Transvascular Transport of \( ^{67}\text{Ga} \) in the Lungs After Cardiopulmonary Bypass Surgery*

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Study objective: To examine the effect of cardiac surgery with cardiopulmonary bypass (CPB) on pulmonary vascular permeability.

Design: A prospective, serial study.

Setting: Department of nuclear medicine and intensive care units of a university hospital.

Patients: Twelve consecutive patients were studied, before and immediately after elective cardiac surgery using CPB (group 1), and 4 consecutive, artificially ventilated patients with acute cardiogenic pulmonary edema (group 2).

Measurements and results: The kinetics in blood and over both lungs were measured, using two mobile probes at the bedside, of intravenously injected \( ^{67}\text{Ga} \), assumed to bind to circulating transferrin, and in vitro \( ^{99m}\text{Tc} \)-labeled red blood cells to account for pulmonary blood volume. From data recorded in time (1 h), a pulmonary leak index (PLI), the time constant of transport of \( ^{67}\text{Ga} \) from the extravascular to the extravascular space of the lung, was calculated and values for both lungs were averaged. In group 1, the PLI (\( 10^{-3}\text{min}^{-1} \), mean ± SD) was 8.2 ± 3.7 before and 17.0 ± 13.5 after CPB surgery (p<0.01) and changes directly related to the duration of CPB. In four patients with a CPB duration ≥120 min, the PLI, 31.1±16.3 \( \cdot 10^{-3}\text{min}^{-1} \), exceeded 2 SD plus mean preoperative PLI. Changes in PLI tended to relate inversely to changes in arterial WBC, which, in turn, inversely related to CPB duration. The \( \text{PaO}_2/\text{FiO}_2 \) ratio decreased and tended to relate inversely to PLI after surgery. No patient developed alveolar pulmonary edema on chest radiograph. In group 2, the PLI was 11.1±3.1 \( \cdot 10^{-3}\text{min}^{-1} \) (NS from group 1 preoperative PLI).

Conclusions: Cardiopulmonary bypass induces a pulmonary vascular leak, as assessed by \( ^{67}\text{Ga} \) kinetics using a bedside detection technique, in some cardiac surgery patients with prolonged CPB. This leak may reflect pulmonary vascular injury and increased permeability, following activation of leukocytes by CPB and subsequent pulmonary sequestration, rather than increased filtration through pressure factors. It may contribute to impaired gas exchange, even in the absence of manifest alveolar edema of the lungs, after surgery.

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Surgery using cardiopulmonary bypass (CPB) results in ischemia/reperfusion of the pulmonary arteries, liberates proinflammatory mediators, and activates neutrophils.1-14 These factors may injure pulmonary vessels and induce permeability edema of the lungs and adult respiratory distress syndrome (ARDS).3,7,8,12,15-20 Indeed, many patients undergoing cardiac surgery with CPB have impaired pulmonary gas exchange and need artificial ventilation for some time after the operation.1,3,8,12,21-23 It is unclear, however, whether a pulmonary vascular leak contributes to these changes, since extravascular lung water may increase in only a minority of patients undergoing cardiac surgery and only 1.7 percent of them may develop ARDS, as defined by classic clinical criteria, with a fatality rate of 50 percent.15,21,22,24 Some investigators found increased clearance of inhaled \( ^{99m}\text{Tc} \)-diethylene-triamine-pentacetate in blood following CPB surgery,23,25 but others did not.13 However, this measure may not be specific for a vascular injury.12,23,25 In dogs, 90 to 120 min of CPB may result in increased vascular permeability and edema of the lungs.12,25 and intestines.36 On light and electron microscopy, biopsy specimens of the lung after CPB show swollen endothelial cells, interstitial edema, accumulation of neutrophils, and damaged septal cells and pneumocytes, particularly if CPB lasts for more than 150 min.7,21,25,27

Methods developed to detect increased permeability noninvasively and to discriminate between permeability and cardiogenic edema of the lungs utilize intravenously (IV) injected radionuclide-labeled proteins and radioactivity measurements over the lung and in blood over time, thereby yielding an index of pulmonary transvascular protein transport.7,20,25,29-33 However, many of these methods may have methodologic drawbacks and limited clinical applicability at the bedside, hampering serial measurements. For instance, measuring the kinetics of the IV injected positron emitter \( ^{68}\text{Ga} \), considered to bind to circulating transferrin, by nonmobile cameras, may be useful to diagnose permeability edema of the lungs and ARDS, but an intravascular tracer, to correct for pulmonary blood volume, was not used.20,32 We therefore use a

