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# Association between gastric intramucosal pH and splanchnic endotoxin, antibody to endotoxin, and tumor necrosis factor- $\alpha$ concentrations in patients undergoing cardiopulmonary bypass

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**Objectives:** To determine the association between gastric intramucosal pH, a minimally invasive marker reflecting the adequacy of oxygen delivery to the gastrointestinal tract, and splanchnic endotoxin, antibody to endotoxin, and tumor necrosis factor (TNF)- $\alpha$  concentrations in patients undergoing cardiopulmonary bypass.

**Design:** Single-arm, prospective study.

**Setting:** University hospital.

**Patients:** Adults (n = 10) free of hepatic, pulmonary, and renal disease undergoing non-emergent coronary artery bypass surgery.

**Interventions:** After induction of general anesthesia and endotracheal intubation, a tonometer nasogastric tube was positioned in the stomach, and triple-lumen fiberoptic catheters were inserted into the hepatic vein and pulmonary artery. Hepatic venous and mixed venous blood samples were analyzed for endotoxin, antibody to endotoxin, and TNF- $\alpha$  at six times: 30 mins after induction of anesthesia (time 1); during vena caval cannulation (time 2); after 15 mins of hypothermic cardiopulmonary bypass (time 3); during spontaneous left ventricular ejection after release of the aortic cross-clamp, but before termination of cardiopulmonary bypass (time

4); 15 mins after termination of cardiopulmonary bypass (time 5); and 1 hr after termination of cardiopulmonary bypass (time 6). Gastric intramucosal pH, systemic oxygen delivery ( $\dot{D}_{O_2}$ ), mixed venous oxygen saturation, hepatic venous oxygen saturation, and hepatic venous lactate concentrations were recorded at these same times. Data for each variable were compared with baseline values (time 1) for statistical significance.

**Measurements and Main Results:** Cardiopulmonary bypass was associated with an increase ( $p < .05$ ) in systemic endotoxin concentrations from ventricular ejection until the end of the study. Virtually identical changes in the splanchnic circulation at this time approached, but did not reach, statistical significance, because hepatic venous endotoxin concentrations were higher than the mixed venous endotoxin concentrations at baseline ( $41.6 \pm 11.2$  vs.  $16.9 \pm 4.9$  pg/mL). Gastric intramucosal pH was abnormal ( $<7.35$ ) at 15 mins ( $p > .05$ ) and at 1 hr after termination of cardiopulmonary bypass ( $p > .05$ ). The relationship between endotoxin and gastric intramucosal pH was not statistically significant ( $p = .15$ ). The decrease in endotoxin antibody was small and statistically insignificant. TNF- $\alpha$  was not detected in any patient. Systemic  $\dot{D}_{O_2}$  decreased ( $p < .05$ ) after 15 mins of hypothermic cardiopulmonary bypass, but returned to baseline values thereafter. There were no significant changes in mixed venous and hepatic venous oxygen saturation values. Splanchnic lactate concentrations increased at cannulation ( $p < .05$ ), after 15 mins of hypothermic cardiopulmonary bypass ( $p < .05$ ), and 15 mins after termination of cardiopulmonary bypass ( $p < .05$ ).

**Conclusions:** These observations are consistent with the hypothesis that impaired gut-barrier function is responsible for endotoxemia

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**occurring during cardiopulmonary bypass. It is unclear whether increased mucosal permeability and mucosal acidosis are causally related phenomena or simply independent markers of damage to gut epithelium. (Crit Care Med 1993; 21:210-217)**

**KEY WORDS: cardiopulmonary bypass; splanchnic perfusion; gastric mucosa; ischemia; cardiac surgery; hepatic vein, catheterization; tonometry; cytokines; endotoxin; tumor necrosis factor- $\alpha$ ; lactate**

Measurement of tissue pH in gastrointestinal (GI) tract mucosa (intramucosal pH) using tonometry is an indirect method of assessing the adequacy of tissue oxygenation (1). Experimental data indicate that mucosal acidosis is one of the earliest indicators of mesenteric ischemia (2, 3). This finding is consistent with the hypothesis that intestinal villi are among the tissues at greatest risk for ischemia during low flow states, because the associated shunting of oxygen from arterioles to venules in the counter-current system within the mucosa renders the villous tips relatively hypoxic (4). Animal studies (3) also show that measurement of intramucosal pH in the stomach is linearly related to intramucosal pH in the small and large intestine during controlled blood loss. In patients undergoing open-heart surgery, reductions in gastric intramucosal pH commonly occur in the period surrounding termination of cardiopulmonary bypass (5, 6).

