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Biomarker dynamics in cardiac surgery: a prospective observational study on MR-proADM, MR-proANP, hs-CRP and sP-selectin plasma levels in the perioperative period

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**ABSTRACT**

**Background:** For many biomarkers in cardiac surgery, there is a lack of knowledge regarding the normal dynamics of plasma levels during the perioperative course. The aim of this study was to investigate the perioperative dynamics of MR-proADM, MR-proANP, hs-CRP and sP-selectin in cardiac surgery.

**Method:** A prospective observational pilot study with 20 patients scheduled for open cardiac surgery procedures with cardiopulmonary bypass (CPB). Plasma samples were taken for each patient and biomarker during the pre-, peri- and postoperative period until Day 6 postoperatively.

**Results:** MR-proADM increased significantly from 0.62 [IQR; 0.54–0.93] nmol/L preoperatively to 1.20 [1.04–1.80] nmol/L postoperative Day 1. MR-proANP increased significantly from 125 [77–152] pmol/L preoperatively to 198 [168–307] pmol/L on weaning from CPB. hs-CRP increased significantly from 2.5 mg/L [0.4–12] preoperatively to peak at 208 mg/L [186–239] postoperative Day 3. The preoperative level of sP-selectin at 23.0 [21.3–26.3] ng/mL initially fell at weaning from CPB, followed by a significant peak of 25.5 [22.7–27.7] ng/mL 8 h postoperatively.

**Conclusions:** The findings in this study may help to understand the physiology of the biomarkers analysed and their response to cardiac surgical trauma including CPB. Furthermore, these findings will guide us in further research on the clinical usefulness of these biomarkers.

**Introduction**

Certain biomarkers can provide useful information in cardiac surgery both in pre- and postoperative prognostic evaluation, as well as in clinical guidance during the perioperative period (Shahian and Grover 2014). Even when designing the leading risk scoring model for cardiac surgery (EuroSCORE II), the authors stressed that it is important that biomarkers are included in preoperative risk evaluation. At present, however this is not possible due to lack of relevant data (Nashef et al. 2012).

There are several aspects of cardiac surgery where biomarkers are of interest, such as: heart failure, cardiac ischemia and organ dysfunction including renal, cerebral, pulmonary or splanchnic dysfunction. Furthermore, the inflammatory state and general stress response during the perioperative period is of great interest, in particular oxidative stress due to major surgical trauma and cardiopulmonary bypass (CPB) (Clermont et al. 2002). Some biomarkers are used routinely in association with cardiac surgery, such as troponins and brain natriuretic peptides (BNP) (Lurati Buse et al. 2014, Fox 2015), while others are still undergoing research.

To be able to implement novel biomarkers as tools in cardiac surgery and intensive care, it is important that we understand the normal dynamic response of the biomarker throughout the perioperative period. We already know the perioperative kinetics of some biomarkers in clinical use such as NT-proBNP and copeptin (Reyes et al. 2005, Holm et al. 2018), but for other potential biomarkers data are lacking or incomplete.

The aim of this study was to explore the dynamic responses of four biomarkers by following their plasma levels in patients undergoing open cardiac surgery.

The biomarkers included were


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We believe the findings in this study may help to understand the physiology of the biomarkers analysed and their response to open cardiac surgical trauma including cardiopulmonary bypass. Furthermore, these findings will guide us in further research on the clinical usefulness of these biomarkers in cardiac surgery.

Clinical significance

- We believe the findings in this study may help to understand the physiology of the biomarkers analysed and their response to open cardiac surgical trauma including cardiopulmonary bypass.

Materials and methods

Patients and design

Between February and September 2015, we prospectively included 20 patients scheduled for open heart surgery with CPB. We analysed the four biomarkers named above pre-, per- and postoperatively until Day 6. We included various open cardiac surgical procedures including coronary artery bypass grafting (CABG, n = 17), aortic valve replacement (AVR, n = 2) and left ventricular assist device (LVAD, n = 1).

We present the cohort in two groups. One group consisting of the whole cohort representing an unselected population and one cohort of patients with a normal uneventful perioperative course, ‘restricted normal cohort’. Based on the limited population, we have not done any statistical comparisons between the groups.

The study was conducted as a prospective longitudinal observational single centre pilot study conducted at a cardiothoracic department, Linköping University Hospital, Sweden. For diagram of patient flow chart see Figure 1.

