Cardiovascular Topics

Effect of different priming fluids on extravascular lung water, cell integrity and oxidative stress in cardiopulmonary bypass surgery

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Abstract

Background: Discussions continue on the ideal priming fluid in adult cardiac surgery. The purpose of this prospective study was to evaluate the effects of different types of priming fluids on extravascular lung water, cell integrity and oxidative stress status.

Methods: Thirty elective coronary artery bypass surgery patients were randomised prospectively into two groups. The first group received colloid priming fluid, while the second group received crystalloid priming fluid. Extravascular lung water index, advanced oxidative protein products, total thiol, free haemoglobin, ischaemic modified albumin and sialic acid levels were measured. Moreover, intra-operative and postoperative outcomes were reviewed.

Results: There were no significant differences between the groups with regard to extravascular lung water index, oxidative stress parameters or cell integrity ($p > 0.05$). Similarly, no significant differences were observed between the patients with regard to intra-operative and postoperative outcomes ($p > 0.05$).

Conclusions: The presumed superiority of colloidal priming for cardiopulmonary bypass could not be confirmed in our study.

Keywords: priming fluid, extravascular lung water index, oxidative stress, cell integrity

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Coronary artery bypass grafting (CABG) causes an acute inflammatory response, which results in systemic inflammatory response syndrome (SIRS), leading to organ damage.[1-3] In cardiopulmonary bypass (CPB) circuits, non-physiological environmental factors such as foreign surfaces, haemodilution, non-pulsatile flow and temperature variations can induce an inflammatory response. Furthermore, the balance between pro- and anti-oxidant mediators is disturbed, resulting in excessive accumulation of reactive oxygen species.[4] In turn, this redox imbalance, which is called oxidative stress, triggers the inflammatory response and initiates an oxidative vicious circle.[2,5] Inflammatory processes accompanied by oxidative stress can affect the barrier function of the plasma membrane, leading to changes in intra- and extravascular volume status.[6]

Pulmonary oedema is a complication following CABG. Accumulation of extravascular lung water (EVLW), as a consequence of increased permeability or increased hydrostatic pressure in the pulmonary capillaries after CABG, is increased in the oedematous lungs and has been described in several studies.[7-10] Transpulmonary thermodilution technique is used to monitor the cardiac preload volume through the global end-diastolic volume (GEDV) and estimates EVLW volume, which is considered a reliable estimate of interstitial lung oedema.[11]

Different types of priming fluids were used in CPB circuits to provide organ protection and perfusion.[12-14] Crystalloid and colloid priming fluids are still in use, and, to date, no standard solution has gained general acceptance.[15,16] Crystalloid-based priming fluids were found to reduce colloid oncotic pressure (COP) and cause CABG-related oedema.[17] However, 6% hydroxyethyl starch 130/0.4 (6% HES) as a synthetic colloid can increase the COP.[18] Despite all that is known, the effects of the composition of the priming fluid on the outcome parameters, such as EVLW, duration of extubation and intensive care unit (ICU)/hospital stay in CABG remain unclear.[13,19,20]

The primary aim of this study was to test the hypothesis that colloid priming fluid provides protective effects against oxidative stress and interstitial pulmonary oedema in CABG. As a secondary aim, we compared the short-term outcome parameters.

Methods

After the study protocol was approved by the ethics committee (ATADEK-723) and written informed consent was obtained

from each patient, 30 consecutive patients scheduled for elective CABG were selected for the study. The patients were randomly allocated to two groups. The patients in group 1 (n = 15) were primed with a 6% HES (1 200 ml 6% HES, Voluven®; Fresenius Kabi, Germany), while the patients in group 2 were primed with a crystalloid solution (1 200 ml 0.9 % NaCl; n = 15, Polifleks®; Polifarma, Istanbul, Turkey).

