Early Detection of Gut Ischemia-Reperfusion Injury During Aortic Abdominal Aneurysmectomy: A Pilot, Observational Study

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Objective: **D-lactate is the enantiomer of L-lactate, which is measured routinely in clinical practice to assess cell hypoxia. D-lactate has been proposed as a specific marker of gut ischemia-reperfusion (IR), particularly during surgery for ruptured abdominal aortic aneurysms. The aim of this study was to compare the use of D-lactate measurement and colonic tonometry (taken as a reference method) for gut IR detection during elective infrarenal aortic aneurysm (IrAA) surgery.**

Design: **Prospective, monocenter, observational study.**

Setting: **Vascular surgery unit, university hospital.**

Participants: **Candidates for elective IrAA surgery.**

Interventions: **Patients without (controls) and with gut IR (defined as $\Delta CO_2 > 2.6$ kPa) were compared retrospectively.**

Measurement and Main Results: **D-lactate levels were compared with colonic perfusion levels (ΔCO_2), as assessed by colonic tonometry, at 7 time points during surgery and until 24 hours after surgery. D-lactate also was measured in mesenteric vein blood before and after gut reperfusion. Plasma TNF-α level was measured at the same time points to assess systemic inflammatory response. Eighteen patients requiring elective IrAA surgery were included. The ΔCO_2 and TNF-α level varied significantly over time. There was a significant ΔCO_2 peak at the end of clamping (2.6 ± 1.8 kPa, $p = 0.006$) and a significant peak in TNF-α level after 1 hour of reperfusion (183 ± 53 ng/L, $p = 0.05$). D-lactate levels were undetectable in systemic and mesenteric blood in all the patients throughout the study period. Gut IR patients ($n = 6$) experienced a longer overall duration of intraoperative hypotensive episodes and received more catecholamines than the controls ($n = 12$).**

Conclusions: **Compared with colonic tonometry, D-lactate was not a reliable biomarker of gut IR during elective IrAA surgery.**

KEY WORDS: aortic aneurysm, abdominal, mesenteric vascular occlusion, reperfusion injury, inflammation mediators, D-lactate

GUT HYPOXIA (ischemia-reperfusion [IR]) often occurs during aortic aneurysm surgery as a result of clamping of the aorta, reduced intraoperative blood pressure, and anesthesia.[1,2] It is associated with an increased incidence of postoperative complications including systemic inflammatory response and multiple-organ dysfunction syndrome.[3,4] Early detection of gut injury, thus, is essential for the best management.

The diagnosis and assessment of gut hypoxia are challenging. Inadequate splanchnic perfusion can be detected indirectly from an increase in lactate levels. Monitoring of intestinal perfusion by intestinal tonometry can detect early mucosal ischemia, as reflected by a decrease in intramucosal intestinal pH (pHi) or widening of the regional-arterial PCO_2 gradient (ΔCO_2).[5] Both pHi and ΔCO_2 are reliable prognostic indicators for the development of organ failure after major surgery.[6] However, arterial lactate concentrations have poor sensitivity as an index of gut hypoxia and as a predictor of postoperative organ failure.[4] Serum D-lactate levels, on the other hand, may prove to be an early indicator of intestinal ischemia.[7-10]

Each lactate isomer results from the reduction of a pyruvate molecule (optically neutral) by a specific lactate dehydrogenase. An L-lactate dehydrogenase produces L-lactate, and a D-lactate dehydrogenase produces D-lactate. Mammals only possess L-lactate dehydrogenase, whereas micro-organisms, particularly bacteria, have D-lactate dehydrogenase and produce D-lactate during fermentation.[11] A leaky mucosal barrier might cause permanent translocation and accumulation of D-lactate.[10] Thus, D-lactate might be a useful clinical marker for the early diagnosis of acute intestinal insult in clinical practice.[9,10,12]

However, the evidence for an association between circulating D-lactate levels and ischemia-induced intestinal injury is conflicting.[13,14] The aim of this study was to compare D-lactate levels and tonometry ΔCO_2 values as early indicators of postoperative gut hypoxia after elective infrarenal aortic aneurysm (IrAA) surgery.