Restricted normal group criteria

From the whole cohort (n = 20) a subgroup (n = 11) of patients with normal uneventful perioperative course was analysed separately. Criteria for this subgroup included: normal preoperative renal function with a glomerular filtration rate (GFR) > 60 mL/min/1.73 m²; uneventful course during surgery and CPB (evaluated from the anaesthesia and surgical charts); and an uneventful postoperative course, that is, left ICU within 24 h postoperatively, no reoperation due to bleeding, tamponade or infection, no postoperative renal
failure (defined as a maximal increase in postoperative plasma creatinine by >50% of the preoperative value), no sign of stroke (defined as a focal neurological deficit persisting more than 24 h with signs of cerebral injury on CT-scan).

Clinical management
Premedication, induction and maintenance of anaesthesia were standardised for all patients in the study. After an overnight fast, the patients were premedicated with oxazepam 5–10 mg orally (PO), and paracetamol 1 g PO. General anaesthesia was induced with thiopental and fentanyl intravenously (IV). Rocuronium bromide IV was used for neuromuscular blockade. Anaesthesia was maintained with isoflurane and intermittent doses of fentanyl. All patients were nonoxygenated. Surgical procedures were performed with standard techniques for cannulation and CPB. The CPB was conducted with a roller pump and a coated membrane oxygenator, integrated arterial filter and a combined cardiomyocyte–venous reservoir. Before cannulation, heparin was administered IV. The extracorporeal circuit was primed with 1500 mL of Ringer solution (Fresenius Kabi) and 200 mL of Mannitol (Fresenius Kabi 150 mg/mL). Aortic cross clamping was used in all patients but one in whom a HeartMate II- Left ventricular assist device (LVAD) was implanted. During cross-clamp, cardiac protection was achieved with cold blood cardioplegia using one part blood and four parts cardioplegia solution (50 mL Cardioplegia APL with potassium 0.8 mmol/mL and procaine 13.6 mg/mL dissolved in 2000 mL Ringer-Acetate®, Fresenius Kabi).

Blood sampling and data collection
Samples for all four biomarkers were taken on the day before surgery (D-1), on the day of surgery in the operating theatre before induction of anaesthesia (OR ind), at weaning from CPB (CPB off), upon arrival at the intensive care unit (ICU arr), 8 h postoperatively (8H), on the morning Day 1 from CPB (CPB off), upon arrival at the intensive care unit (ICU arr), 8 h postoperatively (8H), on the morning Day 1 after surgery (D1) and thereafter every morning until postoperatively Day 6 (D2–6). A total of 11 blood samples were collected from each patient. Of the total sample collection, 13 samples went missing (one at induction, three on arrival at the ICU, three on postop. Day 4, two on postop. Day 5 and four on postop. Day 6), rendering a final total of 828 samples for analysis. Blood samples were obtained in EDTA-tubes and Na-citrate tubes and immediately transported to the clinical chemistry department at the hospital. In the laboratory, the blood was centrifuged and plasma pipetted into cryotubes, then stored at −70 °C pending analysis. Cryotubes were thawed only once for analysis.

Analyses of NT-proBNP were performed with an electrochemiluminescence immunoassay on a Roche Elecsys 2010 automated platform (Roche Diagnosis, Basel, Switzerland). The inter-assay coefficient of variation was <4% at NT-proBNP 180 and 2000 ng/L.

Analyses of MR-proADM and MR-proANP were performed using a Kryptor Compact Plus platform (BRAHMS, Hennigsdorf, Germany). The inter-assay coefficient of variation for MR-proADM was 5.3% at 0.75 nmol/L and 4.3% at 4.52 nmol/L. The inter-assay coefficient of variation for MR-proANP was 2.2% at 104 pmol/L and 1.2% at 506 pmol/L.

Analysis of hs-CRP was done with Cobas c 502 platform (Roche/Hitachi, Mannheim, Germany). Hs-CRP inter-assay coefficient of variation was 1.42% at 1.19 and 1.16% at 12.06 mg/L. P-selectin was analysed as soluble (sP-selectin) using ELISA from R&D (Abingdon, UK). The intra-assay coefficient of variation (CV) was approximately 5% and the inter-assay CV approximately 9%.

Statistics
Data are presented as median and interquartile range (IQR) or proportions with percentages as appropriate. Analyses for the biomarkers’ respective plasma levels over time were performed using repeated measurements according to Friedmans ANOVA. Wilcoxon test with Bonferroni correction was used for analysis of differences between levels within the release curves. Bonferroni correction was adjusted based on ten comparisons or less within the release curves. We considered differences statistically significant if p < 0.05 (for the Wilcoxon test we considered p < 0.05 to be equal to p < 0.005 with Bonferroni correction). Statistical analyses were made with Statistica® version 13.2 (StatSoft, Inc., Tulsa, OK, USA).

