The intraoperative decrease of selenium is associated with the postoperative development of multiorgan dysfunction in cardiac surgical patients

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Objective: The trace elements selenium, copper, and zinc are essential for maintaining the oxidative balance. A depletion of antioxidant trace elements has been observed in critically ill patients and is associated with the development of multiorgan dysfunction and an increased mortality. Cardiac surgery using cardiopulmonary bypass provokes ischemia-reperfusion-mediated oxidative stress. We hypothesized that an intraoperative decrease of circulating trace elements may be involved in this response.

Design: Prospective observational clinical study.

Setting: University hospital cardiothoracic operation theater and intensive care unit.

Patients: Sixty patients (age 65 ± 14 yrs) undergoing cardiac surgery with the use of cardiopulmonary bypass.

Measurements and Main Results: Whole blood concentrations of selenium, copper, and zinc were measured after induction of anesthesia and 1 hr after admission to the intensive care unit. All patients were separated in a priori defined subgroups according to the development of no organ failure, single organ failure, and ≥2 organ failures in the postoperative period.

Results: Fifty patients exhibited a significant selenium deficiency already before surgery, whereas copper and zinc concentrations were within the reference range.

In all patients, blood levels of selenium, copper, and zinc were significantly reduced after end of surgery when compared to preoperative values (selenium: 89.05 ± 12.65 to 70.84 ± 10.46 μg/L; zinc: 5.15 ± 0.68 to 4.19 ± 0.73 mg/L; copper: 0.86 ± 0.15 to 0.65 ± 0.14 mg/L; p < .001).

During their intensive care unit stay, 17 patients were free from any organ failure, while 31 patients developed single-organ failure and 12 patients multiple organ failure.

Multilogistic regression analysis showed that selenium concentrations at end of surgery were independently associated with the postoperative occurrence of multiorgan failure (p = .0026, odds ratio 0.8479, 95% confidence interval 0.7617 to 0.9440).

Conclusions: Cardiac surgery using cardiopulmonary bypass resulted in a profound intraoperative decrease of whole blood levels of antioxidant trace elements. Low selenium concentrations at end of surgery were an independent predictor for the postoperative development of multiorgan failure. (Crit Care Med 2011; 39:000–000)

Key Words: cardiopulmonary bypass; systemic inflammatory response syndrome; multiple organ failure; trace elements; antioxidants; selenium

Oxidative stress is increasingly being recognized as contributing to the development of organ failure in critically ill patients (1). The generation of cytotoxic reactive oxygen species and reactive nitrogen-oxygen species results in cellular injury (2) and activates proinflammatory pathways (3). In mammalians, a sophisticated endogenous defense system protects tissues from oxidative stress. Several enzymes, such as catalase, superoxide dismutase, and glutathione peroxidase (GPx) are specifically designed to neutralize reactive oxygen species and reactive nitrogen-oxygen species (4). For these antioxidant (AOX) enzymes, the trace elements selenium (Se), zinc (Zn), and copper (Cu) serve as essential cofactors. Particular interest has been developed for Se since Se is involved in multiple steps of intracellular AOX defense mechanisms (4, 5). A depression of circulating and tissue AOX concentrations has been repeatedly observed in critically ill patients with a systemic inflammatory response and/or multiorgan dysfunction and was shown to be associated with the severity of illness, a progression of organ failure, and mortality (6–10).

Cardiac surgery with the use of extracorporeal circulation may elicit a systemic inflammatory response (11, 12) and provokes ischemia-reperfusion-related oxidative stress with the release of reactive oxygen species (13–16). Although the occurrence of multiorgan dysfunction after cardiac surgery significantly contributes to perioperative mortality (17), the pathophysiological role of AOX trace elements in multiorgan injury following cardiac surgery is still only poorly understood.
The aim of the present study was therefore to investigate whole blood levels of Se, Cu, and Zn in adult patients before and immediately after elective cardiac surgery using cardiopulmonary bypass (CPB). We hypothesized that cardiac surgery with the use of CPB is associated with a significant decrease of circulating AOX trace element concentrations and that an intraoperative depletion of circulating AOX micronutrients would be correlated with the severity of postoperative organ dysfunction and hence with the postoperative outcome of cardiac surgical patients.

