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Cardiopulmonary bypass with physiological flow and pressure curves: pulse is unnecessary!☆

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Abstract

Objective: Advocates of pulsatile flow postulate that the flow pattern during extracorporeal circulation (ECC) should be similar to the physiological one. However, the waveforms generated by clinically used pulsatile pumps are by far different from the physiological ones. Therefore, we constructed a new computer-controlled pulsator which can provide nearly physiological perfusion patterns during ECC. We compared its effect (group 1) with pulsatile (group 2) and non-pulsatile (group 3) perfusion generated by a conventional roller pump. **Methods:** Thirty pigs (10 per group) underwent 180 min ECC with an aortic cross-clamp time of 120 min. Pulse pressure, peak aortic flow, dp/dt_{max}, pulsatility index and energy-equivalent pressure were measured online. Renal and intestinal blood flow was calculated by fluorescent microspheres. The inflammatory response was assessed by the level of interleukin 6/1ra, the haemolysis by the free haemoglobin, and the escape rate of plasma protein by the disappearance rate of Evans Blue dye. **Results:** When compared to the preoperative curves, pulsatile waveforms during ECC were similar in group 1 and severely damped in group 2. Inflammatory response increased without significant differences between the groups. There were no differences between groups in renal and bowel blood flow. Free haemoglobin after ECC was higher in the pulsatile groups (group 1 = 43 ± 144 mg dl^{-1}, group 2 = 40 ± 164 mg dl^{-1}, group 3 = 11 ± 4 mg dl^{-1}; group 1 vs 2 (ns); group 1 or 2 vs 3 ($p < 0.001$)). The escape rate of Evans Blue increased after ECC in group 1 1.8-fold ($p < 0.05$), in group 2 1.45-fold ($p < 0.05$) and in group 3 1.27-fold (ns). **Conclusion:** Even when using pulsatile flow patterns which mimic closely the physiological waveforms, there is no advantage concerning organ perfusion or inflammatory response. Moreover, the extent of haemolysis and capillary leak is higher compared to non-pulsatile perfusion. Efforts to optimise pulsatility are not justified.

Keywords: Extracorporeal circulation; Pulsatile flow; Non-pulsatile flow; Microcirculation; Energy-equivalent pressure; Capillary leak

1. Introduction

The use of extracorporeal circulation (ECC) is fundamental for the majority of cardiac operations. Despite continuous technical improvements, multiple organ dysfunctions after ECC induced by a systemic inflammatory response syndrome (SIRS) are still a significant clinical problem [1,2]. The perfusion mode (pulsatile vs non-pulsatile) may play an important role in this process. However, more than half a century after the clinical introduction of ECC, data whether pulsatile perfusion is superior to non-pulsatile perfusion are still controversial [3,4]. In the early 1950s, pulsatile pumps were used in experimental setups for animal perfusion. These pump systems were technically unreliable, very expensive and difficult to sterilise. Therefore, non-pulsatile roller pumps that were safe, cheap and easy to handle were used in cardiac surgery. These systems were compatible with patient survival, and, as confidence increased, non-pulsatile perfusion was routinely established in cardiac surgical practice. Progress in pump technology during the 1960s and 1970s led to a new interest in pulsatile flow patterns in ECC. By this time, additional experimental evidence had been reported, and most of this favoured the use of pulsatile flow. Taylor's group, working in Glasgow, was the first to introduce pulsatile flow in clinical practice and reported a better patient outcome [5]. In the 1980s these findings led to the temporary adoption of pulsatile flow in clinical routine by using modified roller pumps for ECC, which were able to generate some pulsatility by periodic acceleration and deceleration of the pump. However, most clinical studies performed subsequently did not detect a benefit associated with pulsatile

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perfusion [6]. Consequently, currently, the more simple non-pulsatile flow has been widely re-established as the standard perfusion mode in cardiac surgery.

There are, however, still advocates of pulsatile flow, who assume that the adverse reactions to ECC may be linked to the lack of pulsatility. The diversity of results in previous studies has been attributed to the variety of pulsatile flow, which makes it difficult to compare the results [3,4]. A clear definition of pulsatile flow does not exist. In most studies, only the brand names of pulsatile devices are mentioned, but there is no information of the actual pulsatile flow pattern. In other studies, only the pulse pressure is used to define pulsatility. In general, a pulse pressure of more than 15 mmHg is considered to be pulsatile, but even this is much lower than the pulse pressure generated by the human heart in the blood circulation. In most cases, other relevant parameters, such as dp/dt, stroke volume or ejection time, are not mentioned. Until now, the clinically approved pumps for pulsatile perfusion do not reproduce the exact physiological flow pattern due to technical limitations, thus generating a pulsatile flow pattern, which is far from the one produced by the human heart [4].

The aim of our study was to design a new ECC pump system capable of reproducing a physiological flow pattern and pressure profile, which mimics as closely as possible the physiological one. In order to investigate the effect of physiological pulsatility, we conducted an experimental study comparing the new pulsatile ECC pump system, with a conventional pulsatile roller pump, and a non-pulsatile roller pump.

2. Methods

The experiments were approved by the Bavarian authorities (reference number 209.1-2531-80/01), and the animals received humane care in compliance with the Guide for the Care and Use of Laboratory Animals (NIH publication 85-23).

2.1. Experimental design

Thirty domestic pigs (10 in each group) underwent ECC:

Group 1: Physiological pulsatile flow with the new pulsatile ECC pump system.
Group 2: Conventional pulsatile flow by roller pump.
Group 3: Non-pulsatile flow by roller pump.

ECC was performed in all animals for 180 min with a cross-clamp time of 120 and 60 min of reperfusion. One litre of cardioplegia (Bretschneider solution) was administrated at the beginning of ECC and an additional half litre was administrated after 1 h of ECC. During cross-clamp time mild hypothermia of 32 °C was induced. After ECC, the animals were observed for 360 min. Central vein pressure, aortic pressure, aortic flow and ECG were recorded during the entire experiment. During the experiment, arterial blood samples for laboratory tests were taken from the left femoral artery. Protein loss was determined by the escape rate of Evans Blue prior to and 240 min after ECC. For investigation of the regional blood flow (renal and gut), we used the microsphere technique. The microspheres were injected before ECC, after 120 min off cross-clamp time, after 60 min of reperfusion and 180 and 360 min after ECC. Samples of the explanted kidney and gut (duodenum, ileum and colon) of each animal were taken for fluorescence measurement of the microspheres. A schematic illustration is given in Fig. 1.

