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Effects of Dexamethasone on Intravascular and Extravascular Fluid Balance in Patients Undergoing Coronary Bypass Surgery with Cardiopulmonary Bypass

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Background: **Cardiac surgery with cardiopulmonary bypass is often associated with postoperative hemodynamic instability. In this regard beneficial effects of corticosteroids are known. The purpose of this study was to investigate whether these effects are due mainly to a modification of the intravascular and extravascular volume status or whether a more direct improvement of cardiovascular performance by corticosteroids is the underlying mechanism.**

Methods: **Twenty patients undergoing elective coronary bypass grafting were included in this randomized double-blind study. Patients of the treatment group received 1 mg/kg^{-1} dexamethasone after induction of anesthesia. In addition to the use of standard monitors and detailed fluid balance assessments, the transpulmonary double-indicator technique was used to measure extravascular lung water, total blood volume, and intrathoracic blood volume. Measurements were done after induction of anesthesia and 1 h, 6 h, and 20 h after the end of surgery.**

Results: **After cardiopulmonary bypass, no relevant increase in extravascular lung water was observed, despite highly positive fluid balances in all patients. A significantly smaller increase in extravascular fluid content was observed in the dexamethasone group. Total blood volume and intrathoracic blood volume did not differ in the two groups. Patients pretreated with dexamethasone had a decreased requirement for vasoactive substances and, in contrast with the control group, no increase in pulmonary artery pressure.**

Conclusions: **Extravascular fluid but not extravascular lung water is increased in patients after surgery with cardiopulmonary bypass. Pretreatment of adult patients with 1 mg/kg^{-1} dexamethasone before coronary bypass grafting decreases extravascular fluid gain and seems to improve postoperative cardiovascular performance. This effect is not caused by a better intravascular volume status.**

HEMODYNAMIC instability occurs frequently in the postoperative period after cardiac surgery with cardiopulmonary bypass (CPB). Several factors contribute to this problem: (1) significant fluid shifts from the intravascular to the extravascular space during surgery and CPB because of decreased colloid osmotic pressure and increased capillary permeability[1,2]; (2) a systemic inflammatory response due to the exposure of blood to the nonphysiologic surfaces of the CPB circuit[3,4]; (3) impairment of myocardial functional reserve, which occurs preoperatively in many patients; (4) cardiac arrest, which despite cardioplegia and other cardioprotective measures, inevitably causes ischemic stress as well as reperfusion injury, which in turn may cause postoperative dysfunction[5]; and (5) significant cardiodepression, which more recent evidence suggests is caused by not only the ischemia–reperfusion phenomena but also myocardial edema after CPB[6] and the direct effects of proinflammatory cytokines on the myocardium.[7,8]

A rational therapeutic strategy to improve cardiovascular performance after cardiac surgery with CPB would involve not only optimal myocardial protection but also the prevention of an excessive inflammatory reaction. Studies 30 yr ago showed some evidence of the beneficial effects of corticosteroids in patients undergoing cardiac surgery.[9] More recently, it was demonstrated that the inflammatory response could be markedly suppressed by preoperative application of steroids.[4,10] Steroids also improved perioperative fluid balances[11–13] and enhanced postoperative cardiovascular stability.[12,14–16]

Some aspects of steroid therapy remain to be elucidated. In particular, more recent knowledge about the impact of myocardial edema on myocardial function and further insights on the antiinflammatory properties of corticosteroids, including better understanding of immunomodulating effects, have led investigators to question how corticosteroids affect intravascular and extravascular fluid balance as well as cardiovascular performance in this setting. The goal of this study was to determine whether, in a double-blind randomized investigation, corticosteroids improve hemodynamic stability by reducing capillary leakage, as indicated by both extravascular lung water and total fluid balances.

Materials and Methods

After approval by the institutional ethics committee and written informed consent, 20 patients undergoing elective coronary artery bypass grafting were included in a randomized double-blind study. Patients older than 75 yr or with restricted left ventricular function (ejection fraction <50%), unstable angina, left main coronary artery stenosis, valvular disease, kidney or liver dysfunction, diabetes mellitus, or peripheral arterial occlusive

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disease were excluded. Patients with a known allergic diathesis or previously treated with corticosteroids and patients being treated with aspirin or nonsteroidal antiinflammatory drugs were also excluded.