Exclusion criteria were assigned as the patient's age not being between 18 and 65 years, left ventricular ejection fraction < 40%, emergent/urgent operations, additional valvular diseases, impaired renal function (estimated glomerular filtration rate > 60 ml/min) and co-morbid disease (except for hypertension).

Anaesthetic and surgical management of the patients was performed by the same anaesthetist and surgical team. A standard monitoring regimen, including invasive arterial pressure, central venous pressure, peripheral oxygen saturation, five-lead electrocardiogram, regional cerebral oxygen saturation and end-tidal CO_2 monitoring was performed. A 5-Fr femoral arterial thermistor-tipped catheter connected to the pulse index contour continuous cardiac output analysis monitor (PiCCO Technology, Pulsion Medical Systems, Germany) was inserted into each patient. The extravascular lung water index (ELWI), stroke volume index (SVI), systemic vascular resistance index (SVRI), cardiac index (CI) and global end-diastolic volume index (GEDI) were measured using the thermodilution and pulse contour analysis methods.

The anaesthesia regimen was intravenously induced with fentanyl and propofol. Tracheal intubation was intravenously facilitated with rocuronium. Anaesthesia was maintained with sevoflurane at one minimum alveolar concentration in air/oxygen and a maintenance dose of rocuronium and fentanyl. Ventilation of the patients was adjusted to maintain normoxia and normocapnia. Heparin (300 IU/kg) and additional heparin were given until the activated clotting time was > 400 seconds. As the CPB concluded, protamine sulphate was administered at the same dosage as the initially administered heparin dose to antagonise the heparin effect. Dopamine, dobutamine, norepinephrine, epinephrine, or combinations thereof were used as inotrope or vasopressors. The patients were transferred to the cardiac ICU after surgery.

Standard CPB techniques were employed. The CPB circuit was primed according to each patient's study group. During CPB, standard cannulation of the ascending aorta and right atrium was performed. Pump flows at 2.0–2.4 l/min/m^2 of the body surface area, moderate systemic hypothermia (32°C) and intermittent anterograde blood cardioplegia was used. Homogenous cooling and rewarming were provided.

Packed red blood cells were transfused to maintain haemoglobin levels between 6 and 8 g/dl during the pump period and between 8 and 10 g/dl after reperfusion. Fresh frozen plasma and platelet transfusions were used, according to the laboratory and clinical findings. Normal saline solution was administered to meet the volume loss by evaporation and through the urine.

In addition to PiCCO and oxidative stress status measurements, heart rate, mean arterial pressure, the partial pressure of carbon dioxide and oxygen (pCO_2–pO_2), and serum level of haematocrit, glucose and lactate were recorded. The duration of extubation and ICU/hospital stay were also determined.

Haemodynamic variables [heart rate (beats/min), mean arterial pressure (mmHg)], blood gas analysis [pH, pCO_2 (mmHg), pO_2 (mmHg), lactate (mmol/l) and biochemical variables (glucose (mg/dl), hematocrit (%)] were obtained at the following times: T0 (zero time point), T1 (after anaesthesia induction), T2 (five minutes after the initiation of CPB), T3 (after cross-clamping), T4 (after weaning from CPB), T5 (at admission to the ICU), T6 (third hour after ICU admission) and T7 (24th hour after ICU admission).

Using the transpulmonary thermodilution and PiCCO methods, ELWI, SVI, SVRI, CI and GEDI were evaluated at the T1, T4, T5, T6 and T7 time points. In addition, blood samples were obtained to evaluate the oxidative stress status and cellular integrity. For this purpose, serum advanced oxidative protein products (AOPP), total thiol (T-SH), free haemoglobin (fHb), ischaemic modified albumin (IMA) and sialic acid (SA) levels were measured at the T0, T5 and T7 time points.

