]	88 (±11)	87 (±10)	91 (±12)	0.17
Troponin T (mg/dl)	0.01 (0.01–0.01)	0.01 (0.01–0.01)	0.01 (0.01–0.01)	0.28
Waist Circumference [cm]	104 (±13)	102 (±13)	104 (±13)	0.86
Operation duration [min]	240 (±60)	244 (±60)	239 (±59)	0.91
CPB duration [min]	113 (±36)	113 (±38)	114 (±34)	0.41
X-Clamp duration [min]	82 (±30)	81 (±29)	85 (±30)	0.90
HbA1c [%]	6.0 (5.6–6.6)	5.9 (5.6–6.4)	6.0 (5.7–7.2)	1.0
CK [mg/dl]	80 (55–116)	80 (60–118)	100 (57–122)	0.97
Myoglobin [mg/dl]	44 (31–54)	46 (32–59)	37 (29–52)	0.15
C-reactive protein [mg/dl]	0.3 (0.1–0.6)	0.3 (0.1–0.6)	0.2 (0.1–0.3)	0.33

Data are mean (±SD), number (%) or median (IQR). CABG: coronary artery bypass grafting, CPB: cardio pulmonary bypass, X-Clamp: Aortic clamping.

h-FABP was associated with the incidence of AKI independent from age and preoperative eGFR.

7 (10%) of the patients had an positive Troponin T (>0.05 mg/dl). Neither in uni- nor in multivariate analyses preoperative troponin T showed a statically significant association with the incidence of AKI ($p > 0.05$).

Discussion

In our study preoperative h-FABP serum concentration was associated with the incidence of postoperative AKI as well as with a longer stay on the ICU.

Previous studies have shown that postoperative h-FABP elevation was a marker for intraoperative myocardial damage with postoperative ECG changings and elevation of established ischemia markers [5,7]. In a similar setting, serum and plasma levels of h-FABP without an ischemic incident were found to be associated with poor outcome in end-stage heart failure patients with circulatory support [25]. The pathophysiology for the poorer outcome was explained by the myocardial damage

indicated by h-FABP elevation. None of the studies investigated a possible association between preoperative h-FABP concentrations with postoperative complications, although h-FABP has been linked to preoperative risk factors like heart failure, metabolic syndrome, chronic kidney disease or diabetes mellitus [1,2,9,11,26]. None of the cited studies have approached our hypothesis.

The incidence of AKI is higher in our cohort than in recent literature. This might be due to the rigorous definitions of AKIN with only a slight creatinine increase of 0.3 mg/dl. In particular as our study was performed during the summer months, the preoperative fastening status thus potentially causing hypovolemia might have sensitised the kidney for intraoperative stress and thus the incidence of AKI. It was reassuring though that only few patients experienced more severe stages of AKI including dialysis as we also did not observe any perioperative mortality.

However, postoperative urinary l-FABP has been shown in several recent studies as a promising marker for the

Table 2 Postoperative results

Variable	All patients (n = 70)	AKI (n = 45)	No AKI (n = 25)	P-value
h-FABP [ng/dl]	9.9 (9.5–10.1)	9.9 (9.7–10.4)	9.9 (9.2–10.1)	0.79
Creatinine Peak Within 48 h [mg/dl]	1.4 (±0.6)	1.7 (±0.6)	1.0 (±0.2)	<0.001
C-reactive protein [mg/dl]	0.2 (0.1–0.5)	0.2 (0.1–0.4)	0.1 (0.1–0.2)	0.54
CK [mg/dl]	230 (145–375)	244 (175–438)	254 (138–422)	0.87
Myoglobin [mg/dl]	261 (182–410)	300 (212–424)	210 (137–446)	0.38
Troponin T [µg/l]	0.3 (0.1–0.5)	0.4 (0.2–0.7)	0.2 (0.1–0.5)	0.29

Data are mean (±SD), number (%) or median (IQR). CABG: coronary artery bypass grafting, CPB: cardio pulmonary bypass, X-Clamp: Aortic clamping.

Table 3 Ventilation time, ICU stay and hospitalization time

Variable	All patients (n = 70)	AKI (n = 45)	No AKI (n = 25)	P-value
Hospitalization [d]	12 (11–15)	13 (11–15)	12 (10–15)	0.35
ICU Stay [h]	44 (21–83)	46 (22–92)	22 (18–47)	0.030
Ventilation Time [h]	16 (12–20)	15 (11–20)	15 (12–21)	0.49

Data are mean (±SD), number (%) or median (IQR). CABG: coronary artery bypass grafting, CPB: cardio pulmonary bypass, X-Clamp: Aortic clamping.

extent of AKI [21-24]. Preoperative levels of urinary or serum levels of h-FABP have not been reported to be associated with AKI yet.

h-FABP as a marker for comorbidities

Patients with higher h-FABP values were older, had higher creatinine values and thus lower eGFR in the present study. Age and preoperative h-FABP were related to postoperative AKI. These findings were similar to the results in previous studies. A possible explanation is the association of h-FABP with a wide spectrum of comorbidities evident in patients undergoing cardiac surgery. DM and metabolic syndrome, which have been described as risk factors for AKI after CABG, were known to cause elevated h-FABP levels [11,18,27-31]. We did not screen for all symptoms of metabolic syndrome, but for waist circumference, and HbA1c. Neither waist circumference nor HbA1c were associated with AKI or with elevated preoperative h-FABP. But in CABG patients HbA1c and waist circumference were higher than in patients with valve surgery. In a larger cohort of CABG patients an association between metabolic syndrome, h-FABP and AKI might be detected.

