The Effect of Cardiopulmonary Bypass on Intestinal and Pulmonary Endothelial Permeability*

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Study objective: To quantify simultaneously the pulmonary and gastrointestinal (GI) damage that occurs during uncomplicated surgery requiring cardiopulmonary bypass (CPB), and to examine the relationships between markers of such damage.

Design: Prospective, open.

Setting: Adult ICU of a national referral hospital.

Patients: Twenty patients undergoing elective CPB surgery.

Measurements and results: Pulmonary vascular injury was assessed using the protein accumulation index (PAI), a double isotope technique specific for high permeability pulmonary edema. The relationships of the PAI with percent neutrophils in bronchoalveolar lavage (BAL), serum, and BAL myeloperoxidase (MPO), and bypass time were examined. Splanchnic vascular injury was assessed using tonometry to measure intramucosal pH (pHi) and the ratio of absorbed lactulose to L-rhamnose (L/R ratio) to determine gut mucosal permeability. Positive correlations were observed between bypass time and PAI (r=0.64, p<0.01), percent neutrophils in the postoperative BAL and PAI (r=0.51, p<0.05), and postoperative serum MPO and PAI (r=0.77, p<0.001). The L/R ratio rose significantly following CPB from 0.04 ± 0.01 in controls to 0.48 ± 0.05 (p<0.0001). The L/R ratio in patients who developed a low pHi was 0.59 ± 0.06 compared with 0.32 ± 0.07 in those whose pHi remained normal (p<0.05). No significant correlation between bypass time and pHi (r=−0.3, p=0.33), bypass time and L/R ratio (r=0.27, p=0.26), PAI and L/R ratio (r=0.2, p=0.42), PAI and pHi (r=−0.34, p=0.16), postoperative serum MPO and L/R ratio (r=0.03, p=0.90), or postoperative serum MPO and pHi (r=−0.10, p=0.67) could be demonstrated.

Conclusions: Pulmonary and GI injury are detectable following uncomplicated CPB. The absence of any relationship between the respective markers of dysfunction suggests that differing pathologic processes are responsible.

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ARDS=adult respiratory distress syndrome; BAL=bronchoalveolar lavage; CPB=cardiopulmonary bypass; DO2=O2 delivery; FIO2=fraction of inspired oxygen; GI=gastrointestinal; ICU=intensive care unit; 113mIn=113mIn-dium; L/R ratio=lactulose:L-rhamnose ratio; Mab=monoclonal antibody; MPO=myeloperoxidase; 3-O-M-D-glucos=3-0-methyl-D-glucose; PAI=protein accumulation index; pHi=gastric intramucosal pH; 99Tc=99technetium

Key words: cardiopulmonary bypass; pulmonary vascular permeability; splanchnic vascular injury; tonometry

Respiratory and gastrointestinal (GI) complications associated with surgery involving cardiopulmonary bypass (CPB) are uncommon, but remain major causes of morbidity and mortality in the postoperative period, partly due to the large number of patients now undergoing such procedures.1-4 Subtle abnormalities of pulmonary and GI function occur more frequently and have also been identified and characterized. Thus, increased pulmonary endothelial permeability and a fall in the diffusing capacity of the lung for carbon monoxide are known to occur even in patients undergoing uncomplicated surgery.5,6 More recently, gastric tonometry has been used to study prospectively changes in gastric intramucosal pH (pHi) that occur following CPB,6 particularly in relation to splanchnic oxygen delivery (DO2)7 and endotoxin levels in the splanchnic circulation.8 In parallel with observations made in critically ill patients,9 a perioperative fall in pHi is predictive of increased morbidity and mortality8 in patients undergoing CPB. Low pHi is thought to reflect GI ischemia,10 which leads to a loss of mucosal integrity, the translocation of endotoxin and bacteria from the gut lumen into the systemic circulation, and possibly a rise in the incidence of nosocomial infection.10 Despite such observations,

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whether increased mucosal permeability and intramucosal acidosis are causally linked or are independent markers of damage to gut epithelium remains unknown.