METHODS

This was a prospective, observational, single-center study conducted in a vascular surgery unit. The study compared 2 diagnostic techniques for gut hypoperfusion; namely, measurement of D-lactate levels and colic tonometry. Both indirectly assess gut mucosal perfusion. The institutional Ethics Committee on Human Research approved the study protocol, and written informed consent was obtained from all the patients before surgery.

Patients requiring elective IrAA surgery between January and September 2002 were enrolled in the study. The main criteria for

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exclusion were age <18 years, recent colonic surgery or pre-existing colonic disease, a diagnosis of mycotic aneurysm, recent inflammatory syndrome (fever above 38°C or recent history of infection), recent gastrointestinal bleeding, pre-existing chronic renal insufficiency (creatinine clearance <15 mL/min), and participation in another clinical trial less than 30 days before enrollment. Patients with iliac aneurysms and in whom a need for bifurcation grafts or suprarenal clamping was foreseen also were excluded.

Patients were premedicated with 1.5 mg/kg of hydroxyzine orally. Anesthesia was induced with sufentanil, propofol, and vecuronium and maintained after orotracheal intubation with isoflurane-nitrous oxide, sufentanil, and vecuronium. The inspired oxygen fraction was maintained at 0.4. Epidural anesthesia was not administered.[15] A triple-lumen catheter was inserted into the internal jugular vein, and a radial artery catheter was used for arterial pressure monitoring and blood sampling. All patients received 10 to 15 mL/kg/h of isotonic sodium chloride intraoperatively. Colloid infusion was given to maintain a stable hemodynamic state (systolic arterial pressure >90 mmHg and urine output >50 mL/h). Solutions containing lactate ions (eg, lactated Ringer's) were not used. Vasopressor agents (dopamine or norepinephrine) were started when fluid resuscitation was not sufficient to correct hypotension (systolic arterial pressure <90 mmHg).[16] The choice of vasoactive agent was free. Blood collected by the cell saver was infused in the normal way. Patients with a hemoglobin concentration <10 g/dL received packed red blood cells to achieve a 10 g/dL concentration.

The aorta was approached via a midline laparotomy. It was clamped below the renal artery and above the inferior mesenteric artery. The inferior mesenteric artery was not reimplanted.

The patients' age, sex, body weight, and comorbidities were recorded. The following intraoperative data were recorded: duration of aortic clamping, duration of surgery, blood transfusion volumes, cell saver transfusion volumes, number of hypotensive episodes, duration of hypotension, fluid management and load (total, crystalloid, and colloid), arterial pressure, cardiac frequency, catecholamine dose, and urinary output. Postoperative data were duration of sedation, duration of mechanical ventilation, blood transfusion and fluid resuscitation, urinary output, unspecific clinical symptoms compatible with ischemic colitis (diarrhea and blood), and in-hospital mortality. The number of hypotensive episodes (systolic arterial pressure <90 mmHg) was noted and their overall duration determined.

To assess the robustness of tonometry, 2 groups of patients were assembled retrospectively according to the ΔCO_2 value measured at the end of aortic occlusion (T2). The control group had a ΔCO_2 below 2.6 kPa and the gut IR above 2.6 kPa at T2. A 2.6-kPa threshold was chosen because outcomes are poor when the value is higher.[4,19-21] The 2 groups of patients were compared retrospectively on the basis of patient demographics, intraoperative data (listed previously), postoperative data, and TNF-α values after 1 hour of reperfusion. The intraoperative variables influencing ΔCO_2 at T2 and the relationship between ΔCO_2 and the overall duration of intraoperative hypotensive episodes were analyzed.

All parameters were performed at 7 time points: before aortic cross-clamping (T1), at the end of aortic cross-clamping time (just before aortic cross-clamp release, T2), 15 minutes (T3), 1 hour (T4), 3 hours (T5), 6 hours (T6), and 24 hours (T7) after aortic clamp release. Ischemia was defined as the period between aortic cross-clamp and aortic cross-clamp release; reperfusion was defined as the period after aortic cross-clamp release.