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dual-radionuclide method and a sensitive, mobile probe system to allow for repeated measurements, at the bedside, of the kinetics of a commonly available, permeable tracer, 67Ga, binding to transferrin, and an intravascular tracer, 99mTc-labeled red blood cells. Although transvascular protein transport in the lung has been suggested to be specific for permeability, independently of microvascular pressure factors, it is unclear whether this applies for gallium, since binding to circulating transferrin may be less avid than for indium.34

The questions for the present study, therefore, were as follows: Does CPB surgery result in a pulmonary vascular leak, using the dual-radionuclide technique mentioned? Is this leak specific for increased pulmonary vascular permeability, independently of pressure factors? How often does CPB lead to a pulmonary vascular leak and does the latter relate to the duration of CPB? Does this leak contribute to the postoperative impairment of pulmonary gas exchange?

METHODS

Patients

We studied two groups of patients. Group 1 consisted of 12 consecutive patients, scheduled for cardiac surgery with CPB. Group 2 consisted of four patients needing artificial ventilation in the intensive care unit because of acute cardiogenic pulmonary edema. The study was approved by the Ethical Committee of the Free University Hospital. Informed consent was obtained in each patient.

Therapeutic Protocol

Group 1: On the day of surgery, anesthesia was induced with intravenous fentanyl, 0.3 μg·kg⁻¹·min⁻¹, pancuronium bromide, 0.1 mg·kg⁻¹·min⁻¹ and diazepam, 0.1 mg·kg⁻¹·min⁻¹, and it was maintained with supplemental doses of these drugs. After intubation, patients were ventilated with an O₂/vitiated air mixture. A balloon-tipped pulmonary artery catheter (Pentacath SP55078FS, Spectramed, Bilhoven, the Netherlands) was inserted. All patients received 100 mg of dexa-methasone IV prior to CPB. In patients undergoing coronary artery bypass grafting or aortic valve replacement, the ascending aorta and left atrium were cannulated and the left ventricle was vented via the ascending aorta or the pulmonary vein (patients 9 and 11). In patients undergoing mitral valve replacement, the ascending aorta and both caval veins were cannulated and the left ventricle was vented via the pulmonary artery or vein (patient 3). The extracorporeal circuit consisted of a roller pump, a silicone membrane oxygenator (Utrax-1, Scimed Life Systems Inc, Minneapolis, Minn), an arterial filter, a soft-shell venous reservoir, and a cardiomyotomy reservoir with a polyvinyl tubing system. The extracorporeal circuit was primed with 2,000 ml of Ringers' lactate solution, 200 ml of human albumin 20 percent (Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, Amsterdam, the Netherlands), 50 ml of sodium bicarbonate 8.4 percent, 100 ml of mannitol (10 percent), and heparin (5,000 IU). A nonpulsatile flow of 2.4 to 3.0 L·min⁻¹·m⁻² was used during cooling and rewarming phases. Patients were cooled to 28°C to 32°C nasopharyngeal temperature. Heparin (300 IU·kg⁻¹) was given IV before CPB was started, and subsequent doses were given whenever the activated clotting time was less than 400 s. During CPB and cooling, the aim was to maintain a hematocrit of ~23 percent. Patients received high-potassium, cold (4°C), crystalloid cardioplegia solution for myocardial protection after cross-clamping the aorta. During aorta cross-clamping, ventilation of the lungs was stopped and positive end-expiratory pressure (PEEP) was kept at 4 cm H₂O. After surgery, the patients were weaned of CPB and received dopamine, 2 μg·kg⁻¹·min⁻¹ and nitroglycerine, 2 μg·kg⁻¹·min⁻¹ or higher, if necessary on clinical grounds. Heparin was neutralized by protamine-sulfate after termination of CPB. After transport to the surgical intensive care unit, IV fluids were given, consisting of sodium chloride, 0.45 percent glucose 2.5 percent, 1,500 ml/24 h, with additional infusion of sodium chloride, 0.9 percent, modified gelatin, and human albumin 20 percent to maintain pulmonary capillary wedge pressure (PCWP) at 8 to 12 mm Hg and mean arterial blood pressure between 70 and 90 mm Hg. In the intensive care unit, packed red blood cells were infused if the hematocrit fell below 27 percent. The total fluid infusion rate in the intensive care unit was 640 ± 284 ml·h⁻¹.

