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Pulsatile Versus *Nonpulsatile Flow*

No Difference in Cerebral Blood Flow or Metabolism during Normothermic Cardiopulmonary Bypass in Rabbits

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Background: **Although pulsatile and nonpulsatile cardiopulmonary bypass (CPB) do not differentially affect cerebral blood flow (CBF) or metabolism during hypothermia, studies suggest pulsatile CPB may result in greater CBF than nonpulsatile CPB under normothermic conditions. Consequently, nonpulsatile flow may contribute to poorer neurologic outcome observed in some studies of normothermic CPB. This study compared CBF and cerebral metabolic rate for oxygen (CMR_{O_2}) between pulsatile and nonpulsatile CPB at 37°C.**

Methods: **In experiment A, 16 anesthetized New Zealand white rabbits were randomized to one of two pulsatile CPB groups based on pump systolic ejection period (100 and 140 ms, respectively). Each animal was perfused at 37°C for 30 min at each of two pulse rates (150 and 250 pulse/min, respectively). This scheme created four different arterial pressure waveforms. At the end of each perfusion period, arterial pressure waveform, arterial and cerebral venous oxygen content, CBF (microspheres), and CMR_{O_2} (Fick) were measured. In experiment B, 22 rabbits were randomized to pulsatile (100-ms ejection period, 250 pulse/min) or nonpulsatile CPB at 37°C. At 30 and 60 min of CPB, physiologic measurements were made as before.**

Results: **In experiment A, CBF and CMR_{O_2} were independent of ejection period and pulse rate. Thus, all four waveforms were physiologically equivalent. In experiment B, CBF did not differ between pulsatile and nonpulsatile CPB (72 ± 6 *vs.* 77 ± 9 ml · 100 g^{-1} · min^{-1}, respectively (median ± quartile deviation)). CMR_{O_2} did not differ between pulsatile and nonpulsatile CPB (4.7 ± 0.5 *vs.* 4.1 ± 0.6 ml O_2 · 100 g^{-1} · min^{-1}, respectively) and decreased slightly (0.4 ± 0.4 ml O_2 · 100 g^{-1} · min^{-1}) between measurements.**

Conclusions: **During CPB in rabbits at 37°C, neither CBF nor CMR_{O_2} is affected by arterial pulsation. The absence of pulsation *per se* is not responsible for the small decreases in CMR_{O_2} observed during CPB. (Key words: Anesthesia: cardiovascular. Brain: blood flow; metabolism. Cardiopulmonary bypass: pulsatile flow.)**

A long-standing question in cardiopulmonary bypass (CPB) management is whether arterial pulsation is necessary to maintain adequate blood flow and aerobic metabolism in key organs, most importantly, the brain. Studies conducted in normothermic (37°C) dogs indicated microvascular perfusion was impaired[1,2] and cerebral blood flow (CBF) was reduced ~20% during nonpulsatile flow.[3,4] In contrast, studies conducted at moderate hypothermia (27°C), both in humans[5] and in our rabbit model of CPB,[6] detected neither CBF differences nor differences in cerebral metabolic rate for oxygen (CMR_{O_2}) between pulsatile and nonpulsatile CPB. Collectively, these observations suggest hypothermia may attenuate CBF and CMR_{O_2} differences between pulsatile and nonpulsatile CPB that are otherwise present during normothermia.

The cerebral physiology of normothermic CPB is assuming greater clinical relevance because of the recent interest in and adoption of normothermic ("warm") cardioplegia and CPB.[7,8] Some authors estimate that nearly 10% of all adult cardiac procedures now use normothermic techniques.[9] The extent to which neurologic outcome is influenced by "warm *versus* cold" CPB is unclear. One study found no difference in neurologic outcome between techniques,[10] whereas another study found evidence of worse neurologic outcome with warm CPB.[9] If pulsation is important for the maintenance of adequate CBF and CMR_{O_2} during normothermia, then nonpulsatile CPB may contribute to the neurologic injuries and cognitive deficits noted after "warm" heart surgery.

Using our rabbit model of CPB, we tested the hypothesis that during normothermic (37°C) conditions, CBF and CMR_{O_2} would be greater with pulsatile as compared to nonpulsatile CPB.

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Materials and Methods

Experimental protocols were approved by the Animal Care and Use Committee of the University of Iowa in accordance with the *Guide for the Care and Use of Laboratory Animals*.§ The following procedures were common to both experimental protocols.

Basic Preparation

Anesthesia was induced in New Zealand white rabbits (weight, 4.0–4.8 kg) by intravenous administration of 2 mg/kg diazepam and 10–15 μg/kg fentanyl *via* a 22-G ear vein catheter. After local infiltration with 1% lidocaine, a tracheotomy was performed and the trachea intubated with a 3.0 cuffed endotracheal tube. Thereafter, the animals' lungs were mechanically ventilated to achieve normocarbia, and anesthesia was maintained with 2% isoflurane in oxygen for the remainder of pre-CPB preparation. Animals were paralyzed with a succinylcholine/lactated Ringer's infusion (4 $ml \cdot kg^{-1} \cdot h^{-1}$) and placed prone. After a midline sagittal scalp incision, a 2-mm burr hole was drilled over the right frontoparietal cortex, and a 1-mm thermocouple (K-type, L-08419-02, Cole Parmer, Chicago, IL) was introduced under the cranium to rest on the dural surface. A posterior midline craniectomy was performed, exposing the confluens sinuum. Heparin was administered as a bolus (200 U/kg intravenously) and was added to the succinylcholine/lactated Ringer's infusion to give a maintenance dose of 200 $U \cdot kg^{-1} \cdot h^{-1}$. The tip of a saline-filled polyethylene catheter (PE-90, Intramedic, Parsippany, NJ) was placed in the confluens sinuum, permitting collection of cerebral venous blood. The cortical thermocouple and cerebral venous catheter were secured with bone wax and fast-drying cyanoacrylate cement, and the animals were placed supine.