2.2. New ECC pulsatile pump system

The new ECC 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 aortic cannula in the arterial line (see Fig. 2A). The basic flow (80 ml kg^{-1} min^{-1}) is continuously generated by the roller pump. The pulsator induces the pulsatile flow by reducing the flow to the aorta during the filling phase and augmenting the flow to the aorta during the ejection phase. A backflow into the heart–lung machine is avoided by a unidirectional restrictor valve. The piston is moved by an electric motor (Baumüller, Nuremberg, Germany) and an interposed ball-bearing spindle (Pfaff-Silberblau-Hebezeuge), as illustrated in Fig. 2B. The electric motor has a freely programmable control system (National Instruments Corporation, Austin, TX, USA), which allows an individual setting (stroke distance, forward/backward velocity, acceleration and frequency) according to the flow characteristics (minimal/maximal pressure, basic flow, systolic/diastolic time and pulse frequency) of the animals, which were individually analysed before ECC. For the adjustment of the pulsator to the systolic blood pressure, a proportional plus integral plus derivative (PID) controller was implemented. For systolic blood pressure regulation, preoperative systolic blood pressure and continuously measured systolic blood pressure were compared online during ECC with the pulsator. The PID controller regulates the systolic pressure by modulating the stroke distance of the piston pump. Reducing the stroke distance leads to a reduction in systolic blood pressure and increasing the stroke distance of the piston pump leads to an increased systolic blood pressure.

2.3. Anaesthesia, preparation, instrumentation and ECC

Domestic pigs weighing 35.2 ± 0.7 kg were pre-medicated with an intramuscular injection of ketamine (5 mg kg^{-1}, Ketanest®, Parke Davis, Munich, Germany) and an atropine sulphate injection (25 μg kg^{-1}, Braun, Melsungen, Germany).

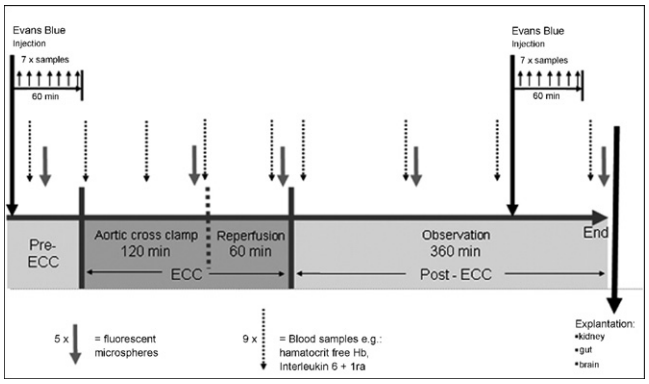

Fig. 1. Experimental design.

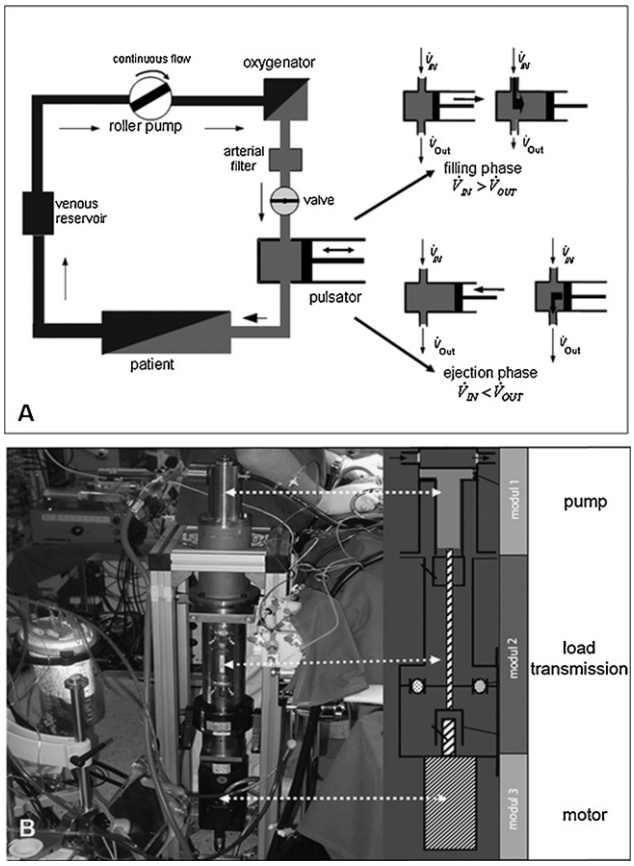

Fig. 2. (A) Schematic of the ECC in group 1. The pulsator converts the constant flow of the roller pump to a pulsatile one by reducing the blood flow in the filling phase and increasing in the ejection phase. (B) The pulsator consists of a piston pump, a load transmission by a spindle, and an electric motor for effective forward and backward movements.

General anaesthesia was induced by intravenous injection of thiopental sodium (12.5 mg kg^{-1}, Trapanal, Byk-Gulden®, Konstanz, Germany). Anaesthesia was maintained by continuous intravenous application of sufentanil citrate (Sufentanildihydrogencitrat 0.375 mg 5 ml^{-1}, Jansen-Cilag GmbH, Neuss, Germany) and midazolam (Midazolam-ratiopharm® 5 mg 5 ml^{-1}, Ratiopharm GmbH, Ulm, Germany) through a syringe pump. Muscle relaxation was induced by pancuronium bromide (Pancuronium Curamed®, CuraMED Pharma GmbH, Karlsruhe) IV 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. Arterial pCO_2 was fixed to a range between 35 and 45 mmHg and pO_2 between 100 and 120 mmHg, base excess was kept at ±2 and plasma K^+ at 4.5–5 mmol l^{-1}. The central venous pressure (CVP) was maintained between 3 and 8 mmHg. In all experiments no catecholamines were used.

Catheters were inserted into the jugular vein (Arrow-Howes™ Quad-Lumen central venous catheter, Arrow International Inc., USA) and the left femoral artery (Cavafix® Certo® 358, 16G, B. Braun Melsungen AG, Melsungen, Germany) for blood sampling, monitoring of the CVP and application of infusions and drugs. Through the right femoral artery, a catheter tip manometer (Millar MIKRO-TIP® SPC-350, Houston, TX, USA) 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 flow probe (A-Serie, Transonic Systems Inc., Ithaca, NY, USA) was placed at the descending aorta above the crossing of the pulmonary veins. Another flow probe (C-Serie, Transonic Systems Inc., Ithaca, NY, USA) was placed around the arterial line between the pulsator and aortic cannula. For injection of the fluorescent microspheres, a catheter (Cavafix® Certo® 455, 14G, B. Braun Melsungen AG, Melsungen, Germany) was placed in the left atrium.