The patients were premedicated with 0.03 mg/kg flunitrazepam (maximum 2 mg) orally on the evening before surgery and again before transport to the operating room. In the anesthesia induction room, a central venous catheter was placed under local anesthesia with use of the Seldinger technique. In addition, a 5-French introducer (Pulsion Medical Systems, Munich, Germany) with side-port for arterial blood pressure measurement was placed into the left femoral artery.

After preoxygenation, anesthesia was induced with 2 μg/kg sufentanil, and patients were paralyzed with 0.1 mg/kg pancuronium. The trachea was intubated and mechanical ventilation was instituted. Anesthesia was maintained with a continuous infusion of 1–1.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ sufentanil and 45–90 $\mu g \cdot kg^{-1} \cdot h^{-1}$ midazolam. If deemed clinically necessary, additional boli of sufentanil or midazolam were given.

After induction, a 7-French Swan–Ganz thermodilution catheter was placed *via* an 8.5-French introducer (Arrow International, Reading, PA) in the right internal jugular vein. In addition, a combined 4-French fiberoptic–thermistor catheter (Pulsiocath PV 2024; Pulsion Medical Systems, Munich, Germany) was inserted *via* the introducer in the left femoral artery, 40 cm up into the descending aorta. The fiberoptic catheter was connected to a commercially available optoelectronic device (COLD-System Z 021; Pulsion Medical Systems, Munich, Germany), which allows simultaneous recording of thermal and dye dilution curves.

Individuals were randomized into two groups under controlled, double-blind conditions. To patients of the control group we administered 10 ml of normal saline after induction of anesthesia, and to patients of the verum group we administered 1 mg/kg dexamethasone, drawn up in a syringe to 10 ml with normal saline. Throughout the entire study, the care of the patients was managed by anesthesiologists and intensivists who were not involved in the study.

Perioperative treatment was standardized according to our clinical routine, with the following guidelines:

1. Priming solution for CPB included 1,150 ml Ringer's lactate solution, 250 ml glucose [5%], 500 ml hydroxyethyl starch [6%], and 100 ml sodium bicarbonate [8.4%].
2. Basic fluid substitution during the first 20 postoperative hours was 40 $ml \cdot kg^{-1} \cdot h^{-1}$ balanced crystalloid solution.
3. Packed erythrocytes were administered if the hemoglobin concentration was <8 g/dl.
4. Albuminous solutions (20%) were administered if the serum total protein concentration decreased to <4 g/dl.
5. If either arterial blood pressure or "filling pressures" decreased, a rapid infusion of 200–300 ml crystalloid solutions was given as the first measure. If the response was insufficient, colloids (hydroxyethyl starch, 6%) were administered.
6. Clinical increases in bleeding tendency caused by coagulation disorders and validated by appropriate laboratory studies were treated by adjusted transfusion of fresh frozen plasma or platelets or both.
7. During the investigation period, a minimum diuresis of 1 $ml \cdot kg^{-1} \cdot h^{-1}$ was maintained with furosemide, if needed.
8. Inotropes were used only when hemodynamic stabilization could not be achieved by fluid administration or when there was other evidence of impaired contractility. The only inotropes used were epinephrine and dopamine. Dopamine was never used for purely renal purposes.

Surgery was performed with extracorporeal circulation and moderate hypothermia (approximately 30°C). Cardiopulmonary bypass involved the use of a centrifugal pump (Bio Medicus Bio-Pump; Medtronic, Eden Prairie, MN) and a membrane oxygenator (Maxima Hollow Fiber Oxygenator; Johnson & Johnson Cardiovascular, Anaheim, CA) for gas exchange.

Measurements of standard hemodynamics were performed after induction of anesthesia (baseline) and 1 h, 6 h, and 20 h postoperatively. In addition, at the same time, net balances of all fluids were calculated and double-indicator dilution measurements were performed.

Fluid Balances

At each measurement and at the end of surgery, a detailed assessment of the net balance of all fluids was performed. For this, crystalloid solutions, colloid solutions, and erythrocyte volumes were recorded separately. The components of the CPB priming solution were included in the assessment; the erythrocyte concentrates corresponded to an erythrocyte volume of 60%, a colloid volume of 39%, and a water content of 1%. Part of the input balance was the autotransfusion of blood collected during surgery from the field with a "cell-saver." The mean of the hematocrit values measured every 20 min was considered the hematocrit value of the collected blood in the corresponding collecting interval. For processing, the collected blood was centrifuged and washed with normal saline solution. The lost plasma volume of the blood was included in the colloid output, whereas 58% of the volume of the processed blood was added to the crystalloid input. The remaining volume in the pump at the end of surgery and postoperative losses *via* the drainage tubes were included in the output balances for erythrocytes and colloids, just as for the individually estimated intraoperative blood loss. Whereas the water losses by diuresis and gastric tubes

could be measured exactly, the perspiratio insensibilis had to be estimated; we calculated that 25 ml/h during surgery and spontaneous breathing and 12.5 ml/h during mechanical ventilation were part of the crystalloid output balance.