METHODS

Patients

After approval by the institutional review board committee and obtaining of written informed consent, 60 patients undergoing elective cardiac surgery with the use of CPB participated in this observational study. Patients with emergency operations, pregnancy, an age < 18 yrs, and those who were unable to give informed consent were excluded.

Anesthesia

In all patients, anesthesia was performed according to our institutional routine Induction of anesthesia: etomidate (0.1 mg·kg⁻¹), sufentanil (0.5–1 μg·kg⁻¹), rocuronium (1 mg·kg⁻¹); maintenance of general anesthesia: sufentanil (1 μg·kg⁻¹·hr⁻¹) and sevoflurane (0.5–1 minimum alveolar concentration).

CPB

CPB was performed in moderate hypothermia (28°C–32°C) on a conventional CPB circuit with cardiac arrest induced by the antegrade infusion of cold crystalloid cardioplegic solution. Extracorporeal circulation was performed with a pump flow of 2.2 L·min⁻¹·m⁻². Before CPB, 300 U kg⁻¹ heparin were administered to achieve an activated clotting time of > 400 secs. After weaning from CPB, heparin was antagonized with protamine in a ratio of 1:1.

Hemodynamic Management

Intraoperative treatment was standardized according to our clinical routine. Basic fluid substitution was performed with 1 mL·kg⁻¹·hr⁻¹ balanced crystalloid solutions. Packed red blood cells were transfused when the hemoglobin content was below 7.5 g·dL⁻¹. The administration of additional fluids, vasopressors, or inotropic drugs was left at the discretion of the attending physicians.

Intensive Care Unit (ICU)

After completion of surgery, all patients were transferred to the ICU. Tracheal extubation was performed when standard extubation criteria were fulfilled. The Simplified Acute Physiology Score II (18) and the Sequential Organ Failure Assessment score (19) were determined once within 24 hrs of admission.

In addition to the duration of mechanical ventilation, and the ICU and the hospital length of stay, we documented the incidence of systemic inflammatory response syndrome, sepsis, severe sepsis, and septic shock according to the American College of Chest Physicians/Society of Critical Care Medicine consensus conference criteria (20). The following organ failure variables were used to determine the incidence of any organ dysfunction (21): Arterial hypoxemia (PaO₂/FIO₂ < 300 mm Hg), acute kidney injury (urine output < 0.5 mL·kg⁻¹·hr⁻¹ for at least 2 hrs despite adequate fluid resuscitation or creatinine increase > 0.5 mg·dL⁻¹ or 44.2 μmol·L⁻¹), coagulation abnormalities in the absence of pharmacologic anticoagulation (international normalized ratio > 1.5 or a partial thromboplastin time > 60 secs), hypotension (mean arterial pressure < 70 mm Hg) despite adequate fluid replacement, thrombocytopenia (platelet count < 100,000·L⁻¹), hyperbilirubinemia (plasma total bilirubin > 2 mg·dL⁻¹ or 34.2 μmol·L⁻¹), and neurologic dysfunction (Glasgow Coma Score below 15 in absence of sedation or metabolic impairment).

Laboratory Tests

Central venous whole blood samples were obtained after induction of anesthesia and 1 hr after admission of the patients to the ICU and stored at room temperature in EDTA tubes. Whole blood trace element concentrations were measured with electrothermal atomic absorption spectroscopy using a graphite furnace absorption spectrometer (5100 PC, Perkin-Elmer, Paris, France) (22).