After intravenous injection of 500 U kg^{-1} heparin sodium (Liquemin® N25000, Hoffmann-La Roche AG, Grenzach-Wyhlen, Germany) the ascending aorta (24 F aortic cannula, Stöckert® Instrumente GmbH, München, Germany) and the right atrium (Venous catheter, 32F, Stöckert® Instrumente GmbH, München, Germany) were cannulated for cardiopulmonary bypass. The aorta was cross-clamped and 1000 ml Bretschneider's cardioplegia (Custadiol®, Dr Franz Köhler Chemie GmbH, Alsbach-Hähnlein, Germany) was infused for cardiac arrest. During the time of cardiac arrest, the left ventricle was vented through the apex. After the end of ECC, all cannulae were removed and 1000 I.E. ml^{-1} of protamine (Protamin®, ICN Pharmaceuticals GmbH, Frankfurt/Main, Germany) was given. The chest and the pericardium were loosely adapted for the rest of the experiment.

2.4. Haemodynamic measurements

The haemodynamic analogue signals were recorded on multi-channel chart recorders (TA 5000, Gould, Valley View, USA). To describe the quality of pulse, we use the following parameters:

1. Pulse pressure (PP):

   $$PP = P_{max} - P_{min}$$

   where P_{max} is the maximal aortic pressure and P_{min} the minimal aortic pressure.
2. Peak aortic flow (pAoF):

   $$pAoF = V_{max}[l\,min^{-1}]$$

   where V_{max} is the peak of systolic blood flow velocity.
3. Maximal aortic velocity of pressure rise = (dp/dt_{max}) [mmHg s^{-1}].
4. The pulsatility index (PI):

   $$PI = \frac{V_{max} - V_{min}}{V_{mean}}$$

   where V_{max} is the peak of systolic blood flow velocity, V_{min} the minimum of diastolic blood flow velocity and V_{mean} the mean blood flow velocity.
5. Percentage of difference from the mean arterial pressure (MAP) to energy-equivalent pressure (EEP):

   $$EEP = \frac{\int f\,p\,dt}{\int f\,dt}$$

where f is the pump flow rate, p the arterial pressure (mmHg) and dt indicates that the integration is performed over time (t). The unit of EEP is mmHg. The difference between the EEP [mmHg] and MAP [mmHg] is the extra energy generated by pulsatility.

2.5. Blood analyses

Blood samples were drawn before ECC, at the beginning of ECC, after 60 and 120 min of cross-clamp, after 60 min of reperfusion, after protamin administration, and 120, 240 and 360 min after ECC. Blood samples were analysed for haemoglobin concentration, platelet and red and white blood cell count. Furthermore, free haemoglobin concentration (derivative spectroscopy), lactate dehydrogenase concentration (COBAS® INTEGRA Lactate Dehydrogenase IFCC, Roche Diagnostics, Mannheim, Germany) and lactate concentration (COBAS® INTEGRA Lactate, Roche Diagnostics, Mannheim, Germany) were measured. Enzyme-linked immunoassays (ElAs) were performed for the assessment of interleukin 6 (IL6) (Quantikine®, R&D Systems, Wiesbaden-Nordenstadt, Germany) and interleukin 1 receptor antagonist (IL1ra) (Quantikine®, R&D Systems, Wiesbaden-Nordenstadt, Germany) concentration.

2.6. Measurement of regional blood flow

Regional blood flow was assessed using fluorescent microspheres (FluoSpheres®, Molecular Probes, MoBiTec, Göttingen, Germany) with a diameter of 15 μm. We used the colours yellow–green, blue–green, red, orange and crimson. A total of 10^6 microspheres 10 kg^{-1} were drawn off the stock solution into a plastic syringe, which was filled with 17 ml of saline solution. Fifteen seconds before starting the microsphere injection, a pump for blood sample collection was started. The injection time was 30 s, and the pump continued for another 105 s after injection. The injection was administered into the left atrium through a catheter. During cardiopulmonary bypass, the microspheres were injected close to the end of the arterial cannula to guarantee an optimal mixture between the microspheres and the blood. After withdrawal, the blood sample was put onto the filter of a sample processing unit (SPU). The filter was washed thrice with 10 ml of phosphate buffer. Later, the filters were stored in a refrigerator. To analyse tissue samples, the animals were euthanised at the end of the experiment. Both kidneys and gut segments from duodenum, ileum and colon were removed and fixed into a 4.5% formaldehyde solution for 2 weeks. After fixation, both kidneys and the gut segments were dissected. After measuring the weight of the tissue samples, the fluorescent microspheres were recovered by tissue digestion. After successful digestion of the tissue samples, the content of the filter was sucked through a mesh opening (7 μm) by a negative pressure. The filter was washed thrice with a phosphate 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. For this purpose, 2 ml of Cellosolve-acetate was poured 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 applied for all collected blood samples. With the fluorescence intensity values of the tissue samples, the withdrawn blood samples and the rate of pump withdrawal (6.5 ml min^{-1}), the regional blood flow was calculated by using the following formula:

$$\mathrm{RBF} = \frac{E_{\mathrm{tissue}} R_{\mathrm{pump}}}{E_{\mathrm{blood}} W_{\mathrm{tissue}}} \ \mathrm{ml\,min^{-1}\,g^{-1}}$$

where RBF is the regional blood flow, E_{tissue} the emission of the tissue sample, R_{pump} the rate of pump withdrawal, E_{blood} the emission of the blood sample and W_{tissue} the weight of the tissue sample.

2.7. Escape rate of albumin

The escape rate of albumin from the intravascular compartment was assessed indirectly by the loss of extinction from Evans Blue (EB, Sigma, Deisenhofen, Germany) within 60 min. The measurements were performed prior to CPB and 4 h after weaning from CPB. The methods have been previously described and discussed in detail [7].

2.8. Statistical analysis

According to the previous publication by Ündar and coworkers [11] we hypothesised a difference of 20% in regional blood flow between a pulsatile and non-pulsatile perfusion mode. Thus, a sample size of 10 was calculated to be adequate for meaningful statistical comparison. 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. After testing of normal distribution, for comparison of the escape rate of Evans Blue, the Wilcoxon matched-pairs signed rank test was used. A p value <0.05 was considered significant.

