Capillary leak syndrome after cardiopulmonary bypass in elective, uncomplicated coronary artery bypass grafting operations: Does it exist?

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Objective: Operations coupled with cardiopulmonary bypass may provoke a systemic inflammatory response, and it has been suggested that this response causes capillary leakage of proteins, edema formation, and even organ failure. However, capillary leak syndrome is mainly a clinical diagnosis and has not been verified as yet by actual demonstration of protein leakage from the circulation. We have therefore measured the disappearance of labeled plasma protein before and after cardiopulmonary bypass.

Methods: Sixteen patients scheduled for elective coronary artery bypass grafting were enrolled in a prospective controlled study. The cardiopulmonary bypass circuit was primed with crystalloids only. Tumor necrosis factor α, interleukin 6, interleukin 8, anaphylatoxin C3a, and terminal complement complex C5b9 levels were determined before, during, and 3 hours after cardiopulmonary bypass. The transvascular escape rate of plasma protein from the intravascular compartment was assessed by measuring the disappearance of intravenously injected Evans blue dye before and during the third hour after cardiopulmonary bypass.

Results: A significant inflammatory response could be demonstrated by means of the 5 measured mediators after bypass. The maximal increase, as compared with the baseline value, was found for interleukin 6 (36-fold). The transvascular escape rate of Evans blue dye was similar before and after bypass (7.6 ± 0.6%/h vs 7.3 ± 0.6%/h).

Conclusions: The above data confirm the systemic inflammatory response induced by cardiopulmonary bypass. Contrary to expectations, the transvascular escape rate of Evans blue dye did not change when comparing values before and after bypass. The data do not support the concept of increased protein leakage in the exchange vessels after bypass. We were unable to demonstrate a capillary leak syndrome.

Cardiopulmonary bypass (CPB) induces a well-described systemic inflammatory response syndrome (SIRS).1 A number of patients have organ dysfunction, which may delay postoperative recovery and may influence morbidity and mortality.2,3 SIRS has been defined by the American College of Chest Physicians/Society of Critical Care Medicine in a consensus conference.4 SIRS after CPB
may lead to adult respiratory distress syndrome and multiorgan failure by means of the same mechanisms that occur in septic conditions. The release of a variety of inflammatory mediators has been implicated in the pathogenesis of SIRS during CPB: tumor necrosis factor $\alpha$ (TNF-$\alpha$) and interleukin (IL) 1, IL-6, and IL-8. Lipid and arachidonic metabolites, platelet-activating factor, and activation of the coagulation cascade are also involved in the inflammatory response and in a physiologic anti-inflammatory reaction.

It has been hypothesized that capillary leak syndrome is induced by the above-described inflammatory reaction. Capillary leak syndrome is defined as a shift of fluid and protein from the intravascular to the interstitial space, which results in hypovolemia. However, capillary leak syndrome after CPB has only been clinically diagnosed and has not yet been verified by the determination of protein leakage from the circulation. Increased capillary permeability after CPB was demonstrated for isolated organs (eg, in the lungs and also in the gut). Concerning the whole body, in contrast, no capillary leakage had been measured in an animal model after CPB. Therefore, the disappearance of labeled plasma protein (PP), plasma cytokines, and complement were measured before and after CPB in patients.

**Methods**

The present investigation was performed in accordance with the principles of the declaration of Helsinki (1964) and its later revisions. The study protocol was approved by the ethical committee of the Technical University of Munich. Written informed consent was obtained from each patient.