The pathophysiologic state of lung injury following CPB has been attributed to a CPB-associated systemic inflammatory response. Possible etiologic factors include activation of the complement and coagulation cascades, kallikrein and fibrinolysis together with subsequent neutrophil activation induced by the contact of blood with nonphysiologic surfaces. In contrast, the pathogenesis of CPB-associated gut injury following CPB is thought to be ischemic in origin, leading to endotoxemia, the effect of which may be to augment the systemic inflammatory response. The ischemia is probably consequent in part on nonpulsatile perfusion during CPB, a potent stimulus for the release of endogenous splanchnic vasoconstrictors such as angiotensin II, and which also activates platelets and leukocytes to form cellular aggregates capable of occluding vessels within the microcirculation. Intestinal villi are especially sensitive to a fall in DO2 because the associated shunting of oxygen from arteries to veins in a counter-current system within the villi renders the superficial layers of the mucosa relatively hypoxic. Consequently, the alterations that have been seen in the GI tract and lungs following CPB may be causally linked.

The aims of this study were threefold: (1) to quantify simultaneously the pulmonary and GI damage that occurs following uncomplicated surgery requiring CPB; (2) to examine the interrelationships between indices of damage to the lungs and GI tract and markers of inflammation and ischemia; and (3) to establish more precisely the relationship between gut permeability and pH i.

METHODS

Patients

Patients undergoing elective surgery necessitating CPB performed by a single surgeon were recruited into the study. Prior to surgery, all patients gave their informed consent to participate in the investigation, the protocol for which was approved by the Ethical Committee of the Royal Brompton National Heart and Lung Hospital.

Perioperative Management

Patients were premedicated with 10 to 20 mg of oral temazepam (Wyeth Laboratories, Maidenhead, Berks, UK) 2 h prior to surgery. A radial artery cannula was inserted and general anesthesia was induced with fentanyl (Janssen Pharmaceutical Ltd; Wantage, Oxon, UK) (20 µg/kg), etomidate (Janssen Pharmaceutical Ltd) (0.2 mg/kg), and pancuronium (Organon Laboratories Ltd, Cambridge, Cambs, UK) (0.15 mg/kg). The trachea was intubated and positive pressure ventilation was initiated. A urinary catheter was inserted at this time. The fraction of inspired oxygen (FIO2) concentration was maintained at 0.4. Anesthesia was continued with 0.5 to 1% isoflurane (Abbott Laboratories Ltd; Maidenhead, Berks, UK), with incremental doses of fentanyl and midazolam (Roche Products Ltd; Welwyn Garden City, Herts, UK) as appropriate. Cardiopulmonary bypass was undertaken using a membrane oxygenator (Bard HF5700, Bard, Crawley, UK) primed with crystalloid (2 L Hartmann’s solution). The bypass circuit was comprised of polyvinyl chloride tubing, a roller pump (Stockert Roller Pump 10.10.00; Stockert Instrumente GmbH; Munich, Germany), and cardiomyopathy suction that was filtered. After administration of heparin (300 IU/kg), bypass commenced with an initial mean flow of 2.4 L/min/m² at 37°C. Patients were cooled to 25 to 29°C during bypass, and flow rates were reduced to between 1.5 and 2.1 L/min/m². The myocardium was protected by cold blood cardioplegia in 15 patients, cross clamp and fibrillation in 1 patient, and crystalloid cardioplegia (St. Thomas’s solution) in the other together with topical cooling. During bypass, the lungs were not mechanically ventilated, but remained collapsed at functional residual capacity. Systemic arterial pressure was maintained at a mean of 50 to 60 mm Hg. After rewarming, mechanical ventilation was recommenced with an FiO2 of 1.0, and normal circulation was reestablished. The effects of heparin were reversed with protamine (CP Pharmaceuticals Ltd; Wrexham, Chwyd, UK) (4.5 mg/kg). The patients, who continued to be mechanically ventilated with an FiO2 of 0.4, were transferred to the ICU where the postoperative measurements were taken.

