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A randomised controlled trial of roller versus centrifugal cardiopulmonary bypass pumps in patients undergoing pulmonary endarterectomy

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Abstract

Objectives: There is some controversy as to whether there is a benefit from the use of a centrifugal pump compared with a roller pump during cardiopulmonary bypass to facilitate cardiac surgery. We compared the two pumps, with the primary aim of determining any difference in the effects on inflammation after pulmonary endarterectomy surgery which required prolonged cardiopulmonary bypass and deep hypothermic circulatory arrest.

Methods: Between September 2010 and July 2013, 58 elective patients undergoing pulmonary endarterectomy were included in this prospective, randomised, controlled study; 30 patients were randomly allocated to the control group, which used a roller pump, and 28 patients to the treatment group, which used a centrifugal pump. Interleukin-6, procalcitonin, C-reactive protein, thromboelastographic parameters, P-selectin, international normalised ratio, activated prothrombin time, free haemoglobin, haematocrit, red blood cell count, white blood cell count, platelet count and protein S100β were recorded during and after the procedure. We also recorded the length of intensive care unit stay, blood loss and transfusion, neurological outcomes and respiratory and renal failure.

Results: There was a significant difference in the primary outcome measure: Interleukin-6 was significantly higher in the roller pump group (587±38 $ng \cdot l^{-1}$ vs. 327±37 $ng \cdot l^{-1}$; $p<0.001$) 24 hours after surgery, which we interpreted as an increased inflammatory response. This was confirmed by a significant rise in the procalcitonin level in the roller pump group 48 hours following surgery (0.79 (0.08-25.25) $ng \cdot ml^{-1}$ vs. 0.36 (0.02-5.83) $ng \cdot ml^{-1}$; $p<0.05$). There were, however, no significant differences in clinical outcome data.

Conclusions: We have shown that the use of a centrifugal pump during prolonged cardiopulmonary bypass and deep hypothermic circulatory arrest is associated with a reduced inflammatory response compared to the standard roller pump. Larger multi-centre trials in this area of practice are required.

Keywords

pulmonary endarterectomy; cardiopulmonary bypass; roller pump; centrifugal pump; cardiac surgical procedure; inflammatory mediators

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Introduction

Cardiopulmonary bypass (CPB) requires a pump to propel the blood and the two most common types are the roller pump and the centrifugal pump. Most cardiac surgical procedures are carried out with CPB and a roller pump, despite its propensity to generate shear forces, which can cause haemolysis, lipid membrane ghosts and spallation from the tubing that may contribute to impaired microcirculation.[1,2] The centrifugal pump, on the other hand, is thought to be associated with less blood trauma and inflammation; however, it is more expensive and is, therefore, only used sparingly, especially in Europe.[3,4] Evidence favouring one pump over the other is somewhat controversial; some studies have suggested that the centrifugal pump is superior in routine elective adult cardiac surgery.[5–7] However, two recently published papers concluded that there was no evidence favouring either type of pump. A best-evidence topic analysed 15 studies[8] and a meta-analysis, including almost 2000 patients from randomised clinical trials, showed no differences in terms of haematological data, postoperative blood loss, blood transfusion, neurological outcomes or mortality.[9]

The majority of studies comparing different types of CPB pumps have studied patients undergoing relatively short surgical procedures, such as coronary artery revascularisation or valve surgeries, using normothermia or mild to moderate hypothermia.[9,10] Therefore, we decided to study patients undergoing pulmonary endarterectomy (PEA), for which CPB must be long (often up to 5 or 6 hours) and deep hypothermic circulatory arrest is required. Our aim was to investigate whether a centrifugal CPB pump would have of any benefit over a roller pump when prolonged CPB is employed. We hypothesised that the use of a centrifugal CPB pump would reduce both the inflammatory response and haemolysis and, therefore, improve clinical outcomes.

Methods

After local ethics committee approval, the patients were asked to provide written informed consent if they were undergoing pulmonary endarterectomy between 30th September 2010 and 10th July 2013. Patients were randomly assigned to the control group (standard CPB using roller pump) or the treatment group (CPB using centrifugal pump), using a sealed envelope technique.