The study was performed in 16 consecutive patients with stable angina in New York Heart Association class III who were scheduled for elective coronary artery bypass grafting (CABG). Exclusion criteria were as follows: age greater than 75 years; body weight greater than 30% more or less than ideal body weight; left ventricular ejection fraction of 40% or less; hemodynamic instability or emergency operations; additional valvular diseases; complete bundle branch block; third-degree atrioventricular block; renal (creatinine level >1.2 mg/dL) or hepatic failure; and hemocrit of less than 30%. Monitoring included continuous recording of electrocardiography, ST-segment analysis of leads II and V5, and pulse oximetry (Marquette, Milwaukee, Wis). Before induction of anesthesia, a 20-gauge radial artery catheter (Arrow, Reading, Pa), a pulmonary artery catheter (7.5F; Baxter, Irvine, Calif) through the right internal jugular vein with an 8.5F introducer sheath (Arrow, Reading, Calif), and 2 large-bore intravenous catheters were placed. After orotracheal intubation, mechanical ventilation with 100% oxygen was provided. Tidal volume was adjusted to achieve normoventilation and controlled by means of mass spectrometry and blood gas analysis to maintain normal levels of arterial carbon dioxide. Measurements of hemodynamics included heart rate (HR), mean arterial pressure, mean pulmonary artery pressure, pulmonary capillary wedge pressure, and cardiac output. Cardiac output was measured in triplicate by the thermodilution technique. The cardiac index and systemic vascular resistance were calculated on the basis of the patient’s body surface area.

**Anesthesia Technique**

Induction of anesthesia was done as a total intravenous technique. Anesthesia was induced using 1 $\mu$g/kg sufentanil, 0.04 mg/kg midazolam, and 0.1 mg/kg pancuronium; an additional dose of 6 $\mu$g/kg sufentanil and 0.3 mg/kg midazolam was given before sternotomy, followed by an infusion of 0.5 $\mu$g $\cdot$ kg$^{-1}$ $\cdot$ h$^{-1}$ sufentanil and 0.02 mg $\cdot$ kg$^{-1}$ $\cdot$ h$^{-1}$ midazolam until the end of the operation. A preoperative volume load with hydroxyethylstarch (500 mL) was used for the purpose of avoiding a drop in arterial blood pressure caused by induction of anesthesia. Every patient did receive the volume before starting the measurement and an infusion of a low dose of dopamine (3 $\mu$g $\cdot$ kg$^{-1}$ $\cdot$ min$^{-1}$), which was used throughout the procedure for maintenance of adequate urine output. Before separation from CPB, dopamine was increased to 5 $\mu$g $\cdot$ kg$^{-1}$ $\cdot$ min$^{-1}$. After termination of CPB, the infusion rate was set according to the

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**Figure 1.** Study protocol to assess the transvascular escape rate of albumin (TER) and the inflammatory response to CPB in patients undergoing CABG. Plasma albumin was labeled by means of intravenous Evans blue dye. Hemodynamic measurements included HR, mean arterial pressure (MAP), central venous pressure (CVP), cardiac index (CI), and systemic vascular resistance (SVRI). COP, Plasma colloidal osmotic pressure.
patient’s circulatory state. A cardiac index of 2.3 L · min⁻¹ · m⁻² or greater and a mean arterial pressure of 60 mm Hg or greater were the targets. In the intensive care unit the patients were sedated with 0.25 µg · kg⁻¹ · h⁻¹ sufentanil and 0.01 mg · kg⁻¹ · h⁻¹ midazolam.

**CPB Technique**

The extracorporeal circuit was primed with 1500 mL of lactated Ringer solution supplemented by 100 mmol of sodium bicarbonate, 5000 IU of heparin (Ratiopharm, Ulm, Germany), and 2 × 10⁶ KIU of aprotinin. CPB was instituted at a flow rate of 2.4 L · min⁻¹ · m² body surface area after systemic heparinization. The rectal temperature was reduced to 28°C by means of cooling on bypass. After crossclamping the aorta, 1000 mL of cold crystalloid cardioplegic solution (Bretschneider = Custodiol; Köhler Chemie, Alsbach-Hähnlein, Germany) was administered. The remaining blood of the bypass circuit was prepared with a Cell Saver (Haemonetics, München, Germany) before retransfusion.

**Protocol of Data Assessment**

The protocol of data assessment is shown in Figure 1. The following variables were assessed: central venous pressure, mean arterial pressure, HR, cardiac index, systemic vascular resistance, and plasma levels of TNF-α, IL-6, IL-8, anaphylatoxin C3a, and terminal complement complex C5b9. Data were sampled before skin incision, immediately before the end of CPB, 2 hours after CPB, and 3 hours after CPB.