Group 2: Patients were admitted into the medical intensive care unit and were treated with diuretics, vasoactive drugs, supplemental oxygen, and others, if needed. After failure of initial therapy for pulmonary edema, all patients were intubated and mechanically ventilated. They all received a continuous infusion of dopamine because of heart failure.

Study Protocol

Autologous red blood cells were labeled with 99mTc (300 μCi/11 MBq, physical half-live 6 h), using a modified in vitro method. Ten minutes after injection of the labeled red blood cells, transferrin was labeled in vitro following IV injection of 67Ga-citrate (100 μCi/4 MBq, physical half-live 78 h; Mallincrodt Diagnostica, Petten, the Netherlands). At 5, 8, 11, 15, 20, 25, 30, 40, 50, and 60 min after 67Ga injection, a total of 9 (5 studies) or 10 (19 studies) blood samples (2 ml) were drawn from an indwelling IV cannula. In some patients, we measured, in vitro, the binding of 67Ga to plasma proteins, using alcohol precipitation. From total 67Ga radioactivity, 98.3 ± 1.7 percent (n = 2) was in the protein precipitate in blood taken 5 min after IV injection of 67Ga for the preoperative study and 98.5 ± 0.3 percent (n = 2) for the postoperative study. For blood taken 60 min after IV 67Ga injection, it was 98.4 ± 1.4 percent (n = 4) for the preoperative study and 96.6 ± 2.1 percent (n = 3) for the postoperative study.

Patients were in the supine position and two scintillation detection probes, each consisting of a sodium-iodine crystal (1.5-1.5 in, Canberra Packard, Schaumberg, Ill) fitted with a 2.025-mm thick lead collimator (inner diameter 4.45 cm), extending 7.5 cm in front of the crystal, were positioned over the right and left lung apex. Each probe was connected with a separate board (Acurrtec/Nal Plus Board, 540051A, Canberra Packard, Ill) and was installed in a personal computer (M300, Olivetti, Milan, Italy). Starting at the time of IV injection of 67Ga, radioactivity was detected for 53 s/min, during 1 h. For each measurement interval, the entire spectrum of photon energies was stored on floppy disk. During processing, three peaks were used: the 140-keV peak of 99mTc and the 184- and 300-keV peaks of 67Ga, with windows of 20 percent centered around each peak. The 99mTc and 67Ga count rates were corrected for background activity, physical half-live, spillover of 99mTc into the 99mTc window, obtained by in vitro measurement of 99mTc, and expressed as counts per minute (cpm) per lung field. Each blood sample was weighed and radioactivity of 1 ml blood was measured by a sodium-iodine well-counter (Berthold, Betron Scientific, Rotterdam, the Netherlands). Four peaks were used: 140 keV (99mTc) and 93, 194, and 300 keV (67Ga), with windows of 20 percent centered around each peak. After correction for background, physical half-life, and spillover, results were expressed as cpm·g⁻¹·h⁻¹.

For each blood sample, a time-matched cpm over each lung was taken. A radioactivity ratio was calculated, (C67Ga/99mTc) (C67Ga/99mTc) and plotted against time. In accordance with the literature,35 the pulmonary leak index (PLI) was calculated, using linear
regression analysis, from the slope of increase of the radioactivity ratio divided by the intercept, representing physical factors in radioactivity detection (Fig 1). A linear correlation coefficient was calculated. By taking pulmonary blood volume and thus presumably surface area into account, the radioactivity ratio represents the ratio of extravascular to intravascular $^{67}$Ga radioactivity. The PLI then represents the transport rate of $^{67}$Ga from the intravascular to the extravascular space of the lungs. Values for both lungs were averaged and the percentual deviation from the mean was calculated.