On the day of surgery, the patients were premedicated with 0.25 mg of alprazolam (Neurol, Zentiva, Slovakia) orally and transferred to the operating theatre. Total intravenous anaesthesia with invasive monitoring of arterial, central venous and pulmonary artery pressures was administered. It consisted of sufentanil (Sufentanil Torrex, Chiesi CZ, Prague, Czech Republic) in a total intravenous dose of 2-3 $\mu g \cdot kg^{-1}$, muscle relaxant rocuronium (Esmeron, Organon Ltd., Swords, Ireland) in a total intravenous dose of 1-2 $mg \cdot kg^{-1}$ and propofol (Propofol, Fresenius Kabi, Bad Homburg, Germany) given intravenously as a bolus dose of 1.5 $mg \cdot kg^{-1}$ followed by a continuous infusion of 3-4 $mg \cdot kg^{-1}$. The patients' lungs were mechanically ventilated using a pressure control mode with positive end-expiratory pressure of 8 cmH_2O and a tidal volume up to 6 $ml \cdot kg^{-1}$ to achieve normocapnia (end-tidal CO_2 pressure 30-35 mmHg). Neither N_2O nor volatile anaesthetics were used. During surgery, the body temperature was measured in the hypopharynx, the rectum and the bladder. Routine antibiotic prophylaxis was administered one hour before the skin incision and continued for forty-eight hours.

After sternotomy, a 3 $mg \cdot kg^{-1}$ dose of heparin was administered. After reaching an activated clotting time of 480 seconds, CPB was initiated, using either a roller or a centrifugal blood pump. The patients were actively cooled to a bladder temperature of 16-18 degrees Celsius. The patients received 1000 ml of cold antegrade crystalloid cardioplegia solution for myocardial protection (Custodiol, HTK Solution, Köhler Chemie GmbH, Bensheim, Germany). Circulatory arrest was used with two short periods of reperfusion to allow endarterectomy of each pulmonary artery. The patients' heads were covered in a "cool cap" (ArcticFlow, DonJoy, Vista, CA, USA) and near infrared spectroscopy (Invos Oxymeter, Somanetics, Troy, MI, USA) was used for cerebral monitoring. We also actively maintained the blood glucose level between 6 and 10 $mmol \cdot l^{-1}$, using a sliding scale of insulin. After finishing the endarterectomy, the patients were rewarmed and weaned from CPB before being given an equipotent dose of protamine (Protamin, Meda Pharma GmbH, Vienna, Austria) for heparin reversal (in a ratio of 1 mg of protamine to 1 mg of the total dose of heparin). After sternal closure, all patients were transferred to the intensive care unit sedated and their lungs mechanically ventilated.

The CPB setup consisted of the heart–lung machine (Stockert S5, Sorin Group Deutschland GmbH, Munich, Germany) with a blood parameter monitoring system (CDI™ System 500, Terumo Cardiovascular Systems, Ann Arbor, USA), a hollow-fibre oxygenator (HILITE 7000 LT System, Medos Medizintechnik AG, Stolberg, Germany) and a heparin-coated tubing set (Medos Medizintechnik AG). When patients were randomly assigned to the centrifugal pump, we used the Sorin Centrifugal Pump System (Sorin Group Deutschland GmbH) with the centrifugal pump Revolution (Sorin Group Italia, Mirandola, Italy). Flow rate was maintained at 2.4 $l \cdot m^{-2}$ in both groups during both cooling and rewarming and alpha-stat acid-base management was used in all patients.

Table 1. Demographic and perioperative data. Values are mean±SEM or frequency (proportion).

	RP	CP	p-value
Age / years	62.9±2.05	59.1±2.26	0.218
Male gender [a)]	14 (47%)	8 (29%)	0.156
BMI / kg·m^{-2}	28.3±0.65	26.3±0.61	0.029*
ECC / min	276.5±5.96	258.2±4.96	0.022*
CCT / min	99.6±2.51	98.8±3.51	0.862
DHCA / min	28.6±1.29	28.6±1.40	0.996
Min T / °C	17.0±0.04	17.1±0.04	0.060

Note. P-values are based on the independent samples t-tests; p-value is derived from the Chi-square test; *p<0.05; RP - roller pump, CP - centrifugal pump, BMI - body mass index, ECC - extracorporeal circulation, CCT – cross-clamp time, DHCA - deep hypothermic cardiac arrest, Min T - minimal body temperature.