The escape rate from plasma of intravenously injected Evans blue dye was determined after induction of anesthesia and during the third hour after weaning from CPB. The blood samples for measurement of Evans blue dye were also analyzed for PP concentration and plasma colloid osmotic pressure.

**Plasma Analyses**

PP concentration was measured by a using biuret test kit (Boehinger Mannheim, Mannheim, Germany). Plasma colloid osmotic pressure was determined with a membrane osmometer (Gonotec, Berlin, Germany; molecular mass cutoff, 10 kd). Plasma concentration of TNF-α, IL-6, and IL-8 was assessed by using 2-site chemiluminescent enzyme immunometric assays (Immunoassay System; Diagnostic Products Corporation, Los Angeles, Calif.). Plasma levels of C3a and C5b9 were analyzed with enzyme immunometric assays (Immogeneics, Heiden, Germany).

**Escape of Plasma Albumin, Plasma Volume, and Intravascular Protein Pool**

The transvascular escape rate of PP from the intravascular compartment (TER) was assessed by measuring the disappearance of intravenously injected Evans blue dye (Ophthalmic Laboratories, Brookvale, Australia). The method has been previously described and discussed in detail.¹¹

Blood samples were taken before the first injection of Evans blue dye to determine the blank absorbance of plasma (7 samples within 0.5 hours). After intravenous injection of Evans blue dye (0.2 mg/kg), samples were obtained every 10 minutes (at 10, 20, 30, 40, 50, and 60 minutes). The absorbance of plasma was determined in a spectrophotometer (Lamba 40; Perkin Elmer, Neuried, Germany) at a λ value of 620 nm and a λ value of 740 nm. Linear regression was calculated from the absorbance of undyed plasma (A) at these 2 wavelengths:

\[
A_{620} = a + b \times A_{740} 
\]

The absorbance of dyed plasma at 620 nm (Evans blue dye [EB₆₂₀]) was corrected for blank absorbance calculated by (1) and from the following:

\[
EB_{620\text{corr}} = EB_{620} - (a + b \times EB_{740})
\]

Specific protein dying (sEB) was calculated from (2) and PP concentration:

\[
sEB = \frac{EB_{620\text{corr}}}{PP}
\]

The decay of sEB with time was fitted as follows:

\[
sEB_t = sEB_0 \times e^{-k \times t}
\]

using the following transformation:

\[
\ln(sEB_t) = [\ln(sEB_0)] - k \times t
\]

with sEB₀ indicating theoretic sEB at the time of dye injection and immediate complete mixing with plasma volume, sEB₁ indicating sEB at any time t, and k indicating the disappearance rate constant. sEB₀ and k were obtained by calculating the linear regression from the sampling times t and the corresponding sEB₁ values.

TER was calculated as follows:

\[
TER = (1 - e^{-k \times 60}) \times 100 \text{ [% \times h}^{-1}\]

Plasma volume (PV) was calculated from the injected dose of EB (EBᵢ) and EB₀:

\[
PV = \frac{EB_i}{EB_0}
\]

with EB₀ indicating PP concentration.

### TABLE 1. Demographic and operative data of 16 patients undergoing CABG

| Age (y) | 61 ± 3 |
| Sex (M/F) | 14/2 |
| NYHA class III (n) | 16 |
| Higgins score¹² | 2.1 ± 0.3 |
| EF (%) | 62 ± 3 |
| Weight (kg) | 81 ± 2 |
| No. of patients with diabetes | 6 |
| No. of patients with peripheral vascular disease | 8 |
| Operative time (min) | 207 ± 9 |
| CPB time (min) | 79 ± 5 |
| Crossclamp time (min) | 54 ± 4 |
| No. of bypasses | 2.8 ± 0.1 |
| Postoperative ventilation (h) | 14 ± 4 |

NYHA, New York Heart Association; EF, ejection fraction.
The intravascular protein pool (IVP) was calculated from the PP concentration and from plasma volume as follows:

$$\text{IVP} = \text{PP} \times \text{PV} \quad (8)$$

### Statistical Analysis

The data are presented as means ± SEM. The data were subjected to Friedman distribution-free 2-way analysis of variance. The significance of differences between control and subsequent data were evaluated by the Wilcoxon matched-pairs signed-rank test at a $P$ value of less than .05 (2-tailed). The statistical software SPSS 10.0 for Windows (SPSS, Inc, Chicago, Ill) was used for these calculations.