The pathophysiologic consequences of mucosal ischemia have been explored in the mesenteric artery occlusion model. Radiolabeled endotoxin placed in the canine colon can be recovered in the bloodstream within 30 mins of ischemia (7, 8). Circulating endotoxin is a potent stimulus for the production of tumor necrosis factor (TNF)- $\alpha$ , one of the principal biological mediators believed to be responsible for initiating multiple organ dysfunction (9). To a limited extent, plasma endotoxin levels are lowered by formation of antigen-antibody complexes with circulating immunoglobulin G antibody (10). Endotoxin (11, 12) and TNF- $\alpha$  (13) production have been reported in patients undergoing open-heart surgery, but endotoxin antibody has not.

We hypothesized that there was a causal relationship between gut mucosal acidosis and the appearance of gut-derived endotoxin in the circulation. To test this hypothesis, we measured gastric intramucosal pH and endotoxin, antibody to endotoxin, and TNF- $\alpha$  concentrations in the splanchnic (i.e., hepatic vein) and systemic (i.e., pulmonary artery) circulations of patients

undergoing cardiopulmonary bypass. We defined mucosal acidosis as gastric intramucosal pH <7.35, because clinical studies (14, 15) suggested that when gastric intramucosal pH decreases below this value, splanchnic perfusion decreases below the level where local oxygen transport can sustain aerobic energy production. Systemic oxygen delivery ( $\dot{V}O_2$ ) and other variables reflecting the adequacy of oxygen transport, including mixed venous oxygen saturation, hepatic venous oxygen saturation, and hepatic venous lactate concentrations, were also monitored.

## MATERIALS AND METHODS

Ten patients (10 male, 0 female) scheduled for non-emergent coronary artery bypass surgery were studied. Mean age was 55 yrs (range 42 to 65). Entry criteria for enrollment included a left ventricular ejection fraction of  $\geq 50\%$  and the absence of clinically important renal, pulmonary, or hepatic dysfunction as determined by routine biochemical testing. All patients gave informed consent to participate in this protocol, which was approved by the Copenhagen Medical Ethics Committee.

On the morning of surgery, each patient received morphine (0.1 mg/kg im) and ranitidine (150 mg orally). After cannulation of the radial artery, induction of anesthesia and endotracheal intubation were achieved using a high-dose fentanyl-pancuronium-oxygen technique. A nasogastric tube with a silicone rubber balloon at its tip (gastric tonometer and sump, Tonometrics, Worcester MA) was positioned in the stomach. Correct placement was confirmed by auscultation, and the tonometer balloon was charged with 2.5 mL of room-temperature normal saline. At the same time, a 7-Fr, heparin-bonded, triple-lumen thermodilution fiberoptic catheter (Abbott Critical Care, Mountain View, CA) was inserted under fluoroscopic guidance into the right hepatic vein through an 8.5-Fr sheath situated in the femoral vein. Correct position was confirmed by injection of contrast material; verification was performed by an attending staff radiologist. An identical catheter was inserted into the pulmonary artery.