3. Results

3.1. Haemodynamic/pulse quality

Compared to the physiological pulse before ECC, the pulse generated by the new pulsatile pump system (group 1) was very similar, except for some additional oscillations. In contrast, the pulsatile flow delivered by a pulsatile roller pump (group 2) was considerably damped and the non-pulsatile roller pump (group 3) still induced a minimal undulation of the aortic flow and pressure curve under ECC (Fig. 3A). This observation was confirmed by analysis of the curves.

Pulse pressure: The average PP in group 1 before ECC was 36.8 ± 5.3 mmHg and thus very similar to 39 ± 7.9 mmHg on ECC (p = ns). In group 2, we measured a PP of 39.5 ± 5.1 mmHg before and 24.4 ± 4.7 mmHg on ECC ($p < 0.001$). In the non-pulsatile group, the PP was

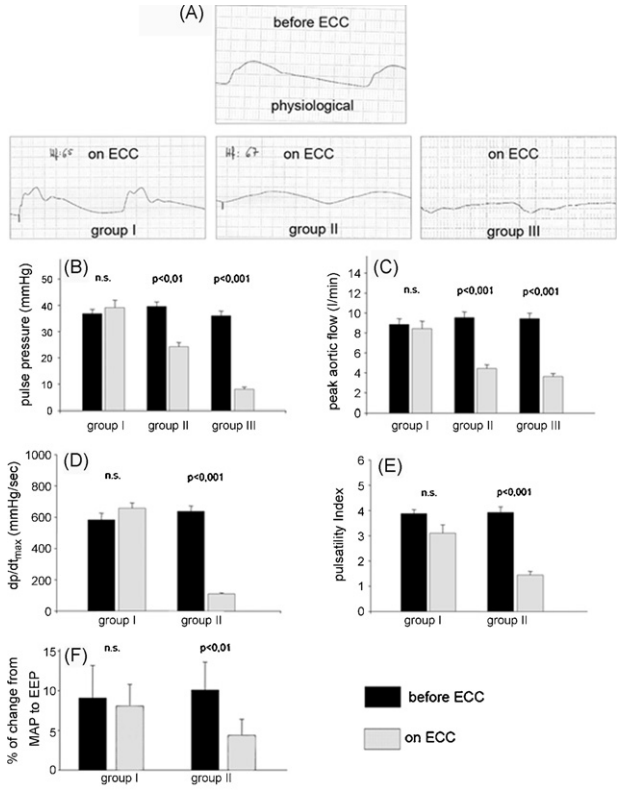

Fig. 3. (A) Original registration of pressure curves. Only in group 1 (pulsator) nearly equal values of pulse pressure (B), peak aortic flow (C), dp/dt_{max} (D), pulsatility index (E), and percentage *of difference from MAP to EEP* before and on ECC were found, indicating the similarity of the pulse curves in this group.

36 ± 5.7 mmHg before and 8 ± 2.3 mmHg during ECC ($p < 0.001$); see Fig. 3B.

Peak aortic flow: In group 1, the pAoF showed no significant difference before and on ECC (8.9 ± 1.8 l min^{-1} vs 8.4 ± 2.4 l min^{-1}). In groups 2 (9.5 ± 1.7 l min^{-1} vs 4.4 ± 1.1 l min^{-1}) and 3 (9.4 ± 1.8 l min^{-1} vs 3.6 ± 1 l min^{-1}) 1) the pAoF decreased significantly ($p < 0.001$) on ECC; see Fig. 3C.

dp/dt_{max}: There was no significant difference for the dp/dt_{max} before (583.3 ± 133.6 mmHg s^{-1}) and on (657.4 ± 108.4 mmHg s^{-1}) ECC in group 1. In group 2, the dp/dt_{max} decreased from 637 ± 106.1 mmHg s^{-1} before ECC to 109.4 ± 20.3 mmHg s^{-1} on ECC ($p < 0.001$); see Fig. 3D.

Pulsatility index: In group 1, the PI showed no significant difference before and on ECC (3.88 ± 0.5 vs 3.1 ± 1.04). In group 2, the PI decreased significantly from 3.92 ± 0.68 to 1.44 ± 0.42 during CPB; see Fig. 3E.

Percentage of difference from MAP to EEP: In group 1, no significant changes in the difference between *MAP* and *EEP* were found comparing before ECC ($9.1 \pm 4.1\%$) and during ECC ($8.1 \pm 2.7\%$). In group 2, the percentage of difference from MAP to EEP was significantly ($p < 0.002$) lower during ECC ($4.4 \pm 2.0\%$) compared to the value before ECC ($10.1 \pm 3.5\%$); see Fig. 3F.

Over the entire duration of the experiment, the three groups did not show significant differences in mean arterial pressure (Fig. 4A) and peripheral resistance (Fig. 4B) in the presence of an equal course of haemoglobin concentration (Fig. 4C). There were no significant differences in volume substitution between the groups. The maximal pressure in the arterial line, between the pulsator and the aortic cannula, was three- to fourfold ($p < 0.001$) higher in group 1 (295.1 ± 77.4 mmHg)