### Results

#### Surgical Data

Surgical data are given in Table 1. The operation time ranged from 155 to 300 minutes (mean, 207 minutes). The CPB time was 43 to 109 minutes (mean, 79 minutes). The aorta was crossclamped for 28 to 80 minutes (mean, 54 minutes). The number of the distal coronary artery anastomoses was 2 to 3 (mean, 2.8). Except for 1 patient, a left thoracic artery was used in all cases to bypass the left anterior descending artery vessel. All patients were weaned from CPB without problems and showed an uneventful postoperative recovery.

#### Hemodynamics

The hemodynamic data before and after the operation are summarized in Table 2. HR was 54 ± 2 beats/min before skin incision and increased to 80 to 90 beats/min during the third hour after the operation. Mean arterial blood pressure was elevated from 80 ± 3 to 98 ± 4 mm Hg 3 hours after CPB. Central venous pressure during the third hour after CPB was not significantly different from the control level. Cardiac index was increased from 2.9 ± 2 to about 4 L · min⁻¹ · m⁻². At the beginning of the third hour after CPB, systemic vascular resistance was significantly lower (−15%) than before the operation.

### Systemic Inflammatory Response

Data on systemic inflammatory response are given in Table 3. TNF-α was doubled at the end of CPB and remained at this level until 3 hours after CPB. IL-6 was approximately 15-fold greater than the baseline value at the end of CPB and further increased to a 36-fold level during the next 3 hours. IL-8 was run in parallel with IL-6 but reached only a 4-fold level 3 hours after CPB. C3a and C5b9 were elevated 7- and 6-fold, respectively, at the end of CPB and decreased after CPB. Three hours after CPB, C3a and C5b9 were 5- and 2-fold baseline values, respectively.

### PP-related Data

PP-related data are given in Table 4. Plasma volume was about 53 mL/kg before the operation. The values obtained 2 hours after weaning from bypass were not significantly different from the pre-CPB values. Plasma colloid osmotic pressure was 22.7 ± 0.7 mm Hg before starting the surgical intervention. Three hours after CPB, it was reduced to 20.6 ± 0.7 mm Hg. The intravascular PP pool was calculated as 3.09 ± 0.16 g/kg before the operation. Two hours after CPB, it was decreased to 2.29 ± 0.17 g/kg.

The decay of the specific color of PP after intravenous injection of Evans blue dye was 7.6% ± 0.6%/h before the operation. During the third hour after CPB, the mean escape rate of the dye was 7.3% ± 0.6%/h. The 2 measurements showed no systematic difference. The postoperative/preoperative ratio of the paired determinations was 1.04 ± 0.11.
**Discussion**

The present study in patients undergoing CABG confirms that CPB in combination with cardioplegic cardiac arrest is followed by a systemic inflammatory response, which was not associated with an increased disappearance rate of labeled PPs, whereas the intravascular protein content was reduced after CPB. These results, however, give no simple answer to the question of the existence of a capillary leak syndrome after CPB.

The capillary leak syndrome is characterized by generalized edema formation and ascites caused by an increase in microvascular permeability to PPs, which is related to inflammatory cytokines and the activation of the complement system. The existence of a capillary leak syndrome related to CPB in cardiac surgery has been repeatedly suggested for pediatric patients. It has been concluded that this is the case from a decrease in PP concentration soon after the onset of CPB. PP concentration, however, reflects not only the intravascular protein pool but also changes in plasma water, which may be increased after institution of CPB, depending on the priming volume of the extracorporeal circuit, on the type of cardioplegia, and on subsequent fluid substitution. Furthermore, for the following reason, it seems rather unlikely that the inflammatory response to CPB causes a pathologic protein extravasation early during CPB, as described elsewhere. The inflammatory response is moderate during CPB but becomes most pronounced 2 to 4 hours after CPB. Therefore, in the present study the disappearance of Evans blue dye was assessed during the third hour after CPB.