The AOPP levels were measured to determine the protein oxidation using a modified method of Hanasand *et al*.[21] The measurement of IMA levels was performed to show three-dimensional modification of plasma albumin using a modification of the Bar-Or *et al*. method.[22] The measurement of T-SH determination was performed to thiol modification of protein, which is based on the method of Sedlak and Lindsay.[23] The SA levels were determined by the method of Sydow.[24] The level of fHb was determined to show the oxidant-mediated homolysis using the method by Harboe.[25]

Statistical analysis

After the determination of distribution of data sets using the Kolmogorov–Smirnov and Shapiro–Wilk tests, all data are presented as mean ± SEM. Statistical analysis was performed using GraphPad Prism v5.0 (GraphPad Software, La Jolla, CA, USA). The sample size was estimated using G*Power software (version 3.1; Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany). To this, the study power was accepted as 80%, the type 1 alpha error was 0.05 and the effect size was accepted as 58% according to the ELWI change,[26] as primary outcome. A comparative analysis of the two groups at the same time point was performed using the unpaired t-test and one-way ANOVA. The Bonferroni *post hoc* test was used for repeated measurements. Differences between values were considered statistically significant at $p < 0.05$.

Results

Table 1 shows haemodynamic, biochemical and arterial blood gas measurements at seven time points in the groups. There were similar results in both groups at all time points ($p > 0.05$). For the colloid group, the IMA levels (ABS units) were measured as 0.511 ± 0.047 at T1, 0.475 ± 0.059 at T5 and 0.457 ± 0.055 at T7. For the crystalloid group, the IMA levels (ABS units) were measured as 0.388 ± 0.074 at T1, 0.355 ± 0.063 at T5 and 0.424 ± 0.080 at T7.

For the colloid group, the T-SH levels (µmol/g protein) were measured as 33.6 ± 2.1 at T1, 76.7 ± 10.4 at T5 and 77.7 ± 20.7 at T7. For the crystalloid group, the T-SH levels (µmol/g protein) were measured as 39.2 ± 4.1 at T1, 55.3 ± 5.8 at T5 and 64.1 ± 6.7 at T7.

For the colloid group, the AOPP levels (mmol/g protein) were measured as 24.5 ± 2.2 at T1, 34.9 ± 3.4 at T5 and 30.6 ± 3.8 at

Table 1. Haemodynamic, biochemical and arterial blood gas measurements in the two groups

Time	Grp	HR (beats/min)	MAP (mmHg)	pCO_2 (mmHg)	pO_2 (mmHg)	Haemato-crit (%)	Glucose (mg/dl)	Lactate (mmol/l)
T1	G1	62.2 ± 4.0	74.1 ± 3.0	36.0 ± 0.7	159.4 ± 4.0	36.1 ± 2.1	129.4 ± 15.3	1.2 ± 0.1
	G2	57.0 ± 3.0	80.3 ± 4.0	36.5 ± 1.3	179.2 ± 10.2	40.0 ± 1.5	116.6 ± 6.8	1.5 ± 0.2
T4	G1	80.5 ± 4.0	69.5 ± 2.0	35.5 ± 0.9	123.8 ± 12.9	29.0 ± 1.8	165.2 ± 18.6	1.8 ± 0.3
	G2	74.7 ± 4.0	67.0 ± 2	36.2 ± 0.9	113.7 ± 6.5	27.1 ± 1.0	139.7 ± 10.7	1.8 ± 0.2
T5	G1	85.5 ± 6.0	88.8 ± 4.0	33.4 ± 1.0	135.2 ± 13.6	31.7 ± 1.2	166.5 ± 17.0	1.7 ± 0.3
	G2	77.7 ± 2.0	77.0 ± 5.0	31.7 ± 1.1	118.8 ± 10.1	29.6 ± 1.1	142.6 ± 12.0	1.9 ± 0.2
T6	G1	93.8 ± 4.0	79.0 ± 3.0	34.6 ± 1.1	131.8 ± 8.5	33.1 ± 1.3	163.9 ± 10.5	2.3 ± 0.3
	G2	94.9 ± 4.0	76.4 ± 3.0	34.3 ± 1.7	149.7 ± 7.6	31.8 ± 1.1	144.9 ± 11.3	2.3 ± 0.3
T7	G1	87.5 ± 3.0	83.1 ± 3.0	36.4 ± 1.0	96.0 ± 6.6	29.9 ± 1.3	175.0 ± 10.5	2.0 ± 0.4
	G2	83.9 ± 4.0	82.2 ± 3.0	38.4 ± 0.9	99.8 ± 6.7	30.0 ± 1.0	183.5 ± 7.0	2.2 ± 0.3