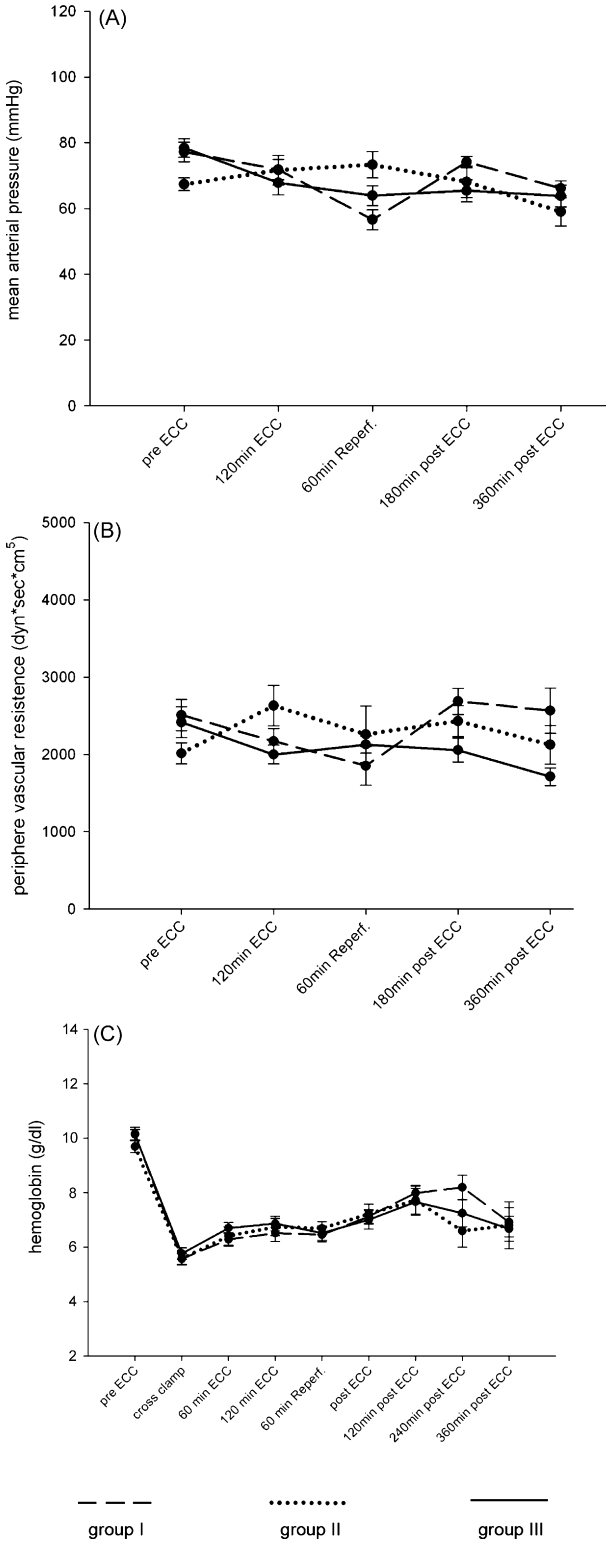

Fig. 4. No significant differences were found in the course of mean arterial pressure (A), peripheral vascular resistance (B), and haemoglobin (C).

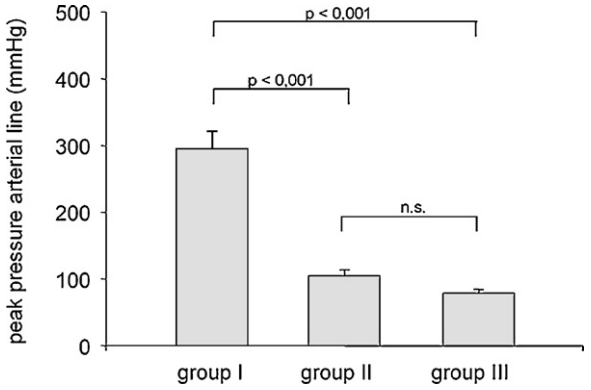

Fig. 5. Peak pressure in the arterial line measured between the pulsator and the aortic cannula.

compared to groups 2 (104.6 ± 24.2 mmHg) and 3 (78.8 ± 17.8 mmHg); see Fig. 5. The difference between groups 2 and 3 was not significant.

3.2. Regional blood flow

Kidney: Regional renal blood flow did not differ between the groups and did not change during the course of the experiments (Fig. 6A). The correlation in regional blood flow between the left and right kidney was $r = 0.99$ in all measurements.

Gut: Continuous perfusion did not result in reduced blood flow in any segment of the gut (e.g., for colon: 0.24 ± 0.06 ml min^{-1} g^{-1} before ECC, 0.27 ± 0.06 ml min^{-1} g^{-1} after 180 min). Neither roller pump pulsatility (0.29 ± 0.11 ml min^{-1} g^{-1} before ECC, 0.28 ± 0.06 ml min^{-1} g^{-1} after 180 min ECC), nor the pulsator (0.27 ± 0.06 ml min^{-1} g^{-1} before ECC, 0.29 ± 0.12 ml min^{-1} g^{-1}after 180 min ECC) resulted in significant changes during any measurement period (Fig. 6B).

3.3. Inflammation

There were no significant differences in IL6 and IL1ra concentrations in serum between the three groups at any time during the experiment. The concentration of IL6 increased significantly ($p < 0.001$) in all groups during the experiment and reached its maximum 6 h after ECC (group 1: 18.4 ± 14.7 vs 433.3 ng l^{-1} vs 354.7 g l^{-1}; group 2: 52.6 ± 17.5 ng l^{-1} vs 518.3 ± 113.4 ng l^{-1}; group 3: 29.4 ± 29.3 ng l^{-1} vs 332.57 ± 157.9 ng l^{-1}); see Fig. 7A. The IL1ra concentration also increased significantly ($p < 0.001$) in all groups during the experiment and reached its maximum 2 h after ECC (group 1: 116.5 ± 135.6 ng l^{-1} vs 1290 ± 865.7 ng l^{-1}; group 2: 244.4 ± 188.4 ng l^{-1} vs 1077.8 ± 545.2 ng l^{-1}; group 3: 376.6 ± 418 ng l^{-1} vs 987.3 ± 465.8 ng l^{-1}); see Fig. 7B.

3.4. Lactate

During the beginning of ECC, the lactate concentration increased significantly in all groups. The maximum was reached 60 min after the beginning of ECC (group 1: 6.69 ± 3.75 mmol l^{-1}; group 2: 8.03 ± 2.44 mmol l^{-1}; group 3: 8.43 ± 3.25 mmol l^{-1}). After finishing ECC, the lactate concentration decreased continuously, and dropped to its basic value or below 120 min after ECC. There were no significant differences in lactate concentrations between the three groups at any time of the experiment (Fig. 7C).