In all patients with an ICU stay > 1 day (n = 29), serum GPx activity was determined in serum probes that had been obtained simultaneously with the whole blood probes (i.e., after induction of anesthesia and 1 hr after admission to the ICU) and stored at −80°C, using a method coupling the peroxidase reaction with the reduction of oxidized glutathione (23). One unit of GPx activity is defined as that which oxidizes 1 mol of NADPH/min in the assay system (24).

The reference values for the normal population in whole blood are 100–140 μg/L for Se, 4.0–7.5 mg/L for Zn, and 0.70–1.24 mg/L for Cu. The normal reference GPx activity is 96–150 units/L (25).

Statistical Analysis

Data were statistically analyzed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA).

As a primary end point, we evaluated the whole blood Se concentrations before and immediately after cardiac surgery, which were compared using repeated measures analysis of variance (26). The sample size of this pilot observational trial was calculated based on previous unpublished measurements. Power analysis revealed a minimal sample size of 27 patients to detect a 20% difference in pre- and postoperative Se levels, when a level of significance of .05 and a power of 90% were to be achieved. To allow further subgroup analysis (see below), we included 60 patients to generate a sample size comparable to that being analyzed in the available literature on this topic (9, 10).

Patients were separated in three a priori-defined subgroups: patients with no organ failure during the observation period (group NOF), patients developing a single organ failure during ICU stay (group SOF), and patients showing dysfunction of ≥ 2 organs (group MOF) during the postoperative time course. After testing for normal distribution (Shapiro-Wilk W test), differences between groups were tested using corresponding analysis of variance tests (26). Post hoc testing was performed using Bonferroni adjustments for multiple measurements (27). Proportions were compared using the chi-square test. For correlation studies, linear regression analysis was used. The predictive value of trace element concentrations for the development of MOF at any time during ICU stay was calculated from the area under the curve using receiver operating characteristics. Analysis of prognostic variables associated with the development of MOF was performed using a forward stepwise logistic regression model. In all cases, a level of p < .05 was considered statistically significant.

RESULTS

Preoperative Status and Intraoperative Data

Biometric and demographic data and data on surgery are given in Table 1. Subgroups did not differ regarding preoperative status and/or data during surgery (Table 1), with the exception that isolated coronary artery bypass grafting was performed more frequently in the SOF group, while isolated valvular surgery was most often performed in NOF patients.
Postoperative Time Course

During their postoperative stay in the ICU, 17 patients were free from any organ failure, while 31 patients developed SOF and 12 patients a MOF syndrome (for details see Table 2). Already on the first postoperative day, the MOF group was characterized by higher Simplified Acute Physiology Score II and Sequential Organ Failure Assessment values and a higher degree of postoperative inflammation, as indicated by serum procalcitonin levels (Table 2). MOF patients received significantly more packed red blood cells during their first day in the ICU, since hemoglobin concentration at ICU admission was lowest in this group (Table 2). MOF patients had a significantly longer duration of mechanical ventilation and ICU stay.

Three patients died during the observation, one patient in the NOF group due to an acute postoperative rupture of the ascending aorta and two patients in the MOF group as a result of postoperative cardiogenic (and later additionally septic) shock.

Trace Element Status

Fifty patients exhibited a Se deficiency already before surgery whereas preoperative Cu and Zn concentrations were within the reference range for the normal German population (Fig. 1). At ICU admission, all patients showed a significant decrease in whole blood trace element concentrations when compared to baseline values.

Trace Element Status and Postoperative Outcome

Preoperatively, trace element concentrations did not differ between the different subgroups (Table 3). Intraoperatively, circulating trace element concentrations decreased most pronouncedly in patients developing MOF postoperatively (Fig. 2, Table 3). This decrease was neither associated with intraoperative fluid balance nor with postoperative albumin levels.