Measurements

Assessment of Bronchoalveolar Lavage (BAL) Fluid: A flexible fiberoptic bronchoscope (Olympus UK; Keymed Ltd; Southend, UK) was passed via the endotracheal tube into a segment of the right lower lobe and wedged. Bronchoalveolar lavage was then performed using three 60-mL aliquots of 0.9% sodium chloride buffered with 8.4% sodium bicarbonate (0.275 mL; 8.4% NaHCO3 in 500 mL 0.9% NaCl) to a pH of 7.0. Each aliquot was injected and allowed to settle for 5 s before being aspirated into a siliconized glass vessel. The pooled fluid was centrifuged at 300 g for 10 min at 4°C. The cell pellet was resuspended in Hank’s balanced salt solution and cellular analysis was carried out in accordance with the guidelines of the BAL task group. Briefly, following resuspension, the total counts of nucleated cells were made by staining with 1% crystal violet in 1% acetic acid, counting the cells (Improved Neubor Counting Chamber), and the results were expressed as number of cells per milliliter of BAL fluid recovered. Neutrophil counts were obtained by using cytocentrifuge slide preparations of the cells (Shandon Cytospin; Shandon Southern Instruments; Southhampton, UK) using 100 µL aliquots of cell suspension, air dried, and stained with May-Grumwald-Giemsa stain. Differential cell counts were made by counting at least 300 cells in random fields. The neutrophil content is expressed as a percent of the total cells recovered.

The urea concentration in each BAL sample was determined using standard laboratory techniques.

Assessment of Neutrophil Activation: Myeloperoxidase (MPO) is a hemoprotein synthesized within the neutrophil and released extracellularly on activation. The MPO-EIA method (Biotech; Bonneuil-Marne, France) was used to assay levels of MPO in the BAL fluid and plasma. Briefly, this is an enzyme-linked immunoassay of the ELISA (enzyme-linked immunosorbent assay) type. Samples are incubated in the walls of a sectionable microplate that have been coated first with a monoclonal antibody (MAb) to MPO. The MPO-Mab complex is labeled with a biotin-linked polyclonal antibody. The final step of the assay is based on a biotin-avidin coupling in which avidin has been covalently linked to alkaline phosphatase. The amount of MPO in each sample is measured enzymatically on addition of 4-nitrophenyl-phosphate by colorimetric reading of the microplate at the 405-nm absorbance wavelength and expressed as nanograms per milliliter.

Measurement of Gastric Intramucosal pH (pHi): Following induction of anesthesia, a gastric tonometer (TRIP TGS catheter,
Tonometrics Inc, Bethesda, Md) was passed nasogastrically. Correct positioning was ascertained by auscultating over the stomach as 50 mL of air was injected through the tonometer and confirmed radiologically postoperatively. Intramuscular pH was measured as instructed by the manufacturer. Briefly, the silicone balloon of the tonometer was filled with 2.5 mL 0.9% saline solution after elimination of air. After equilibration (see below) of Pco2 between the saline solution and the stomach lumen, an anerobic sample of the last 1.5 mL saline solution from the tonometer was drawn at the same time as an arterial blood sample. The tonometer CO2 and the arterial bicarbonate were measured immediately (Ciba Corning 278 Blood Gas System, Corning Medical, Medfield, Mass), and pH was calculated by a modification of the Henderson-Hasselbach equation:

\[
\text{pHi} = 6.1 + \log_{10} \left( \frac{F \times \text{tonometer saline solution } \text{Pco}_2}{\text{arterial bicarbonate concentration}} \right)
\]

where F is a factor dependent on the equilibration time and is supplied by the tonometer manufacturer. We considered pHi values below 7.32 as clinically significant, which represents the mean minus 2 SDs of that seen in normal subjects.

**Assessment of Pulmonary Endothelial Permeability:** Endothelial permeability was quantified using the protein accumulation index (PAI); a double isotopic technique that measures the rate at which a radiolabeled plasma protein (transferrin) accumulates within the lung interstitium. The PAI has been shown to be specific for high-permeability pulmonary edema. 16-18 Briefly, 40 MBq of 113mIndium (113mIn) was administered intravenously to label transferrin in vivo. Two scintillation counters (Oakfield Instruments; Oxford, UK) were firmly attached to the patient’s chest wall in the midclavicular line 3 cm below the clavicle. A third detector was placed over the heart representing the intravascular pool. Following intravenous administration of stannous chloride (0.03 mL/kg), red blood cells were labeled in vivo with 20 MBq of 99Technetium (99Tc). Counts arising from both isotopes from the three probes were monitored after a 15-min period to allow for mixing and distribution. The relative extravascular accumulation of 113mIn-transferrin in both upper lung zones was derived by computer acquisition of the following ratio:

\[
\frac{113m\text{In lung counts}}{99\text{Tc lung counts}} \times \frac{113m\text{In heart counts}}{99\text{Tc heart counts}}
\]

A ratio for each lung is calculated for each 3-min epoch during a 54-min data acquisition. The PAI is derived from the slope of the regression line of the ratios plotted against time.