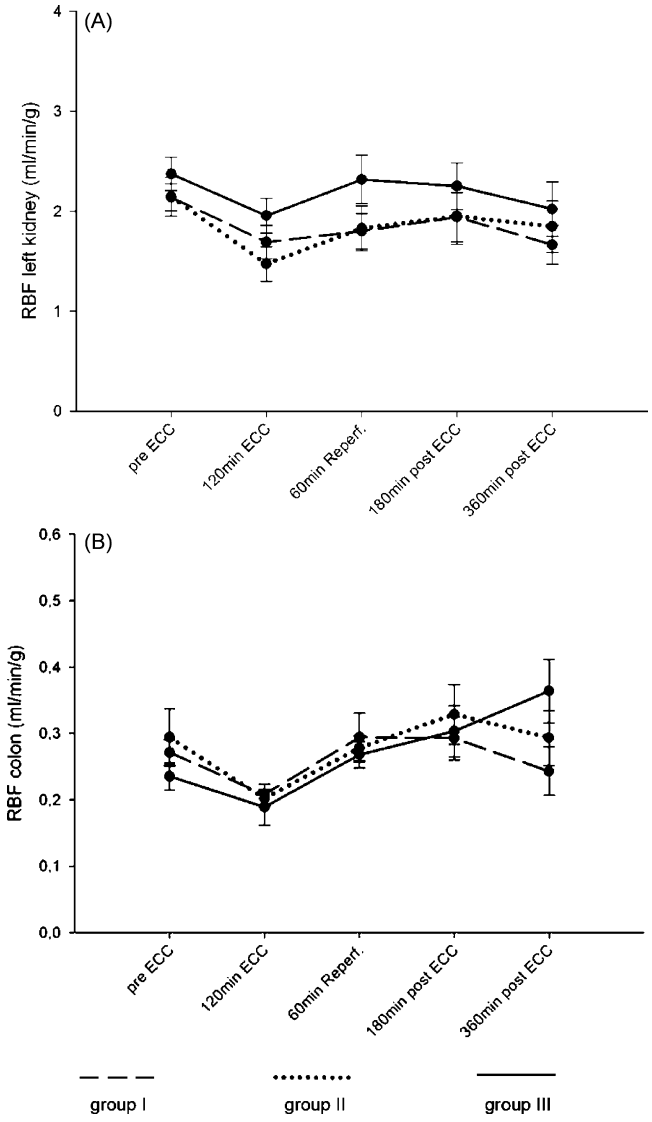

Fig. 6. Regional blood flow of kidney (A) and colon (B). No significant differences were seen between the groups.

3.5. Haemolysis

Free haemoglobin: The concentration of free haemoglobin was similar in both pulsatile groups. The concentration increased significantly ($p < 0.001$) after 120 min of ECC (group 1: 7.39 ± 2.44 mg dl^{-1} vs 43.89 ± 14.89 mg dl^{-1}; group 2: 11.73 ± 5.11 mg dl^{-1} vs 39.37 ± 13.82 mg dl^{-1}). In group 3, the free haemoglobin concentration also increased significantly ($p < 0.001$) during the experiment and reached its maximum after 60 min of reperfusion. The differences between both pulsatile and the non-pulsatile groups were significant ($p < 0.001$); see Fig. 7D.

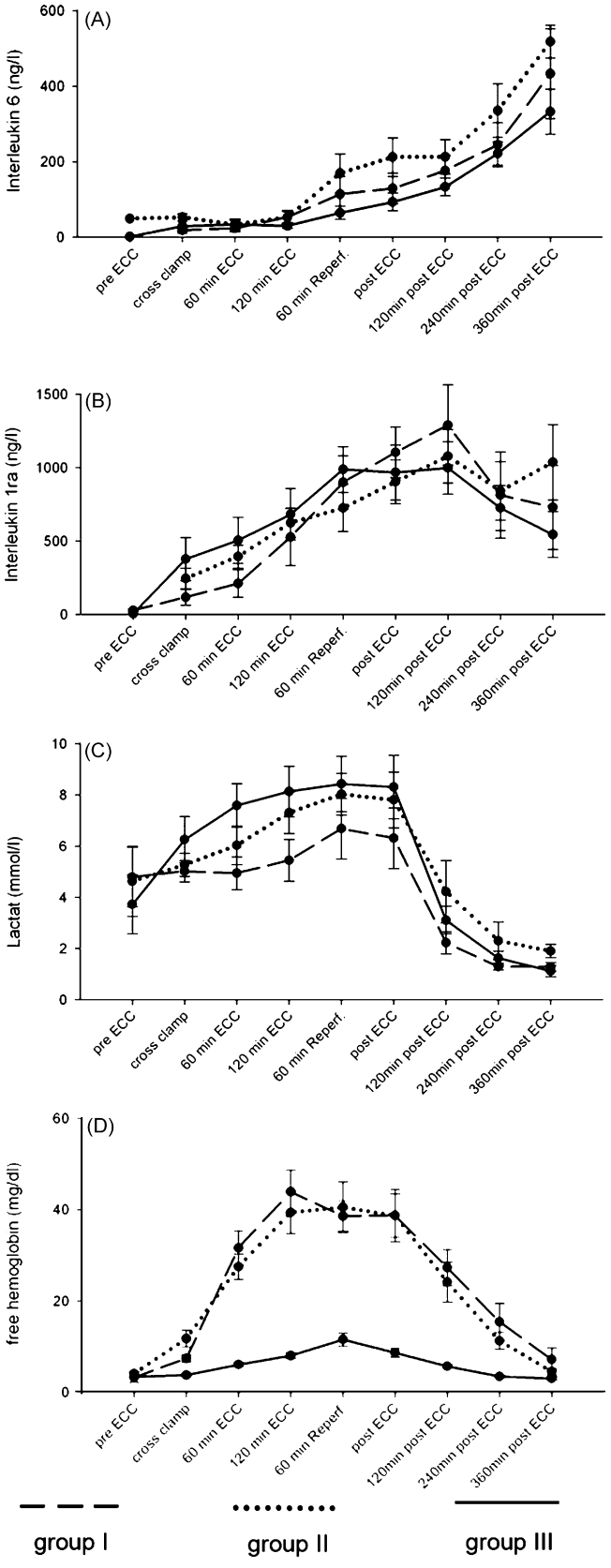

Fig. 7. Time-dependent course of interleukin 6 (A), interleukin 1ra (B), lactate (C), and free haemoglobin (D). Significantly higher values for free haemoglobin, indicating haemolysis, were only found in the two pulsatile groups.

3.6. Escape of albumin (capillary leak)

The transvascular escape rate of Evans Blue dye increased after ECC in group 1 1.8-fold (18.7% h^{-1} vs 34% h^{-1}, $p < 0.05$); in group 2, 1.45-fold (17.4% h^{-1} vs 25.4% h^{-1}, $p < 0.05$); and in group 3 1.27-fold (19% h^{-1} vs 24.3% h^{-1}, p: ns); see Fig. 8.