**Group 1:** Patients scheduled for cardiac surgery were studied 1 to 2 days before surgery at the department of nuclear medicine. On the day of the study, a chest radiograph was ordered. Directly after the study, venous blood was obtained for WBC (Coulter JS, Coulter Electronics, Luton, United Kingdom). After start of mechanical ventilation and operation on the day of surgery, but immediately before onset of CPB, arterial blood was obtained for measurement of $\text{PO}_2$, corrected for body temperature (blood gas analyzer CIBA-Corning, 179/2298, Corning Medical and Scientific, Medfield, Mass) and the $\text{FiO}_2$ and PEEP level were read from the ventilator. Duration of CPB and the time that the aorta was cross-clamped were recorded. After arrival in the surgical intensive care unit, a chest radiograph was obtained and a second PLI was measured, $3.8 \pm 0.9$ h after discontinuing CPB. Arterial blood was taken for measurement of $\text{PO}_2$, total protein (biuret method), and albumin (biuret method) concentrations, and WBC. All patients were mechanically ventilated and the $\text{FiO}_2$ and PEEP level were recorded. The mean pulmonary arterial pressure and PCWP (mm Hg) were measured (Viggo-Spectramed, Spectramed, Bilthoven, the Netherlands; monitor Transcorm, Marquette Electronics, Milwaukee, Wis) at end-expiration with patients in the supine position, after calibration and zeroing to atmospheric pressure at the midchest level. A chest radiograph was also obtained at 7 AM on the first postoperative day.

**Group 2:** Patients with acute cardiogenic pulmonary edema were studied as soon as a clinical diagnosis was established after admission into the medical intensive care unit or onset of pulmonary edema. All patients were intubated and artificially ventilated. Between a repeated chest radiograph, obtained to confirm the presence of cardiogenic pulmonary edema for inclusion into the study, and the PLI measurement $3.8 \pm 1.1$ h had elapsed. The $\text{FiO}_2$ and PEEP level were read from the ventilator and the $\text{PO}_2$ was measured in arterial blood. A pulmonary artery catheter had been inserted in three patients, and mean pulmonary arterial pressure and PCWP had been measured at admission or onset of pulmonary edema. In these patients, arterial blood was obtained when the PLI was measured for determination of total protein and albumin concentrations.

In both groups, chest radiographs were scored by one of the investigators, unaware of the PLI, for the presence and extent of pulmonary edema according to the following: 0 = normal; 1 = mild interstitial edema; 2 = severe interstitial edema; 3 = alveolar edema in one to two quadrants; and 4 = alveolar edema in three to four quadrants.

**Calculations and Statistical Analysis**

The pulmonary microvascular hydrostatic pressure ($P_m$) was calculated from $P_m = (\text{mean pulmonary arterial pressure} - \text{systemic arterial pressure}) - \text{Paw}$.  

**Table 1—Characteristics of Patients Undergoing Cardiac Surgery (Group 1)**

<table>
<thead>
<tr>
<th>Patient/Sex/</th>
<th>Type of Surgery</th>
<th>CPB Time, min</th>
<th>Aortic Cross-Clamp Time, min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/F/60</td>
<td>AVR</td>
<td>127</td>
<td>90</td>
</tr>
<tr>
<td>2/F/75</td>
<td>CABG (1x)</td>
<td>40</td>
<td>18</td>
</tr>
<tr>
<td>3/M/49</td>
<td>MVR</td>
<td>160</td>
<td>114</td>
</tr>
<tr>
<td>4/M/50</td>
<td>CABG (2x)</td>
<td>82</td>
<td>48</td>
</tr>
<tr>
<td>5/F/60</td>
<td>CABG (3x)</td>
<td>120</td>
<td>73</td>
</tr>
<tr>
<td>6/M/71</td>
<td>CABG (4x)</td>
<td>165</td>
<td>81</td>
</tr>
<tr>
<td>7/F/66</td>
<td>MVR</td>
<td>116</td>
<td>80</td>
</tr>
<tr>
<td>8/M/51</td>
<td>CABG (4x)</td>
<td>163</td>
<td>98</td>
</tr>
<tr>
<td>9/M/66</td>
<td>AVR</td>
<td>136</td>
<td>105</td>
</tr>
<tr>
<td>10/M/61</td>
<td>CABG (2x)</td>
<td>64</td>
<td>41</td>
</tr>
<tr>
<td>11/M/65</td>
<td>AVR</td>
<td>124</td>
<td>93</td>
</tr>
<tr>
<td>12/M/64</td>
<td>CABG (5x)</td>
<td>125</td>
<td>88</td>
</tr>
</tbody>
</table>

*AVR = aortic valve replacement; MVR = mitral valve replacement; CABG = coronary artery bypass graft (number of grafts); CPB = cardiopulmonary bypass.