**Measurement of Gut Absorption and Permeability:** Four saccharides, 3-O-methyl-D-glucose (3-O-M-D-glucose), D-xylose, L-rhamnose, and lactulose, were employed to assess active carrier-mediated, passive carrier-mediated, transcellular, and paracellular transport in the small intestine, respectively, as described in full elsewhere. 19 Briefly, 100 mL of water containing 0.2 g 3-O-M-D-glucose, 0.5 g D-xylose, 1.0 g L-rhamnose, and 5.0 g lactulose was instilled into the stomach via the integral nasogastric tube in the tonometer. For the following 5 h, all urine was collected, at the end of which time the total volume of urine was noted. A 40-mL aliquot was frozen immediately and stored at -20°C until analyzed. Patients remained nil-by-mouth for 8 to 12 h prior to surgery and for the duration of the study. Urinary saccharide analysis was performed using gas chromatography/mass spectroscopy (Shimadzu GCMS-QP2000, Dyson Instruments, Tyne and Wear, UK) and results expressed as a percent of enterally administered saccharide. Using these results, the lactulose: L-rhamnose (L/R) ratio was calculated to provide a specific index of gut permeability.

<table>
<thead>
<tr>
<th>Patient No./Age, yr/Sex</th>
<th>Operation</th>
<th>Bypass Time, min</th>
<th>Cross-Clamp Time, min</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/69/M</td>
<td>CAVG</td>
<td>108</td>
<td>65</td>
</tr>
<tr>
<td>2/49/M</td>
<td>CAVG</td>
<td>80</td>
<td>34</td>
</tr>
<tr>
<td>3/66/M</td>
<td>AVR+CAVG</td>
<td>92</td>
<td>74</td>
</tr>
<tr>
<td>4/41/M</td>
<td>CAVG</td>
<td>112</td>
<td>70</td>
</tr>
<tr>
<td>5/63/M</td>
<td>CAVG (redo)</td>
<td>183</td>
<td>89</td>
</tr>
<tr>
<td>6/60/M</td>
<td>CAVG</td>
<td>134</td>
<td>48</td>
</tr>
<tr>
<td>7/70/M</td>
<td>CAVG</td>
<td>150</td>
<td>104</td>
</tr>
<tr>
<td>8/70/M</td>
<td>AVR</td>
<td>184</td>
<td>143</td>
</tr>
<tr>
<td>9/64/M</td>
<td>CAVG</td>
<td>131</td>
<td>83</td>
</tr>
<tr>
<td>10/80/F</td>
<td>AVR+CAVG</td>
<td>128</td>
<td>93</td>
</tr>
<tr>
<td>11/57/F</td>
<td>CAVG</td>
<td>126</td>
<td>86</td>
</tr>
<tr>
<td>12/46/M</td>
<td>AVR</td>
<td>146</td>
<td>118</td>
</tr>
<tr>
<td>13/66/M</td>
<td>CAVG</td>
<td>97</td>
<td>62</td>
</tr>
<tr>
<td>14/61/M</td>
<td>CAVG</td>
<td>131</td>
<td>74</td>
</tr>
<tr>
<td>15/53/M</td>
<td>CAVG</td>
<td>115</td>
<td>65</td>
</tr>
<tr>
<td>16/60/M</td>
<td>CAVG</td>
<td>47</td>
<td>28</td>
</tr>
<tr>
<td>17/74/M</td>
<td>AVR</td>
<td>180</td>
<td>115</td>
</tr>
<tr>
<td>18/67/M</td>
<td>CAVG</td>
<td>120</td>
<td>82</td>
</tr>
<tr>
<td>19/63/M</td>
<td>CAVG</td>
<td>101</td>
<td>65</td>
</tr>
<tr>
<td>20/72/M</td>
<td>AVR+CAVG</td>
<td>173</td>
<td>128</td>
</tr>
</tbody>
</table>

Mean±SEM, 62.6±2.2—126.9±8.0, 81.3±6.7

*CAVG=coronary artery vein graft; AVR=aortic valve replacement.

