Elevated endothelin-1 level is a risk factor for nonocclusive mesenteric ischemia

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Objective: Nonocclusive mesenteric ischemia may occur after cardiac surgery, commonly in conjunction with the use of cardiopulmonary bypass. Some evidence suggests that endothelin-1 serum levels are increased in patients with mesenteric ischemia, but the association of endothelin-1 and nonocclusive mesenteric ischemia has not been studied. The objective was to investigate whether elevated levels of endothelin-1 could be found in patients exhibiting nonocclusive mesenteric ischemia.

Methods: In an observational cohort study, nonocclusive mesenteric ischemia developed in 78 of 865 patients undergoing elective cardiac surgery. Control patients were identified from the cohort through 1:1 propensity score matching. Preoperative and postoperative endothelin-1 serum levels were determined by means of enzyme-linked immunosorbent assay. Odds ratios (with 95% confidence interval) were calculated by logistic regression analyses to determine the risk of endothelin-1 for the development of nonocclusive mesenteric ischemia.

Results: Patients with nonocclusive mesenteric ischemia had higher preoperative (11.3 vs 9.3 pg/mL; $P = .001$) and postoperative (15.7 vs 11.1 pg/mL, $P < .001$) levels of endothelin-1 than the controls. The probability of developing nonocclusive mesenteric ischemia increased with each picogram/milliliter endothelin-1 level preoperatively (odds ratio, 1.29; 95% confidence interval, 1.12-1.49) and each picogram/milliliter postoperatively (odds ratio, 2.04; 95% confidence interval, 1.54-2.72). Receiver operating characteristic analyses showed that elevated endothelin-1 serum levels had a high accuracy to predict nonocclusive mesenteric ischemia (optimal cutoff value of 14.5 pg/mL, area under the curve of 0.77, sensitivity 51%, and specificity 94%).

Conclusions: Endothelin-1 seems to predispose patients undergoing cardiac surgery to develop nonocclusive mesenteric ischemia. In addition, it may be a useful marker to identify patients at risk for nonocclusive mesenteric ischemia after cardiac surgery. (J Thorac Cardiovasc Surg 2015;149:1436-42)

See related commentary pages 1443-4.

Supplemental material is available online.

Nonocclusive mesenteric ischemia (NOMI) is a dreaded gastrointestinal complication after cardiopulmonary bypass (CPB) with mortality rates of up to 90%.[1,2] It is considered as a form of intestinal blood flow impairment with extreme reduction or maldistribution of splanchnic blood flow.[2,3] Intestinal ischemia leads to compromised mucosal integrity, bacterial translocation, bacteremia, and the development of multiorgan failure. Nevertheless, the exact pathomechanism leading to nonocclusive disease is currently unknown.[2]

We have previously identified perioperative risk factors for the development of NOMI after cardiac surgery, such as the use of an intra-aortic balloon pump, catecholamine support, or loss of sinus rhythm.[4] However, these risk factors are not apparently related to common physiologic mechanisms that are important to understand if NOMI is to be prevented.

In a porcine model, experimental application of endothelin (ET)-1 has been shown to reduce microvascular blood flow of the distal jejunum and ileum.[5] Specific ET_A and ET_B blockade with tezosentan were shown to improve microcirculatory blood flow in the ileal mucosa during experimental endotoxemia.[6] We previously observed that CPB leads to jejunal ischemia, which is associated with upregulation of ET-1 and changes in ET receptor expression.[7]

Although these observations indicated a role of ET in intraoperative visceral malperfusion, it is still unclear whether these findings are transferable to humans and to

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Abbreviations and Acronyms
CI = confidence interval
CPB = cardiopulmonary bypass
ET = endothelin
NOMI = nonocclusive mesenteric ischemia
OR = odds ratio
ROC = receiver operating characteristic

the setting of NOMI. If ET should be involved in human NOMI, treatment with ET receptor antagonists might become a clinical strategy. We decided to investigate whether elevated serum ET-1 levels are associated with an increased risk for the occurrence of NOMI in patients undergoing elective cardiac surgery.

MATERIALS AND METHODS

Patients

After approval by the local ethics committee (Landesärztekammer des Saarlandes; Reference Identification: 199/09), a prospective cohort study was performed from January 1, 2010, to March 31, 2011. During the study period, 1272 patients underwent cardiac surgery with extracorporeal circulation, of whom 94 underwent urgent surgery and 15 underwent emergency surgery. Of the 1163 adult patients who underwent elective cardiac surgery, 298 refused participation, resulting in the study population of 865 individuals (74%) (Table E1). Written informed consent was obtained from all patients. Blood samples were obtained prospectively on all patients at regular intervals and stored for subsequent analysis.