Data were collected continuously during surgery and blood samples were taken for laboratory analysis after the induction of anaesthesia, after the administration of protamine and 24 and 48 hours after surgery. Thromboelastography (TEG 5000 Thrombelastograph® Hemostasis Analyzer System, Haemonetics, Braintree, MA, USA) was performed after the induction of anaesthesia and after the administration of protamine.

Plasma levels of procalcitonin (PCT) were analysed using the Kryptor test (BRAHMS AG, Hennigsdorf, Germany); the sensitivity of the analytic method was 0.02 ng·ml^{-1}. Plasma concentrations of C-reactive protein (CRP) and interleukin 6 (IL-6) (ELISA, Immunotech, Paris, France) were also determined. The intra- and inter-assay coefficients of variation were below 5%. Protein S100β as a marker of cerebral injury was measured using the ECLIA method on a Elecsys 2010 Roche analyser (Roche Diagnostics Limited, Rotkreuz, Switzerland). The examination of P-selectin as a marker of platelet and endothelium activation was performed using a Human sP-selectin™ Elisa kit (R&D Systems Europe, Abingdon, UK; error of measurement: 5.1% - 5.6%, laboratory standard for healthy people: serum sP-sel level 57.16 -148.83 ng·ml^{-1}, plasma sP-sel level 21.96 -78.29 ng·ml^{-1}).

Our primary outcome variable was IL-6; a previous study has shown that IL-6 increases from a mean (IQR) of 25 (21-39) ng·l^{-1} to 522 (416-645) ng·l^{-1} 24 hours after pulmonary endarterectomy.[9] We proposed that a 30% reduction in IL-6 would be clinically important and our power study (alpha 0.05, 80% power) showed that 27 patients would be required in each group; we decided to recruit 30 in each group to account for data loss or drop-outs. Distribution of data was tested using the Kolmogorov-Smirnov test. Normally distributed variables were reported as mean ± standard error of the mean (SEM). Differences between the groups were tested using the independent samples t-test, the two-way analysis of variance (ANOVA) Mann-Whitney U-test or the Chi-square test. P-values below 0.05 were considered to be statistically significant. Statistical analyses were performed using SPSS 17 (SPSS Inc., Chicago, IL, USA) and Statistica 12 (StatSoft, Inc., Tulsa, OK, USA).

Results

A total of 60 patients were recruited and 30 were randomly assigned to each group. Two patients from the centrifugal group were removed due to massive perioperative surgical bleeding, necessitating several transfusions and the institution of veno-arterial extracorporeal membrane oxygenation support in one case. This patient later died from septic complications in the intensive care unit (ICU). The two groups were similar except that patients in the control group (roller pump) had a higher body mass index (BMI) and duration of CPB, although the differences were numerically relatively small (Table 1). We, therefore, included body mass index (BMI) and duration of CPB as continuous covariate variables for further analysis of data.

Postoperative inflammation was greater in the control group (roller pump), as shown by a higher peak IL-6 levels 24 h after surgery compared to patients in the centrifugal pump group (587±38 ng·l^{-1} vs. 327±37 ng·l^{-1}, p<0.001; actual power=0.99, respectively; Figure 1). The PCT levels were also increased 48 h after surgery in the control group compared with the centrifugal pump group (0.79 (0.08-25.25) ng·ml^{-1} vs. 0.36 (0.02-5.83) ng·ml^{-1}, unadjusted p=0.0283, respectively; Figure 1). Controlling for confounders did not alter the result.

There was no difference between the two groups in free haemoglobin, white blood cell count, platelet count, P-selectin or haematocrit; the red cell count was also similar when adjusted for covariates, p=0.055 (Figure 2). Results of thromboelastography (TEG) and other coagulation data were also similar (Figure 3A), as was protein S100ß (Figure 4).

No differences were shown in any of the clinical outcome data and three patients from the centrifugal pump group with postoperative neurological complications suffered a Type II injury with transient confusion only (Table 2).