4. Discussion

Even more than half a century after the clinical introduction of cardiopulmonary bypass, the controversy concerning the benefits of pulsatile versus non-pulsatile flow during ECC continues. The intuitive estimation that nature knows best suggests that pulsatile flow as the physiological one should be imitated during ECC. Different theories served as a rationale for advocating pulsatile flow [3,4,8]: (1) even with equal flow rates, pulsatile flow contains a higher energy, ensuring a better patency of the vascular bed; (2) pulsatile flow reduces oedema formation by increased lymph movements; (3) pulsatile flow allows for more efficient metabolism at lower flow rates; and (4) the cardiovascular regulating system is adapted to pulsatile flow. Therefore, pulsatile flow is important to maintain the proper function of neuroendocrine reflexes, which are triggered by baroreceptors.

The use of pulsatile flow for cardiopulmonary bypass in human patients was most popular during the 1980s and the early 1990s; however, until now, most clinical studies have failed to demonstrate any benefit of the pulsatile flow mode [6].

This can be attributed to the fact that there really is no benefit of pulsatility, or that the quality of the pulse is not sufficient to achieve the benefits postulated in theory. Due to technical limitations and several damping components such as the oxygenator and arterial filter, the properties of pulsatile flow used in the clinical setting are far from the ones of physiological pulsatile flow [9,10].

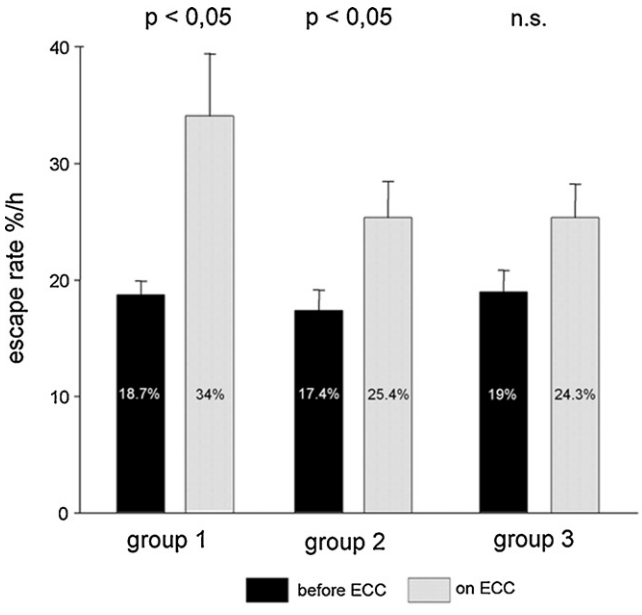

Fig. 8. Escape rate of Evans Blue as marker for the capillary leak.

The fundamental problem of comparing the different perfusion modes or different types of pulsatile flow is the lack of a clear definition or a precise quantification of pulsatility. The majority of investigators used only the pulse pressure to compare different perfusion modes. However, the generation of pulse also depends on the energy gradient. Hence, both arterial pressure and pump flow waveforms must be used to quantify different perfusion modes. Therefore, several authors [3,4] argued that the maximal aortic velocity of pressure rise (dp/dt_{max}), and more complex parameters such as the EEP or the PI are mandatory to describe pulsatile waveforms. In our study, the pulse was exactly quantified by pulse pressure, peak aortic flow, dp/dt_{max}, PI and the difference from EEP to MAP, allowing a valid comparison between pulsatile and non-pulsatile flow.

Advocates of pulsatile flow postulate that the type of flow we need is similar to the one produced by the normal left ventricle [4]. Based on this point of view, it was our hypothesis that the superiority of pulsatile flow can only be clearly demonstrated by using physiological flow during ECC.

To avoid the above-mentioned disadvantage of conventional pulsatile ECC systems, we added a complementary, speedy accelerative pump (pulsator) behind the oxygenator. The pulse pressure 'waveform' does not only depend on the pulse pump system, but also on the vascular resistance of the organism. In order to maintain comparable haemodynamic states, we used the same flow rate (80 ml kg^{-1} min^{-1}) during ECC, used no catecholamines and maintained a constant CVP level in all study groups. A significant vasoconstriction during ECC, such as has been described by several authors before, was not seen in any of our study groups. The same was seen in respect to the MAP. This may be contributed to our constant volume substitution. To reduce the restrictive effect of the aortic cannula, we used a 24 F cannula, which was the largest one that could be introduced in the relatively small piglet aorta. Nevertheless, a kind of injection jet inducing aortic vibration could not be avoided, which probably caused the cocks-comb-like wave oscillations in the pulsator group. Despite this limitation, we were able to mimic a nearly physiological pulsatile flow profile during ECC within the pulsator group. This was proven by the similar values for PP, pAoF, dp/dt_{max}, difference from EEP to MAP and PI as compared to the situation before ECC. In contrast, we found that pulsatile flow produced by a conventional roller pump differs significantly from the physiological flow profile.

Although we were able to mimic the physiological blood flow with our new pump system, we did not find any advantages of regional blood flow compared to the pulsatile or non-pulsatile roller pump groups. Using a self-designed blood pump for ECC, Ündar and co-workers [11] described a decreased renal blood flow in non-pulsatile versus pulsatile flow only during deep hypothermic bypass (at 18°: 53 ml 100 g^{-1} min^{-1} vs 82 ml 100 g^{-1} min^{-1}; after deep hypothermic cardiac arrest: 55 ml 100 g^{-1} min^{-1} vs 41 ml 100 g^{-1} min^{-1}), but not during normothermic bypass (124 ml 100 g^{-1} min^{-1} vs 126 ml 100 g^{-1} min^{-1}). Similarly, an experimental study by Cook and co-workers [12] on dogs confirmed that renal blood flow was affected by temperature, but not by pulsatility.

The use of ECC is associated with a variety of pathophysiological mechanisms that might influence the perfusion of the splanchnic region as an important cause of postoperative complications [13]. Sack and co-workers [14] in an experimental study on pigs, found an ECC-induced micro-vascular perfusion injury despite normal macro-haemodynamic perfusion. In our setting, no significant difference in respect to the perfusion mode was seen. Ohri and co-workers [15] using laser Doppler flow measurements of the gastric wall at 37 °C, described a significantly ($p = 0.03$) increased gastric mucosal flow with pulsatile versus non-pulsatile perfusion only in one of 12 measuring points. In addition, in this study, the temperature was of greater importance than the perfusion mode.

