A Computer-Controlled Pulsatile Pump System for Cardiopulmonary Bypass and Its Effects on Regional Blood Flow, Haemolysis and Inflammatory Response

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Abstract

The benefit of pulsatile perfusion during cardiopulmonary bypass is still controversial.In this study we examined the non-pulsatile perfusion generated by a roller pump, the pulsatile perfusion induced by a roller-pump and the "physiological" pulsatile perfusion generated by a new device on renal and gut tissue perfusion, haemolysis and inflammatory response.In the group with the new computer-controlled pump system there was no significant difference for haemodynamic data between the measurement before and under ECC. The degree of haemolysis was similar in both pulsatile groups but less in the non-pulsatile group. There was no difference on serum concentration of IL 6, IL 1ra and on regional blood flow between the groups.There are no advantages for pulsatile perfusion on haemolysis, inflammatory response and regional organ blood flow.

1. Introduction

Multiple organ dysfunctions after ECC are still a significant clinical problem. The mechanisms of organ injury after ECC are not fully understood, the perfusionmode (pulsatile versus non-pulsatile) may play an important role in this process. Data are still controversial whether pulsatile perfusion is more beneficial than non-pulsatile perfusion [1,2]. There are many reasons for the divergent results of different studies. First, because of the various types of generated pulsatile flows it is difficult to compare the results of previous studies. A clear definition for pulsatile flow does not exist [3]. Second, the not optimal setup of the cardiopulmonary bypass system (e.g. art. cannula) plays a major roll why the results are different. The purpose of this study was to investigate the effects of different types of pulsatile perfusion (physiological, roller pump) versus non-pulsatile flow. The different types of pulsatile perfusion are well defined by various haemodynamic datas. The effect of the different perfusion modes were investigated on regional renal and gut blood flow using fluorescent m icrospheres. The inflammatory response was evaluated by measuring the proinflammatory Interleukin 6 and the antiiflammatory Interleukin 1ra. The haemolysis was quantified by assessing the concentration of free haemoglobin and lactate dehydrogenase.

2. Methods

Experimental design: Thirty domestic pigs (10 in each group) underwent ECC (*group I:* physiological pulsatile flow, *group II:* pulsatile flow, *group 3:* non pulsatile flow) for 180 min, 120 min crossclamped and 60 min of reperfusion. After ECC all animals were observed for 6 hours. The central vein pressure, aortic pressure, aortic flow and ECG were recorded during the whole experiment. While the time of ECC the flow and pressure in the arterial line were measured as well. During the experiment at nine stages arterial blood samples were taken from the left femoral artery. For investigation of the regional renal and gut blood flow we used the microsphere technique. The microspheres were injected before ECC, after 120 min crossclamped, after 60 min of reperfusion and 180 and 360 min after ECC.

The new CPB pulsatile pump system is composed of a Stöckert roller pump and an additional piston pump (pulsator). The pulsator is integrated between the oxygenator and the aortal cannula in the arterial line. The base flow is generated by the non-pulsatile roller pump and after the oxygenator the new device impresses a pulsatile profile on the non-pulsatile base flow. To avoid a backflow into the cardiopulmonary circuit a valve was placed between the oxygenator and the pulsator.

Animals and anesthesia Thirty domestic pigs weighing 35.2 ± 0.7 kg were premedicated with intramuscular ketamine and atropine sulfate injection. General anesthesia was induced by intravenous injection of sodium thiopental. Anesthesia was maintained by continuous intravenous application of sufentanil citrate and midazolam through a syringe pump. Muscle relaxation was induced by pancuronium bromide i.v. and maintained by continuous delivery of pancuronium

bromide by a syringe pump. After endotracheal intubation, the pigs were placed on a respirator and ventilated with a mixture of oxygen and nitrogen dioxide. The fraction of inspirate oxygen (FIO_2) was set on 0,5. Every 30 min arterial pCO_2, pO_2, base excess and K^+ values were checked. pCO_2 was fixed to a range between 35 – 45 mmHg and pO_2 between 100 – 120 mmHg, base excess was kept at ± 2 and plasma K^+ at 4,5 – 5mmol/l.

Preparation Catheters were inserted in the jugular vein and the left femoral artery for blood sampling, monitoring of the central vein pressure and application of infusions and drugs. Via the right femoral artery a catheter tip manometer was placed in the descending aorta for monitoring the aortic pressure. After a median sternotomy the thymus was removed and the pericardium was opened. For measuring the aortic flow a perivascular ultrasonic flowprobe was placed at the descending aorta above the crossing of the pulmonary veins. For the injection of the fluorescent microspheres a catheter was placed in the left atrium.