After insertion of vena caval and aortic cannulas, nonpulsatile cardiopulmonary bypass was conducted in standard fashion using a membrane oxygenator (SAFE-1, Polystan A/S, Vaerloese, Denmark). Pump prime consisted of 2 L of lactated Ringer's solution and 4000 IU of heparin. Cardiac standstill was induced and maintained by intermittent administration of approximately 2 L hyperkalemic cardioplegic solution. Other features of cardiopulmonary bypass included moderate hypothermia (28°C), pump flow rates of approximately 2 L/min/m<sup>2</sup>, mean arterial pressure of 55 to 65 mm Hg,

topical cooling of the myocardium, and hemodilution to a hematocrit of 20% to 25%. No vasoactive medications were administered during cardiopulmonary bypass. As surgical correction was nearing completion, the body was rewarmed and the aortic cross-clamp was removed to resume total cardiac perfusion (reperfusion period). Patients were weaned from cardiopulmonary bypass as soon as the heart started to beat spontaneously, core temperature was  $\geq 38^{\circ}\text{C}$ , and sufficient surgical hemostasis had been achieved.

Blood samples were collected from the hepatic vein and pulmonary artery for determination of endotoxin, endotoxin antibody, and TNF- $\alpha$  concentrations at the following times: time 1, 30 mins after fiberoptic catheterization (baseline); time 2, during vena caval cannulation; time 3, after 15 mins of hypothermic cardiopulmonary bypass; time 4, during the reperfusion period (i.e., during left ventricular ejection after release of the aortic cross-clamp, but before termination of cardiopulmonary bypass); time 5, 15 mins after termination of cardiopulmonary bypass; time 6, 1 hr after termination of cardiopulmonary bypass. In addition, the following variables were recorded at each time period: a) hepatic venous and mixed venous oxygen saturations (Oximetrix<sup>®</sup> 3 oxygen saturation/cardiac output computer, Abbott Critical Care); b) total elapsed time from induction; c) core temperature (obtained from the pulmonary artery catheter thermistor); d) cardiac output (measured in triplicate, averaged, and indexed for body surface area); e) bicarbonate concentration; and f) arterial hemoglobin. Arterial hemoglobin was also obtained after 1 hr of cardiopulmonary bypass.

For samples obtained during cardiopulmonary bypass, pump flow rates were substituted for cardiac output. Mixed venous oxygen saturation was obtained from an oxygen saturation monitor (SM 0100, Oxysat<sup>®</sup> Meter, Bentley Laboratories, Irvine, CA) attached to the venous side of the cardiopulmonary bypass circuit, and the temperature of venous blood returning to the cardiopulmonary bypass machine was substituted for core temperature. After collection of the last specimen, the hepatic catheter was removed from the patient.

At time 1 and at each time thereafter, the first 1 mL of normal saline from the tonometer balloon (dead-space) was collected and discarded, and the remaining fluid was collected and immediately analyzed for  $\text{Pco}_2$ . The tonometer was recharged with 2.5 mL room-temperature normal saline after each collection. Gastric intramucosal pH was calculated using the Henderson-Hasselbalch equation:  $\text{pH} = 6.1 + \log \left( \frac{[\text{HCO}_3^-]}{\text{Pco}_2 \times 0.03} \right)$ , where  $[\text{HCO}_3^-]$  is the calculated bicarbonate concentration in arterial blood and  $\text{Pco}_2$  is the calculated steady-state partial pressure of  $\text{CO}_2$  at  $37^{\circ}\text{C}$ . Because equilibration of  $\text{CO}_2$  between saline in

the balloon, gastric juice, and gastric mucosa is a time- and temperature-dependent phenomenon,  $\text{Pco}_{2(\text{ss})}$  was obtained by multiplying the measured  $\text{Pco}_2$  by correction factors appropriate for dwell time and core temperature (16).