Discussion

Our prospective randomized controlled study has shown that, in patients undergoing pulmonary endarterectomy using prolonged CPB with deep hypothermic circulatory arrest, the use of the centrifugal pump causes less inflammatory activation compared with the standard roller pump. Compared to other authors who also studied the activation of inflammation using different

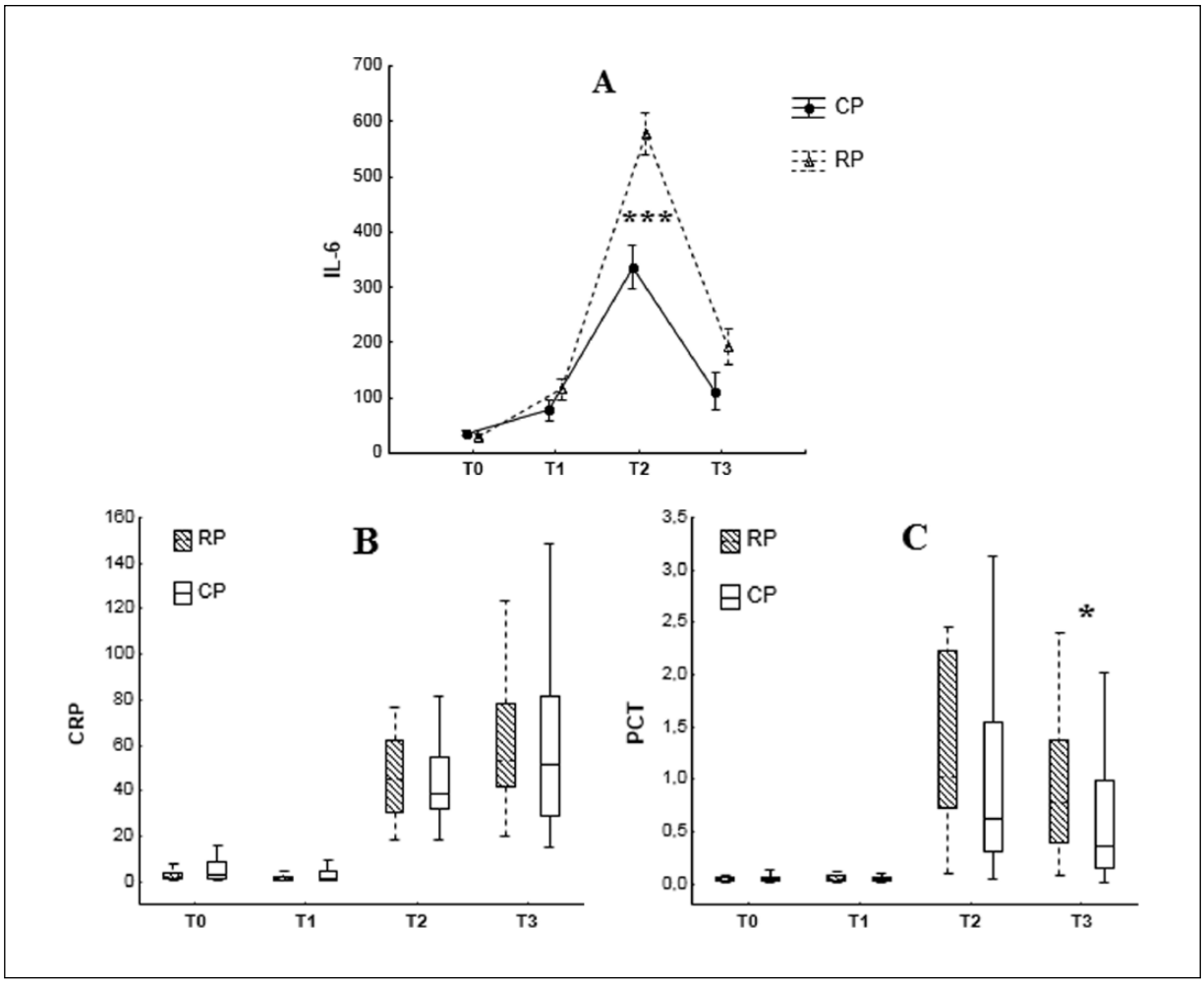

Figure 1. The course of markers of inflammation.
A. IL-6 = Interleukin 6 (ng·l^{-1}): normal variables are depicted as mean±SEM
B. CRP = C reactive protein (mg·l^{-1})
C. PCT = Procalcitonin (ng·ml^{-1})
Non-normal variables are represented by box-plots, whiskers constitute a non-outlier range;
T0 = pre pump; T1 = post pump; T2 = 24h post surgery; T3 = 48h post surgery; RP = roller pump; CP = centrifugal pump; * $p< 0.05$, *** $p< 0.001$.

