Biomarkers and prognosis in cardiac surgery in the ICU

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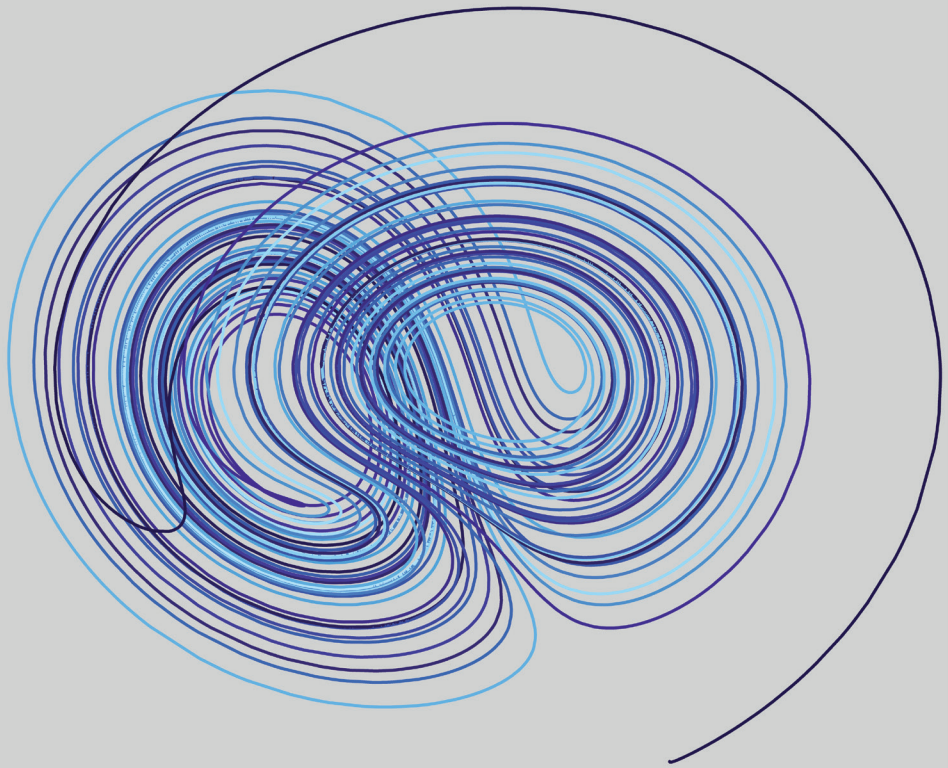

CHAPTER **3**

Postoperative ProADM levels predict mortality in thoracic surgery patients – comparison with APACHE IV score.

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Abstract

Objectives: Risk assessment in ICU patients using commonly used prognostic models may be influenced by using different data definitions and by errors in data collection. We investigated if a set of biomarkers (procalcitonin, MR-pro-adrenomedullin, CT-pro-endothelin-1, CT-pro-arginine vasopressin, and MR-pro-atrial natriuretic peptide), alone or as a panel could be useful in postoperative risk assessment for hospital mortality in comparison to the APACHE-IV score.

Design: In a prospective observational cohort study, we analyzed 800 consecutive patients undergoing elective cardiac surgery. We assessed biomarker levels on admission to the ICU and every six hours thereafter for 24 hours. For every postoperative time point and for every biomarker we determined the predictive value for hospital mortality and made a comparison with the Acute Physiology and Chronic Health Evaluation IV score.

Setting: Intensive care of an academic referral hospital.

Patients: A total of 800 consecutive patients undergoing elective cardiac surgery.

Interventions: None.

Measurements and Main Results: MR-pro-adrenomedullin is a good predictor of mortality (c-statistic at time point 6 hours after admission to the ICU: 0.940; CI-95 0.918 - 0.956) and performed better than the Acute Physiology and Chronic Health Evaluation IV score (c-statistic 0.842; CI-95 0.811 - 0.868). The c-statistic did not change significantly on the time points 6, 12 and 18 hours after admission. Using a cutoff value for proADM taken 6 hours after admission on ICU (Time point 2) of 3.2 nmol/l sensitivity was 81.8% and specificity 93.9%, the positive Likelihood Ratio was 13.3, positive predictive value 31.0% and negative predictive value 99.4%. Patients with a MR-proADM above this cutoff level had an odds ratio of 68.9 (95% CI 22.2 – 213.1) for not surviving their hospital stay. The other biomarkers had less predictive power.

Conclusions: In elective cardiac surgery, MR-pro-adrenomedullin measured between 6 and 18 hours after admission to the ICU is a better predictor of hospital mortality in comparison with the Acute Physiology and Chronic Health Evaluation IV score.