*Endotoxin, Endotoxin Antibody, and TNF- $\alpha$  Analysis.* Endotoxin was measured using the limulus amoebocyte lysate test in combination with a rocket immunoelectrophoretic assay (17). The sensitivity of the test is 0.8 pg/mL, as measured using *Escherichia coli* (055:B5 standard endotoxin, M.A. Bioproducts, Walkersville, MD). Endotoxin antibody was measured using an enzyme-linked immunosorbent assay (ELISA) method and values were corrected for hemodilution using the following equation:  $\text{endotoxin antibody}_{\text{corrected}} = \text{endotoxin antibody}_{\text{uncorrected}} \left[ \frac{(\text{Hct}_{\text{ind}} - \text{Hct}_{\text{cpb-1h}})}{\text{Hct}_{\text{ind}}} \right]$ , where  $\text{Hct}_{\text{ind}}$  is the arterial hematocrit at induction and  $\text{Hct}_{\text{cpb-1h}}$  is the arterial hematocrit after 1 hr of cardiopulmonary bypass. TNF- $\alpha$  concentrations were measured using a commercially available ELISA method (T Cell Sciences, Cambridge MA). The sensitivity of this test is 10 pg/mL.

*Statistical Analysis.* Differences between time points on the outcome variables and changes from baseline were evaluated by analysis of variance for repeated measures. In the presence of significant time differences, pairwise comparisons against baseline values were evaluated using multiple paired *t*-tests. Change from baseline was also evaluated. A Bonferroni adjustment was made to compensate for the additive type-1 error due to multiple comparisons. The analysis of variance was performed using an unbalanced, repeated-measures program (5V, BMDP Statistical Software, Los Angeles, CA) (18). Autoregressive, structured covariance matrices were used, as these matrices resulted in maximum Akaike's information criteria. Restricted estimation by maximum likelihood was used to estimate the covariance structure. In addition, gastric intramucosal pH was regressed on each other variable and time to determine if significant relationships existed between the variables. A  $p < .05$  was considered significant. Values were reported as mean  $\pm$  SEM.

## RESULTS

Mean duration of cardiopulmonary bypass and cross-clamping of the aorta was  $103 \pm 10$  mins (range 71 to 163) and  $66 \pm 6$  mins (range 45 to 96), respectively. Weaning from cardiopulmonary bypass was achieved without inotropic support or artificial pacing, and recovery from surgery was unremarkable for all ten patients.

Significant overall effects of time were observed for gastric intramucosal pH,  $\dot{\text{D}}\text{o}_2$ , hepatic venous lactate,

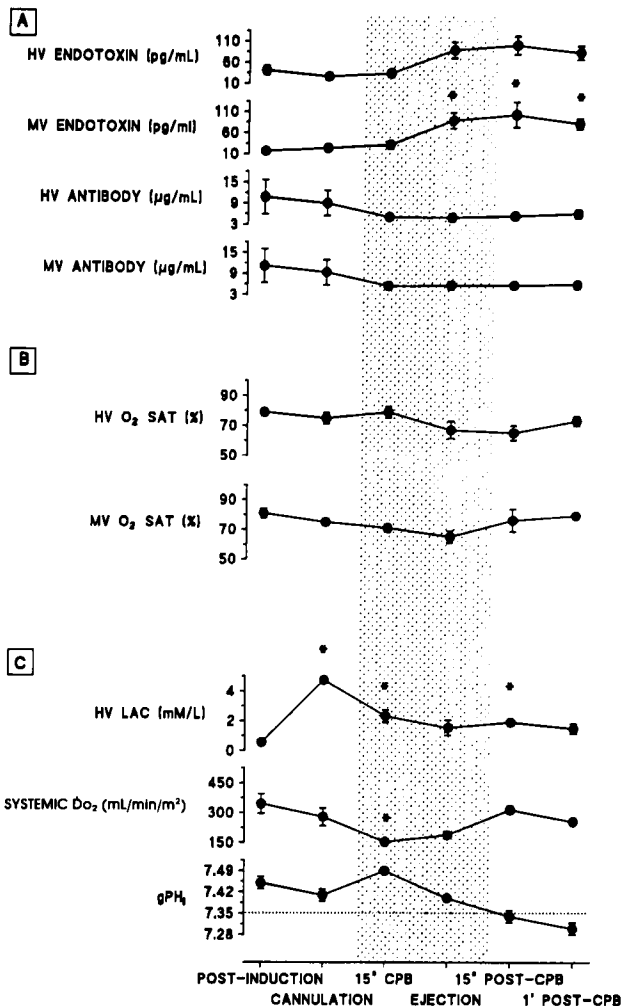
endotoxin, oxygen saturation, and mixed venous endotoxin and mixed venous oxygen saturation. Significant overall effects of time were observed for changes from baseline for the same variables. Pairwise comparisons lacked sufficient power to detect statistically significant differences between specific time points after adjusting for multiple comparisons for gastric intramucosal pH, mixed venous oxygen saturation, hepatic venous endotoxin, and hepatic venous oxygen saturation. The relationship between gastric intramucosal pH and endotoxin at both sites was not significant ( $p = .15$ ).