Ethics
After written informed consent the patients were enrolled into the study. The study was performed according to the Helsinki Declaration of Human Rights. The study was approved by the Regional Ethics Review Board at the University Hospital in Linköping (EPN 2014/50-31).

Results
Baseline data
The median age in the complete cohort (n = 20) was 71 (64–77) years, with 20% being females. The overall median preoperative risk score according to the EuroSCORE II model was 1.7 (1.3–2.7). Preoperative plasma concentration of NT-proBNP was 740 (175–1200) ng/L. The median CPB time was 76 (65–120) min. The median hospital stay was 9 days (8–14) and there was no hospital or 30-day mortality. Detailed data are presented in Table 1.

In the restricted normal uneventful cohort (n = 11) (see ‘Material and Methods’ section) the overall preoperative risk profile was lower (EuroSCORE II 1.3 (1.1–1.7)) than the risk profile for the whole cohort. Also the preoperative level of NT-proBNP (190 (160–950) ng/L) was lower in the restricted cohort than the level for the whole cohort.

Perioperative MR-proADM levels
There was no difference between plasma levels of MR-proADM at D-1 and at induction. However, plasma levels increased during the perioperative period, reaching significance already on arrival at the ICU with a further increase on
postoperative D1 for both the whole cohort (0.62 vs. 1.20 nmol/L; \( p < 0.005 \)) and the restricted uncomplicated cohort (0.55 vs. 1.07 nmol/L; \( p < 0.005 \)). From Day 1, values remained stable until Day 3. From Day 3, the plasma levels fell. On Day 5, plasma levels were significantly lower than on Day 3 (1.20 vs. 0.98 nmol/L; \( p < 0.005 \)). In general, the whole cohort tended towards higher plasma levels postoperatively than did the restricted normal cohort (Table 2, Figures 2 and 3).

**Perioperative MR-proANP levels**

The dynamics for both cohorts behaved similarly in the early phase of the perioperative period with significant increases compared to preoperative values already at weaning from CPB (whole cohort: 125 vs. 198 pmol/L \( p < 0.005 \) and restricted normal cohort 122 vs. 179 pmol/L \( p < 0.005 \)). In the whole cohort, there was a tendency towards further increase on Days 2–4 that remained throughout the perioperative period, with a peak value D4 of 240 pmol/L (169–394). In the restricted normal cohort, there was a peak median level of 212 pmol/L (122–253) on Day 1 after surgery with a tendency towards decreasing values at the end of the perioperative period. There were no significant changes in plasma levels in either groups postoperatively (Table 2, Figures 2 and 3).

**Perioperative hs-CRP levels**

hs-CRP showed an initial decrease in plasma levels from D-1 to CPB off, that was almost significant for the whole cohort (2.5 vs. 1.0 mg/L). Thereafter, levels rose and 8h after arrival at the ICU were significantly higher than the preoperative value both for the whole cohort (2.5 vs. 16 mg/L, \( p < 0.001 \)) and for the restricted normal cohort (2.1 vs. 13 mg/L, \( p < 0.005 \)). The increase in levels continued reaching a peak on Day 3 for both the whole cohort 208 mg/L (186–239) and the restricted normal cohort 201 mg/L (151–237). Thereafter, there was a significant decrease in levels in the whole cohort by Day 4 (208 vs. 157 mg/L, \( p < 0.005 \)) and in the restricted normal cohort by Day 5 (201 vs. 123 mg/L, \( p < 0.005 \)) (Table 2, Figures 2 and 3).

**Perioperative sP-selectin levels**

sP-selectin showed an initial decrease in levels, that, for the whole cohort, reached statistical significance at CPB off (23.0 vs. 20.8 ng/mL, \( p < 0.005 \)). After surgery, levels increased to a peak 8h postoperatively. For the whole cohort, the peak value at 8h was significantly higher than at CPB off (25.5 vs. 20.8 ng/mL, \( p < 0.001 \)). The restricted normal cohort showed similar dynamics with a peak at 8h postoperatively with 25.4 ng/mL (22.6–27). In both cohorts levels of sP-selectin decreased after 8h and tended to reach preoperative values by Day 6 (Table 2, Figures 2 and 3).
In this study on patients undergoing open heart surgery with CPB, we describe the perioperative dynamics of plasma levels of the four biomarkers MR-proADM, MR-proANP, hs-CRP and sP-selectin. All four biomarkers displayed dynamics showing significant changes in plasma levels during the perioperative period.