†Patients with a significant pulmonary vascular leak.
Table 2—Results in Patients Undergoing Cardiac Surgery (Group 1)*

<table>
<thead>
<tr>
<th>Before Surgery</th>
<th>During Surgery Before CPB</th>
<th>After Surgery and CPB</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLI, <em>10^-3 min^-1 (r)</em></td>
<td>Radiograph‡</td>
<td>PEEP</td>
</tr>
<tr>
<td>ptions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>8.5 (0.97)</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>7.9 (0.91)</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>4.6 (0.92)</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>12.6 (0.97)</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>4.3 (0.88)</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>6.9 (0.87)</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>4.8 (0.90)</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>6.2 (0.97)</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>7.1 (0.94)</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>9.8 (0.94)</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>17.4 (0.98)</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>7.9 (0.86)</td>
<td>0</td>
</tr>
<tr>
<td>Mean</td>
<td>6.2 (0.93)</td>
<td>4.4</td>
</tr>
<tr>
<td>SD</td>
<td>3.7 (0.04)</td>
<td>0.7</td>
</tr>
</tbody>
</table>

*Abbreviations are explained in text.
†Linear correlation coefficient (r) in parentheses.
‡Radiograph score of pulmonary edema (see text); for scores after surgery and CPB: on the day of PLI/first postoperative day.
§PLI after surgery and CPB > 2 SD + mean PLI before surgery.

PCWP(0.4) + PCWP: The protein colloid osmotic pressure (P_m) was calculated, using a nomogram, from total protein and albumin concentrations. The difference between P_m and P_end is the estimated net intravascular filtration pressure. To test for differences between groups, the Wilcoxon signed rank and rank-sum tests were used for paired and unpaired data, respectively. The Spearman rank correlation coefficient (r) was used to express relations, except for the relation between PLI and CPB duration, where nonlinear regression analysis was used. A p<0.05 was considered statistically significant. Data are expressed as mean ± SD.

RESULTS

Group 1

Seven patients undergoing coronary artery bypass grafting and five patients undergoing replacement of a cardiac valve were studied (Table 1). All patients survived to discharge from the hospital.

Table 2 shows results for PLI measurements. The difference in PLI between left and right lungs, expressed as percentage of mean values, was 8.7 ± 6.7 and 9.1 ± 6.2 percent for preoperative and postoperative measurements, respectively. The mean PLI after surgery was greater than before surgery. In only 4 patients, however, did the PLI after surgery exceed 2 SDs above the mean preoperative PLI (15.6 ± 10^-3 min^-1). In these 4 patients, the postoperative PLI was 31.1 ± 16.3 vs 9.9 ± 2.2 ± 10^-3 min^-1 in the other 8 patients (p<0.01), with an increase over preoperative values by a factor of 5.8 ± 2.6 in the former and 1.1 ± 0.3 in the latter (p<0.01). There was no difference in the correlation coefficient in the regression analysis of the radioactivity ratio vs time used to compute the PLI before and after surgery or for patients with and without a significantly elevated PLI. All coefficients were significant (p<0.005).

The PLI after surgery (y) related exponentially to the duration of CPB (x), according to y = 10.9 + (0.0008·EXP^0.062·x) (r = 0.64, p<0.05). Changes in PLI also related exponentially to the duration of CPB (r = 0.60, p<0.05). The CPB duration in the 4 patients with an elevated PLI was equal or greater than 120 min and averaged 152 ± 21 min, vs 102 ± 35 min in the other 8 patients (p<0.05). Conversely, 4 of 8 patients with a CPB time equal or exceeding 120 min, but none of those with a less prolonged CPB, had a significantly elevated PLI. There was no relation of PLI to aortic cross-clamp time: 91 ± 18 min in patients with and 70 ± 31 min in those without an elevated PLI (NS). Before surgery, the venous WBC was 6.6 ± 1.9 and after surgery the arterial WBC was 11.4 ± 3.6 ± 10^9 L^-1 (p<0.01). The postoperative arterial WBC and its change vs preoperative venous values inversely related to the duration of CPB: r = -0.79 (p<0.01) and -0.90 (p<0.005), respectively. The WBC in the 4 patients with and in the 8 patients without an elevated PLI increased by a factor of 1.3 ± 0.4 and 2.1 ± 0.6, respectively (p<0.05). Changes in PLI tended to relate inversely to changes in WBC (r = -0.59, p = 0.05).