HR, heart rate; MAP, mean arterial pressure; pCO_2, partial pressure of carbon dioxide; pO_2, partial pressure of oxygen.

Table 3. Time-dependent parameters measured with PiCCO technology in the two groups

Time	Group	PiCCO CI (l/min/m²)	PiCCO SVI (ml/m²)	PiCCO GEDI (ml/m²)	PiCCO GEF (%)	PiCCO ELWI (ml/kg)
T1	G1	2.3 ± 0.2	33.3 ± 3.4	642 ± 61	20.0 ± 2.2	11.7 ± 1.6
	G2	2.1 ± 0.1	29.3 ± 2.8	628 ± 33	21.0 ± 1.4	8.4 ± 0.7
T4	G1	2.3 ± 0.3	26.6 ± 1.7	717 ± 84	16.6 ± 2.1	11.8 ± 1.3
	G2	2.4 ± 0.2	31.2 ± 2.0	614 ± 31	23.2 ± 1.6	9.5 ± 1.2
T5	G1	2.4 ± 0.2	27.5 ± 2.9	749 ± 83	17.6 ± 2.6	10.6 ± 1.2
	G2	2.3 ± 0.1	29.2 ± 1.0	607 ± 90	21.3 ± 0.8	8.6 ± 0.7
T6	G1	2.6 ± 0.2	27.6 ± 2.8	711 ± 81	17.0 ± 2.6	8.5 ± 0.7
	G2	2.5 ± 0.1	26.0 ± 1.3	639 ± 50	19.4 ± 1.6	7.7 ± 1.0
T7	G1	3.0 ± 0.1	33.9 ± 1.8	848 ± 28	18.5 ± 2.0	9.4 ± 1.1
	G2	2.9 ± 0.2	34.5 ± 2.2	698 ± 48	19.7 ± 0.9	7.3 ± 0.6

PiCCO, pulse index contour continuous cardiac output; CI, cardiac index; SVI, stroke volume index; GEDI, global end-diastolic index; GEF, global ejection fraction; ELWI, extravascular lung water index.

T7. For the crystalloid group, the AOPP levels (mmol/g protein) were measured as 34.0 ± 3.8 at T1, 42.1 ± 6.0 at T5 and 37.4 ± 4.8 at T7.

For the colloid group, the fHb levels (g/l) were measured as 0.08 ± 0.02 at T0, 0.19 ± 0.04 at T5 and 0.06 ± 0.01 at T7. For the crystalloid group, the fHb levels (g/l) were measured as 0.14 ± 0.03 at T1, 0.24 ± 0.06 at T5 and 0.08 ± 0.04 at T7.

For the colloid group, the SA levels (mg/g protein) were measured as 0.38 ± 0.03 at T1, 0.55 ± 0.06 at T5 and 0.66 ± 0.08 at T7. For the crystalloid group, the SA levels (mg/g protein) were measured as 0.48 ± 0.06 at T1, 0.56 ± 0.06 at T5 and 0.69 ± 0.09 at T7.