Double-indicator Dilution

Double-indicator dilution measurements were simultaneously performed with the indicators cold and indocyanine green (ICG). Indocyanine green (22.5 mg) was dissolved in 15 ml ice-cooled water for injection and given as a bolus through the proximal lumen of the pulmonary artery catheter. Measurements were performed in triplicate and mean values were calculated. After each bolus injection, pulmonary artery and aortic thermodilution curves, and an aortic dye dilution curve, were recorded simultaneously.

Cardiac output was calculated according to the Stewart–Hamilton principle, from the aortic and pulmonary artery thermodilution curves. For further calculations the average of both values was used at each measurement.

Extravascular lung water (EVLW) was measured from the fiberoptically recorded aortic thermal and ICG dilution curves by a modified mathematical algorithm.[17] The EVLW value is the difference between the intrathoracic distribution volumes of cold and ICG:

$$EVLW = ITTV - ITBV \quad (1)$$

where ITTV = intrathoracic thermal volume and ITBV = intrathoracic blood volume.

ITTB and ITBV are calculated from the product of blood flow (cardiac output [CO]) and the mean transit times through the thoracic compartment of the indicator cold (mtt_{TD}) and the dye ICG (mtt_{ICG}), respectively:

$$ITTV = CO \times mtt_{TD} \quad (2)$$

and

$$ITBV = CO \times mtt_{ICG} - 1.63\ ml\ kg^{-1} \quad (3)$$

Total blood volume (TBV) was calculated from the rate of hepatic ICG elimination. A modified method, described previously in more detail,[18] was applied. At each measurement (baseline, 1 h, 6 h, 20 h), hematocrit was determined, and 5, 6, 7, 8, 9, 12, 15, 18, 21, 24, 27, and 30 min after bolus injection of ICG, mixed venous blood samples were taken. Start of injection of ICG was defined as time point 0. Plasma was separated and the ICG plasma concentration was measured by spectrophotometry (MR-3000; Milton Roy, Ivyland, PA). The entire spectrum of light intensities from 600 to 900 nm was recorded. ICG concentration was then determined by multilinear fitting of the entire spectrum to a calibration spectrum. Calibration spectra were constructed for each measurement at baseline, 1 h, 6 h, and 20 h, with use of the blank blood sample, into which a known amount of ICG was titrated. Calibration therefore referred directly to whole blood, thereby avoiding any corrections for hematocrit.

The resulting concentration–time course for ICG, c(t), was fitted to a biexponential decay according to

$$c(t) = a \times e^{-k1t} + b \times e^{-k2t} \quad (4)$$

where a and b = weighting factors and k1 and k2 = time constants.

Since complete mixing of ICG in the volume of distribution requires several minutes, the virtual concentration at time of injection (c_0) cannot be measured directly. C_o was therefore obtained by back-extrapolation, basically by adding the fitted parameters a and b:

$$c_0 = a + b \quad (5)$$

.

Determination of TBV is based on the principle of conservation of mass. Thus, TBV is calculated from the amount of the injected indicator (m_0) and its blood concentration, c_0:

$$TBV = m_0/c_0/BW \quad (6)$$

where BW = body weight in kilograms.

The differences between TBV and the corresponding cumulated fluid balances were regarded as changes in extravascular fluid content (EVFC).

Statistics

On the basis of a previous study, in which we investigated the effect of colloid *versus* crystalloid priming of the CPB on EVLW,[19] a sample size of 20 patients (10 per group) was estimated. A power analysis yields, for a 25% effect on EVLW 1 h postoperatively with a level of significance of 5% and power of 80%, a sample size of eight patients per group. All data in the tables and figures are presented as mean ± SD. All statistical procedures were performed on a personal computer with use of a commercial software package (Statistica for Windows, version 4.0; Statsoft, Tulsa, OK). $P \geq 0.05$ was considered statistically significant. To test for significant differences, demographic data were subjected to the Kruskal–Wallis and chi-square tests (table 1). Differences in the other parameters were statistically tested with an analysis of variance for repeated measurements. If significant differences were revealed, *post hoc* comparisons were performed in and between the patient groups with use of the Tukey honest significant difference test.