Hepatic venous and mixed venous endotoxin concentrations closely paralleled one another during the study period (Fig. 1A, upper two panels). Small and insignificant changes in hepatic venous endotoxin were observed from baseline to cannulation ( $41.6 \pm 11.2$  to  $26.5 \pm 8.3$  pg/mL, respectively) and from cannulation to 15 mins of cardiopulmonary bypass ( $26.5 \pm 8.3$  to  $34.3 \pm 9.3$  pg/mL, respectively). Minor variations (from  $16.9 \pm 4.9$  to  $24.4 \pm 9.0$  pg/mL and from  $24.4 \pm 9.0$  to  $31.9 \pm 7.9$  pg/mL;  $p > .05$ ) also were noted in mixed venous endotoxin over the same time period. Mixed venous endotoxin subsequently increased at ventricular ejection ( $88.7 \pm 19.0$  g/mL;  $p < .05$ ), at 15 mins after cardiopulmonary bypass ( $102.0 \pm 29.9$  pg/mL;  $p < .05$ ), and at 1 hr after termination of cardiopulmonary bypass ( $80.1 \pm 12.6$  pg/mL;  $p < .05$ ). Because hepatic venous endotoxin was higher than mixed venous values at time 1, virtually identical endotoxin concentrations in the hepatic vein ( $88.8 \pm 18.9$ ,  $100.0 \pm 21.4$ , and  $82.0 \pm 15.4$  pg/mL, respectively) did not reach statistical significance. Endotoxin antibody (Fig. 1A, lower two panels) and oxygen saturation (Fig. 1B) in the splanchnic and systemic vascular beds did not change significantly during the study period.

Hepatic venous lactate concentrations (Fig. 1C, top panel) increased from baseline values at cannulation ( $4.75 \pm 0.15$  mM/L;  $p < .05$ ), after 15 mins of hypothermic cardiopulmonary bypass ( $2.33 \pm 0.42$  mM/L;  $p < .05$ ), and at 15 mins after termination of cardiopulmonary bypass ( $1.91 \pm 0.19$  mM/L;  $p < .05$ ). Systemic  $\dot{D}O_2$  decreased ( $p < .05$ ) from an initial value of  $345 \pm 49.5$  to  $155 \pm 5.5$  mL/min/m<sup>2</sup> after 15 mins of cardiopulmonary bypass. Systemic  $\dot{D}O_2$  returned to baseline values thereafter (Fig. 1C, middle panel).

Gastric intramucosal pH increased from  $7.45 \pm 0.02$  (baseline) to  $7.49 \pm 0.01$  ( $p > .05$ ) after 15 mins of cardiopulmonary bypass, but steadily decreased thereafter. It was abnormal (i.e.,  $<7.35$ ) 15 mins after termination of cardiopulmonary bypass ( $7.34 \pm 0.02$ ;  $p > .05$ ) and reached  $7.30 \pm 0.02$  ( $p > .05$ ) by the end of the study (Fig. 1C, bottom panel).

TNF- $\alpha$  was not detected in any patient, and hence, is not depicted.