No significant differences in oxidative stress and cellular injury parameters were found between the colloid and crystalloid group at any time (Table 2) ($p > 0.05$). The changes in all PiCCO parameters are presented in Table 3. There was no significant difference between the groups ($p > 0.05$). ELWI (ml/kg) was measured as 11.7 ± 1.6 (T1), 11.8 ± 1.3 (T4), 10.6 ± 1.2 (T5), 8.5 ± 0.7 (T6) and 9.4 ± 1.1 (T7) in group 1 and as 8.4 ± 0.7 (T1), 9.5 ± 1.2 (T4), 8.6 ± 0.7 (T5), 7.7 ± 1.0 (T6) and 7.3 ± 0.6 (T7) in group 2. No significant differences were found between the two groups ($p > 0.05$). The ELWI course at the different time points is presented in Fig. 1.

Discussion

In this study, we compared two different priming fluids for EVLW, oxidative stress, cell integrity and ICU/hospital length of stay during CABG. A minimal increase in EVLW that did not reach statistical significance was observed in the crystalloid priminge fluid compared to the colloid priming fluid at all time points. Colloid and crystalloid priming fluids were also similar in their effects on cell integrity and oxidative stress. Furthermore, there were no differences between the groups in terms of postoperative ventilation times and length of ICU or hospital stay.

Performing coronary revascularisation using the CPB technique is an effective and safe technique, but fluid accumulation in the extravascular space is a phenomenon associated with the CPB technique.[27] Fluid extravasation leads to increased water content in the tissues, which results in cardiac and pulmonary dysfunction. The mechanisms contributing to this fluid shift are complex and attributed to a decrease in plasma oncotic pressure with the use of priming fluids during CPB, SIRS secondary to the exposure of blood to foreign surfaces, hypothermia or ischaemia–reperfusion injury.

This study was undertaken primarily to investigate changes in EVLW and oxidative stress status when different types of priming fluids were used for CPB. It was hypothesised that the crystalloid priming group (group 2) would have higher levels of ELWI, which would have apparent clinical effects, while the colloid priming fluid was expected to have beneficial effects during the peri-operative period.

It was previously believed that transcapillary fluid shift is determined solely by the balance between hydrostatic pressure and COP.[28] However, the revised Starling equation, which has

Table 2. Time-dependent changes in oxidative stress and cellular injury parameters in the two groups

Time	Group	IMA (ABS units)	T-SH (umol/g protein)	AOPP (mmol/g protein)	fHb (g/l)	SA (mg/g protein)
T1	G1	0.511 ± 0.047	33.6 ± 2.1	24.5 ± 2.2	0.08 ± 0.02	0.38 ± 0.03
	G2	0.388 ± 0.074	39.2 ± 4.1	34.0 ± 3.8	0.14 ± 0.03	0.48 ± 0.06
T5	G1	0.475 ± 0.059	76.7 ± 10.4	34.9 ± 3.4	0.19 ± 0.04	0.55 ± 0.06
	G2	0.355 ± 0.063	55.3 ± 5.8	42.1 ± 6.0	0.24 ± 0.06	0.56 ± 0.06
T7	G1	0.457 ± 0.055	77.7 ± 20.7	30.6 ± 3.8	0.06 ± 0.01	0.66 ± 0.08
	G2	0.424 ± 0.080	64.1 ± 6.7	37.4 ± 4.8	0.08 ± 0.04	0.69 ± 0.09

IMA, ischaemic modified albumin; T-SH, total thiol; AOPP, advanced oxidative protein products; fHb, free haemoglobin; SA, sialic acid.

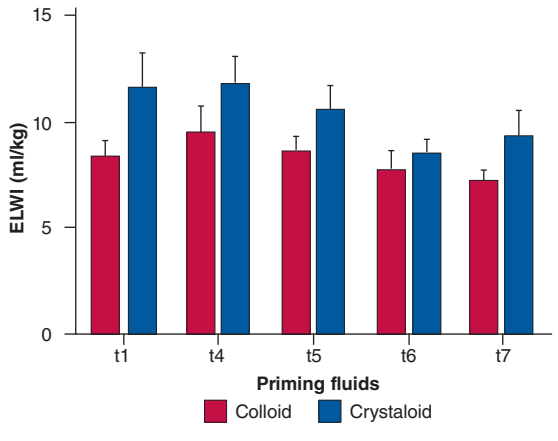

Fig. 1. Time-dependent changes in ELWI (ml/kg) in the two groups. ELWI, extravascular lung water index.

been accepted in recent years, has changed the view on fluid balance.[29] According to this equation, fluid movement from the intravascular space to the tissue is less affected by COP.