Introduction

Risk assessment of ICU patients is important for quality, scientific and economic reasons. For risk assessment of ICU patients and quality comparison between ICU's the Acute Physiology and Chronic Health Evaluation (APACHE) IV is widely used. It has been validated in almost all patient categories including cardiothoracic surgery patients (1). The APACHE-IV score estimates the risk of hospital mortality from actual clinical data in the first 24 hours after ICU admission, patient characteristics, chronic health evaluation, reason of admission, and diagnostic categories. The need to collect much data requires an elaborate and precise system. Furthermore, risk assessment may be greatly influenced by the used data definitions (e.g., for chronic respiratory failure or immunosuppression) or using data taken prior to ICU admission (lead time bias) (2). It would be of great value if the simple assessment of a biomarker could aid in the risk assessment of ICU patients, improve the APACHE IV score, or even replace it.

Several assays for pro-hormones have been developed that give information about important pathophysiologic pathways in cardiac surgery such as the inflammatory pathway (Procalcitonin [PCT]), the vasomotor response (MR-pro-Adrenomedullin [MR-proADM] and CT-pro-Endothelin-1 [CT-proET-1]), the neurohumoral response (CT-pro-Arginine Vasopressin [CT-proAVP]) and the cardiohumoral response (MR-pro-Atrial Natriuretic Peptide [MR-proANP]).

The aim of this study was to investigate whether the postoperative levels of the aforementioned biomarkers could aid in the prediction of hospital-mortality, to compare their predictive value with the APACHE IV score and to determine in which timeframe the postoperative sample should be taken.

Material and Methods

Study population

The study was performed at the Leiden University Medical Center, a 500-bed tertiary referral hospital. Study participants were consecutive patients undergoing elective cardiac surgery. Patients more than 18 years who could read and understand the informed consent and the study information were eligible for entrance in the study. Patients were only included after signing the informed consent. Exclusion criteria were pregnancy, active infection, emergency surgery, and participation in another study. We adhered to the Helsinki protocol and standard of good clinical practice. The study was approved by the Medical Ethical Committee (Protocol P 05.045).

Operative procedure

Anesthesia was standardized and consisted of premedication with lorazepam (1-1.5 mg) the night and the morning before operation. Induction was achieved with propofol 1-1,5 mg/kg bolus and a remifentanil bolus of 20-40 µg. Anesthesia was maintained with propofol 5-6 mg/kg/h continuously and remifentanil 800-1600 µg/hour continuously. Heparin was administered before the start of cardiopulmonary bypass, if applied, at a dose of 300 IU/kg bolus and subsequently at a maintenance dose adapted to maintain the activated clotting time above 400 seconds. At the end of cardiopulmonary bypass heparin was antagonized with protamine sulphate titrated 1:1 to the initial dose of heparin (3 mg/kg). Ventilation was set at low pressure (BIPAP 10/4 cm H_2O) and low frequency just to prevent atelectasis of the lung.

Bypass priming included 1000 ml of a 6% HES 130/0.4 solution (Voluven, Fresenius Kabi) and 200 ml Ringers solution, 100 ml Mannitol 20%, 5000 IU Heparin, Cyclokapron™ 1000 mg and Cefazolin 1000 mg. After venous and arterial cannulation, bypass was commenced using a heart-lung machine (S3, Sorin Group; München, Germany), with a centrifugal blood pump (Revolution; Sorin Group, Mirandola, Italy). Oxygenation was accomplished with a hollow fiber oxygenator (Quadrox-i, Maquet; Hirlingen, Germany). Tubing was coated with bio inert heparin-free polymers (Safeline, Maquet; Hirlingen, Germany). Flow was laminar with rates set at 2.0-2.6 l/m^2/min. Intermittent warm antegrade blood cardioplegia was instituted every 15-20 min for a period of two minutes at a flow of 300-450 ml/min with a pressure of 200-250 mm Hg. During bypass, the core temperature was maintained at 34-36 °C. Standard surgical prophylaxis consisted of Cefazoline 1 g intravenously, given within one hour to first incision.

ICU care

After surgery patients were transferred to the ICU for postoperative care. Care given on the ICU was standardized as much as possible. When patients were extubated and stable, they were transferred to the thoracic surgery ward the next day.

Biomarker Sampling

Blood samples (9 ml Vacuette® Lithium-Heparin, Greiner Bio-One, VWR; Radnor, PA) were drawn at arrival on the ICU (T1) and every 6 hours thereafter (T2, T3, T4) until 24 hours after admission (T5). The blood samples were immediately processed (centrifuged for 5 minutes with 4000 rpm) and plasma was stored at -80 °C until analysis. Sampling was stopped when the patient was discharged to the ward or needed a rethoracotomy.