The PCWP was lower than 15 mm Hg in each patient (for the group 9.0 ± 3.1 mm Hg) when the PLI after surgery was measured. The difference between P_m and P_end (Table 2) in patients with and without an elevated PLI was -1.9 ± 5.7 and -3.8 ± 4.7 mm Hg, respectively (NS). The PLI did not relate to either pressure or their difference. The fluid infusion rate during the PLI measurement was 591 ± 369 ml h^-1.

Transvascular Transport of 68Ga after Bypass Surgery (Rajmakkers et al)
Table 3—Characteristics and Results in Patients With Acute Cardiogenic Pulmonary Edema (Group 2)*

<table>
<thead>
<tr>
<th>Patient/Sex/ Age, yr</th>
<th>Underlying Disease</th>
<th>PLI, (10^{-1} \text{ min}^{-1}) (r)†</th>
<th>Radiograph‡</th>
<th>PEEP</th>
<th>PaO₂/FI₀₂</th>
<th>(P_{max})</th>
<th>(P_{min})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/62</td>
<td>Ventricular fibrillation; cardiopulmonary resuscitation; remote myocardial infarction</td>
<td>11.5 (0.98)</td>
<td>4</td>
<td>6</td>
<td>192</td>
<td>23.4</td>
<td>24.1</td>
</tr>
<tr>
<td>2/M/74</td>
<td>Acute myocardial infarction; hypertension</td>
<td>9.3 (0.97)</td>
<td>4</td>
<td>8</td>
<td>160</td>
<td>21.6</td>
<td>19.0</td>
</tr>
<tr>
<td>3/M/75</td>
<td>Remote myocardial infarction; pacemaker; cardiomegaly, triple-vessel disease, and pulmonary congestion on autopsy</td>
<td>15.2 (0.98)</td>
<td>3</td>
<td>7</td>
<td>249</td>
<td>23.6</td>
<td>20.3</td>
</tr>
<tr>
<td>4/M/62</td>
<td>Concentric left ventricular hypertrophy on echocardiogram; hypertension</td>
<td>8.4 (0.95)</td>
<td>4</td>
<td>1</td>
<td>190</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Mean</td>
<td>11.1 (0.97)</td>
<td>5.5</td>
<td>198</td>
<td>22.9</td>
<td>21.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>3.0 (0.01)</td>
<td>3.1</td>
<td>37</td>
<td>1.1</td>
<td>2.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Abbreviations are explained in text.
†Linear correlation coefficient (r) in parentheses.
‡Radiograph score of pulmonary edema (see text).

and did not differ between patients with or without an elevated PLI.

The PaO₂/FI₀₂ ratio decreased \((p<0.01)\) from 367 ± 56 before to 314 ± 58 after CPB surgery, while the PEEP level increased \((p<0.01)\) from 4.4 ± 0.7 to 6.3 ± 1.0 cm H₂O (Table 2). After surgery, the ratio was 275 ± 56 in patients with vs 333 ± 52 in those without an elevated PLI \((p=0.10)\), while the PEEP level did not differ. For postoperative values, the PaO₂/FI₀₂ ratio at the time of PLI tended to relate inversely to the PLI: \(r_{PLI} = -0.57\) \((p=0.05)\). No patient developed alveolar pulmonary edema on chest radiograph, either shortly after surgery or on the first postoperative day. The lowest PaO₂/FI₀₂ ratio during artificial ventilation in the intensive care unit, 8.8 ± 6.3 h after discontinuing CPB, was 256 ± 52, at a PEEP level of 5.7 ± 1.4 cm H₂O. The duration of artificial ventilation in the intensive care unit was 20.2 ± 5.8 h in patients with and 16.6 ± 3.2 h in those without an elevated PLI (NS).

**Group 2**

Patient characteristics and results are shown in Table 3; one patient (patient 3) finally died in cardiogenic shock in the intensive care unit 1 day after the PLI measurement. In each patient in whom it was measured, the PCWP was above 16 mm Hg \((n=3): 18.3 ± 2.1 \text{ mm Hg})\). The difference in PLI between left and right lungs, expressed as percentage of mean values, was 4.8 ± 4.3 percent. The PLI did not differ from group 1 preoperative values and never exceeded 2 SDs plus the mean of the latter. The PLI differed \((p<0.05)\) from postoperative values in group 1 patients with an elevated PLI but not from those in the other patients.