types of pump, we have demonstrated quite different results. Lindholm et al. who focused on CPB biocompatibility, showed significantly higher elevation of IL-8 during the rewarming phase of CPB, but neither IL-6 nor tumour necrosis factor-α exhibited significant differences between the groups throughout the CPB or during the following 24 hours.[11] Although they included patients who underwent coronary artery bypass grafting (CABG) and CABG + aortic valve replacement surgery, their CPB times (145±9 and 149±7 minutes) were much shorter than in our patients. Also, Baufreton et al., in their small study, showed peak levels of IL-6 six hours following the start of CPB, with no significant differences between the two groups.[12] Tumour necrosis factor-α and IL-8 levels peaked even earlier, without any differences. Also, in this study, the CPB times (124±38 and 140±42 minutes) were shorter than in our patients. Even though the inflammatory response to CPB might have been attenuated by the aprotinin given to patients in the second study, we speculate that the type of pump may become an important factor with respect to cytokine release and profound pro-inflammatory reaction, depending on the duration of CPB, which is not yet precisely defined. This may be supported by a study done by Ashraf et al.[13] who also failed to show a significant IL-6 level difference between the roller pump and the centrifugal pump in their paediatric patients.

IL-6 is one of the major pro-inflammatory cytokines involved in the acute phase response, as well as in the pathogenesis and outcome of systemic inflammatory