**Protocol**

Bronchialalveolar lavage was performed following the induction of anesthesia, but prior to the start of surgery (lateral segment, right lower lobe). A second lavage was carried out immediately after the patient arrived in the ICU postoperatively (anterior segment, right lower lobe). The recovered BAL fluid was analyzed for cellular content, MPO, and urea concentration. Ten milliliters of blood was obtained from each patient simultaneously with each lavage, and serum concentrations of MPO and urea were determined. Gastric pH was measured after 90 min of CPB or just prior to the termination of bypass, whichever was the shorter, and 150 min after initiation of the saccharide solution. Pulmonary endothelial permeability, and gut absorption and permeability were each measured once, studies being commenced within 3 h of the patient’s return to the ICU. The MPO assay was also performed on blood samples from eight normal control subjects. Ten normal volunteers, fasted for 10 h, also underwent bowel permeability studies following an identical protocol.

**Calculations and Statistics**

Data are expressed in the text and tables as mean±SEM. Least squares regression analysis was used to assess correlation between the measured variables. Student’s t test was used to assess differences in BAL and blood samples. The Mann-Whitney U test was used to analyze unpaired data, and p values less than or equal to 0.05 were considered statistically significant.

**Results**

A total of 20 patients undergoing elective CPB surgery (18 male; age range, 41 to 50 years) were studied. Their demographic and clinical data are displayed in Table 1. Sixteen were ex-smokers and 4 were lifelong nonsmokers. The mean bypass and cross-clamp times were 126.9±8.0 (range, 47 to 184) min and 81.3±6.7 (range, 28 to 143) min, respectively. All patients made...
an uneventful clinical recovery following surgery with the exception of patient 5 who developed adult respiratory distress syndrome (ARDS) and required ventilatory support for 6 days postoperatively. The preoperative BAL samples in patients 8 and 15 could not be analyzed due to contamination with blood. Technical failure prevented the measurement of PAI postoperatively in patients 16 and 20.

The mean MPO concentration in plasma obtained from controls was 66.11±10.52 ng/mL and from the patients preoperatively 43.34±11.27 (p=0.13). Postoperatively, the serum MPO concentration rose to 136±15.3 ng/mL (p<0.001 cf preoperative value). The BAL MPO concentration rose from 6.59±2.61 ng/mL preoperatively to 20.32±6.04 ng/mL postoperatively (p<0.05). The BAL/serum MPO ratio rose from 0.017±0.003 preoperatively to 0.061±0.007 postoperatively (p<0.05). The BAL/serum MPO ratio rose from 0.059±0.02 preoperatively to 0.196±0.07 postoperatively (p<0.05). The BAL neutrophil content rose significantly from 20.34±5.7% preoperatively to 48.1±5.3% postoperatively (Fig 1, p<0.001). The mean PAI was 1.57±0.29×10⁻³, (range, 0 to 4.4×10⁻³) compared with <1.0×10⁻³ for normal controls measured previously by our own group and others. Positive correlations were observed between bypass time and PAI (Fig 2, r=0.64, p<0.01), postoperative BAL neutrophil content and PAI (r=0.51, p<0.05), and postoperative serum MPO concentration and PAI (r=0.77, p<0.001).

The quantity of saccharide recovered and the L/R ratio for the controls and patients are shown in Table 2. A profound fall in 3-O-M-glucose and D-xylose absorption was observed in the patients postoperatively compared with the controls. The fall in the absorption of L-rhamnose was of a greater magnitude than that of lactulose, such that the L/R ratio rose significantly compared with the control group. In 12 patients (60%), a low pH (<7.32) was recorded during and/or after surgery, while in the remainder, pH remained normal throughout. The L/R ratio in patients who developed an intramucosal acidosis was 0.59±0.06, compared with 0.32±0.07 in those whose pH remained normal throughout (p<0.05, Fig 3). No difference in L/R ratio was seen between patients with or without evidence of a metabolic acidosis (arterial pH<7.35, p=0.15; base deficit >2, p=0.55). No significant correlation between bypass time and pH (r=−0.3, p=0.33), bypass time and PAI.