**Figure 1.** A) Hepatic venous (HV) and mixed venous (MV) concentrations of endotoxin and antibody to endotoxin (ANTIBODY). B) Hepatic venous and mixed venous oxygen saturation (O<sub>2</sub> SAT). C) Hepatic venous lactate (LAC) concentration, systemic oxygen delivery ( $\dot{D}O_2$ ), and gastric intramucosal pH (gPH<sub>g</sub>). The dotted line indicates the lower limit of normal gastric intramucosal pH (7.35). The duration of cardiopulmonary bypass is represented by the shaded area. \* $p < .05$  compared with baseline values (time 1). POST-INDUCTION, 30 mins after induction of anesthesia (time 1); CANNULATION, vena caval cannulation (time 2); 15' CPB, 15 mins after the onset of hypothermic cardiopulmonary bypass (time 3); EJECTION, spontaneous ejection from the left ventricle before termination of cardiopulmonary bypass (time 4); 15' POST-CPB, 15 mins after termination of cardiopulmonary bypass (time 5); 1' POST-CPB, 1 hr after termination of cardiopulmonary bypass (time 6).

## DISCUSSION

Translocation of intestinal bacteria into the circulation of experimental animals has been reported in many settings, including circulatory shock and endotoxin challenge (19, 20, 21). We hypothesized that systemic endotoxemia in patients undergoing open-heart

surgery (11, 12) was linked to reductions in splanchnic blood flow during extracorporeal circulation (22) and collateral ischemic damage to gut mucosa. Accordingly, we monitored direct and indirect markers of oxygen transport to the GI tract, along with corresponding endotoxin concentrations in the hepatosplanchnic and systemic circulations, at identical times in the perioperative period.

*Gastric Intramucosal pH.* Data presented here are in agreement with the findings of our previous study (6) in suggesting that the decrease in gastric intramucosal pH to abnormal values is in proportion to the duration of cardiopulmonary bypass. In both investigations, gastric intramucosal pH increased from baseline values during the hypothermic phase of cardiopulmonary bypass. Subsequently, it decreased to 7.30 after 103 mins of extracorporeal circulation in the present study, whereas it decreased to 7.26 after 141 mins of nonpulsatile flow in our earlier investigation (6). Even though these differences are not statistically significant, they do suggest that inadequate oxygen transport to the GI tract in the postoperative period may be related to the duration of cardiopulmonary bypass. The fact that duration of bypass (23) and duration of gastric mucosal acidosis on the day of surgery (5) are sensitive predictors of major complications after cardiac surgery lend additional support to this argument.

*Pathogenesis of Increased Intestinal Permeability and Its Sequelae.* Our results also provide some insight into the pathogenesis of endotoxemia arising during cardiopulmonary bypass. Figure 1 shows that endotoxin concentrations in the systemic circulation increased during ventricular ejection. Virtually identical changes in the splanchnic circulation did not achieve statistical significance because concentrations in the hepatic vein were higher than in the pulmonary artery at baseline (i.e.,  $41.6 \pm 11.2$  vs.  $16.9 \pm 4.9$  pg/mL, respectively). Nevertheless, these findings are consistent with the hypothesis that systemic endotoxin originates in the mesenteric vascular bed, where it is transported to the liver and then to other tissues via the portal circulation. Under normal circumstances, the intestinal tract mucosa provides an effective barrier to the >500 species of bacteria colonizing the intestine and their endotoxins. While the mechanisms responsible for alterations in gut-barrier function in this patient population are incompletely understood, events surrounding cardiopulmonary bypass undoubtedly play a key role.

"Environmental" endotoxins are the first intraoperative factors to be considered in the pathogenesis of mucosal injury. Studies (24–26) show that administering endotoxin to animals triggers mesenteric vasoconstriction and translocation of bacteria and their

endotoxins. O'Dwyer and co-workers (27) found that injection of a single dose of endotoxin (4 ng/kg) to healthy volunteers significantly compromises gut mucosal barrier function. These observations have important clinical implications, because there are indications that patients undergoing open-heart surgery routinely receive environmental endotoxins in the pump prime (mean 11 pg/mL, range 0 to 64) and cardioplegic solutions (mean 6 pg/mL, range 0 to 125) (11). Assuming these data are typical, each of our patients received 22 ng of exogenous endotoxin at the start of cardiopulmonary bypass (pump prime) and another 12 ng in the cardioplegic solution. Additional contributions from cardiac suction tubing and ice slush used for topical cooling are not included in this calculation.