ECC After intravenous injection of 500U/kg heparin sodium the ascending aorta and the right atrium were cannulated for cardiopulmonary bypass. The aorta was crossclamped and Bretschneiders cardioplegic was infused for cardiac arrest. During the time of cardiac arrest the left ventricle was vented via the apex. After the end of extracorporeal circulation, all cannulae were removed and the effect of heparin was neutralized by an intravenous injection of protamine. The chest and the pericardium were not closed for the rest of the experiment.

Measurement of regional blood flow Regional blood flow was assessed using fluorescent microspheres with a diameter of 15 µm. We used the colors yellow-green, blue-green, red, orange and crimson. 10^6 microspheres/10 kg were drawn off the stock solution into a plastic syringe which was filled with 16 to 17 ml of saline solution. Fifteen seconds before starting the microspheres injection, a pump for blood sample collection was started. The injection time was 30 seconds and the pump continued for another 105 seconds after injection. The injection was given into the left atrium via a catheter. During the cardiopulmonary bypass the microspheres were injected near by the end of the arterial cannula to guarantee an optimal mixture between the microspheres and the blood. After withdrawn, the blood sample was put onto the filter of a sample processing unit (SPU)[4]. The filter was washed three times with 10 ml of phosphat buffer. Afterwards the filters were stored in a refrigerator. To analyze tissue samples, animals were euthanised at the end of experiment, both kidneys and the gut were removed and fixed into a 4.5 % formaldehyde solution for 2 weeks. After fixation both kidneys and the gut were dissected. After measuring the weight of the tissue samples, the fluorescent microspheres were recovered by tissue digestion. After digestion of the tissue samples was successful the content of the filter was sucked by a negative pressure through the filter (mesh opening = 7 µm). The filter was washed three times with a phosphat buffer and dried between the three washing steps by centrifugation at 2800 rpm. The filter was set back in the SPU to extract the dyes from the Microspheres. Therefore 2ml of Cellosolve-acetate was given onto the filter membrane, followed by 2 min of vortexing and a centrifugation time of 5 min at 2800 rpm. The sample tube of the SPU was disconnected and the fluorescent intensity of the solution in the sample tube was measured by using an automated luminescence spectrometer. The same procedure was done for all collected blood samples. With the fluorescence intensity values of the tissue samples, the withdrawn blood sample and the rate of pump withdrawn (6.5 ml/min) the regional blood flow was calculated by using the following formula:

$$RBF = \frac{E_{tissue} \times R_{pump}}{E_{blood} \times W_{tissue}} \qquad ml/min/g$$

RBF = regional blood flow
E_{tissue} = emission of the tissue sample
E_{blood} = emission of the blood sample
W_{tissue} = weight of the tissue sample

Statistical Analysis Differences between independent groups were assessed by analysis of variance. The level of significance was adapted by using the Bonferroni correction. A change was considered significant when the p value was < 0.01. Results are given as means ± SEM

3. Results

Haemodynamics The new pulsatile pump system generated a pulsatile flows similar to those before ECC. The modified roller pump delivered a pulsatile flows but not similar to those before ECC and the roller pump in Group III generated a non-pulsatile perfusion. Figure 1 showed representative pressure curves of all groups on ECC. To define measurement categories for physiological pulsatile flow we selected the pulsatility index (PI), pulse pressure (PP), dp/dt_{max} and peak aortic flow (PAF) (Figure 1).

pulse pressure The average PP in group I before ECC was 36.8 ± 5.3 mmHg and 39 ± 7.9 mmHg on ECC. The difference was not significant. In group II we measured a PP of 39.5 ± 5.1 mmHg before and 24.4 ± 4.7 mmHg on ECC. In the non pulsatile Group the PP was 36 ± 5.7 mmHg before and 8 ± 2.3 mmHg. The differences in group II and III were with p < 0,001 significant.

dp/dt$_{max}$ There was no significant difference for the dp/dt$_{max}$ before (583.3 ± 133.6 mmHg/sec) and on (657.4 ± 108.4 mmHg/sec) ECC in group I. In group II the dp/dt$_{max}$ decreased from 637 ± 106.1 before ECC to 109.4 ± 20.3 mmHg/sec on CPB ($p < 0{,}001$).

pulsatility index In Group I the PI showed no significant differences before and during ECC (3.88 ± 0.5 vs. 3.1 ± 1.04). In group II the PI decreased significant from 3.92 ± 0.68 to 1.44 ± 0.42 during CPB.