**Assessment of Transvascular Protein Leakage**

Microvascular leakage of PPs is monitored by the disappearance rate of intravenously applied labeled proteins. In the present study endogenous PPs were labeled in vivo with Evans blue dye. The disappearance rate of Evans blue dye reflects the extravasation of protein if the dye is readily bound to protein. Evans blue dye binds firmly to albumin (>99.2%), and the Evans blue dye-binding capacity of albumin is 13 mol of Evans blue dye per mole of albumin. For the present study, it can be calculated that only 1 of 1000 binding sites were occupied. Therefore, unbound Evans blue dye should not have been present, and the calculated disappearance rate of Evans blue dye represents the transvascular leakage of albumin.

**Baseline Disappearance Rate of Albumin**

Studies in conscious, healthy men showed a mean disappearance rate for albumin of 4.5%/h to 5.5%/h or 7.4%/h to 8.5%/h. The present baseline data correspond with these rates but do not necessarily represent normal values. The standard protocol of anesthesia included a preoperative volume load with hydroxyethylstarch (500 mL) and an infusion of a low dose of dopamine (3 µg · kg⁻¹ · min⁻¹). The volume load increased plasma volume, and a 25% increase in plasma volume by albumin or dextran was shown to increase the disappearance rate of albumin from less than 5%/h to 8%/h. Furthermore, the patients showed a rather high central venous pressure caused by the volume load and positive-pressure ventilation, and an elevation in venous pressure increases the extravasation of macromolecules.

Concerning dopamine, low-dose dopamine (4 µg · kg⁻¹ · min⁻¹) was demonstrated to enhance splanchic blood flow, and an increase in intestinal blood flow by isoproterenol was shown to increase the capillary filtration coefficient as a result of an increase in microvascular filtration area. Accordingly, increased microvascular filtration can be assumed to occur during low-dose dopamine administration, at least in the splanchic circulation.

On the other hand, different types of anesthesia (halothane and pentobarbital) were shown to reduce the disappearance rate of intravenous labeled albumin by 30% to 40% in normovolemic dogs because of their hemodynamic action. Data on the effect of sufentanil-midazolam on the escape rate of albumin are not available. Sufentanil-midazolam is known, however, to have only minor hemodynamic effects and therefore should not significantly affect the disappearance rate of albumin.

**Albumin Disappearance Rate After CPB**

The present study gives no indication of an increased protein leakage after CPB. This does not exclude, however, an increased microvascular permeability to protein.

Transvascular transport of macromolecules depends not only on microvascular permeability but also on exchange area and fluid filtration. The latter variables depend on the microvascular perfusion, microvascular blood pressure, and colloid osmotic pressure. The hemodynamic and colloid osmotic pressure data after CPB, however, do not support a compromised microvascular filtration compared with that at baseline. Thus, it seems rather unlikely that the microvessels had become leaky to proteins after CPB.

**Inflammatory Mediators and Microvascular Protein Leakage**

Inflammatory cytokines have been repeatedly shown to increase capillary permeability to macromolecules. Accordingly, during sepsis and after the application of endotoxin, which are well known to activate inflammatory mediators, increased microvascular leakage of macromolecules has been observed in patients and in experimental animals.

