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Nonocclusive mesenteric infarction after cardiac surgery: potential biomarkers

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ABSTRACT

Background: Nonocclusive mesenteric ischemia can cause intestinal infarction but the diagnosis is challenging. This prospective study evaluated three plasma biomarkers of intestinal infarction after cardiac surgery.

Materials and methods: Patients were recruited after cardiac surgery if they required laparotomy (with or without intestinal resection) for suspected nonocclusive mesenteric ischemia. Plasma levels of D-lactate, intestinal fatty acid–binding protein (i-FABP), and smooth muscle actin (SMA) before laparotomy were measured.

Results: Twenty patients were recruited (68 ± 9 y, EuroSCORE: 8.7 ± 2.8, mortality 70%). A positive laparotomy ($n = 13$) was associated with no change in D-lactate ($P = 0.95$), decreased i-FABP ($P = 0.007$), and increased SMA ($P = 0.01$). All patients with high SMA had a positive laparotomy. A subgroup analysis was undertaken in the eight patients who required multiple laparotomies. D-lactate increased between the two laparotomies in nonsurvivors ($n = 4$). Plasma i-FABP ($P = 0.008$) and SMA ($P = 0.036$) significantly decreased after the bowel resection, regardless of survival outcome.

Conclusions: None of the biomarkers were accurate enough to reliably diagnose intestinal infarction. However, all patients with high values of SMA developed intestinal infarction, thus warranting further investigation. An increasing D-lactate after intestinal resection suggests impending death.

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Introduction

Nonocclusive mesenteric ischemia (NOMI) occurs in 2/100,000 patients,[1] is less common than occlusive mesenteric ischemia,[2] and carries a mortality rate of up to 80%.[3-5] First described 60 years ago,[6] the pathogenesis of NOMI remains poorly understood. It can develop in a wide range of critical illnesses,[7] after major surgery,[6,8] in ventilated patients and those on hemodialysis.[9,10]

NOMI remains a substantial diagnostic challenge, as in most patients it has an insidious onset.[11,12] In a minority of patients, NOMI becomes severe, and full thickness intestinal infarction ensues, with the potential sequelae of perforation and peritonitis. The diagnostic challenge is two-fold: the detection of all those with NOMI and those with NOMI who require intestinal resection.

The diagnostic accuracy of plasma biomarkers of intestinal ischemia has been reviewed.[13] Although some appear promising, for instance D-lactate[14-16] and intestinal fatty acid–binding protein (i-FABP),[17,18] their performance in the context of NOMI after cardiac surgery has not been tested.[13] Two recent studies in infants with necrotizing enterocolitis, with some similarities to NOMI, suggested that α-smooth muscle actin (SMA) might be a useful marker for severe intestinal ischemia.[19,20]

We aimed to prospectively evaluate three plasma biomarkers (D-lactate, i-FABP, and SMA) for diagnosing intestinal infarction after cardiac surgery. The purpose of this study was to evaluate these biomarkers as diagnostic markers and not as prognostic markers.

Material and methods

Eligibility and patient consent

This prospective, observational pilot study was undertaken in the Cardiothoracic and Vascular Intensive Care Unit between September 2010 and December 2012. All patients were managed by the same team of surgeons, anesthetists, and intensivists. Patients were recruited after cardiac surgery if they required laparotomy based on suspicion of intestinal infarction due to NOMI. Exclusion criteria were age <18 y; consent from the patient or family withheld or withdrawn; occlusive mesenteric ischemia.

Written prospective consent was obtained from the patient whenever possible. When not possible, consent was obtained from the patients' next of kin, and retrospective consent was obtained on recovery. This study was approved by the New Zealand Northern Region Ethics Committee A (NTX/10/006/053).

Laparotomy and data collection

Patients were recruited after a clinical decision that laparotomy was necessary. This was based on a consensus between intensivists, cardiac, and general surgeons. The clinical decision was based on multiple factors including the presence of abdominal distension, ileus, peritonism, hematochezia, pneumatosis, hepatic portal venous gas, and usually in association with a further deterioration in the patient's overall physiological status. At the time of recruitment, EuroSCORE (European System for Cardiac Operative Risk Evaluation, model I; http://euroscore.org) was calculated. A positive laparotomy indicates full thickness intestinal infarction and was followed by resection (when survivable). Resected specimens were sent for histopathology. Some patients had additional laparotomies as a planned "second look" to confirm anastomotic integrity, intestinal viability, or to restore intestinal continuity.

The findings at laparotomy and clinical details were recorded on a standardized form and entered into computerized database from the date of recruitment to hospital discharge or death.

Biomarker assays

Immediately before each laparotomy, plasma was collected for routine laboratory testing and subsequent assays of candidate biomarkers. Plasma was obtained by drawing blood into K_2 EDTA vacutainers, centrifuging at 1472 × *g* for 10 min, and freezing the supernatant at −80°C. The plasma levels of biomarkers were determined using commercial kits: D-lactate assay (Cat#ab83429, Abcam, Cambridge, UK); enzyme-linked immunosorbent assay (ELISA) for i-FABP (Cat#HK406-02, Hycult Biotech, Uden, The Netherlands); and SMA (Cat#A-BIN364996, antibodies-online, GA). Manufacturers' instructions were followed. Samples were analyzed at least in duplicate. Absorbance was measured with SpectraMax 340PC plate reader (Molecular Devices, CA), and plasma concentration was estimated using the Softmax Pro version 5.4.3 software (Molecular Devices, CA).

Data analysis

Differences in plasma biomarker levels were analyzed using the analysis of variance model to determine significant differences and expressed as model-estimated mean with 95% CIs and *P* values.

A receiver-operating characteristic (ROC) curve analysis was used to determine the ability of each biomarker to discriminate a positive and negative laparotomy and to determine an optimal cutoff point for each biomarker.[21] A 2 × 2 contingency table was created for each biomarker using the optimal cutoff point to derive the sensitivity, specificity, positive and negative predictive values, and diagnostic accuracy.[22,23] Two-tailed *P* values were calculated using the Fisher's exact test.

Student *t*-test or signed rank test (selected after normality testing of data) was performed on the subgroup of eight patients who had multiple laparotomies, to determine the changes in biomarker levels from the positive first laparotomy to the last laparotomy performed in the same patients. The analysis was also performed for those eight patients to test the difference between survivors and nonsurvivors ($n = 4$ each) using the analysis of variance or Kruskal–Wallis test if the data were not normally distributed.