Biomarkers

Specifications on the biomarkers assayed are given in detail in the references. In short, PCT is considered a marker of inflammation and is raised especially in, but not limited to,

invasive bacterial infection (3) (4). Its maximum level is reached within 24 hours after the onset of infection and subsides with a half-life of about 24 hours after the inflammatory stimulus has disappeared (5) (6). CT-proAVP is the C-terminal fragment of the pro-hormone of arginine vasopressin (or anti diuretic hormone [ADH]). AVP has a central role in water homeostasis, as antidiuretic hormone reducing free water clearance in hyperosmolar states and in volume depletion. Moreover, it acts as a potent vasoconstrictor and is released in the circulation in acute hypotension and shock because of various causes (7). In severe chronic systolic heart failure, it is elevated in an apparent attempt to maintain an adequate effective circulating volume (8). The prohormone is more stable compared to the active hormone. Its concentration adequately reflects the levels of bioactive ADH and thus can be used as an alternative (9). MR-proANP is a stable fragment of the prohormone of ANP. It is produced and stored in the atria. It is secreted in low levels in healthy states and in higher levels upon atrial stretch (10). ANP promotes natriuresis and vasodilation, thereby acting as an agent against volume overload (11) (12). It has a strong association with N-terminal pro-B type natriuretic peptide and in studies has been shown to predict morbidity and mortality in patients after myocardial infarction (13) (14). The pro-hormone is more stable than the hormone itself and can be assayed as an alternative (12).

MR-proADM is a stable midregional fragment of the prohormone of adrenomedullin that is involved in vasomotor regulation and homeostasis (14). Its levels are elevated in subjects with cardiac failure (15). The prohormone is more stable than the hormone itself and can be used as an alternative (16).

CT-proET-1 is the C-terminal fragment of the prohormone of endothelin-1. Endothelin-1 is a potent vasoconstrictor and has an important role in the vasomotor homeostasis (17) (18). The pro-hormone is more stable compared to the hormone and can be used as an alternative (19).

Analysis of biomarkers was done on coded samples in an external laboratory independent of the clinical team and without knowledge of outcome or access to patient data, at the courtesy of Thermo Fischer Scientific / B.R.A.H.M.S. (Hennigsdorf, Germany). In short, MR-proADM, PCT, MR-proANP and CT-proET-1 where all analyzed with the Thermo Fisher / B.R.A.H.M.S. KRYPTOR® using Time Resolved Amplified Cryptate Emission technology, which is described in detail elsewhere (20) (21) (22). CT-proAVP was analyzed with sandwich immunoluminometric assay developed by Thermo Fisher / B.R.A.H.M.S. (9).

Patient Data

Patient characteristics were derived from their medical records. Operative data were derived from a database held by de department of cardiac surgery. Perioperative and postoperative data from the operating room and ICU were derived from the Patient Data

Management System used in the ICU (Metavision© IMDsoft™, USA). APACHE-IV scores were derived with Mediscore software (Mediscore, Itémedical, Tiel, the Netherlands) using definitions provided by the Dutch National Intensive Care Evaluation (NICE) registry (23).

Statistical considerations

Biomarker data are not complete for all patients due to errors in the collection of samples, processing of samples or laboratory processing. This was a complete random process. On average 13% of the samples was missing on T1, T2 and T3, 25% was missing on T4 and 68% was missing on T5 for all biomarkers. The amount of missing data increased over time by protocol due to discharges of patients to the ward (therefore leaving the study). We decided to analyze all post-operative time points separately and only for those patients who had both an APACHE IV score and a biomarker value at that time point (table 2). This means that for every time-point and for every biomarker a slightly different patient population was analyzed.

Significance of differences between outcome groups is tested using t-test, Pearson Chi-squared or Fischer exact where appropriate. Receiver operating characteristics (ROC) analysis was done for all biomarkers on all mentioned time points, as well as for the corresponding APACHE IV score. The c statistics of biomarker and APACHE IV was compared according to the method described by De Long et al (24), and a p value reported. A reported p value less than 0.05 was interpreted as a significant difference between the c statistic of the biomarker compared with the APACHE IV score. For pro-ADM a cutoff value was calculated with a high sensitivity and specificity based on the coordinates of the ROC curve.

All analysis was done with STATA-12 MP (StataCorp LP, College Station, TX).