Among the trace elements, only postoperative Se and Zn concentrations had predictive accuracy for the later development of MOF (Fig. 3). Forward stepwise logistic regression analysis showed that only CPB duration ($p = .03$, odds ratio 1.02, 95% confidence interval 1.0013 to 1.03) and Se concentrations measured 1 hr after admission to the ICU ($p = .003$, odds ratio 0.85, 95% confidence interval 0.76 to 0.94) were independently associated with the development of MOF later in the postoperative time course (whereas preoperative trace element concentrations, postoperative Zn and Cu concentrations, postoperative hemoglobin, the units of packed red blood cells administered, Simplified Acute Physiology Score II and procalcitonin values at day 1, the duration of surgery, ischemia time, and EuroScore were not). Postoperative Se concentrations correlated with the ICU length of stay ($r = -0.36, p = .005$) and with procalcitonin concentrations at day 1 ($r = -0.27, p = .036$). The intraoperative Se decrease correlated with the Sequential Organ Failure Assessment score at day 1 ($r = -0.27, p = .035$).

Gpx Activity

In the 29 patients staying >1 day in the ICU, we could observe a decrease of serum Gpx activity 1h after admission to the ICU (98 ± 22 U/L vs. preoperative 117 ± 19 U/L, $p < .001$). Furthermore, a positive correlation between serum Gpx activity and whole blood Se concentrations could be found ($r = .52, p < .001$).

DISCUSSION

In the present study, we could demonstrate a significant decrease of Se, Zn, and Cu during open-heart surgery with the use of CPB. This intraoperative decrease was most pronounced in patients developing organ dysfunctions later in the postoperative time course. Se concentrations measured 1 hr after completion of surgery were independently associated with the development of MOF and were correlated with perioperative inflammation and ICU length of stay.

In critically ill patients, the importance of the endogenous AOX capacity has been repeatedly demonstrated. In particular, reductions in Se concentrations were found to be associated with the development of inflammatory and infectious complications, progression of organ dysfunction, and mortality (8–10, 28). In contrast, data on the importance of trace element status for the outcome from elective surgery are sparse. Most studies including surgical patients report only postoperative Se concentrations (8, 10), which are however affected also by the use of CPB. This intraoperative decrease in whole blood trace element concentrations when compared to baseline values.

Table 1. Preoperative status, data on surgery, and cardiopulmonary bypass

<table>
<thead>
<tr>
<th>Trace Element Status and Postoperative Outcome</th>
<th>All (n = 60)</th>
<th>No Organ Failure (n = 17)</th>
<th>Single Organ Failure (n = 31)</th>
<th>≥ Two Organ Failure (n = 12)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biometric/Demographic data</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>68 (20–87)</td>
<td>72 (20–83)</td>
<td>64.5 (20–81)</td>
<td>69 (46–87)</td>
<td>.107</td>
</tr>
<tr>
<td>Sex, male (n [%])</td>
<td>42 (70)</td>
<td>12 (71)</td>
<td>24 (68)</td>
<td>6 (50)</td>
<td>.517</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>171 ± 9</td>
<td>170 ± 10</td>
<td>172 ± 10</td>
<td>169 ± 8</td>
<td>.585</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80 (52–180)</td>
<td>80 (52–180)</td>
<td>82 (52–108)</td>
<td>74.5 (50–111)</td>
<td>.313</td>
</tr>
<tr>
<td>Euroscore</td>
<td>5 ± 3</td>
<td>5 ± 3</td>
<td>5 ± 3</td>
<td>7 ± 4</td>
<td>.421</td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated coronary artery bypass grafting [n [%]]</td>
<td>37 (62)</td>
<td>8 (47)</td>
<td>24 (77)</td>
<td>5 (42)</td>
<td>.033</td>
</tr>
<tr>
<td>Isolated valvular surgery [n [%]]</td>
<td>7 (11)</td>
<td>5 (29)</td>
<td>1 (3)</td>
<td>1 (8)</td>
<td>.024</td>
</tr>
<tr>
<td>Aortic surgery [n [%]]</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>.621</td>
</tr>
<tr>
<td>Combined procedure [n [%]]</td>
<td>15 (25)</td>
<td>4 (24)</td>
<td>5 (17)</td>
<td>6 (50)</td>
<td>.070</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>209 (150–605)</td>
<td>192 (155–420)</td>
<td>209 (150–605)</td>
<td>285 (162–503)</td>
<td>.089</td>
</tr>
<tr>
<td>Ischemia time (min)</td>
<td>66 ± 39</td>
<td>72 ± 41</td>
<td>60 ± 37</td>
<td>71 ± 41</td>
<td>.334</td>
</tr>
<tr>
<td>Cardiopulmonary bypass time (min)</td>
<td>104 (45–366)</td>
<td>98 (45–243)</td>
<td>100 (52–294)</td>
<td>145 (84–366)</td>
<td>.113</td>
</tr>
</tbody>
</table>