Results

Eighty sets of measurements were performed for 20 patients. Data on the demographic characteristics of patients, CPB, and intraoperative blood loss and volume of autotransfusion are summarized in table 1. Despite randomization, the number of male patients was higher in the

Table 1. Demographic Data of Patients, Data on Cardiopulmonary Bypass, and Data on Intraoperative Blood Loss and Volume of Autotransfusion

	PLC	DXM
Height (cm)	165 ± 6	173 ± 6†
Weight (kg)	71 ± 10	86 ± 11*
Body surface (m^2)	1.78 ± 0.15	1.99 ± 0.13†
Age (yr)	66.8 ± 3.7	62.5 ± 9.5
Sex (m/f)	6/4	9/1
Perfusion time (min)	101 ± 34	103 ± 39
Ischemic time (min)	65 ± 25	67 ± 28
Cellsaver (ml)	871 ± 447	738 ± 314
Blood loss (ml)	1369 ± 357	1599 ± 713

mean ± SD.

* $P < 0.05$: Kruskal Wallis-resp. chi-test; † $P < 0.01$.

PLC = placebo group (n = 10); DXM = dexamethasone group (n = 10).

dexamethasone group (9 *vs.* 6). To normalize the data, all fluid compartments, rates, and balances are related to body weight or body surface. No differences between the two groups with respect to age, cross-clamp times, duration of extracorporeal circulation, intraoperative blood loss, and volume of autotransfusion were observed.

Baseline hemodynamic values after induction of anesthesia were comparable in the two groups (table 2). An increase in heart rate and cardiac index was observed in both groups over the entire study period. Patients in the placebo group showed small but significantly higher mean pulmonary artery pressures in the early postoperative period (1 h and 6 h). Accordingly, pulmonary vascular resistance was higher at these times in the placebo group.

Vasoactive substances, applied during the study period, were recorded and evaluated. Over the entire postoperative period (from end of surgery until 20 h postoperatively), 4 of 10 patients in the dexamethasone group did not receive any epinephrine, whereas only 1 of 10 patients in the placebo group could be treated without any epinephrine. In addition, only one patient in the dexamethasone group required dopamine, *versus* four patients in the placebo group. However, mean doses of epinephrine and dopamine were low, and these differences did not show any statistical significance.

The EVLW value was in the upper normal range (normal: <6 ml/kg in the method described) in both groups at baseline and remained unchanged in the placebo group throughout the entire study (table 3). In the treatment group a progressive decrease in EVLW was observed, which became significant by 20 h after surgery.

Cumulated net fluid balances, diuresis findings, and doses of furosemide are presented in table 4. In order to

Table 2. Hemodynamic Variables

		Baseline	1h	6h	20h
HR (min^{-1})	PLC	63 ± 16	91 ± 8**	92 ± 17**	88 ± 21**
	DXM	61 ± 11	87 ± 15**	94 ± 13**	92 ± 11**
MAP (mmHg)	PLC	70 ± 12	84 ± 8	71 ± 4	76 ± 12
	DXM	76 ± 9	78 ± 15	77 ± 13	77 ± 11
			†	†	
MPAP (mmHg)	PLC	19 ± 6	24 ± 2*	23 ± 4*	21 ± 4
	DXM	16 ± 5	19 ± 3	19 ± 3	18 ± 4
CVP (mmHg)	PLC	11 ± 4	11 ± 2	11 ± 2	9 ± 3
	DXM	9 ± 5	10 ± 4	9 ± 3	7 ± 3
PCWP (mmHg)	PLC	12 ± 5	13 ± 4	13 ± 3	13 ± 3
	DXM	12 ± 6	12 ± 3	12 ± 2	10 ± 3
CI ($l \cdot min^{-1} \cdot m^{-2}$)	PLC	2.3 ± 0.6	3.0 ± 0.9*	3.1 ± 0.8*	3.1 ± 0.6*
	DXM	2.3 ± 0.5	2.7 ± 0.7	3.1 ± 0.5*	3.3 ± 0.8**
SVI (ml/m^2)	PLC	38.5 ± 9.2	33.1 ± 8.7	33.5 ± 6.5	35.5 ± 4.3
	DXM	37.6 ± 6.5	31.3 ± 7.0	33.7 ± 5.1	36.3 ± 7.3
			‡	†	
PVRI ($dyn \cdot sec \cdot m^{-2} \cdot cm^{-5}$)	PLC	211 ± 67	312 ± 176*	258 ± 87	227 ± 90
	DXM	162 ± 61	206 ± 57	187 ± 52	194 ± 43
SVRI ($dyn \cdot sec \cdot m^{-2} \cdot cm^{-5}$)	PLC	2137 ± 533	2102 ± 722	1636 ± 438	1804 ± 557
	DXM	2456 ± 737	2077 ± 614	1816 ± 608	1777 ± 670

mean ± SD.