Table 1 Baseline Characteristics of the Study Population

	Total n = 800	Hospital survivors n = 768	Hospital non-survivors n = 32
Sex (male)	542	521	21
Age (Median; IQR)	67; 59 – 75	67; 58 – 75	70; 62.5 – 75.5
BMI (Median; IQR)	24.1; 26.3 – 29.3	26.3; 24.0 – 29.3	25.2; 23.9 – 29.1
Diabetes	146	138	8
Hypertension	359	347	12
Peripheral vascular disease	149	142	7
COPD	116	110	6
Chronic Kidney insufficiency	28	22	6[a]
Recent angina, MI	70	68	2

Table 1 Baseline Characteristics of the Study Population *Continued*

	Total n = 800	Hospital survivors n = 768	Hospital non-survivors n = 32
Heart failure (NYHA III/IV)	176	156	20[a]
Pre-operative echocardiographic (765 patients):			
LVF Good (EF ≥ 55%)	399	389	10[b]
LVF Reasonable (EF 55-40%)	232	224	8[b]
LVF Moderate (EF 25-40%)	86	77	9[b]
LVF Poor (EF < 25%)	48	44	4[b]
Pulmonary Hypertension	116	105	11[a]
Surgical procedures[c]			
CABGonly	247	243[a]	3
OffPumpCABG	70	69	1
Combination CABG/valve surgery	161	149	12[a]
Surgery on myocardium	57	48	9[a]
Valve surgery only	374	358	16
Aorta surgery	99	94	5
OR duration (min.) (Median; IQR)	280; 222 - 349	276.5; 222 – 341.5	417; 348.5 – 490.5[a]
EuroScore (Median; IQR)	6; 3-7	5; 3 – 7	7; 6 – 10[a]
APACHE IV Score (Median; IQR)	48; 38 - 59	48; 38 – 58	69; 53 – 9[a]
APACHE IV probability of Death in Hospital (Median; IQR)	0.039; 0.013 – 0.074	0.037; 0.011 – 0.071	0.155; 0.076 – 0.310[a]

IQR = interquartile range, BMI = body mass index, COPD = chronic obstructive pulmonary disease, MI = myocardial infarction, NYHA = New York Heart Association, LVF = left ventricular function, EF = ejection fraction, CABG = coronary artery bypass grafting, OR = odds ratio, APACHE = Acute Physiology and Chronic Health Evaluation.

[a] Statistically significant difference $p \leq 0.05$ (using t-test, Pearson chi-squared or Fischer exact were appropriate). The characteristic is more common or is higher in the column in which [a] is placed.

[b] Statistically significant difference in the whole group with moderate and poor left ventricular function more common in nonsurvivor group.

[c] Combinations of procedures possible and therefore a higher total number of patients.

Results

From December 2006 to August 2010, 817 consecutive patients gave formal written consent to participate in the study. From seventeen patients, accidently, no blood samples were taken. These patients were not analyzed. The median age of the 800 remaining patients was 67; 542 of them were men. There were 32 patients who died in hospital with a median length of stay of 17.5 days (min, 0 days, max, 89 d), 3 patients died during surgery. Patient characteristics are summarized in Table 1.

The median values and (geometric) means of all biomarkers in the non-survivor group were higher than in the survivor group. This difference was significant for all biomarkers at all time points except for CT-proAVP (Supplement - Table 1).

Table 2 shows the discrimination between survivors and non-survivors as measured by the c-statistics for the biomarkers at different time points and also for the APACHE IV scores from the corresponding population. Although the APACHE-IV score is always based on data from the first 24 hours after ICU admission, c-statistics may differ because populations are not identical at different time points. An ROC comparison analysis was performed which showed that the c-statistic for MR-proADM was better than the APACHE-IV score on time point T2, T3 and T4 which means that a MR-proADM sample taken between 6 and 18 hours after operation discriminates better between survivors and non-survivors than the APACHE-IV score in the corresponding patient population. C-statistics for CT-proAVP were worse when compared with APACHE IV scores. No differences in c-statistics were found for CT-proET1, PCT, and MR-proANP compared to the c-statistics of the APACHE IV scores. ROC graphs of different biomarkers compared with the APACHE-IV score for time point T3, are given in the supplement.

Table 2. C-statistics for prediction of mortality of different biomarkers on different time-points and for the APACHE-IV score for the corresponding population. P-value for difference in c-statistic between biomarker and APACHE-IV model.