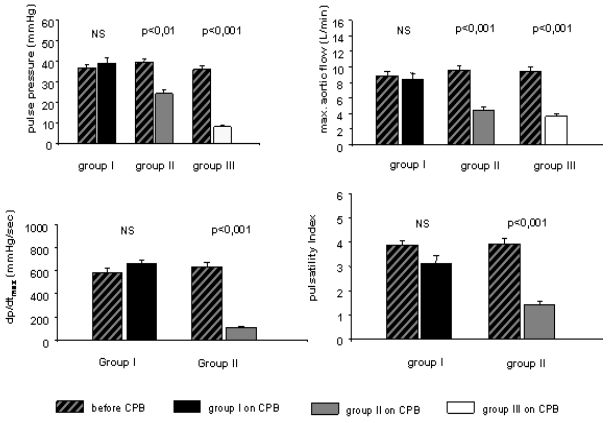

Figure 1 shows the haemodynamic data of pulse pressure, dp/dt$_{max}$, aortic peak flow and pulsatility index

aortic peak flow For the APF there were also no significant differences in Group I between before and on ECC (8.9 ± 1.8 L/min vs. 8.4 ± 2.4 L/min). In Group II (9.5 ± 1.7 vs. 4.4 ± 1.1 L/min) and III (9.4 ± 1.8 vs. 3.6 ± 1 L/min) the aortic peak flow decreased significant on ECC in comparison to APF before ECC.

Haemolysis There were no differences in lactate dehydrogenase concentration between the three groups during the experiment. The concentration of free haemoglobin was similar in both pulsatile groups. The concentration increased significant ($p < 0.001$) after 120 min of ECC 4 fold (group I: 7.39 ± 2.44 vs. 43,89 ± 14,89 mg/dl; group II: 11.73 ± 5.11 vs. 39.37 ± 13.82 mg/dl). In group III the free haemoglobin concentration also increased significant ($p < 0{,}001$) during the experiment and reached his maximum after 60 min of reperfusion. The differences between both pulsatile and the non-pulsatile group were significant ($p < 0{,}001$) (Figure 2)

Inflammation There were no significant differences in Interleukin 6 and Interleukin 1ra concentration in serum between the three groups for any time of the experiment. The Interleukin 6 concentration increased significant ($p < 0.001$) in all groups during the experiment and reached

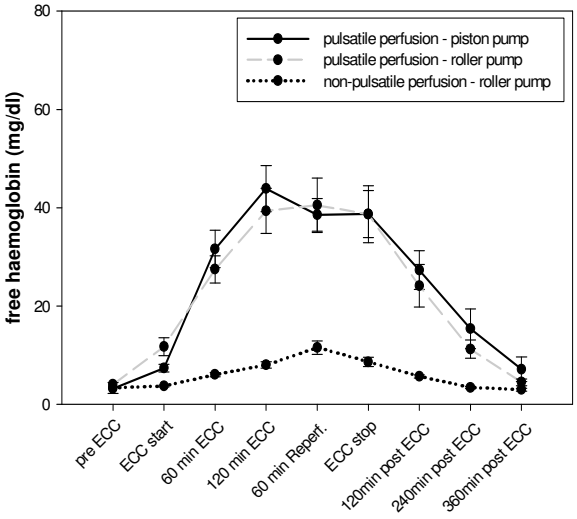

Figure 2 shows the free haemoglobin concentration

his maximum after 6 hours after ECC (group 1: 18.4 ± 14.7 vs. 433.3 vs. 354.7 ng/L; group 2: 52.6 ± 17.5 vs. 518.3 ± 113.4 ng/L; group 3: 29.4 ± 29.3 vs. 332.57 ± 157.9 ng/L). The Interleukin 1ra concentration also increased significant ($p < 0.001$) in all groups during the experiment and reached the maximum after 2 hours after ECC (group 1: 116.5 ± 135.6 vs. 1290 ± 865.7 ng/L; group 2: 244.4 ± 188.4 vs. 1077.8 ± 545.2 ng/L; group 3: 376.6 ± 418 vs. 987.3 ± 465.8 ng/L).