A TRIP tonometer (Tonometrics Division, Instrumental Corp., Helsinki, Finland) was used to measure the regional CO_2 ($PrCO_2$). The tonometer is a silicon 8-F catheter with a balloon tip and a semipermeable membrane that allows diffusion of gases but not fluids. After induction of anesthesia, the tonometer was introduced intrarectally, positioned in the sigmoid colon, and connected to a Tonocap device (Datex, Helsinki, Finland) for gas tonometry. Correct placement of the catheter was checked by radiography before surgery and de visu by the surgeon during laparotomy. The tonometer was maintained in situ throughout the surgery. It was removed 24 hours after aortic cross-clamp release. After automatic calibration, regional CO_2 gut pressure ($PrCO_2$) was measured by infrared spectroscopy. Arterial blood samples were obtained simultaneously to measure $PaCO_2$. The ΔCO_2 was calculated as the gut-to-arterial PCO_2 difference ($P(r-a)CO_2$) as described elsewhere.[17]

Blood specimens were collected in heparinized plastic tubes. Plasma was separated by centrifugation at 3,500 rpm for 10 minutes and stored at −80°C before analysis. Tumor necrosis factor alpha (TNF-α) was determined on duplicate samples by an automated chemiluminescent immunometric assay (DPC Immulite 1000 analyzer, Siemens Healthcare Diagnostics) (detection threshold, 1.7 ng/L). TNF-α levels were measured at the same 7 time points as for D-lactate determinations (stated previously).

After sampling, 1 mL of whole blood was deproteinized with perchloric acid, centrifuged at 3,500 rpm for 20 minutes at 4°C, and stored at −70°C until enzymatic spectrophotometry.[18] A standard curve was obtained before each set of measurements. The technique's sensitivity threshold was 0.14 mmol/L.[13] Arterial D-lactate was determined at 7 time points; additionally, venous mesenteric D-lactate was measured at T1 and T2.

Results were expressed as means ± standard error or medians with ranges. As the data were not Gaussian, differences in variables across multiple time points were tested using the Friedman repeated-measures analysis of variance on ranks, followed by multiple comparisons corrected for multiplicity. The retrospective comparison between groups was performed using the unpaired t-test, multiple regression analysis, and the Spearman correlation test. The significance threshold was $p < 0.05$. Analyses were performed using SPSS 13.3 for the overall analysis, an Excel spreadsheet for post hoc comparisons, and GraphPad Prism version 5.03 for Windows.

RESULTS

Eighteen patients (mean age, 70 ± 2 years) were included in the study (Table 1). All underwent surgery for uncomplicated, elective IrAA. There were no cases of aneurysm of the iliac vessels. The main comorbidities were arterial hypertension (9/18), moderate cardiac insufficiency classes I and II (New York Heart Association classification system) (6/18), and diabetes mellitus (4/18).

Intraoperative and postoperative data are summarized in Table 1. No patient developed clinical symptoms of colonic ischemia. There were no in-hospital mortalities.

The ΔCO_2 varied significantly over time ($p = 0.014$) (Tables 2 and 3). It was 1.8 ± 0.4 kPa (13.5 ± 3 mmHg) before aortic cross-clamping and peaked significantly at the end of clamping (2.6 ± 0.4 kPa [19.5 ± 3 mmHg]; $p < 0.05$). It decreased below 2 kPa (15 mmHg) by 3 hours of reperfusion, but a second significant increase was observed at 6 hours of reperfusion (2.7 ± 0.5 kPa [20.2 ± 3.7 mmHg]; $p < 0.05$). It decreased again to below 2 kPa (15 mmHg) after 24 hours of reperfusion. Overall, 13 patients had a ΔCO_2 above 2 kPa (15 mmHg). If the ΔCO_2 threshold for detecting gut ischemia was taken as 2.6 kPa (19.5 mmHg), 6 patients may have been considered to have experienced gut ischemia (Fig 1).

TNF-α levels varied significantly over time ($p < 0.001$) (Table 2). The level was 34 + 12 ng/L at baseline and peaked at 1 hour of reperfusion to 161 ± 67 ng/L, a value that was significantly higher ($p < 0.05$) than the values before aortic