When discussing the concentrations of the biomarkers included in the study, some considerations must be kept in mind. All patients were exposed to the trauma of open cardiac surgery with CPB, generating an inflammatory response and oxidative stress (Clermont et al. 2002). Furthermore, patients in the study had a median volume overload of almost 4000 mL (Table 1).

Analysis of MR-proADM showed that preoperative plasma concentrations were slightly elevated compared to healthy controls, but in the same range as previously shown among patients with ischaemic heart disease planned for CABG (Morgenthaler et al. 2005; Lorubbio et al. 2018). MR-proADM levels increased to a peak at Days 1–2 postoperatively with a doubling of preoperative levels. These levels, however, were lower than levels measured in patients suffering from sepsis (Morgenthaler et al. 2005). In this study, the increase in MR-proADM was seen already peroperatively and reached statistical significance at weaning from CPB (Table 2). The increase was theoretically expected as a response to vasodilatory and hypotensive effects during anaesthesia, surgery, CPB and volume overload, since the action of ADM is to reduce hyperpermeability during severe inflammatory states (Temmesfeld-Wollbruck et al. 2007; Simon et al. 2017). Postoperative levels remained higher for a longer period in the non-selected cohort indicating that this cohort included patients with a longer period of general inflammation.

Among the natriuretic peptides, brain natriuretic peptide (BNP) and NT-proBNP have been the most studied in the context of cardiac surgery (Litton and Ho 2012). The perioperative kinetics of plasma NT-proBNP during cardiac surgery have been described (Reyes et al. 2005). Although atrial natriuretic peptide (ANP) is not used in clinical practice as much as BNP/NT-proBNP (Krichevskiy and Kozlov 2019), there are data showing that ANP can be of clinical importance as a prognostic factor in cardiovascular disease (Alehagen et al. 2013). In a previous study by Berendes on a cohort of patients undergoing cardiac surgery, they found an earlier increase in ANP compared to BNP (Berendes et al. 2004). In that study, patients were followed up to 48 h postoperatively. Our study indirectly confirms these findings by describing the plasma level dynamics of MR-proANP, where an earlier peak in the level of MR-proANP was observed on Days 1–2 compared to that previously described for NT-proBNP, occurring around Days 3–4 postoperatively (Reyes et al. 2005). It may be that ANP is stored in granules within the myocardium ready for secretion, whereas BNP must be synthesised before secretion (Tanase et al. 2019). Theoretically, this implies that in the early phase after cardiac surgery ANP could be a better prognostic marker than BNP for severe postoperative heart failure.

hs-CRP showed a well-defined dynamic course during the perioperative period. In a previous study on patients...
operated with open heart surgery (Tegnell et al. 2002), CRP was seen to reach a peak level of around 200 mg/L on Day 3 postoperatively. In that study, the first measurement after the preoperative one was on Day 1 postoperatively. Furthermore, measurements in that study used the usual CRP assay and not the high-sensitivity CRP assay, which would have increased the possibility of discriminating minor changes in the early period. In our study, we confirmed this finding (208 mg/L on Day 3). Moreover, we identified an initial but non-significant decrease in level from that preoperatively to that at CPB off, and thereafter a significant increase by 8 h after surgery (Table 2). It has been shown that the induction of CRP secretion from hepatocytes is mainly stimulated by interleukin-6 (IL-6) (McFadyen et al. 2018). It has also been shown that IL-6 increases 10-fold by the end of CPB (Giomarelli et al. 2003). During surgery and on arrival at the ICU there was no sign of elevated plasma levels of hs-CRP (Table 2). One might expect a more rapid increase in hs-CRP than was seen in this study. However, there were several factors that could have influenced the inflammatory response, not least the hemodilution occurring during anaesthesia, surgery and CPB. Also, one patient received an LVAD, which can further aggravate the inflammatory response in this patient specifically.

For sP-selectin, the dynamics at first appeared to be non-specific with rather small changes over time. However, when looking closer at the plasma levels a wave pattern is seen with significant changes over the perioperative course (Figures 2 and 3). The pattern begins with a decrease which is difficult to explain but might simply be the result of dilution. Thereafter, a significant increase was seen which could be a reflection of the inflammatory response and activation of platelets and possibly endothelial cells. This is supported by the fact that the curve in its early phase showed some similarity to the one seen with hs-CRP.