*(**) $P \leq 0.05$ (0.01): 1h, 6h, 20h *vs.* baseline; †(‡) $P \leq 0.05$ (0.01): PLC *vs.* DXM.

PLC = placebo group; DXM = dexamethasone group; HR = heart rate; MAP = mean arterial pressure; MPAP = mean pulmonary artery pressure; CVP = central venous pressure; PCWP = pulmonary capillary wedge pressure; CI = cardiac index; SVI = stroke volume index; PVRI = pulmonary vascular resistance index; SVRI = systemic vascular resistance index; baseline = after induction of anesthesia; 1h (6 h, 20 h) = 1 (6,20) h postoperatively.

Table 3. Extravascular Lung Water

		Baseline	1h	6h	20h
					†
EVLW (ml/kg[1])	PLC	5.8 ± 1.0	6.2 ± 1.3	5.8 ± 1.2	5.8 ± 1.1
	DXM	5.4 ± 1.1	5.1 ± 1.4	4.7 ± 1.1	4.6 ± 0.8*

mean ± SD

* $P \leq 0.05$: 20h *vs.* baseline; † $P \leq 0.01$: PLC *versus* DXM.

PLC = placebo group; DXM = dexamethasone group; baseline = after induction of anesthesia; 1h (6h, 20h) = 1 (6,20) hour(s) postoperatively.

analyze the effects of surgery, extracorporeal circulation, and intraoperative fluid therapy separately, balances at end of surgery are also specified. The input and output of cellular blood components were well-balanced, with differences of <2 ml/kg over the entire study period. As expected, a significant positive fluid balance was seen in all patients at end of surgery; this was caused by excess crystalloid input, which continued to increase up to 6 h after the end of surgery.

In the later postoperative course this accumulated volume decreased slowly and only partially. At 20 h, the cumulated total fluid balances were still +72.4 ml/kg and +60.0 ml/kg, respectively, in the placebo and dexamethasone group. There were significantly fewer positive fluid balances in the dexamethasone group over the entire study period. In both groups, crystalloids were replaced by colloids in the postoperative period, as indicated by the time courses of the detailed balances in table 4. No significant differences in doses of furosemide were seen between the two groups (table 4).

Total blood volume was decreased compared to baseline at 1h and remained at this level during the entire study period after surgery in both groups (fig. 1). ITBV remained remarkably stable, with almost identical time courses in the two groups, as demonstrated in fig. 2.

In all patients an increase in extravascular fluid content was observed; the data are depicted in fig. 3. Significantly more fluid was transferred to the extravascular space in the placebo group, with a maximum difference of >20 ml/kg at 6 h postoperatively.

Discussion

The results of this prospective randomized clinical study demonstrate no relevant changes in EVLW after coronary bypass surgery, despite marked positive fluid balances and total extravascular fluid accumulation. Pretreatment with dexamethasone decreased significantly the extent of positive fluid balances and total extravascular fluid accumulation. Despite these differences in fluid extravasation, time course of TBV and ITBV were remarkably similar in the two groups, as a result of blinded routine clinical management.

As early as 1966, corticosteroids were being administered to patients undergoing cardiac surgery, with the goal of counteracting some of the adverse effects of CPB.[9] The majority of studies performed since than showed an improvement in hemodynamic stability by preoperative administration of steroids. Steroids were therefore recommended in order to stabilize mean arterial blood pressure[12,14] and to increase cardiac index after CPB.[15,16] In the current investigation, we used a 1-mg/kg dose of dexamethasone at least 60 min before CPB, according to previous recommendations.[20] We did