**Extracorporeal Circulation and Microvascular Protein Leakage**

The contact of blood with foreign surfaces during extracorporeal circulation (ECC) is well known to activate inflam-
matory cytokines and the complement system, which in turn should disturb the endothelial barrier function. Only limited information is available, however, concerning the effect of CPB or ECC on microvascular leakage of PPs. An increased transvascular escape rate of albumin has been described in patients after CPB. In experimental animals after ECC without CPB, an increase in intestinal, pulmonary, coronary, and global microvascular permeability to proteins has been reported.31,34

The present results contradict these studies, but they are in accordance with a recent animal study from our laboratory with CPB and cardiopulmonary cardiac arrest according to the clinical standard protocol.11 Probably, the inflammatory response in the present study was not sufficient to injure the endothelial barrier to proteins, as opposed to other studies, which showed increased microvascular protein leakage at severalfold higher levels of inflammatory mediators after CPB34,35 or ischemia-reperfusion of the lower body.36

**Intravascular Protein Pool**

In the present examination intravascular protein was decreased by about 25% after CPB. This does not mean, however, that there was an increased microvascular permeability to proteins but may be related to several other factors. First, an unknown loss of plasma occurs during and after the operation as the result of the surgical procedure (eg, surgical blood loss, blood remaining in the CPB circuit, and plasma loss caused by hemococoncentration in the cell saver). Second, protein is trapped at the surfaces of the ECC circuit, which was found to be in the order of 2 g during 90 minutes for the circuit used in our institution. Third, the return of extravasated protein by lymph nodes is reduced during anesthesia because lymph node transport by the muscle pump is not present as the result of the immobilization.25 Finally, protein is shifted to the extravascular compartment early during CPB by an increased microvascular filtration after hemodilution by the crystalloid priming volume of the ECC circuit, which increases microvascular filtration pressure by decreasing plasma colloid osmotic pressure.

**Conclusion**

In recent years, the attractive hypothesis was proposed that the inflammatory response to CPB in cardiac surgery increases capillary leakiness and causes an enhanced extravasation of proteins and fluid. The present data confirm the inflammatory response after CPB in patients undergoing elective CABG. The escape rate of albumin, however, gives no indication of an increase in microvascular permeability. Thus, a capillary leak triggered by the inflammatory response after CPB seems rather unlikely. Nevertheless, PPs may be shifted from the intravascular to the extravascular compartment by means of an increased fluid filtration during CPB as a consequence of hypocoonic hemodilution by crystalloidal priming of the CPB circuit and the use of a crystalloidal cardiopulmonary solution.

**References**

Discussion

Dr Edward D. Verrier (Seattle, Wash). I have an academic interest in this area. Did you notice any evidence of either weight gain, differences in fluid administration, or other end-organ function, such as a difference in an alveolar oxygen gradient, creatinine clearance, or lung compliance? If you take any inflammatory mediators, such as IL-8, IL-6, or any of the anaphylactic toxins of complement, each one of them, in almost any animal model, will cause edema. They will create a change in either the Starling forces or the membrane itself, leading to transcapillary extravasation of fluid. I am concerned that you might have a methodological problem, even with the Evans blue dye or the timing of it, because it is counterintuitive and it goes against most of our experimental evidence.

Dr Tassani. I think these experimental situations in which the inflammatory mediators are causing edema are mostly a problem of the concentration. There have been several studies done in patients with sepsis in which these inflammatory mediators are manyfold higher, as during CPB, and more important, the duration of the inflammatory mediators in sepsis is longer, more often several days. In contrast, during CPB, the duration of elevated levels of inflammatory mediators is only 1 to 2 hours, and the concentrations approach normal values very fast. What we are postulating is that the capillary leakage, which is a clinical diagnosis found often in operating on infants, is mostly the result of hemodilution just to fluid transition and probably not a reaction or a result of the inflammatory reaction.

Dr Michael C. Maxwell (Charlotte, NC). Most often when we see capillary leak syndrome clinically, it is in patients who are on the pump a long time, 2.5, 3.0, or 3.5 hours. Your average pump time was 84 minutes. Did you analyze a subset that had longer time was 84 minutes. Did you analyze a subset that had longer pump runs to see if that was an influence? Your average pump time was 84 minutes. Did you analyze a subset that had longer pump runs to see if that was an influence? Dr Tassani. That is a very good comment. What we are trying at the moment is to do the same study in a population of infants with a long pump time. However, during the presented investigation, even a slight elevation of the Evans blue dye disappearance rate should have been able to be measured with this rather reliable and precise method.