Data are presented as median (range), as mean ± SD or as absolute numbers (with the percentage [%] of the whole).
for whole blood selenium concentrations. Based on this value, we found in >80% of the included patients a Se deficiency already preoperatively, most probably due to a reduced Se intake, which has been previously demonstrated for most European countries (29).

As animal data demonstrate that Se deficiency before the onset of oxidative stress is associated with a worsening of oxidative damage when compared to a normal preinjury Se status (31), an adequate preoperative micronutrient status should theoretically be of paramount importance to curtail perioperative oxidative stress. On the other hand, preoperative concentrations of neither trace element were predictive for or independently associated with postoperative organ dysfunction in our study, pointing at the importance of the intraoperative period in which the suboptimal preoperative Se status was further aggravated. Our findings are confirmed by data of Al-Bader et al (32) who observed a comparable decrease of micronutrients during surgery with CPB but unfortunately did not report its impact on patient outcome.

Our observations add evidence to a key role for Se, which was found in a logistic

**Table 2. Organ failures according to subgroup analysis and postoperative outcome data**

<table>
<thead>
<tr>
<th>Subgroups and Outcome</th>
<th>Total (n = 60)</th>
<th>No Organ Failure (n = 17)</th>
<th>Single Organ Failure (n = 31)</th>
<th>≥ Two Organ Failure (n = 12)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial hypoxemia</td>
<td>38 (63)</td>
<td>n.a.</td>
<td>29 (94)</td>
<td>9 (75)</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>9 (15)</td>
<td>n.a.</td>
<td>0</td>
<td>9 (75)</td>
<td></td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>5 (8)</td>
<td>n.a.</td>
<td>1 (3)</td>
<td>4 (33)</td>
<td></td>
</tr>
<tr>
<td>Shock</td>
<td>4 (7)</td>
<td>n.a.</td>
<td>0</td>
<td>4 (33)</td>
<td></td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>5 (8)</td>
<td>n.a.</td>
<td>1 (3)</td>
<td>4 (33)</td>
<td></td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>1 (2)</td>
<td>n.a.</td>
<td>0</td>
<td>1 (8)</td>
<td></td>
</tr>
</tbody>
</table>

Incidence of systemic inflammatory response syndrome/sepsis (n [%])

<table>
<thead>
<tr>
<th>Systemic inflammatory response syndrome/sepsis</th>
<th>Total (n = 60)</th>
<th>No Organ Failure (n = 17)</th>
<th>Single Organ Failure (n = 31)</th>
<th>≥ Two Organ Failure (n = 12)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>POD 1</td>
<td>53 (88)</td>
<td>POD 1 13 (76)</td>
<td>POD 1 29 (94)</td>
<td>POD 1 11 (92)</td>
<td>0.195</td>
</tr>
</tbody>
</table>