Table 4. Cumulative Fluid Balances and Furosemide Application

		Baseline - eos	Baseline - 1h	Baseline - 6h	Baseline - 20h
		‡	‡	‡	‡
Crystalloids (ml/kg[1])	PLC	70 ± 19	68 ± 19	62 ± 18	42 ± 17
	DXM	50 ± 14	45 ± 15	40 ± 14	27 ± 10
Erythrocytes (ml/kg[1])	PLC	0.5 ± 3.7	1.5 ± 3.8	0.7 ± 3.9	1.4 ± 4.2
	DXM	0.6 ± 3.7	0.2 ± 3.5	0.7 ± 4.2	0.2 ± 4.5
Colloids (ml/kg[1])	PLC	6 ± 9	11 ± 11	23 ± 14	29 ± 20
	DXM	10 ± 8	17 ± 10	27 ± 14	33 ± 15
		‡	‡	‡	‡
Total fluid balance (ml/kg[1])	PLC	**77 ± 26**	**81 ± 28**	**86 ± 32**	**72 ± 31**
	DXM	**60 ± 15**	**62 ± 20**	**67 ± 22**	**60 ± 18**
			†	†	†
Diuresis (ml/kg[1])	PLC	25 ± 21	34 ± 21	49 ± 24	83 ± 32
	DXM	17 ± 5	26 ± 5	38 ± 6	60 ± 11
Furosemide (mg)	PLC	—	10.5 ± 18.0	13.5 ± 17.3	30.5 ± 39.5
	DXM	—	17.0 ± 14.2	18.0 ± 15.5	33.5 ± 26.0

mean ± SD

†(‡) $P \leq 0.05$ (0.01): PLC *vs.* DXM.

PLC = placebo group; DXM = dexamethasone group; baseline = after induction of anesthesia; eos = end of surgery; 1 h (6 h, 20 h) = 1 (6,20) h postoperatively.

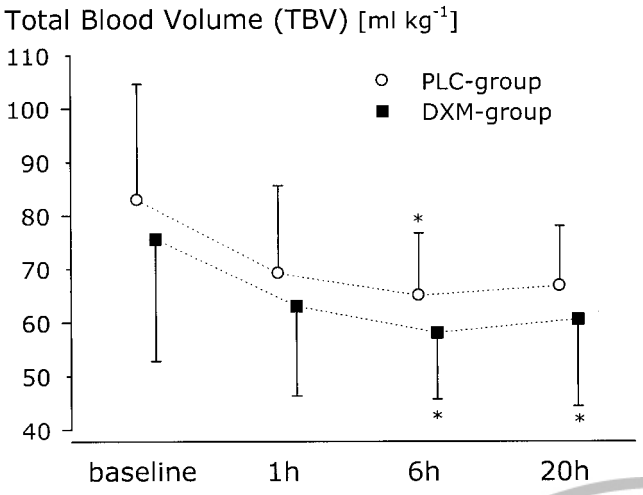

Fig. 1. Time course of total blood volume (TBV) from baseline until 20 h postoperatively. TBV is postoperatively significantly decreased in both groups in comparison with baseline, but no significant differences between the groups are demonstrated. PLC = placebo group; DXM = dexamethasone group; baseline = after induction of anesthesia; 1h, 6h, and 20h = postoperative hours 1, 6, and 20; *$P \geq 0.05$ (6h, 20h *versus* baseline).

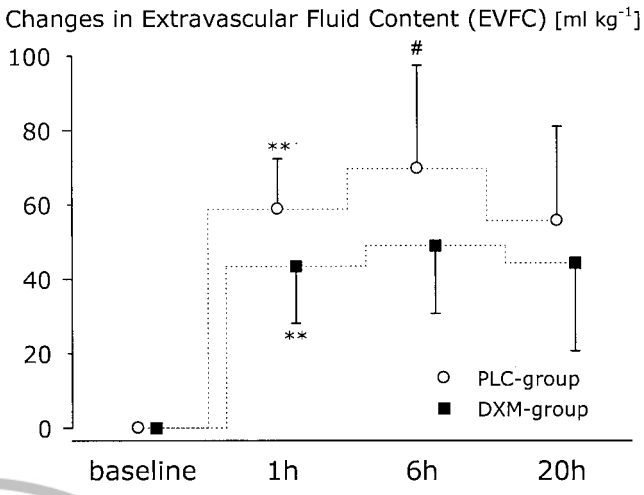

Fig. 3. Cumulated absolute changes in extravascular fluid content (EVFC) from baseline until 20 h postoperatively. Significantly less fluid was transferred to the extravascular space in the dexamethasone group, with a maximum difference at 6 h postoperatively. PLC = placebo group; DXM = dexamethasone group; baseline = after induction of anesthesia; 1h, 6h, and 20h = postoperative hours 1, 6, and 20; **$P \geq 0.01$ (1h *vs.* baseline); #$P \geq 0.05$ (PLC *vs.* DXM).

not observe significant differences in cardiac index between the verum group and the placebo group, and a slightly decreased need for epinephrine or dopamine during the postoperative course in the dexamethasone group was the only evidence of better cardiovascular performance. In principle, any improvement of hemodynamics could be due to either an improved cardiac contractility or changing loading conditions, which in turn could be influenced by fluid extravasation.

