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Clinical Outcomes of Pulsatile and Non-Pulsatile Mode of Perfusion

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Abstract: A longstanding debate remains over whether or not pulsatile flow provides better perfusion during cardiopulmonary bypass (CPB). This paper provides a guide for clinical investigation, as well as current laboratory and clinical evidence concerning pulsatile and non-pulsatile perfusion. This evidence is in the form of in vitro and in vivo experiments and clinical trials. We review the literature and provide personal experience from the Pediatric Cardiac Research Laboratories at the Penn State Hershey Children's Hospital. Pulsatility is emerging as the preferred perfusion method for CPB. Clinical evidence show better cardiac, renal, and pulmonary outcomes in patients receiving pulsatile perfusion. Furthermore, better cytokine, endothelin, and hormone levels and a higher respiratory index are shown in pulsatile perfusion modes compared with non-pulsatile perfusion modes. In recent years, evidence has amounted that supports a shift toward pulsatility in these procedures over non-pulsatility. Currently, more evaluation of circuit components and patient outcomes is needed. **Keywords:** pulsatile perfusion, non-pulsatile perfusion, cardiopulmonary bypass, surplus hemodynamic energy.
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DEBATE: PULSATILE VS. NONPULSATILE PERFUSION

To date, despite increasing evidence in favor of pulsatile perfusion techniques, the debate over the superiority of either pulsatile or non-pulsatile perfusion in cardiopulmonary bypass (CPB) remains (1). This de bate is founded on three main issues. First, pulsatile flow lacks a universal definition, and quantification of arterial pressure and pump flow-waveforms is imprecise. Adequate quantification depends on an energy gradient rather than a pressure gradient (2). Currently, the most precise methods use Shepard's energy equivalent pressure (EEP). EEP can be used to calculate the total hemodynamic energy (THE), and, in conjunction with the mean arterial pressure (MAP), the surplus hemodynamic energy (SHE). THE represents EEP in units of energy, and SHE represents the extra energy generated caused by pulsatility (3). As stated by Ündar (2), SHE, at adequate levels, maintains more microcirculation perfusion at physiologic levels, decreases the systemic inflammatory response (SIRS), and improves vital organ recovery, leading to better clinical outcomes. These quantification methods allow comparison between perfusion modes and circuit components.

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Second, each component used in the circuit must be selected with attention to their effect on pulsatility. As a result of their geometry and unique characteristics, the membrane oxygenator, arterial filter, aortic cannulae, and tubing all create pressure drops in the circuit that affect the quality of the pulsatility, almost as much as does the pumphead. A lower pressure drop means less blood trauma and a reduced SIRS. Haphazard selection of these components will compromise the pulsatility; therefore, scientific evaluation of each component is necessary for the optimization of the circuit.

Finally, experimental design must not limit the ability to compare measurable outcomes in patients. To see measurable outcomes, pulsatile perfusion must be used for a substantial amount of time, rather than a few minutes, as has been done past experiments (1,2). Additionally, in patients without vital organ failure, the benefits of pulsatile perfusion may occur at subclinical levels, making patient selection an important factor in producing meaningful comparisons (2).

CLINICAL INVESTIGATION OF PULSATILE PERFUSION

Literature Search

The key issues of the debate outlined above allude to the steps necessary to best evaluate pulsatile perfusion.

The first step is a literature review to identify the key factors involved in patient and component selection. A Medline search on 28 May 2008 with the term "Pulsatile CPB" produced 160 publications. Examination of the literature provides insight into the factors that contribute to meaningful comparisons and outcomes (2).

In Vitro Studies

In vitro experiments in a simulated patient, after component selection, familiarize investigators with the operating conditions and highlight the benefits and limitations of each component (2). Simulated CPB patients have been described for both pediatric and adult patients (4,5).

As previously stated, SHE values indicate the extra energy supplied by pulsatile perfusion. Thus, in in vitro experiments, SHE values are the parameter used to investigate each individual component's ability to deliver adequate pulsatility (6). In addition to showing the added energy provided by pulsatile flow, comparisons of SHE values between different versions of circuit components can determine the pumps, membrane oxygenators, arterial filters, and aortic cannulae with the best hemodynamic profiles. Rider et al. (7) described the performance of eight commercial 10-F pediatric arterial cannulae in a simulated infant CPB patient under pulsatile and non-pulsatile conditions. The findings supported the previous evidence that pulsatile flow delivers more SHE and determined that the geometry, length, and most importantly the inner diameter of the cannulae have significant impacts on the pressure drop over their length and the SHE delivered to the simulated patient. These experiments and others like it in in vivo models provide surgeons the tools to select components that exhibit the best known hemodynamic profiles (8–10).

In Vivo Studies

After testing the circuit in a simulated patient, in vivo animal experiments provide further details on vital organ immunohistopathology associated with the procedure and choice of perfusion that are not accessible in human trials. Furthermore, it allows clinical perfusionists the opportunity to tune their technique before human studies (2).

Many in vivo models support using pulsatile perfusion in CPB. Ündar (11) showed that cerebral hemodynamics significantly benefit from pulsatile perfusion. In neonatal piglets, pulsatile perfusion provided higher global cerebral blood flow, improved cerebral metabolic rate, higher cerebral oxygen delivery, and lower cerebral vascular resistance. Furthermore, better myocardial and renal blood flow was shown with pulsatile perfusion. In sheep, Nakamura et al. (12) also found that the outer and middle renal cortices had higher renal blood flow in pulsatile compared with non-pulsatile CPB. Herreros et al. (13) suggested that better peripheral blood flow was seen using a pulsatile pump compared with a centrifugal pump. Many in vivo experiments speak to the benefits of pulsatile perfusion, whereas those that do not show advantages to pulsatile perfusion instead show no difference compared with non-pulsatile perfusion (14).