Admission to the intensive care unit

<table>
<thead>
<tr>
<th>Intraoperative fluid balance (mL)</th>
<th>POD 1 3620 (1000–9048)</th>
<th>POD 2 3512 (1870–6283)</th>
<th>POD 3 3897 (1000–9048)</th>
<th>POD 3 3480 (2052–7051)</th>
<th>0.002</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate (mmol·L⁻¹)</td>
<td>9.8 ± 10.9</td>
<td>9.9 ± 13</td>
<td>9.7 ± 1.4</td>
<td>8.7 ± 0.9</td>
<td>0.024</td>
</tr>
<tr>
<td>First postoperative day</td>
<td>0.6 (0.6–10.1)</td>
<td>1.1 (0.6–10.1)</td>
<td>1.2 (0.2–4.1)</td>
<td>2.3 (1.1–7.0)</td>
<td>0.072</td>
</tr>
</tbody>
</table>

Duration of mechanical ventilation (hrs) 10 (3–361) 12 (4–67) 8 (3–29) 21 (10–361) 0.000

Intensive care unit length of stay (days) 1 (1–21) 1 (1–7) 1.5 (1–10) 3.5 (1–21) 0.000

Hospital length of stay (days) 10 (6–57) 9.5 (7–22) 10 (6–57) 12.5 (2–35) 0.743

Mortality (n [%]) 3 1 0 2 0.078

n.a., nonapplicable; POD, postoperative day, number indicates the earliest postoperative day at which the condition became manifest.

**Figure 1. Perioperative time course of whole blood concentrations of selenium, zinc, and copper. The lower boundary of the box indicates the 25th percentile, the line within the box marks the median, and the upper boundary of the box indicates the 75th percentile. Whiskers indicate the 90th and 10th percentiles, whereas close circles symbolize the 95th and fifth percentile. The gray shaded areas indicate the reference range for each trace element. **

* *p < .01 vs. no organ failure and **p < .001 vs. single organ failure. Data are presented as absolute numbers (percentage %) of the whole, as median (range) or as mean ± sd.
regression analysis to be the only trace element that was independently associated with the later development of MOF. The prominent role of Se might be due to its plethora of biological functions. Both Cu and Zn exert their antioxidant function as cofactors of primarily one particular enzyme (i.e., the Cu-Zn superoxide dismutase) (4). In contrast, Se is incorporated into at least 25 selenoproteins (33) and hence constituent of multiple AOX defense lines (5). Furthermore, Se is involved in the regulation of microvascular tone (34), cell cycling and apoptosis (35), and inhibits proinflammatory transcription factors such as activator-protein-1 (36) or nuclear factor-κB (3, 37). In fact, we could demonstrate a negative correlation between Se concentrations at end of surgery and the degree of postoperative inflammation at day 1, as assessed by procalcitonin levels, consistent with recent findings in critically ill patients (10). Furthermore, an increasing body of evidence indicates a prominent role for Se in the regulation of cardiovascular function. Extreme Se deficiencies are associated with the development of a severe cardiomyopathy, as originally described for regions of endemic Se deficiency in China (“Keshan’s disease”) and in patients given long-term parenteral alimentation without Se supplementation (38). Even mild Se deficiencies result in a reduced AOX capacity, which may aggravate ischemia-reperfusion injury observed following acute myocardial infarction, coronary bypass surgery, heart transplants, and coronary angioplasty (5).

Our data highlight the usefulness of performing very early assays of Se status, since Se concentrations measured already at end of surgery were able to pre-

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**Figure 2.** Intraoperative decreases of antioxidant trace elements (in % from baseline) in the different subgroups. The biggest trace element decrease was observed in patients developing multiorgan failure (MOF) in the postoperative period. The lower boundary of the box indicates the 25th percentile, the line within the box marks the median, and the upper boundary of the box indicates the 75th percentile. Whiskers indicate the 90th and tenth percentiles, whereas close circles symbolize the 95th and fifth percentile. *p < .05 vs. preop.* Data are presented as mean ± SD. The *p* values of the repeated measures analysis of variance are shown separately for the time, group, and interaction (time × group) effects.