Regional blood flow

Duodenum: There were no significant differences between the groups during the experiment in the duodenal regional blood flow. In group I and II there were no significant differences in the course of the experiment in regional duodenal blood flow. In group three the regional blood flow increased significant ($p < 0.001$) at the end of reperfusion concerning to regional duodenal blood flow before ECC (0.31 ± 0.07 vs. 0.56 ± 0.14 ml/min/g).

I*leum:* There were no significant differences between the groups during the experiment in the regional blood flow of the ileum. There were also no significant differences during the course of the experiments in the groups.

Colon: There were no significant differences between the groups during the experiment in the regional blood flow of the colon. There were also no significant differences during the course of the experiments in the groups (before ECC: group 1 = 0.27 ± 0.06; group 2 = 0.29 ± 0.11; group 3 = 0.24 ± 0.06 ml/min/g vs. after ECC: group 1 = 0.29 ± 0.12; group 2 = 0.28 ± 0.06; group 3 = 0.27 ± 0.06 ml/min/g) (Figure 3).

Kidney: There were no significant differences between the groups during the experiment in the regional renal blood flow.

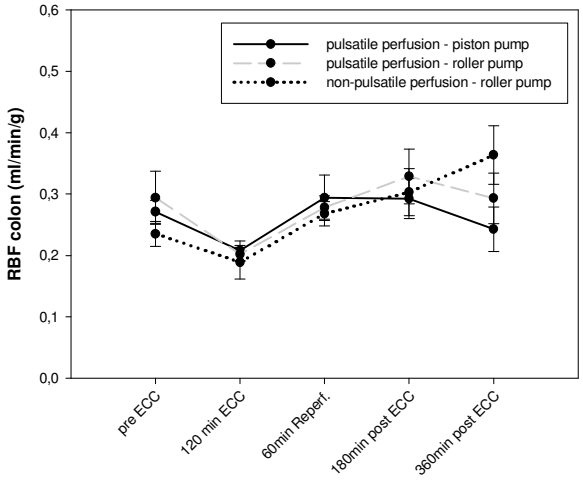

Figure 3 shows the regional blood flow in the colon

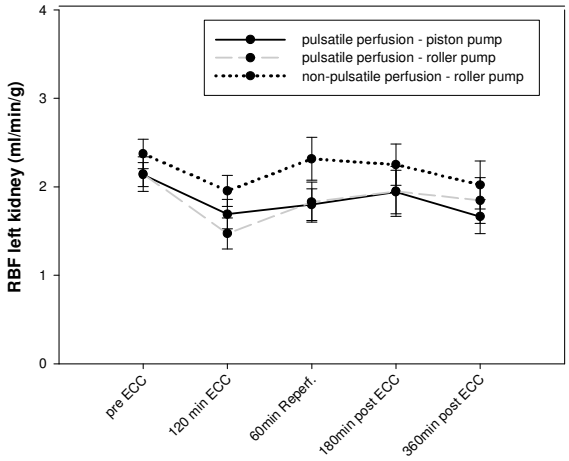

Figure 4 shows the renal regional blood flow

There were also no significant differences during the course of the experiments in the groups (Figure4).

4. Discussion and conclusions

The benefit of pulsatile flow during ECC is still controversial. There are several reasons for the divergent results like the variety of devices used to create the pulsation[1], suboptimal use of pumps, oxygenators and cannulas[5], insufficient hemodynamic datas and limitations in study design. Supporters of pulsatile flow postulate that the type of flow needed should be similar to the one produced by the normal left ventricle[2]. CPB systems used till now failed to achieve this goal. In many studies pulsatile flow profile generated by the pump is dampened by the oxygenator which is connected in series between the pump and the aortic cannula. In order to overcome this disadvantage we added a complimentary, speedy accelerative pump, behind the oxygenator. With this design we were able to mimic a physiological pulsatile flow profile during ECC, proven by the nearly equal values for PP, pAoF, dp/dt *max* and PI as before ECC. In contrast we were able to show that pulsatile flow produced by a conventional roller pump differs significantly from the physiological flow profile. Despite being able we were able to mimic the physiological blood flow with our new pump system we did not find any advantages for regional renal and gut blood flow and inflammatory reaction in the pulsator group compared to the pulsatile or non pulsatile roller pump groups. From our results, we conclude that the use of pulsatile perfusion is unnecessary to increase regional intestinal and renal blood flow or to reduce the systemic inflammatory response after ECC. Our new pulsatile device can be used for further investigations to test the effect on "physiological" perfusion during ECC in selected, vulnerable organ systems. At the moment, efforts to optimize pulsatility do not seem to be justified.

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