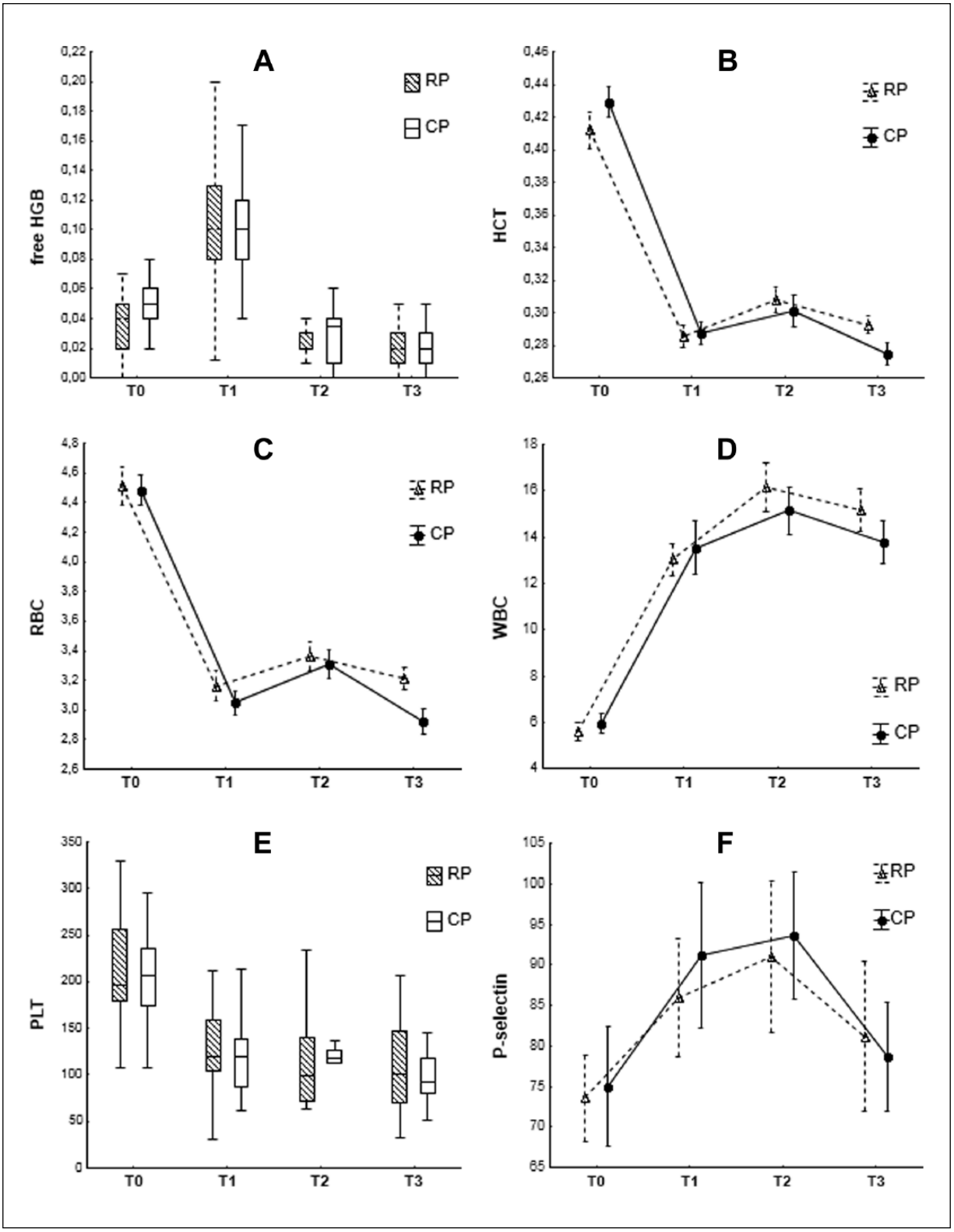

Figure 2. The course of haematological data.
A. Free HGB = free haemoglobin ($g \cdot dl^{-1}$): B. HCT = haematocrit: C. RBC = red blood cell count ($10^{12} \cdot l^{-1}$), D. WBC = white blood cell count ($10^{9} \cdot l^{-1}$), E. PLT = platelet count ($10^{9} \cdot l^{-1}$): non-normal variables are represented by box-plots, whiskers constitute a non-outlier range; F = P-selectin ($ng \cdot ml^{-1}$): normal variables are depicted as mean±SEM.
T0 = pre pump; T1 = post pump; T2 = 24h post surgery; T = 48h post surgery; RP = roller pump; CP = centrifugal pump.
* $p<0.05$.