When interpreting sP-selectin dynamics, one must bear in mind that absolute plasma concentrations can differ between studies as values depend on the method and calibrator used for chemical analysis. No international standard exists and therefore it may be more correct to look at

**Figure 2.** Graphs representing the unselected cohort ($n = 20$) for MR-proADM, MR-proANP, hs-CRP and sP-selectin. D-1: day before surgery; OR ind: on the day of surgery in the operating theatre before induction of anaesthesia; CPB off: weaning from CPB; ICU arr: upon arrival at the intensive care unit; 8 h: hours postoperatively; Day 1: on the morning after surgery; D 2–6: every morning until postoperatively Day 6 (D2–6).
relative levels during the perioperative course rather than absolute values when comparing studies.

Although the exact reasons for the behaviour of each biomarker over time are not obvious, there are theoretical speculations. Patients undergoing cardiac surgery with CPB are exposed to considerable trauma with corresponding systemic inflammation (Desborough 2000; Clermont et al. 2002). There is also considerable fluid retention during surgery and the early postoperative phase. After a few days patients begin to mobilise fluid and permeability is restored to normal (Clermont et al. 2002; Dekker et al. 2019). The dilution effect might be an explanation for the early decrease in both hs-CRP and sP-selectin. Later in the clinical course, both MR-proADM and hs-CRP trended towards a decreasing in values around Days 4–5 postoperatively in the uncomplicated patient cohort. This is theoretically in line with clinical observations, supported by studies on microcirculation, that endothelial hyperpermeability lasts at least 3 days after cardiac surgery (Dekker et al. 2019). Furthermore, we have reported results from two cohorts, one non-selected cohort with patients with different risk profiles and one normal cohort with lower risk profile and uncomplicated perioperative course. Generally, this study indicates that concentrations in the non-selected cohort were higher than in the uneventful cohort, and that these tended to remain elevated for longer periods of time. It illustrates the fact that the normal uncomplicated cohort represents healthier patients with a milder perioperative course with faster recovery to habitual state. This is not surprising and gives some idea how these biomarkers behave in different settings depending on which cohort is being studied.

We believe the laboratory analyses in this study are valid. The biomarkers were thawed once and analysed in batches, so inter-individual relationships between the levels of the biomarkers are most likely correct. Furthermore, the pre-operative baseline plasma concentrations of MR-proADM, MR-proANP and hs-CRP concur with those found in previous studies (Tegnell et al. 2002; Morgenthaler et al. 2005, Charitakis et al. 2016).

Figure 3. Graphs representing the restricted normal cohort (n = 11) for MR-proADM, MR-proANP, hs-CRP and sP-selectin. D-1: Day before surgery; OR ind: on the day of surgery in the operating theatre before induction of anaesthesia; CPB off: weaning from CPB; ICU arr: upon arrival at the intensive care unit; 8 h: hours postoperatively; Day 1: on the morning after surgery; D 2–6: every morning until postoperatively Day 6 (D2–6).
**Limitations**

This is a pilot study with 20 patients included. The limited cohort must, of course, be taken into consideration. The aim of this study was to investigate the perioperative dynamics of four biomarkers in cardiac surgery. As a pilot study we had no plan to evaluate prognostic value or to define cut-off levels for clinical use. This motivated the small cohort. Another aspect to keep in mind is that most patients suffered from ischaemic heart disease and the surgical procedures were predominantly CABG. However, all patients were operated with sternotomy and CPB, which generates a general inflammatory response regardless type of cardiac procedure.

**What this study contributes**

The dynamics of the biomarkers in this study displayed significant changes and trends. We believe that our data may be useful in further understanding the physiology of these biomarkers as well as their response to cardiac surgical trauma and CPB. We also believe that this study provides important information on how to design further analyses when evaluating the prognostic value of these biomarkers and their use in clinical assessment in cardiac surgery.

**Conclusions**

In this study, we investigated the plasma levels of MR-proADM, MR-proANP, hs-CRP and sP-selectin during the pre-, per and postoperative periods until Day 6 after cardiac surgery. We found significant changes and peak values for all four biomarkers. We believe that these data are valid and can be useful in further understanding the physiology of these biomarkers as well as their response to cardiac surgical trauma and CPB. In further studies it would be recommended to address more specifically the prognostic and clinical value of these biomarkers in cardiac surgery. Furthermore, aim for investigations that can define cut-off levels for these biomarkers in order to guide goal-directed therapy in cardiac intensive care. Hopefully, the analysis and implementation of some or all of these biomarkers will be a routine part of everyday clinical practice in the future.

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**Disclosure statement**

No potential conflict of interest was reported by the author(s).

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**Data availability**

The data that support the findings of this study are available on request from the corresponding author, JH. The data are not publicly available due to ethical restrictions, their containing information that could compromise the privacy of research participants.

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