Older age indicates increased risk for AKI after cardiac surgery. Furthermore, elderly patients tend to have higher h-FABP levels [1,2,18-20,30]. Both effects could be observed in our results.

Length of ICU stay

The second finding in the present study was the association between preoperative h-FABP and longer postoperative ICU treatment. A reasonable explanation for this phenomenon was the incidence of AKI, which was associated with a longer ICU stay itself. AKI and renal failure are known factors with an impact on ICU and hospitalization

time in cardiac surgical patients [14]. By being associated with the incidence of AKI, h-FABP was also related to the length of ICU stay. Longer ICU stay is associated with higher costs and ICU capacity frequently is a limiting factor for cardiac surgery departments. Predicting possible lengths of stay for risk patients is of crucial importance for the cost-effectiveness and for decent organisation of departments. Therefore predictive markers need to be identified in further studies.

Postoperative h-FABP

Postoperative h-FABP was not associated with AKI in the current study. h-FABP is a proven marker for myocardial damage and is known to be elevated after cardiac surgery. Postoperative h-FABP correlated with the established myocardial damage markers (myoglobin, troponin T and CK/CK-MB) in this study. None of the postoperative markers had an association with AKI, however, we might have missed true associations due to limited sample size and thus limited statistical power.

The presented study with a small number of patients was designed to create hypotheses for future investigations and has several limitations. A larger cohort is needed for multivariate analyses, e.g. to adjust for the effect of age and to investigate the different AKI stages in more detail to also further explore the association with the length of stay on the ICU. The screening for metabolic syndrome was incomplete, as well as was the information on further pathomechanisms for the incidence of AKI, such as red cell count, left ventricular ejection fraction, and hemodynamic instabilities. However, this information is lacking in literature as well. Other subtypes of FABP (liver, brain) might also interfere with h-FABP and should be measured in future studies. If the rather strict definition of AKI by the KDIGO can be transferred unmodified to cardiac surgical patients needs to be discussed as well.

Conclusions

The findings of our study suggest an association between preoperative serum h-FABP levels and postoperative incidence of AKI and the length of ICU stay. The results justify further research of FABP as a possible predictor for adverse events after cardiac surgery within the setting of prospective studies requiring larger sample sizes.

Table 4 Univariate and multivariate models

Variable	Univariate	Model I	Model II	Model III	Model IV	Final model (p < 0.1) OR (95% CI)
Ln(h-FABP)	2.29 (1.08–4.88)	2.29 (1.08–4.89)	1.82 (0.78–4.24)	2.24 (1.01–4.94)	1.79 (0.73–4.39)	2.29 (1.08–4.88)
eGFR	0.99 (0.97–1.02)	0.99 (0.97–1.02)	-	-	0.99 (0.96–1.02)	-
Age	1.06 (1.00–1.11)	-	1.04 (0.98–1.10)	-	1.03 (0.97–1.09)	-
Ln(TropT)	1.33 (0.74–2.39)	-	-	1.11 (0.60–2.05)	1.15 (0.62–2.13)	-

Determinants of AKI; data is presented as OR (CI95%); ln(h-FABP) to achieve normal distribution ln of FABP was calculated; final model is based on backward elimination.

Abbreviations

AKI: Acute kidney injury; CABG: Coronary artery bypass grafting; CPB: Cardio pulmonary bypass; DM: Diabetes mellitus; ECG: Electrocardiography; FABP: Fatty acid binding protein; h-FABP: Heart-type fatty acid binding protein; ICU: Intensive care unit; I-FABP: Liver-type fatty acid binding protein; IQR: Interquartile range; LV-EF: Left ventricular ejection fraction; SD: Standard deviation.

Competing interests

M Oezkur was supported by a rotational post from the Comprehensive Heart Failure Center Würzburg funded by the German Ministry of Research and Education. PU Heuschmann receives/ received in the recent years research support from the German Ministry of Research and Education (Center for Stroke Research Berlin; Comprehensive Heart Failure Center Würzburg), the European Union (European Implementation Score Collaboration), the German Stroke Foundation, the Charité-Universitätsmedizin Berlin, the Berlin Chamber of Physicians, and the University Hospital of Würzburg.

Authors' contributions

MO conceived, designed, executed the study and had major parts in the statistical analyses. AG substantially contributed to conception and design of the study. JP carried out the patient acquisition, blood sampling and performed the ELISA. ML participated in the laboratory work, especially in the ELISA. PH and MW gave significant input to the statistical analysis and design of the manuscript. CS, RL participated in the design of the study, and gave significant input on the manuscript. All authors read and approved the final manuscript.

Acknowledgements

We thank all patients providing data to the current study as we as we thank the physicians and study personnel for filling in case report forms for study participant and performing study procedures. This publication was funded by the German Research Foundation (DFG) and the University of Würzburg in the funding programme Open Access Publishing. This study was supported by the German Ministry of Education and Research (BMBF) within the setting of the Comprehensive Heart Failure Center Würzburg (BMBF 01EO1004).

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Received: 25 June 2014 Accepted: 5 September 2014

Published: 12 September 2014

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doi:10.1186/1471-2261-14-117

Cite this article as: Oezkur et al.: Preoperative serum h-FABP concentration is associated with postoperative incidence of acute kidney injury in patients undergoing cardiac surgery. *BMC Cardiovascular Disorders* 2014 **14**:117.

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