**Figure 3.** Receiver operating characteristic curves for the significance of preoperative (preop.) and postoperative (postop.) trace element concentrations to predict the development of multiorgan failure (MOF) in the postoperative period. AUC, area under the receiver operating curve.
dict the development of MOF occurring 24–72 hrs later. This observation is supported by experimental findings of rapid Se decreases preceding the clinical onset of septic shock (39) and distinguishes our study from the majority of investigations in critically ill patients in which Se status was determined only up to 48 hrs after admission (8, 9, 40).

The etiology underlying the observed intraoperative trace element decrease remains speculative. Our data do not support the hypothesis that trace elements were diluted intraoperatively with priming and resuscitation fluids. All patients had a similar intraoperative fluid balance, which was not correlated with the observed decreases in trace element concentrations. Several studies could demonstrate a weak correlation between plasma albumin and Se, putatively reflecting Se escape into the interstitial compartment by capillary leakage (8–10). We were unable to find such a relationship, most probably due to the fact that Se concentrations were measured in whole blood in which albumin-bound Se represents only a very small fraction of total Se content (41). It is known from other antioxidants that their circulating concentrations are depleted when scavenging reactive oxygen species during/after CPB (42). The largest amount of plasma Se (53%) is bound to selenoprotein-P (43), which decreases during oxidative stress (40) as a result from its binding to the endothelium at inflammatory sites (44), its translocation into other tissue compartments to exert AOX functions (45), and a downregulation of the hepatic selenoprotein-P synthesis by inflammatory cytokines (46).

In our study, we further observed a close correlation between decreases in serum GPx (accounting for 39% of plasma-bound Se) and whole blood Se, which confirms previous findings in patients with systemic inflammation (9) and demonstrates that the observed Se decrease was in fact interrelated by a reduced AOX capacity. As a possible mechanism, it is important to note that in states of Se deficiency, extra- and intra- cellular GPx is the first Se-containing enzyme to decrease, most probably to allow redistribution of Se to other tissues, e.g., for the synthesis of proteins like selenoprotein-P (47). In any case, further studies are required to elucidate the importance of these respective mechanisms.

We acknowledge that our study has several limitations. First, our study is not suited to resolve the question of whether the observed Se decrease in cardiac surgical patients is causative or “only” indicative for the development of organ injury. This question should be addressed by a Se substitution study in cardiac surgical patients with preoperative Se deficiency. In fact, Berger et al (48) could recently demonstrate a significant attenuation of perioperative inflammation and a nonsignificant reduction of hospital stay in patients receiving AOX supplementation when admitted to the ICU after cardiac surgery. Our data might indicate that Se substitution in Se-deficient cardiac surgical patients should start already preoperatively, in an attempt to prevent intraoperative Se depletion, and to allow GPx activity to be optimized before the exposure to intraoperative oxidative stress. In in vitro models, maximum GPx activities could be achieved already 48 hrs after start of Se incubation (49). Second, it retrospectively appears unnecessary to have separately analyzed a subgroup with only one failing organ since this subgroup virtually showed no differences when compared to the NOF group. However, this result could not be expected by us when we defined the separate subgroups a priori. Combining the NOF and the SOF subgroups to one conjoint group would have even strengthened the validity of our results.

Third, we acknowledge that the number of patients, in particular in the MOF group, is small. The study was however sufficiently powered to allow the detection of a significant difference between pre- and postoperative trace element concentration. The subsequent subgroup analysis has to be considered to be purely explorative and hypothesis-generating.

CONCLUSIONS

AOX trace elements were found to decrease intraoperatively in patients undergoing cardiac surgery with the use of extracorporeal circulation. The intraoperative decrease of circulating Se concentrations was predictive for and independently associated with the postoperative development of MOF, and correlated with the Sequential Organ Failure Assessment score at the first postoperative day. Furthermore, Se concentrations at end of surgery were correlated with the degree of postoperative inflammation and with length of stay in the ICU.

Further studies are warranted to elucidate the exact mechanisms underlying the intraoperative AOX decrease observed during cardiac surgery and to determine both the efficacy and the optimal time point of a preemptive Se substitution being initiated before the onset of perioperative oxidative stress.

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