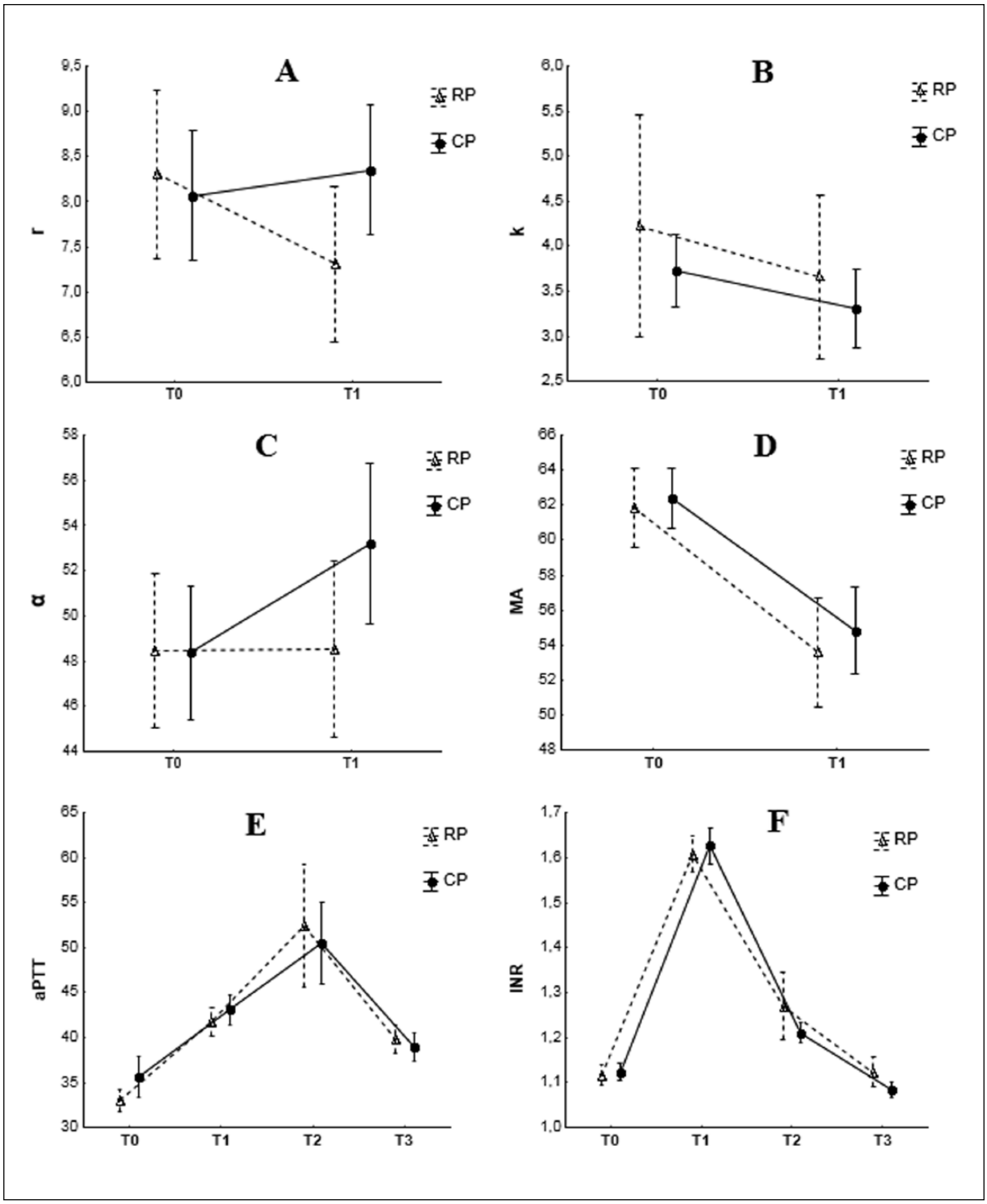

Figure 3. The course of thromboelastographic data (r, k, α, MA), aPTT and INR.
A. r = TEG parameter r (min); B. k = TEG parameter k (min); C. α = TEG parameter α; D. MA = TEG parameter MA (mm); E. aPTT = activated prothrombin time (s); F. INR = international normalized ratio.
Variables are depicted as mean±SEM.
T0 = pre pump; T1 = post pump; T2 = 24h post surgery; T3 = 48h post surgery; RP = roller pump; CP = centrifugal pump.

response syndrome, sepsis and septic shock. Increased levels of IL-6 have been reported in patients undergoing coronary artery bypass surgery with CPB compared with those without CPB.[14] In our study, we have confirmed that CPB leads to the activation of the inflammatory cascade, causing an elevation of cytokines and

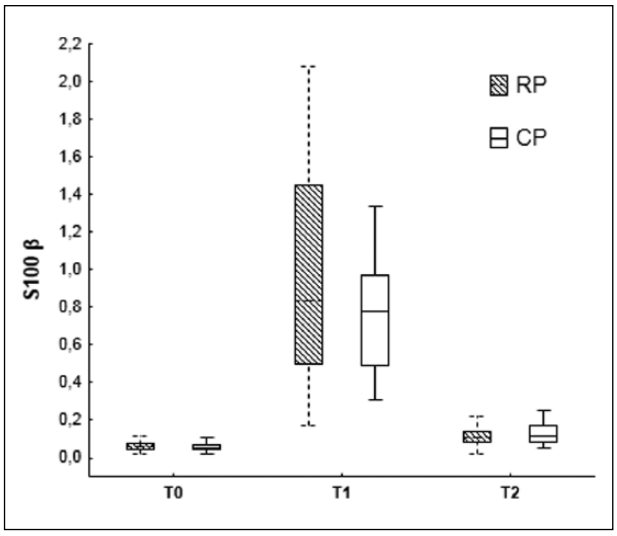

Figure 4. The course of S100 β.
S100 β (μ·l⁻¹): Non-normal variables are represented by box-plots, whiskers constitute a non-outlier range;
T0 = pre pump; T1 = post pump; T2 = 24h post surgery; RP = roller pump; CP = centrifugal pump.

other protein markers. Procalcitonin has been shown to be a marker of bacterial sepsis as well as an inflammatory marker and this was also lower when the centrifugal pump was used. The postoperative rise in PCT in our study was similar to other published work,[10,15] showing peak values 24 – 48 hours after surgery, with gradual normalization in uncomplicated procedures. This was a demonstration that infection did not participate in this post-surgical response. We hypothesize that the slower decline of PCT to normal values in patients in whom the roller pump was used may be due to a more profound aseptic inflammatory response to the pump rather than a reflection of bacterial infection in this group.