**DISCUSSION**

Four of 12 patients who underwent cardiac surgery developed a significant pulmonary vascular leak, as assessed by \(^{67}\text{Ga}\) kinetics, after surgery. The risk for a leak and its severity related to the duration of CPB. The leak reflected a pulmonary vascular injury and increased permeability rather than increased filtration through pressure factors. It may have been caused by activation of leukocytes by CPB and subsequent pulmonary sequestration, and it may have contributed to impaired arterial oxygenation after surgery despite absence of alveolar pulmonary edema on chest radiography.

Cardiac surgery with CPB results in a severe reduction of blood flow in the pulmonary artery during aortic cross-clamping and asystole. In experimental animals, reperfusion after occlusion of a pulmonary artery induces pulmonary endothelial damage, as shown by depressed prostaglandin E₂ uptake and a pulmonary vascular injury and increased permeability for proteins that may be transient.¹⁶-²⁰,²⁶ This reperfusion injury depends on occlusion time, but may occur even after 60 min of occlusion in some models.¹⁶-²⁰ Depending on animal species and models, the injury may be caused by O₂ radicals produced in the lung during reperfusion, although liberation of proinflammatory mediators and activated leukocytes might contribute.¹⁶-²⁰ In our four patients with a pulmonary vascular leak who underwent cardiac surgery, the aortic cross-clamp time was not prolonged, suggesting that the leak was not caused by ischemia/reperfusion of the pulmonary artery, even though residual blood flow during CPB may have varied among patients because of different CPB cannulation techniques. After lung transplantation in man, the PLI does not increase significantly.³³

In contrast, CPB is known to activate the complement cascade, which may lead to activation and microvascular sequestration of circulating neutrophils and may contribute to a fall in arterial WBC immediately after start of CPB.¹³,¹⁰,¹²,¹⁴,¹⁵,²⁵,²⁷ Later during and after CPB, the arterial WBC rises, presumably be-
cause of demargination and release from bone marrow caused in part by activated complement components, even though the rise in arterial is less than in venous blood owing to pulmonary sequestration of neutrophils, particularly after removal of the aortic cross-clamp and restoration of lung perfusion.\textsuperscript{1,2,4,6,12,14} In turn, complement components and activated neutrophils, releasing substances such as proteolytic enzymes and O\textsubscript{2} radicals, may damage the pulmonary endothelium and increase vascular permeability.\textsuperscript{5,7,9,11,13-14} So that prior leukocyte depletion may ameliorate pulmonary vascular injury after CPB, at least in dogs.\textsuperscript{12} In dogs, the increased transvascular flux of radioactive indium-transferrin after CPB was directly related to neutrophil sequestration and lipid peroxidation by O\textsubscript{2} radicals in the lungs after removal of the aortic cross-clamp during CPB.\textsuperscript{7} Although the arterial WBC increased after CPB in our patients, in agreement with the literature,\textsuperscript{1,2,5,6,12,14} the rise was smallest in the four patients developing a pulmonary vascular leak after prolonged CPB, thereby suggesting that the leak was related to neutrophil trapping in the lungs.

The relation between the duration of CPB on the one hand and the risk for a pulmonary vascular leak and its severity on the other hand may be caused by increasing activation of complement and expression of molecules for neutrophil adherence to pulmonary endothelium with time.\textsuperscript{1,4,6,8-10,14} Indeed, the degree of sequestration of leukocytes (neutrophils) in the lung may directly relate to the duration of CPB,\textsuperscript{1,2} agreeing with our data, and lung morphologic changes particularly if CPB duration exceeds 150 min.\textsuperscript{21,37} In dogs, the pulmonary clearance of prostaglandin E\textsubscript{1}, a measure of pulmonary endothelial function, decreases if CPB is applied for at least 3 h,\textsuperscript{36} but in man, the pulmonary clearance of serotonin and propranolol does not diminish after this period of CPB.\textsuperscript{37} Nevertheless, the need for prolonged (>24 h) ventilatory support after cardiac surgery may directly relate to the time on CPB and the degree of complement activation.\textsuperscript{3,9}

Although endotoxin, tumor necrosis factor, and interleukin 1 may be liberated during CPB and may amplify the inflammation cascade on pulmonary endothelium,\textsuperscript{10,11,14} corticosteroids may completely prevent liberation of tumor necrosis factor.\textsuperscript{14} However, the drugs may only partly suppress activation of the complement system by CPB, although the pulmonary sequestration of neutrophils during CPB may diminish and the rebound neutrophilia after CPB might be enhanced.\textsuperscript{2,6,14} Because all our patients received corticosteroids, the increased pulmonary vascular leak after CPB might be associated with activated complement rather than release of cytokines. Together with the use of a membrane oxygenator for CPB, which might cause less activation of complement and neutrophils and less pulmonary sequestration than a bubble oxygenator,\textsuperscript{2,3,6,9} pretreatment with corticosteroids may also have contributed to a relatively low prevalence of a pulmonary vascular leak in our patients.