While environmental endotoxins may initiate gut mucosal injury, the fact that splanchnic endotoxin concentrations at induction and after 15 mins of extracorporeal circulation were essentially the same ( $41.6 \pm 11.2$  vs.  $34.3 \pm 9.3$  pg/mL) raises the possibility that additional factors (e.g., mesenteric hypoperfusion [22]), amplify this process. Reductions in blood flow sufficient to cause intestinal ischemia initially affect the superficial epithelium, where patchy necrosis at the tips of the villi can be demonstrated histologically. As ischemia progresses, the remainder of the mucosa and still deeper layers of the intestinal wall are affected (28–30). Morris and co-workers (31) provided compelling evidence in sheep that bacterial translocation increases when superior mesenteric artery blood flow is reduced 50% by a mechanical occluder, and that translocation is largely prevented if mesenteric flow is preserved by arterial infusion of a vasodilator (sodium nitropruside). The notion that mesenteric hypoperfusion disrupts the functional integrity of gut mucosa is further supported by data that show that bacterial translocation is abrogated when infusions of hydroxyethyl starch and dobutamine are used to preserve normal mesenteric blood flow in acutely endotoxic pigs (32).

Related to this hypothesis are numerous reports (33–37) that indicate that nonpulsatile cardiopulmonary bypass, physiologically a controlled form of circulatory shock, triggers the release of angiotensin II. In animal models of cardiogenic shock, angiotensin II production is responsible for reductions in mesenteric perfusion that are out of proportion to the decrease in cardiac output (38–41). Hence, a causal relationship between the increase in angiotensin II concentrations and reductions in splanchnic blood flow during cardiopulmonary bypass (22) seems likely. Nonpulsatile flow is also associated with activation of platelets and leukocytes to form cellular aggregates capable of occluding vessels within the microcirculation (42). Other factors that reduce mucosal blood flow in this setting include

systemic hyperoxemia (43), hemodilution (hematocrit 20% to 25%) with controlled hypotension (44), hypocapnia (45–47), and the release of other mediators that constrict the splanchnic vascular bed (e.g., vasopressin [48] and thromboxane  $A_2$  [49]).

Based on these and other studies, it can be argued that gut perfusion is impaired by the administration of environmental endotoxins and the release of endogenous vasoconstrictors during cardiopulmonary bypass. According to this line of reasoning, hypothermia delays the onset of mucosal ischemia by reducing oxygen consumption ( $\dot{V}O_2$ ). As core temperature and  $\dot{V}O_2$  increase during the reperfusion period, continued release of endogenous vasoconstrictors attenuates parallel changes in intestinal perfusion, allowing ischemic mucosal damage by widening the gap between  $\dot{D}O_2$  and  $\dot{V}O_2$ . This self-perpetuating cycle is reinforced by restoration of pulsatile flow and expulsion of gut-derived endotoxin, sequestered in the microcirculation, into the portal vein. Indirect evidence suggests that gut mucosal barrier function, which ordinarily returns to normal a few days after surgery (11), is seriously impeded whenever the duration of extracorporeal circulation is protracted (e.g., >3 hrs) and/or a  $\dot{V}O_2/\dot{D}O_2$  mismatch in the GI tract occurring during the rewarming phase of cardiopulmonary bypass persists into the postoperative period (e.g., low cardiac output syndrome) (5, 23).