Biomarkers and corresponding APACHE IV score	T1	T2	T3	T4	T5
MR-proADM					
n	673	674	664	590	250
c-statistic (AUC)	0.912	0.940	0.943	0.949	0.883
95% CI	0.862- 0.962	0.898 - 0.982	0.895 – 0.991	0.896 – 1.000	0.776 - 0.991
APACHE IV					
n	673	674	664	590	250
c-statistic (AUC)	0.861	0.842	0.843	0.824	0.791
95% CI	0.790- 0.932	0.762 - 0.922	0.757 - 0.928	0.729 - 0.918	0.679 - 0.901
p	0.1740	0.0025	0.0032	0.0020	0.2003
CT-proET1					
n	679	670	669	588	249
c-statistic (AUC)	0.784	0.817	0.873	0.882	0.858
95% CI	0.688 – 0.881	0.785 - 0.845	0.845 - 0.897	0.852 - 0.906	0.810 - 0.900
APACHE IV					
n	679	670	669	588	249
c-statistic (AUC)	0.861	0.842	0.841	0.823	0.793
95% CI	0.789 – 0.932	0.812 - 0.869	0.810 - 0.867	0.790 - 0.853	0.735 - 0.840
p	0.2108	0.7095	0.5729	0.4285	0.4936
PCT					
N	673	673	671	590	250
c-statistic (AUC)	0.782	0.862	0.852	0.856	0.830
95% CI	0.748 - 0.812	0.833 - 0.887	0.823 - 0.878	0.825 - 0.883	0.775 - 0.872

Table 2. C-statistics for prediction of mortality of different biomarkers on different time-points and for the APACHE-IV score for the corresponding population. P-value for difference in c-statistic between biomarker and APACHE-IV model. *Continued*

Biomarkers and corresponding APACHE IV score	T1	T2	T3	T4	T5
APACHE IV					
N	673	673	671	590	250
c-statistic (AUC)	0.860	0.842	0.841	0.824	0.790
95% CI	0.832 - 0.886	0.811 - 0.868	0.811 - 0.867	0.791 - 0.854	0.736 - 0.840
p-value	0.0682	0.4963	0.7495	0.3896	0.4339
MR-proANP					
N	682	671	665	589	243
c-statistic (AUC)	0.783	0.820	0.837	0.856	0.837
95% CI	0.750 - 0.813	0.790 - 0.849	0.807 - 0.865	0.827 - 0.883	0.783 - 0.880
APACHE IV					
N	682	671	665	589	246
c-statistic (AUC)	0.861	0.842	0.841	0.824	0.793
95% CI	0.832 - 0.886	0.812 - 0.869	0.811 - 0.868	0.790 - 0.853	0.737 - 0.842
p-value	0.1619	0.6229	0.9371	0.4866	0.6877
CT-proAVP					
N	676	655	657	580	241
c-statistic (AUC)	0.673	0.577	0.626	0.782	0.802
95% CI	0.636 - 0.708	0.538 - 0.615	0.587 - 0.663	0.747 - 0.816	0.745 - 0.849
APACHE-IV					
N	676	655	657	580	241
c-statistic (AUC)	0.866	0.843	0.848	0.824	0.790
95% CI	0.839 - 0.892	0.813 - 0.870	0.818 - 0.874	0.791 - 0.854	0.731 - 0.838
p-value	0.0000	0.0002	0.0106	0.6093	0.8713

AUC = area under curve, APACHE = Acute Physiology and Chronic Health Evaluation.

p value for difference in c-statistic between biomarker and Acute Physiology and Chronic Health Evaluation IV model.

Table 3. Logistic model with both APACHE-IV and ProADM as predictors of hospital mortality.

Model	T1	T2	T3	T4	T5
Observations	673	674	664	590	250
APACHE-IV, p	<0.0005	0.012	0.016	0.099	0.060
ProADM, p	<0.0005	<0.0005	<0.0005	<0.0005	0.005
c-statisti of the model (95% CI)	0. 913 (0.862 – 0.964)	0. 922 (0.849 - 0.996)	0. 918 (0.821 – 1.000)	0. 928 (0.842 – 1.000)	0. 893 (0.788 – 0.999)

A p-value < 0.05 denotes a significant contribution of the parameter to the model.

Table 4. C-statistic of MR-proADM compared with c-statistic of APACHE-IV and c-statistic of combined model with MR-proADM and APACHE-IV

MR-proADM and Models	T1	T2	T3	T4	T5
MR-proADM					
n	673	674	664	590	250
c-statistic (AUC)	0.912	0.940	0.943	0.949	0.883
95% CI	0.862- 0.962	0.898 - 0.982	0.895 – 0.991	0.896 – 1.000	0.776 - 0.991
APACHE-IV					
n	673	674	664	590	250
c-statistic (AUC)	0.861	0.842	0.843	0.824	0.791
95% CI	0.790- 0.932	0.762 - 0.922	0.757 - 0.928	0.729 - 0.918	0.679 - 0.901
P[a]	0.17	0.0025	0.0032	0.0020	0.20
Combined model with MR-proADM and APACHE-IV					
N	673	674	664	590	250
c-statistic (AUC)	0.913	0.922	0.918	0.928	0.893
95% CI	0.862 – 0.964	0.849 – 0.996	0.821 – 1.000	0.842 – 1.000	0.788 – 0.999
p[b]	0.98	0.37	0.24	0.25	0.74

AUC = area under curve, MR-proADM = MR-pro-adrenomedullin, APACHE-IV = Acute Physiology and Chronic Health Evaluation IV.