Many methods for the noninvasive assessment of increased permeability of the pulmonary vasculature may have limited clinical applicability and may hamper repeated studies at the bedside, by utilizing relatively insensitive or nonmobile cameras, or radiolabels, including albumin-bound iodine and transferrin-bound indium, that may not be routinely available.\textsuperscript{7,20,25,29,33}

Others have technical limitations, by lack of assessment of pulmonary blood volume, so that the radioactivity of proteins recorded over the lungs may be confounded by changes in pulmonary blood volume.\textsuperscript{20,29,32} The advantages of our technique to estimate transvascular protein transport in the lungs above that used by others\textsuperscript{7,20,29,33} include the dual-radionuclide technique, using commonly available \textsuperscript{67}Ga, to estimate the transvascular transport rate of transferrin, \textsuperscript{99m}Tc-labeled red blood cells to account for pulmonary blood volume, and a mobile, sensitive detection technique at the bedside. The difference in PLI between the lungs may be viewed as some measure of reproducibility of our measurements. The normal PLI for proteins varies widely between studies, mainly because of differences in methods and models.\textsuperscript{9,20,25,29,34}

The mean preoperative PLI roughly agrees with that measured with \textsuperscript{67}Ga and positron emission tomography,\textsuperscript{36} but it is higher than that measured with radioactive indium-transferrin in healthy volunteers.\textsuperscript{31} This may relate to differences in patients, method, or both. Moreover, gallium may bind less avidly to transferrin than indium.\textsuperscript{34} However, the nonprotein-bound fraction equilibrates more rapidly with the pulmonary extravascular space than the protein-bound fraction, so that the PLI, measured over 1 h, should be largely determined by transferrin transport.\textsuperscript{34}

Increased pulmonary transvascular transport of radiolabeled proteins, including transferrin labeled with the positron emitter \textsuperscript{67}Ga, may be specific for increased vascular permeability.\textsuperscript{20,29,31-33} Nevertheless, transvascular gallium transport might be affected by pressure factors, since both transport of unbound radionuclide, if present, and proteins might increase along with increased fluid flux following an elevated hydrostatic pressure, a decreased colloid osmotic pressure, or both. Indeed, transvascular protein transport may increase above control during cardiogenic pulmonary edema if the PCWP exceeds \textasciitex{\textasciitextless}30 mm Hg.\textsuperscript{29,32} However, our data reinforce the literature on Ga and positron emission tomography,\textsuperscript{20,32} that the PLI assessed by Ga is specific for vascular permeability, since the increase in the four patients who underwent cardiac surgery was not caused by an elevated intravascular fluid filtration pressure in the lung, approxi-
mated by the difference of calculated $P_{mv}$ and $P_{out}$.
Moreover, the PLI was not elevated during cardiogenic pulmonary edema, in accordance with the literature. 29,30,32 Nevertheless, the relatively high PLI before but not after aortic valve replacement in one patient (patient 11) could have been caused by pressure factors. Finally, our data suggest, in accordance with the relation between increased pulmonary vascular permeability for proteins and impaired gas exchange after lung transplantation or during ARDS, 29,33 that a pulmonary vascular leak may contribute to impaired gas exchange after cardiac surgery despite absence of alveolar edema on the radiograph of the lungs. Indeed, extravascular lung water may increase directly after CPB 22,24 only in a minority of patients who undergo cardiac surgery. This can be explained in part by the insensitivity of the chest radiograph in detecting excess lung water. 8 On the other hand, absence of alveolar edema on the chest radiograph of patients with an elevated PLI may be explained if the rise in PLI was only transient, if fluid flux increased less than protein flux, if interstitial fluid was removed by pulmonary lymphatics, or combinations. 20,29,30 Assessment of transvascular protein transport may be more sensitive in detecting a pulmonary vascular leak than the measured extravascular lung water, the chest radiograph, or the arterial $P_{O_2}$. 7,29,30,32

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