The different inflammatory activation caused by a centrifugal pump and a standard roller pump has diagnostic and potential pathogenetic consequences. PCT and IL-6 measurement may enable patients at increased risk of bacterial infection after PEA to be identified and daily monitoring may be indicated. An unexpected rise could prompt antibiotic treatment before the clinical signs of infection can be detected. The highest plasma levels of PCT are found in acute systemic bacterial infections and sepsis and is a valuable prognostic marker in cardiac surgery.[16] However, PCT is not highly specific for infection. In accordance with our previous study and those of other authors,[10,17] we showed that non-infectious factors may contribute to the evolution of serum PCT levels after cardiac surgery in the absence of postoperative complications. Due to the combination of local trauma, CPB and pulmonary and myocardial reperfusion, cardiac surgery leads to substantial changes in the immune system, with activation of cytokine and the PCT response. The increase in PCT and IL-6 seems to be dependent on the surgical procedure, with more invasive procedures associated with higher PCT and cytokine levels.[15] Patients with an uncomplicated course following PEA, thus, presented a continuous reference interval for plasma PCT and cytokine concentrations. A post-surgery increase of inflammatory markers limits their diagnostic value for the early diagnosis of inflammatory complications and it must be taken into consideration in this period.

Elevated cytokine concentrations also have a potential pathogenetic role in haemodynamic instability after PEA. This was demonstrated by Langer et al.[18] in a relatively small group of 14 patients. The authors revealed a positive correlation between maximum vasopressor support and peak levels of IL-6. In our previous study, the duration of catecholamine support was demonstrated as a better parameter reflecting haemodynamic instability than maximum doses of norepinephrine.[19] We documented that the time of post-surgery catecholamine support was related to IL-6 and IL-8 levels.

A major limitation of our study was the relatively small group sizes. The reason for this was the difficulty in recruiting patients undergoing such extensive surgery with prolonged CPB, which we decided was important for this study. Additionally, the study was organised in a single centre. Even though the study was carried out over three years, we did not feel it was possible to continue the study for longer than this to recruit enough patients to allow the study to be powered for clinical outcomes, as we had initially planned. Another limitation of our study is that patients randomly assigned to the roller pump had significantly shorter CPB duration and lower BMI. However, the actual differences were relatively small and we have controlled for these in our analysis of the data.

Despite these limitations, ours is the first study to compare the two devices in major cardiac surgery with prolonged CPB, in contrast to other studies which have examined patients undergoing relatively straightforward cardiac surgery with shorter CPB times.[2,4–6,8,9,20–22]. We propose that a larger multi-centre study comparing the two devices is now indicated, powered for clinical outcomes, which would be too big to carry out in a single centre.

In summary, we have shown that, in patients undergoing PEA using prolonged CPB and deep hypothermic circulatory arrest, the non-occlusive centrifugal pump is associated with reduced inflammation. We propose that future work is needed to define all possible effects of different pumps on outcomes of cardiac surgical procedures with prolonged CPB.

Table 2. Postoperative clinical data. Values are mean ±SEM or median (min; max) or frequency (proportion).

	RP	CP	P-value
AV / hrs	27 (18; 944)	26 (15; 539)	0.963
ICU stay / days	7 (3; 29)	6.5 (3; 37)	0.664
Blood loss / ml	1128±70	1011±75	0.259
pRBC / U	0 (0; 12)	0 (0; 3)	0.584
CRRT	2 (6.7%)	1 (3.6%)	n.t.
pre-Creatinine / µmol/l	96.2±3.46	95.4±3.41	0.869
post-Creatinine / µmol/l	132.6±13.49	112.3±6.82	0.187
Respiratory complication	2 (6.7%)	3 (10%)	n.t.
Neurological complication	0 (0%)	3 (10.7%)	n.t.

Note. P-values are based on the independent samples t-tests for normal and Mann-Whitney tests for non-normal variables; n.t. - significance not tested due to the low particular frequencies within the 2x2 tables.
RP: roller pump, CP: centrifugal pump, AV: artificial ventilation, pRBC: packed red blood cells, CRRT: continuous renal replacement therapy, pre-Creatinine: creatinine before surgery, post-Creatinine: creatinine after surgery.
The study was not powered for clinical outcomes.

Declaration of Conflicting Interest

The author declares that there is no conflict of interest.

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