[a] Difference between c-statistic of MR-proADM and APACHE-IV.

[b] Difference between c-statistic of MR-proADM and combined model.

The c-statistics for MR-proADM at time points T3, T4 and T5 are similar, which means that discrimination between survivors and non-survivors by MR-proADM does not change between 6 and 18 hours after operation. Multiple logistic regression analysis showed that both MR-proADM and the APACHE IV score were independent predictors of hospital mortality for time point T1 to T3 when modeled together. For time point T4 and T5, the APACHE IV score was not a significant contributor in this model (table 3). The c-statistic of the model including MR-proADM and the APACHE IV score at different time points was lower when compared with the c-statistic of MR-proADM alone (table 4), although this finding was not statistically significant. Using a cutoff value for proADM taken 6 hours after admission on ICU (time point 2) of 3.2 nmol/l sensitivity was 81.8% and specificity 93.9%, the positive likelihood ratio was 13.3 (95% CI 9.3 – 19.1), the negative likelihood ratio was 0.19 (95% 0.08 – 0.47), positive predictive value 31.0% (95% CI 19.9% - 44.7%) and negative predictive value 99.4% (95% CI 98.2% – 99.8%). Patients with a MR-proADM above this cutoff level had an odds ratio of 68.9 (95% CI 22.2 – 213.1) for not surviving their hospital stay.

Discussion

The main finding of the study is that a MR-proADM level, taken between 8 and 16 hours postoperative, better discriminates nonsurvivors from survivors than the APACHE IV score in patients after elective cardiac surgery. Both MR-proADM and the APACHE IV score are independent predictors of mortality. However, adding the APACHE IV score to MR-proADM in a prognostic model adds little to the discriminating power of MR-proADM alone.

ADM plays a crucial role in cardiovascular homeostasis. It is not only primarily a potent vasodilator in cardiac-overload situations but also enhances cardiac output and plays a role in the regulation of volume balance (25). Furthermore, ADM is associated with inflammation in heart failure patients and in human endotoxemia models (26) (27). MR-proADM has been investigated in a number of studies as a biomarker for prediction of outcome and diagnosis in different clinical settings. Morgenthaler et al (16) found a median MR-proADM level of 0.56 nmol/l (interquartile range [IQR], 0.08 – 3.9 nmol/l) in patients with cardiovascular disease who were planned for cardiac surgery. In patients with sepsis, they found a median MR-proADM level of 3.7 (IQR, 0.72 – 15.4) nmol/l. Peacock et al (28) investigated several biomarkers in patients with dyspnea because of several causes in the emergency department. They found that patients who died within 14 days had a higher MR-proADM level (median 2.4; IQR, 1.6 – 4.7 nmol/l) than survivors (median 1.4; IQR, 1.0 – 2.0 nmol/l). Travaglino et al (29) found that MR-proADM alone or in combination with PCT (c-statistic 0.694 and 0.790 respectively) could predict hospitalization in febrile patients

admitted to the emergency department. In another study Travaglino et al (30) found that serial measurement of PCT and MR-proADM at admission and after 72 hours predicted 30- and 90-days mortality. Kahn et al (31) investigated the predictive value of MR-proADM for in patients after myocardial infarction and found a statistically significant difference between survivors and non-survivors (median values, 0.71 vs 1.31 nmol/l). The reason why MR-proADM levels are high in the postoperative survivor group could be because of the combined cardiovascular and inflammatory response seen in the postoperative period (32). In the nonsurvivor group, the values of MR-proADM are comparable with septic patients reflecting a more severe cardiovascular and inflammatory response.

The APACHE-IV score is an elaborate tool assessing severity of illness and outcome of ICU patients. It includes among others demographic data, comorbidities, laboratory values, information about cardiac function before surgery and detailed information about the surgical procedure performed (1). It would be of great value if a simple measurement of a biomarker in the first 24 hours post admission offered the same predictive value as the APACHE-IV score. This study indeed shows that for the cardiac surgery patients a single measurement of MR-proADM sampled between 6 and 18 hours after surgery could predict mortality as least as good as the APACHE-IV score. This is important because the APACHE-IV score is a complex score that demands a significant workload, is time consuming, is prone to error and can, in the worst case, be manipulated (2). MR-proADM on the other hand can be incorporated in standard laboratory measurements and is an objective, unbiased measurement. It may be postulated that measuring MR-proADM could potentially be costs saving when compared to the collection of all data needed for calculation of the APACHE IV score. However, this has never been studied yet.