The majority of the individuals had an uneventful postoperative course. On the basis of clinical changes suggestive of mesenteric ischemia, angiography of the superior mesenteric artery was performed in 88 patients.[4] Of these, 78 were found to have NOMI, and the results were normal in 10. To create an adequate control group, 78 patients from the whole cohort were selected by propensity score-matching analysis. The final study population thus consisted of 78 patients with NOMI and 78 patients without NOMI. In these patients, ET-1 serum levels were determined post hoc.

Radiographic Analysis

Arterial angiography was performed if NOMI was suspected. The decision to perform angiography was based on the presence of at least 2 of 4 possible clinical indicators: new onset of oliguria/anuria, abdominal distention with decreased or absent bowel sounds, serum lactate levels greater than 5.0 mmol/L, metabolic acidosis (base excess <-5 mmol/L), or increase of vasopressor support by more than 3-fold from the end of surgery in the absence of hypovolemia. Angiography was performed only in patients with a systolic blood pressure greater than 90 mm Hg or a cardiac index greater than 1.8 L/min/m^2. All images were assessed by an experienced radiologist and an intensivist on consensus basis with respect to vessel morphology, reflux of contrast medium into the aorta, small bowel parenchymal contrast enhancement, and distension and the delay between arterial injection and portal vein filling. In accordance with our previously published scoring system,[3] NOMI was diagnosed whenever the total score was more than 1 (Table E2).

Endothelin-1 Measurements

In the late afternoon before surgery and the early morning after surgery, blood was collected in 2.7 mL ethylenediaminetetraacetic acid tubes (Sarstedt AG and Co, Nümbrecht, Germany) and placed on ice until centrifugation. Blood was obtained from a peripheral vein preoperatively and a central venous line postoperatively. Serum was immediately (<5 minutes) separated by centrifugation (1525*g* for 10 minutes at 4°C), filled into polypropylene tubes (Sarstedt AG and Co), and stored at −80°C for further analysis. The ET-1 concentrations and the standard curves were determined using an enzyme-linked immunosorbent assay kit (Assay Designs, Immunoassay Kit, catalog no. 900-020A, Enzo Life Sciences Inc, Farmingdale, NY) according to the manufacturer's protocol. The sensitivity of the assay was 0.41 pg/mL. All measurements were performed in duplicate by the same person on the same day.

Propensity Score-Matching Analysis

To minimize patient selection bias in this retrospective nonrandomized study, we used a propensity score-matching analysis to evaluate the effect of ET-1 on the development of NOMI. The matching was based on the results of multivariate logistic regression analysis. Control patients were identified from our database, that is, patients who underwent cardiac surgery during the same study period without developing NOMI (n = 787). A P value less than .20 was defined for selecting variables for entry into the final model. Variables were selected from epidemiologic and clinical data (Table 1) including the previously identified preoperative risk factors for NOMI.[4] By using these covariables, a propensity score was calculated for each patient. Finally, each patient who had NOMI was matched to 1 patient who did not have NOMI with the closest propensity score. The maximum difference of propensity score for a matching was less than 0.05. With this technique, comparable patient cohorts (each n = 78) were identified for the final analysis (NOMI and control). There were no significant differences in baseline characteristics between the propensity-matched groups (Table 1).

Statistical Analysis

All data are presented as mean ± standard deviation or with 15th and 85th percentile. Data analysis was performed using SPSS Statistics 19 and R 2.10.1 for Windows (IBM, Ehningen, Germany). In the first step, chi-square tests were performed to compare patients with and without NOMI regarding dichotomous variables. For continuous variables, the differences between the 2 groups were compared with Student t tests (Welch's t tests in case of inhomogeneous variances). The influence of NOMI on the course of ET-1 was analyzed by analysis of variance for repeated measurements.

In the second step, odds ratios (ORs) were calculated by logistic regression analyses to determine the risk of preoperative and postoperative ET-1 to have NOMI in the cohort of 156 study patients (78 matched pairs). Additional models were calculated, adjusted for potential confounders (listed in Table 1). In these models, to avoid collinearity, covariates with a positive correlation greater than 0.3 were excluded.

In the third step, different receiver operating characteristic (ROC) curves were performed to evaluate the predictive power of preoperative and postoperative serum ET-1 levels for the occurrence of NOMI and 30-day mortality. The Youden Index was used to calculate optimal cutoff points for ET-1 for the prediction of NOMI.

In the fourth step, ORs were adjusted for the 7 perioperative risk factors we had previously identified[4]: reexploration for bleeding, intra-aortic balloon pump support, need for more than 2 packed red blood cells, serum lactate level greater than 5 mmol/L, need for norepinephrine greater than 0.1 μg/kg/min, levosimendan therapy, and loss of sinus rhythm. In these models, to avoid collinearity, covariates with a positive correlation greater than 0.3 were excluded. To evaluate the potential role of ET-1 serum levels in the pathogenesis of NOMI, we compared postoperative ET-1 serum levels of the control group (positive for at least 1 risk factor) and the NOMI group.

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