Influence of Corticosteroids on Capillary Leakage

Inflammatory reactions occurring during and after CPB have been well recognized for a long time by open-heart surgeons.[3,4,21] CPB-related inflammatory response comprises a complex reaction including complement activation, release of various cytokines, activation of leukocytes, increased expression of adhesion molecules, and production of numerous substances such as arachidonic acid metabolites, oxygen-free radicals, platelet-activating factor, endothelins, and nitric oxide.[4] These reactions are similar or even identical to a systemic inflammatory response syndrome and may cause several intraoperative and postoperative complications, subsumed under "postperfusion" or "postpump" syndrome.[22] Capillary leakage is a relevant component of this phenomenon,[23,24] and several of the involved inflammatory mediators, which can cause an increase in vascular permeability,[3,4] have been identified. It has been shown that the release of these inflammatory mediators—in particular, the release of TNFα after CPB—can be blocked by steroids.[10,12,25,26]

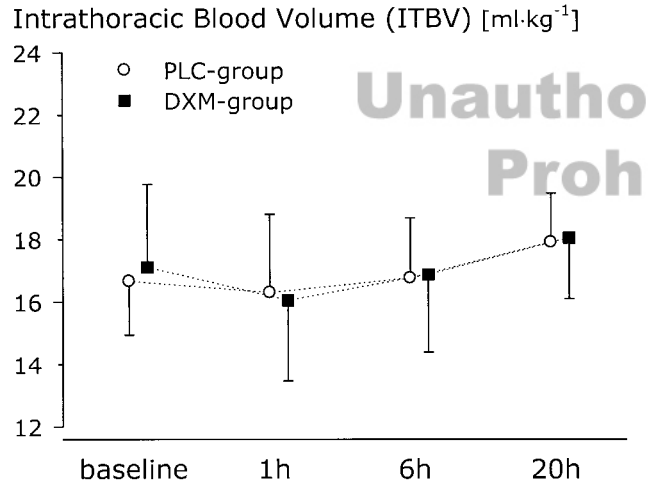

Fig. 2. Time course of intrathoracic blood volume (ITBV) from baseline until 20 h postoperatively. No differences between both groups are demonstrated. PLC = placebo group; DXM = dexamethasone group; baseline = after induction of anesthesia; 1h, 6h, and 20h = postoperative hours 1, 6, and 20.

In fact, several studies demonstrated that steroids also can decrease the positive fluid balances after CPB.[11–13] Most investigators hypothesized that this beneficial effect was caused by less capillary leakage,[1,2,23] which results from the well-known antiinflammatory effects of steroids. To our knowledge, it has not yet been demonstrated that capillary leakage, in terms of net fluid transfer from intravascular to extravascular accumulations, is indeed decreased by steroids. To validate this hypothesis and to assess capillary leakage under clinical circumstances, in the current study we measured EVLW and total fluid shifts to the extravascular space.

In contrast with our expectations, EVLW did not differ from baseline after surgery in the placebo group (table 3). This finding is different from those of previous inves-

tigations, in which a slight but significant increase in EVLW was observed after CPB.[19,27] In fact, EVLW after induction of anesthesia (baseline) was already higher in the current investigation (5.8 ± 1.0 *vs.* 3.8 ± 0.9 ml/kg), whereas EVLW values after surgery were similar in the control groups.[19] It remains unclear whether the type of anesthesia used for induction could be associated with different fluid regimens during the induction period. In the previous study,[19] anesthesia was induced with etomidate and fentanyl, whereas in the current investigation only sufentanil was used. However, despite the fact that EVLW was not increased after CPB, our results—in accordance with those of various studies— confirm highly positive fluid balances in all patients in the early postoperative period, mainly caused by cumulated crystalloids (table 4). Thus, capillary leakage after CPB does not necessarily cause an increase in EVLW.[27]