Pilot Studies

The fourth step, after finalizing the circuit components, is pilot studies with ~20 patients per group. Each group should be selected based on risk stratification, and patient parameters related to the outcome of CPB should not be significantly different between these groups. These parameters should be used to determine the perfusion operating conditions through experimentally developed algorithms. For pilot experiments, pulsatile flow should only be used after the cross-clamp is in place and should be discontinued before cross-clamp removal. Also, pulsatile flow pump rate should be identical across trials. Safety devices must be in place in all human trials. These include bubble detectors and possibly bubble trap systems. Also, transcranial Doppler (TCD) and devices such as the emboli detection and classification (EDAC) quantifier can be used to detect and quantify the number of microemboli within the circuit and patient. TCD can detect emboli >40 μm, whereas EDAC can detect and quantify microemboli >10 μm (2,15,16). Blood samples from each patient before and after the procedure provide biological markers that indicate the level of tissue trauma caused by CPB. These include, but are not limited to, plasma free hemoglobin levels, cytokine and complement levels, and neutrophil and platelet counts. With these considerations, meaningful comparisons can be made between pulsatile and non-pulsatile perfusion.

Alkan et al. (17), used biological markers and clinical outcomes to compare pediatric patients' responses to pulsatile and non-pulsatile CPB. Overall, the pulsatile perfusion group had better clinical outcomes with less inotropic support, lower infusions of dopamine and dobutamine, shorter intubation periods, and shorter time spent in the intensive care unit (ICU) and the hospital, as shown in Table 1. Additionally, urine output was higher during the procedure and during the ICU period with pulsatile perfusion, whereas differences in the two groups between creatinine and enzyme levels and drainage amounts were negligible. Thus, the pulsatile perfusion group compared with the non-pulsatile group benefited with improved cardiac, renal, and pulmonic function after CPB. These data were further confirmed and elaborated on by Alkan et al. (18), in a larger clinical trial containing 215 pediatric patients with congenital heart disease, 151 in the pulsatile group, and 64 in the non-pulsatile perfusion group. In addition to the aforementioned parameters, this trial showed lower adrenalin levels (.026 ± .005 vs. .046 ± .005 μg/kg/min, $p = .021$), lower lactate levels (16.27 ± 2.02 vs. 24.66 ± 3.05 mg/dL, $p = .00034$), and higher albumin levels (3.15 ± .03 vs. 2.95 ± 1.06 mg/dL, $p = .046$) in the pulsatile

Table 1. Statistically significant clinical outcomes between groups (17).

Parameter	Pulsatile	Non-Pulsatile	*p*
Inotropic support (no. agents)	1.5 ± 1.1	2.4 ± 1.0	.0015
Dopamine (μg/kg/min)	6.5 ± 3.3	10.3 ± 4.8	.0023
Dobutamine (μg/kg/min)	3.1 ± 6.6	8.0 ± 9.1	.034
Intubation period (hours)	20.4 ± 17.0	35.4 ± 30.7	.038
ICU stay (days)	2.2 ± 1.1	4.3 ± 4.2	.028
Hospital stay (days)	7.6 ± 2.5	11.8 ± 6.8	.007
Urine output during CPB (mL/d)	553.6 ± 150.9	465.8 ± 151.2	.045
Urine output in ICU (mL/d)	658.8 ± 211.0	528.2 ± 224.7	.039

perfusion group compared with the non-pulsatile perfusion group, further showing the benefits provided by pulsatile perfusion. Similar trends were shown in a recent study by Alkan-Bozkaya et al. (19), with 70 pediatric patients with ventricular septal defects. Alkan-Bozkaya et al. (20) reiterated these finding again in pediatric patients with congenital heart defects and further studied the impact of pulsatility on thyroid hormone homeostasis, showing that the thyroid hormones FT3 and FT4 were less reduced in patients receiving pulsatile perfusion both during CPB and 72 hours post-operative. Although the mechanism for the changes in thyroid hormone homeostasis during CPB is unclear, this suggests that pulsatile perfusion results in better patient outcomes. Orime et al. (21), measured cytokine and endothelin markers to determine the damage incurred by the endothelium during pulsatile and non-pulsatile perfusion in CPB. Patients from the pulsatile perfusion group had lower endothelin-1 and interleukin-8 levels, indicative of decreased endothelial damage. More recently this group provided data consistent with the above trial and elaborated support for pulsatile perfusion. Sezai et al. (22) noted lower levels of epinephrine and norepinephrine, indicating a decreased stress response and a higher respiratory index in patients undergoing pulsatile perfusion during CPB.

Clinical Trials and Use

When enough pulsatile perfusion pilot runs have been completed and the team is content with the CPB procedure and circuit, implementation of routine use is justified. Furthermore, the system can be fine tuned to further improve patient outcomes, including synchronizing pulsatility with the EKG (2,23).

CONCLUSIONS

Although pulsatile perfusion is not a panacea for the problems encountered in CPB patients, it can have a significant impact on clinical outcomes, especially in high-risk patients, provided adequate pulsatility is achieved. Pulsatile perfusion generates greater SHE values than non-pulsatile perfusion, and investigators commonly agree the benefits of pulsatile perfusion could be caused by movement of lymph that prevent edema and sludging in capillaries and maintained microcirculatory flow. Thus, as shown in the literature and above, pulsatile perfusion improves patient outcomes through improved cardiac, renal, and pulmonic function compared with patients undergoing non-pulsatile perfusion. Furthermore, pulsatile perfusion better maintains thyroid hormone homeostasis, which also may provide better patient outcomes.

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