Does mucosal permeability increase without an antecedent episode of intramucosal acidosis? Because endotoxin concentrations increased at a time when gastric intramucosal pH was decreasing yet still within the normal range (i.e., during ventricular ejection, time 4), and because the relationship between these two variables did not reach statistical significance ( $p = .15$ ), our data would appear to support the notion that loss of gut barrier function and mucosal acidosis are independent markers of epithelial injury, rather than causally related phenomena. However, in addition to the limitations imposed by a small sample size, two additional caveats deserve careful consideration. First, gastric intramucosal pH measurements necessitate an equilibration period of  $\geq 30$  mins under relatively steady-state conditions. Such a situation is unusual in the clinical setting, because several factors governing the splanchnic  $\dot{V}O_2/\dot{D}O_2$  relationship (e.g., angiotensin II concentrations [50], mesenteric perfusion pressure, core temperature [51], and sympathetic nervous system activity [52]) change rapidly during the reperfusion period. Second, animal studies (53) suggested that even though tonometric estimates of mucosal pH closely correlate with tissue pH microelectrode measurements in experimental endotoxemia, they underestimate the severity of mucosal acidosis during

mesenteric hypoperfusion. Hence, the net effect of these two factors on intramucosal pH during the terminal phase of cardiopulmonary bypass is uncertain.

The fact that TNF- $\alpha$  was undetectable in any of our patients is perplexing. Laidler and colleagues (13) detected TNF- $\alpha$  in three of five cardiac surgery patients approximately 1 to 2 hrs after aortic cross-clamp release (i.e., time 6 in our study). This latency period presumably represents the time required by macrophages to synthesize and release TNF- $\alpha$  in detectable quantities into the plasma after stimulation by endotoxin. However, neither the duration of cardiopulmonary bypass nor the range of endotoxin concentrations was reported by Laidler et al (13). This omission is relevant because reductions in liver blood flow and/or core temperature, factors that are closely linked to the duration of cardiopulmonary bypass, can impair phagocytic function (54). Accordingly, the possibility that the duration of cardiopulmonary bypass was shorter—hence, the magnitude of the stimulus (i.e., endotoxin) for TNF- $\alpha$  production was more limited in the present study than in the study by Laidler et al. (13)—cannot be excluded.

Finally, our data suggest that endotoxin antibody has a negligible effect in reducing endotoxemia. The increase in endotoxin concentrations during ventricular ejection is additional evidence, suggesting that not only endotoxin antibody but other mechanisms (e.g., reticuloendothelial cell system phagocytosis [55]) are unable to effectively clear endotoxin from the circulation under these conditions.

*Oxygen Transport Variables.* In our initial study (6) of cardiac surgical patients, we found that a decrease in gastric intramucosal pH to 7.26 was associated with significant increases in splanchnic lactate concentration, and significant reductions in systemic  $\dot{D}O_2$ , hepatic venous oxygen saturation, and mixed venous oxygen saturation in the postcardiopulmonary bypass period. Results from the present study, in which the duration of cardiopulmonary bypass was substantially (27%) shorter, are consonant with these findings in demonstrating that milder degrees of mucosal acidosis (gastric intramucosal pH 7.30) are accompanied by correspondingly narrower changes in  $\dot{D}O_2$ , hepatic venous oxygen saturation, and mixed venous oxygen saturation. Not fully explained by our data is the etiology of increased hepatic venous lactate concentrations at vena caval cannulation (time 2), early cardiopulmonary bypass (time 3), and at 15 mins after termination of cardiopulmonary bypass (time 5). It has been suggested (56) that increased splanchnic lactate concentrations, accompanied by gastric mucosal acidosis, hepatic venous oxygen desaturation, and increased hepatic venous pyruvate/lactate ratios, are the result of

inadequate  $\dot{D}_O_2$  to the gut. In contrast, splanchnic hyperlactacidemia, arising within the first hour of cardiopulmonary bypass (when values for these oxygen transport variables are normal), is attributed to a hypothermia-induced defect in pyruvate metabolism. The etiology of increased lactate concentrations before cardiopulmonary bypass remains uncertain.

Our data lend additional support to the hypothesis that gut-barrier function is impaired in patients undergoing cardiopulmonary bypass. It is unclear whether increased mucosal permeability to endotoxin and mucosal acidosis are causally related phenomena, or simply independent markers of injury to gut epithelium induced by endotoxin, splanchnic hypoperfusion, and/or other factors. Further studies will be necessary to clarify events surrounding increased intestinal mucosal permeability in patients undergoing open-heart surgery.

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