From the data of this study it can be deduced that the highest capillary leakage rate occurred during surgery, with approximately 15 ml · kg^{-1} · h^{-1} in the placebo group and 11 ml · kg^{-1} · h^{-1} in the dexamethasone group. It is obvious that fluid extravasation associated with cardiac surgery and CPB can be modified but not prevented by dexamethasone. In light of the other influences on Starling's transmembranous forces (not affected by steroids), this is comprehensible. Of course, changes in vascular permeability due to inflammatory mediators are not the only cause of fluid extravasation under these circumstances. Another important cause of fluid transfer is the decrease in plasma colloid osmotic pressure regularly seen as a result of the priming solution of the CPB circuit.[1,28] At least in the early development of increased intravascular-to-extravascular fluid shift during CPB, the change in colloid osmotic pressure seems to be a major mechanism.[23,29] An increase in venous pressure, sometimes seen with initiation of CPB or caused by postischemic myocardial dysfunction, can also result in an increase in transvascular protein and fluid flux.[30] Finally, an impaired lymphatic flow during or after CPB may be involved in the development of tissue edema.[31]

Influence of Corticosteroids on Cardiac Preload

Theoretically, less fluid loss into the extravascular space could improve intravascular volume status and thereby increase preload and cardiac performance. However, as shown in fig. 1, less fluid loss to the extravascular compartment in the dexamethasone group was not associated with an increase in TBV. Moreover, TBV was even decreased postoperatively to an identical extent in the two groups, despite positive fluid balances in all patients, blinded clinical fluid management, and the observed differences in these balances.

Still, TBV determines only very indirectly cardiac filling, and, with respect to hemodynamic stability, not TBV but the intravascular volume of the intrathoracic compartment holds a key position, as it serves as a blood reservoir for the left ventricle.[32]

In previous studies, ITBV was demonstrated to serve as a more reliable preload parameter, as opposed to the filling pressures, central venous pressure (CVP), and pulmonary capillary wedge pressure (PCWP).[33,34] Theoretically, corticosteroids could redistribute intravascular volume in favor of the intrathoracic compartment and thereby stabilize the post-CPB hemodynamic situation. To investigate this hypothesis we measured ITBV *in vivo* from the concentration–time courses recorded *via* the aortic fiberoptic catheter.[27] As shown in fig. 2, no significant changes in the course of ITBV were seen, and differences in cardiac filling in the dexamethasone group could be clearly ruled out.

Influence of Corticosteroids on Extravascular Fluid Content

Decreased TBV in conjunction with positive fluid balances inevitably results in an increase in EVFC. Investigators in mainly experimental studies have tried to quantify the rise in EVFC.[29] Olthof *et al.*[2] measured changes in interstitial fluid volume by a noninvasive conductivity technique and found an increase in interstitial fluid volume of 14% in 11 patients undergoing coronary bypass surgery, from start to end of operation. Koller *et al.*[1] estimated for a 70-kg person a filtered volume of 3 l/h during extracorporeal circulation. Relative changes in interstitial fluid volume and the extent of filtered volume only during CPB are difficult to compare with our data, and none of the previous study groups investigated the effect of corticosteroids on their findings. Our postoperative measurements demonstrated a massive increase in EVFC, between 40 and 70 ml/kg, compared with the situation after induction of anesthesia (fig. 3). However, at 1 h and 6 h, a highly significant difference was observed between the two groups: the increase in EVFC in the patients pretreated with dexamethasone was up to 20 ml/kg less than in the placebo group (fig. 3).

Influence of Corticosteroids on Left and Right Ventricular Afterload

Neither mean arterial pressure nor systemic vascular resistance was significantly different in the two groups (table 2), representing a comparable left ventricular afterload in both groups.

However, pulmonary vasoconstriction, pulmonary hypertension, and right ventricular dysfunction are common occurrences after CPB,[35] and we also measured a significant increase in pulmonary vascular resistance and mean pulmonary artery pressure in the placebo group 1 h and 6 h postoperatively (table 2). In contrast, this phenomenon was not observed in patients pretreated with dexamethasone. The endothelium is recognized to be central to the pathophysiology of this condition, probably by oxidant-mediated reduction of pulmonary

nitric oxide production.[35,36] Modulation of the inflammatory response by corticosteroids seems also to prevent pulmonary vasoconstriction and improve right ventricular function. In addition, pulmonary hypertension may also contribute to left ventricular myocardial interstitial edema, which in turn might result in left ventricular dysfunction.[6]

In summary, we conclude that a significant increase in extravascular fluid gain but not in EVLW is regularly seen in patients after CPB. The data of this study suggest that pretreatment of patients with 1 mg/kg dexamethasone before CPB decreases extravascular fluid gain but does not cause differences in cardiac filling.

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