The most important factor determining transcapillary fluid movement is the endothelial glycocalyx layer and the COP in the sub-glycocalyx. In our study, sialic acid, one of the glycocalyx damage markers, was found to be similar in both groups. As a result, EVLWI was similar in patients receiving colloid and crystalloid fluids. In a meta-analysis of 29 studies published in 2022, the strategies of crystalloid and colloid priming were compared.[30] The authors emphasised that both priming fluids were similar in terms of COP.

Various types of priming fluids have been researched, but no consensus has been reached on the ideal composition to prevent SIRS and fluid extravasation. The literature contains a few studies related to the effects of priming fluids on ELWI. In a previous study by Hoeft *et al.*,[8] the researchers demonstrated that priming with a colloid fluid attenuated the increase in EVLW when compared to the effects of a pure crystalloid priming solution. Similarly, in a study investigating the effects of a hyperoncotic solution on EVLW and pulmonary function, the researchers found that post-CPB, EVLW was unchanged in the HES group, but elevated by 22% in the crystalloid group.[19] They also indicated that the colloid solution prevented EVLW accumulation in the early post-pump period.

Sade *et al*.[31] designed a study to determine whether there were important differences in the clinical effects of HES, albumin and lactate Ringer's solution (LRS) when used in priming fluid. They found greater somatic and pulmonary fluid accumulation in the LRS group and suggested that colloid was preferable to crystalloid priming fluids. However, no beneficial effects concerning the clinical parameters and patient outcomes could be demonstrated in the majority of the studies using colloid priming fluids.

Our study differs from previous studies in that most prior studies of the effects of different priming fluids on clinical outcomes focused on the impairment of blood coagulation and renal function related to HES usage.[32,33] In our study, we evaluated ELWI together with the oxidative stress status, which are the two main mechanisms that contribute to CPB-related organ damage. We have shown that two different priming fluids with similar results in terms of cell integrity and oxidative stress did not increase lung fluid content. Choi *et al*.[34] studied the effects of HES in comparison with human albumin and found no difference in the inflammatory response. Similarly, Lioi *et al*.[35] compared three different priming fluids (lactate Ringer's solution, human albumin and 10% HES) and found no statistically significant differences between the groups with regard to inflammatory cytokines.

In our study, the oxidative stress parameters were similar in both groups. Although there are numerous methods available for the assessment of oxidative stress, AOPP, IMA, fHb and T-SH levels have been proposed as possible markers of redox status. As an inflammatory marker, SA, which is known to have a significant correlation with other plasma acute-phase proteins, such as C-reactive protein and fibrinogen, was chosen.[36,37] Neither of the priming fluids used in our study caused detrimental effects on the redox or inflammatory status.

As a first limitation of our study, different processes of cellular damage such as apoptosis, inflammation and DNA damage may have taken place in our experimental set-up. However, in order not to spoil the perspective of the study, we only wanted to associate oxidative stress with lung water. The second limitation is that only male subjects should have been included in the study so that hormonal changes did not affect the study. However, to avoid difficulties while generalising the findings, our study was carried out with a mixed-gender population.

Conclusion

In our study, while the oxidative stress parameters were similar in both groups, mild increases in ELWI that did not reach statistical significance were observed in the crystalloid group. The colloid (6% HES) priming fluid was shown to be similar to the crystalloid fluid in terms of ELWI. Further studies on high-risk patients are warranted to explore the effects of different priming fluids on clinical parameters and patient outcomes.

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