Table 2—Saccharide Recovery in Control and Patient Groups, Expressed as a Percentage of the Enterally Administered Dose

<table>
<thead>
<tr>
<th>Saccharide</th>
<th>Controls, %</th>
<th>Patients, %</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-xylose</td>
<td>35.03±1.40</td>
<td>1.24±0.42</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>3-O-M-D-glucose</td>
<td>49.20±1.98</td>
<td>2.30±0.43</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>L-rhamnose</td>
<td>10.02±1.22</td>
<td>0.72±0.14</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lactulose</td>
<td>0.37±0.05</td>
<td>0.27±0.06</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>L/R ratio</td>
<td>0.04±0.01</td>
<td>0.48±0.05</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Figure 1. Preoperative and postoperative percent neutrophils in BAL (p<0.001). Open triangle indicates patients; solid squares, mean value.

Figure 2. Relationship between protein accumulation index (PAI) and bypass time (r=0.64, p<0.01).

Figure 3. Lactulose/rhamnose (L/R) ratio in patients with a gastric intramucosal pH (pHi) less than and greater than 7.32 (p<0.05). Open circle indicates patients; solid triangle, mean value.
L/R ratio (r=0.27, p=0.26), PAI and L/R ratio (r=0.2, p=0.42), PAI and pH (r=−0.34, p=0.16), postoperative serum MPO and L/R ratio (r=0.03, p=0.90), or postoperative serum MPO and pH (r=−0.10, p=0.67) could be demonstrated.

**Discussion**

This study demonstrates that pulmonary and gastrointestinal injuries are detectable following uncomplicated surgery involving CPB, but the absence of any relationship between the respective markers of dysfunction suggests that differing pathologic processes may be responsible. These results are in accordance with the hypotheses that CPB-associated pulmonary injury is the result of an inflammatory process generated, at least in part, by the contact of blood with nonphysiologic surfaces, whereas the GI injury is ischemic in origin, the precise mechanism of which remains uncertain.

A greater increase in PAI than that seen in this study has been documented previously in patients with ARDS, suggesting that increased endothelial permeability characterizes the lung injury associated with this condition. Furthermore, we measured a rise in the BAL/serum urea ratio due to an increase in the diffusion of urea from the circulation into the alveoli, again reflecting the increased pulmonary endothelial permeability. Despite the fact that similar derangements are found in patients with ARDS, only one patient (case 5) developed clinical ARDS postoperatively. The uncomplicated recovery of the other 19 patients implies that CPB-associated pulmonary endothelial damage is transient and self-limited. We have demonstrated previously that the incidence of clinically apparent ARDS following CPB is 1.3%, which is lower than that observed in association with other predisposing conditions such as sepsis. These two observations may reflect the short duration of the initiating insult in these circumstances. Why only some patients develop severe lung injury in these and other situations is unclear, but it is in agreement with other studies that have demonstrated that PAI does not predict the development or outcome of ARDS and that there is a continuum of lung injury. Thus, PAI is a valuable research tool in the assessment of patients with lung injury, but is subject to limitations that are discussed in full elsewhere. In this context, it is interesting that the results recorded for patient 5 were of no value in predicting the onset of ARDS; higher values for PAI, serum MPO, and percent neutrophils in BAL were recorded in other patients who made an uncomplicated recovery.

The increase in pulmonary endothelial permeability following CPB measured in the current study was related to the duration of bypass, and correlated with the postoperative serum MPO and an increase in neutrophil numbers in the lung. These associations, while not absolute, implicate the neutrophil as being central to the development of lung injury following CPB, a hypothesis that has been proposed in ARDS. We have previously demonstrated a significant relationship between PAI and BAL percent neutrophils in patients with full-blown ARDS which reinforces this theory. The rise in the BAL/serum MPO ratio observed was of a similar magnitude to the measured change in the BAL/serum urea ratio. These findings suggest that the increase in pulmonary endothelial permeability was related to the systemic activation of neutrophils. If it were due to a local process occurring within the pulmonary interstitium, a greater rise in the BAL/serum MPO ratio than that seen for urea would be expected due to the local production of MPO. The neutrophil may therefore be central to the process of lung injury following CPB, although the precise underlying mechanisms are unknown despite the many studies documenting high circulating plasma levels of various inflammatory mediators and cellular activation.