A limitation of this study is the small number of patients reaching the end point mortality. Because of this, we could not construct a model with more than two or three parameters because of to the danger of overfitting. Larger studies including more patients will allow building a model with more prognostic parameters. This could potentially improve the prognostic value.

Another point of consideration is that the statements in this article about MR-proADM in comparison with the APACHE IV score are only valid for elective cardiac surgery patients. The results of our study cannot be extrapolated to the ICU population as a whole. Although MR-proADM is a predictor of mortality in other ICU-patient categories (33) (34), these studies did not make a comparison with the APACHE-IV score.

In this study, the population was predominantly male (68%), which is different from the population from which the APACHE IV score was constructed (54,2% men) (1) and could lead to potential bias.

The odds ratio of dying in hospital for patients with a MR-proADM level above 3.2 nmol/l 6 hours after admission should be interpreted with great caution because of the low number of cases and therefore wide confidence intervals. Moreover, although the odds ratio for mortality associated with a MR-proADM higher than 3.2 nmol/l, was very high, i.e., 68.9 (95% CI 22.2 – 213.1), the positive predictive value for mortality was only 31%. The cut-off value of 3.2 nmol/l was arbitrarily chosen based on the ROC curve in this study. We cannot rule out that other cut-off values would be more appropriate in other populations. To confirm our findings, future studies should, ideally, be conducted in multiple centers with more patients and patient categories included.

Conclusions

This is, to our knowledge, the first study, which addresses the question if a biomarker can help in postoperative risk stratification in cardiac surgery patients in comparison with the APACHE IV score.

MR-proADM levels taken between six and eighteen hours postoperatively in elective cardiac surgery patients predict hospital mortality well and even better than the APACHE-IV score. Additional studies should be conducted to confirm these results and to address the question if MR-proADM also predicts hospital mortality in other ICU populations in comparison with the APACHE-IV score. Other studies should address the question whether MR-proADM could be incorporated in risk assessment scores and other quality measurements for ICU care to detect high-risk patients, improve quality of care and survival of patients.

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Supplement

Supplemental Table 1. Inter quartile ranges and geometric mean of all biomarkers for the total population and per outcome group.

Biomarkers – different groups					
MR-proADM nmol/l	T1*	T2*	T3*	T4*	T5*
Total group (n)	673	674	664	590	250
25%	1.07	1.01	1.03	0.99	1.08
Median (50%)	1.42	1.38	1.32	1.27	1.44
75%	1.94	1.95	1.86	1.78	2.12
Geometric mean 95% confidence interval	1.51 1.45 - 1.56	1.48 1.42 - 1.54	1.45 1.39 – 1.51	1.39 1.33 – 1.45	1.60 1.49 – 1.72
Survivors (n)	648	652	644	571	232
25%	1.05	1.00	1.02	0.98	1.07
Median (50%)	1.39	1.34	1.29	1.25	1.38
75%	1.85	1.85	1.82	1.71	1.92
Geometric mean 95% confidence interval	1.46 1.41 - 1.51	1.42 1.37 – 1.47	1.40 1.35 – 1.45	1.33 1.28 – 1.38	1.48 1.39 – 1.58
Non – survivors (n)	25	22	20	19	18
25%	2.44	3.21	3.16	3.24	2.75
Median (50%)	3.02	4.67	4.96	4.79	4.94
75%	5.23	7.61	8.15	6.94	6.48
Geometric mean 95% confidence interval	3.46 2.81 - 4.26	4.97 3.74 – 6.60	5.21 3.74 – 7.27	4.66 3.49 – 6.22	4.41 3.09 – 6.28
CT-proET1 pmol/l	T1*	T2*	T3*	T4*	T5*
Total group (n)	679	670	669	588	249
25%	59.0	90.9	92.4	81.5	82.6
Median (50%)	78.6	125.2	123.5	112.0	108.1
75%	112.0	176.6	170.3	147.4	161.4
Geometric mean 95% confidence interval	82 79 - 85	127 122 - 131	125 121 - 130	113 109 - 118	117 109 - 125
Survivors (n)	654	648	649	569	237
25%	58.7	90.2	92.4	81.5	81.7
Median (50%)	77.8	124.3	121.3	110.3	104.9
75%	108.7	174.0	166.3	144.2	155.3
Geometric mean 95% confidence interval	80 78 - 83	124 118 - 129	122 118 - 127	110 106 - 114	110 104 - 117
Non-survivors(n)	25	22	20	19	12
25%	104.3	173.1	193.3	192.1	197.1