It is known that ECC leads to a SIRS [1], which may be detrimental to patient outcome [2]. We evaluated the inflammatory response by measuring the pro-inflammatory IL6. In accordance with other investigators, we found a significant elevation of IL6 with a peak several hours after ECC [1,16,17]. These data confirm the systemic inflammatory response induced by cardiopulmonary bypass. Like Neuhof and co-workers [16] we found no difference due to the perfusion mode. The same was true for the anti-inflammatory response, which was monitored by the IL1ra levels. These findings confirm that pro- and anti-inflammatory cytokines increase to maintain their balance during cardiac surgery with ECC [18]. In our opinion, including more pro- and anti-inflammatory parameters would probably provide a more sophisticated assessment regarding the inflammatory reaction, but most likely not change the main finding. There are no differences between pulsatile and non-pulsatile groups.

As a consequence of the inflammatory reaction, some authors hypothesised an increased capillary leakage, during and after ECC with loss of plasma proteins, organ failure and oedema formation [19,20]. However, capillary leak was not detectable in humans with aortic cross-clamp times of less than 80 min [21,22]. The aortic cross-clamping time of 120 min chosen in our experiment is considered to provoke pronounced adverse reactions in pigs [23]. A significant increase in transvascular escape rate of Evans Blue as an indicator for the capillary leakage was only seen in both pulsatile groups. In the non-pulsatile group, there was only a trend towards higher capillary leakage with ECC.

The concentration of the serum lactate is an accepted indicator of aerobic/anaerobic metabolism. By using pulsatile perfusion, we found only a trend towards lower lactate levels, even with little advantage of physiologically induced flow by the pulsator. The results of two former studies using pulsatile flow have been controversial: one verified an effect on lactate levels [24], the other did not [25].

In our study the most pronounced difference between pulsatile and non-pulsatile perfusion was found with respect to the amount of haemolysis. Compared to the non-pulsatile group, haemolysis was markedly higher in both pulsatile groups without differences between the physiological pulsator-induced and the 'conventional' roller pump-induced pulsatile flow, thus indicating that haemolysis is induced by the pulsatile perfusion mode itself and not by the new device.

5. Conclusion

With our new pump system we were able to mimic a physiological pulse pressure pattern. Despite this precondi-

tion, as is demanded by the supporters of pulsatile flow, we did not find any advantages on regional blood flow or inflammatory reaction in the pulsator group compared to the pulsatile or non-pulsatile roller pump groups. Moreover, the pulsatile regimes led to an increased haemolysis and an elevated capillary leak. With these findings, we disprove our hypothesis of the superiority of ECC with a physiological pulse pressure waveform. Therefore, we conclude that pulsatile flow during mild hypothermic ECC is unnecessary! Efforts to optimise pulsatility do not seem to be justified. However, the study was conducted in normal healthy subjects. Therefore, a possible benefit of pulsatile perfusion in patients suffering from cerebrovascular disease or renal insufficiency cannot be excluded.

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Appendix A. Conference discussion

Dr A. Liebold (*Rostock, Germany*): This work in my eyes represents an excellent piece of experimental research in a field of still ongoing interest, namely, the improvement of current CPB technologies in order to be less invasive to the patients. The animal study was preceded by developmental engineering of a new pump device designed to produce nearly physiological flow patterns.

The group of Dr Voss tried to answer two complexes of questions. First, is this novel pulsatile pump system able to mimic physiological flow patterns?

And second, can these flow conditions be translated into improved biological outcomes?

It was one of the strengths of the study that the authors tried to precisely quantify their pulse waveforms by different physical parameters, thus, being able to generate a pulse similar to physiologic flow. Whereas this first task was a more physical one, the second one about the effect of pulsatility was much more difficult to answer, I guess.

The experimental setup was tremendous, and I had a chance to read, also, the manuscript.

Finally, it turned out that pulsatility had purely no beneficial effect. Moreover, haemolysis and capillary leakage were increased as compared to continuous flow.

For me it remains questionable whether the lacking effect of pulsatility in this study was simply due to the relatively short duration of perfusion or some technological shortcomings of the procedure itself.

Furthermore, it is likely that other factors, such as cannulation site, the type of arterial cannula, and the outflow design may have an inference on flow characteristics.

I have two brief questions for you. First, would you speculate on the reason of the increased capillary leakage in both pulsatile groups.

And second, do you think it is still justified to care for pulsatile flow in times of well-functioning, long-term running continuous flow pumps in VAD systems?

Dr Voss: Let me answer the last question first: Advocates for pulsatile flow quote that the kind of pulsatile flow we need should be the one which is generated by the beating heart.

However, due to technical limitations and several damping components such as the oxygenator, the properties of 'pulsatile flow' used in the clinical setup are far from the ones of physiological pulsatile flow.

Therefore it is absolutely necessary to use an optimised pulsatile flow to answer the question if pulsatile flow is of benefit or not.

To your first question concerning the capillary leakage: The inflammatory response was equal in all groups, probably leading to vascular damage in all groups. However, a capillary leak was only seen in the pulsatile groups. I think one reason may be the higher peak pressure of the systolic pulse, leading to a higher amount of capillary leak.

Dr D. Birnbaum (*Bad Nauheim, Germany*): Maybe I dare to ask you to make a note to the problem of the delivery of the pulse via the aortic cannula. It depends on the width of the cannula related to aorta and of the 'Windkessel' function of an aorta particularly of a healthy one. Can you comment briefly on this?

Dr Voss: The aortic cannula is of importance due to the pulsatile flow because it's also a component which dams the pulse and disturbed the aortic flow.

Therefore, in this experiment, we applied in the pigs, which weighed about 35 kg, aortic cannulas with 24 French. This is a very large cannula able to perfuse a 100-kilo man.

Dr Birnbaum: Right.

Dr Voss: So I think the aortic cannula is really a limitation in the delivery of pulsatile flow.

Dr Birnbaum: At least it makes it understandable that your data is already optimised; however, it is illusionary to think that big cannulas could routinely be used in human.

Dr Voss: Yes. If you have a look at the pressure curves we saw in the pulsator group, there are some oscillations. And I think it's of course of the cannula leading to some disturbance.

Dr A. Wahba (*Trondheim, Norway*): Yes. It appears to me that the possible advantages of pulsatile perfusion are lost by the blood damage that is being done, and you can see that on the free haemoglobin. Did you in your model try other methods of creating pulsatility, for example, balloon pumping on top of a roller pump?

Dr Voss: No. We only used the setup which I just showed.