Profound impairment of both active (3-O-M-D-glucose) and passive (D-xylene) carrier-mediated absorption of saccharides in the small bowel occurred in the current study and a coincident increase in gut permeability was demonstrated by the rise in the L/R permeability ratio. The reduction in absorption of 3-O-M-D-glucose and D-xylene may be explained by a variety of factors other than GI mucosal injury, including gastric emptying and dilution, small intestinal peristalsis, blood flow, the volume of distribution of saccharides, and alterations in renal clearance. However, the rise in the L/R permeability index we observed postoperatively cannot be explained by such phenomena, because these factors should influence the clearance of both saccharides equally. Permeability refers to the facility with which the intestinal mucosal surface can be penetrated by the unmediated diffusion of specific constituents. Although absorption can be increased or decreased based on the available mucosal surface area, permeability remains unchanged in the healthy bowel. Estimates of permeability can be obtained through measurements of permeation of two markers that are affected equally by the range of relevant factors outlined above, but that pass across the mucosal barrier by differing mechanisms. Lactulose and L-rhamnose meet these criteria. Thus, lactulose is a nonhydrolyzable disaccharide that permeates through intercellular tight junctions, while L-rhamnose, a smaller molecule, is absorbed primarily via the transcellular route. The maintenance of the integrity of tight intercellular junctions between the enterocytes is a dynamic process, actively controlled by ATP-dependent intracellular mechanisms and cytoskeleton. During episodes of hypoperfusion, the integrity of these junctions and therefore of the mucosal barrier

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may become impaired. Our results demonstrate a significant rise in lactulose absorption relative to L-rhamnose following CPB. It is recognized that the gut is a reservoir of microorganisms and endotoxins that can induce septicemia. The consequences of impaired intestinal barrier function are the initiation or perpetuation of inflammatory processes. As all our patients with one exception made an uncomplicated recovery postoperatively, it seems that the splanchnic injury, like the increase in pulmonary endothelial permeability, was probably transient and self-limiting. Further studies are being undertaken to determine the natural history of these changes.

Experimental studies have shown that a reduction in intramuscular pH measured tonometrically reflects gut ischemia. In the current study, the increase in gut permeability seen in association with a low pH supports an ischemic cause for this phenomenon following CPB. The incidence of a low pH seen in this study is similar to that reported elsewhere: other studies have reported abnormally low values for pH in 50 to 60% of patients studied after CPB. Although a sensitive but nonspecific marker of postoperative complications, the nature and effect of any corrective therapy aimed at correcting a low pH remain to be established. Although we have demonstrated increased gut permeability in association with a low pH, there is a degree of overlap between patients with a normal pH and those with an abnormal pH. This may be explained by the fact that gastric tonometry reflects blood flow specifically to the stomach via the celiac artery. Increased GI permeability is a reflection of small-bowel absorption, the blood supply of which is from the superior mesenteric artery. The presence of significant atheromatous disease, from which this population was known to suffer, might contribute to the disruption of blood flow in one or other of these arteries thereby creating local ischemia exacerbated by low systemic perfusion pressures during and after CPB. The result of such a process could be to create areas of localized ischemia that could effect either the pH or L/R ratio in isolation. Studies to further examine this relationship are currently being undertaken.

In conclusion, we have demonstrated that transient pulmonary and splanchnic vascular damage are ubiquitous following CPB, but that there is no correlation between the markers of injury. These findings suggest differing pathophysiologic conditions, involving neutrophil activation in the lung and ischemia of unknown etiology in the GI tract. Patients with low pH demonstrated increased GI permeability, suggesting that mucosal injury occurs peripheratively. The significance of these findings in terms of CPB-associated morbidity and mortality are unclear and warrant further consideration.

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