Supplemental Table 1. Inter quartile ranges and geometric mean of all biomarkers for the total population and per outcome group. *Continued*

Biomarkers – different groups					
Median (50%)	127.2	236.8	277.6	239.9	275.7
75%	187.0	310.8	443.0	347.1	358.4
Geometric mean 95% confidence interval	135 110 - 165	226 173 - 295	271 206 - 357	260 196 - 342	246 184 - 329
PCT ng/ml	T1*	T2*	T3*	T4*	T5*
Total group (n)	673	673	671	590	250
25%	0.07	0.17	0.20	0.18	0.19
Median (50%)	0.10	0.34	0.40	0.37	0.43
75%	0.18	0.79	0.91	0.87	1.38
Geometric mean 95% confidence interval	0.12 0.11 – 0.13	0.38 0.35 – 0.42	0.46 0.42 – 0.50	0.42 0.38 – 0.47	0.56 0.47 – 0.67
Survivors (n)	648	651	651	571	232
25%	0.06	0.17	0.19	0.18	0.19
Median (50%)	0.10	0.33	0.38	0.36	0.39
75%	0.18	0.75	0.88	0.84	1.27
Geometric mean 95% confidence interval	0.11 0.11 – 0.12	0.36 0.33 – 0.39	0.43 0.40 – 0.47	0.40 0.36 – 0.44	0.49 0.41 – 0.58
Non-survivors(n)	25	22	20	19	18
25%	0.15	0.79	0.60	0.48	1.30
Median (50%)	0.24	1.80	1.90	1.75	1.91
75%	0.77	3.24	15.84	11.93	21.7
Geometric mean 95% confidence interval	0.32 0.20 – 0.51	2.11 1.22 – 3.64	3.10 1.51 – 6.35	3.19 1.43 – 7.11	3.60 1.57 – 8.24
MR-proANP pmol/l	T1*	T2*	T3*	T4*	T5*
Total group (n)	682	671	665	589	246
25%	170	153	140	129	134
Median (50%)	251	212	195	180	186
75%	369	308	291	272	290
Geometric mean 95% confidence interval	252 242 - 262	218 209 - 227	202 194 - 211	189 180 - 198	201 186 - 217
Survivors (n)	657	649	645	570	228
25%	170	151	139	127	132
Median (50%)	245	209	195	179	182
75%	360	300	286	270	279
Geometric mean 95% confidence interval	247 237 - 257	213 204 - 222	198 189 - 206	184 175 - 192	192 177 - 207

Supplemental Table 1. Inter quartile ranges and geometric mean of all biomarkers for the total population and per outcome group. *Continued*

Biomarkers – different groups					
Non-survivors(n)	25	22	20	19	18
25%	320	321	283	247	270
Median (50%)	465	394	374	401	329
75%	651	518	501	570	581
Geometric mean 95% confidence interval	449 353 - 571	411 325 - 520	422 321 - 556	420 318 - 553	368 260 - 520
CT-proAVP pmol/l	T1*	T2	T3	T4*	T5*
Total group (n)	676	655	657	580	241
25%	16	58	60	47	39
Median (50%)	39	154	112	85	76
75%	96	300	224	154	141
Geometric mean 95% confidence interval	38.4 35 – 42	121 111 - 133	107 99 - 115	79 73 - 86	75 66 - 85
Survivors (n)	652	633	638	561	223
25%	16	57	58	45	38
Median (50%)	38	152	111	84	71
75%	93	293	219	148	119
Geometric mean 95% confidence interval	37.5 34 – 41	120 109 - 131	106 98 - 114	77 71 - 83	68 60 - 78
Non-survivors(n)	24	22	19	19	18
25%	36	110	106	121	172
Median (50%)	76	190	212	295	303
75%	176	357	358	380	430
Geometric mean 95% confidence interval	73.2 49.5 – 108	185 111 - 308	161 95 - 271	213 140 - 322	215 135 - 341

T1 = Time point admission ICU; T2 = Time point 6 hours post admission; T3 = Time point 12 hours post admission; T4 = Time point 18 hours post admission; T5 = Time point 24 hours post admission.
* Denotes statistically significant difference (Students t-test on logarithm of the mean; p ≤0.05) of biomarker levels on that time point between survivors and non-survivors.

ROC graphs of PCT, MR-proADM, MR-proANP, CT-proAVP, CT-proET-1 on time point 3 compared with the ROC graph of APACHE-IV.