The tip of a saline-filled catheter (PE-90), introduced *via* the right external jugular vein, was advanced to the superior vena cava to measure central venous pressure. An incision was made 2–3 mm inferior to the midportion of the mandibular ramus, and the facial artery was isolated. The carotid sinus and internal carotid artery were not manipulated. The facial artery was cannulated in retrograde fashion with an "end-view" 4-Fr solid-state pressure transducer (model 110-4G, Camino Laboratories, San Diego, CA) such that the tip of the transducer was approximately 8–11 mm distal to the internal/external carotid bifurcation. At selected intervals during CPB (see below), the signal from this catheter was digitized and recorded on a computer hard disk. Both brachial arteries were cannulated (saline-filled PE-160 tubing) for microsphere reference blood sampling. The left brachial arterial catheter also was used for arterial pressure monitoring and collection of arterial blood.

A midline abdominal incision was made. Viscera were covered with a transparent plastic sheet (SaranWrap, Dow Brands, Indianapolis, IN), and the distal abdominal aorta was isolated from surrounding tissue. The sternum was divided in midline, the thymus was retracted, and a Teflon-pledgeted 4-O silk purse-string suture was placed in the right atrium. After systemic anticoagulation with heparin (300 U/kg, intravenously), the distal aorta was ligated and cannulated in retrograde fashion with a 10-Fr pediatric arterial perfusion cannula (Biomedicus, Eden Prairie, MN) 7–10 mm superior to the distal aortic bifurcation. (Our prior technique of bilateral femoral artery cannulation[11] was abandoned because of marked damping of pulsatile waveforms.) A 21-Fr venous cannula (Polystan, Ballerup, Denmark) was placed in the right atrium. The aortic and right atrial cannulas were connected to the perfusion circuit, and normothermic CPB was initiated as described below. Approximately 30 min before CPB, isoflurane, maintenance fluids, and the succinylcholine/heparin infusion were discontinued. Anesthesia was maintained for the rest of the experiment with fentanyl (100-$\mu g/kg$ bolus, 150-$\mu g \cdot kg^{-1} \cdot h^{-1}$ infusion) and diazepam (2-mg/kg bolus, 3-$mg \cdot kg^{-1} \cdot h^{-1}$ infusion). Muscle relaxation was achieved with pancuronium (0.2 mg/kg).

CPB

The CPB circuit consisted of a venous reservoir, a membrane oxygenator/heat exchanger (Capiox 308, Terumo, Piscataway, NJ), a variable-temperature water pump (VWR Scientific, San Francisco, CA), and either a pulsatile perfusion pump (Medical Engineering Consultants, Los Angeles, CA) or a nonpulsatile centrifugal pump (model 540, Biomedicus, BP-50 pump head), depending on the experiment (see below). With the pulsatile pump, the duration of systolic ejection (ejection period, ms), pulse rate (pulse/min), and stroke volume (ml) were each independently variable. Circuit priming fluid consisted of 300 ml 6.5% (weight/vol)

§ National Institutes of Health: Guide for the Care and Use of Laboratory Animals, NIH Publication No. 85-23. Washington, D.C., National Institutes of Health, 1985.

high molecular weight hydroxyethyl starch (McGaw, Irvine, CA) in 0.72 N sodium chloride, 18 mEq sodium bicarbonate, 250 mg $CaCl_2$, and 1,000 U heparin. The priming fluid was circulated through a 40-μm filter for 15–20 min before addition of ~150 ml fresh, filtered, packed rabbit erythrocytes, achieving a priming hemoglobin concentration of 6–10 g/dL (OSM3 (rabbit absorption coefficients), Radiometer, Copenhagen, Denmark).

CPB was initiated and maintained throughout the experiment at a systemic flow rate of 100 ml · kg^{-1} · min^{-1}, monitored with a calibrated in-line electromagnetic flow meter (Biomedicus, TX-40P). The pulmonary artery was clamped to ensure complete venous outflow to the CPB circuit. To prevent left ventricular ejection and/or distension, the tip of a 14-G catheter was placed transapically in the left ventricle to permit drainage to the venous reservoir. Water temperature to the heat exchanger was maintained at 37°C. The oxygenator was ventilated with a variable mixture of oxygen and nitrogen to maintain Pa_{CO_2} near 40 mmHg and Pa_{O_2} near 250 mmHg when measured at an electrode temperature of 37°C (IL1304, Instrumentation Laboratory, Lexington, MA). Shed blood from the surgical field was returned to the venous reservoir after passing through a 40-μm filter. Sodium bicarbonate was given to maintain a base excess greater than −4 mEq/L, calculated at 37°C. Rabbit erythrocytes were given to maintain hemoglobin concentration between 6.7–8.5 g/dL. No pharmacologic or mechanical means were used to control arterial pressure. At experiment completion, animals were killed by discontinuation of CPB and intracardiac administration of KCl solution.

CBF and CMR_{O_2} Measurements

CBF was measured by the radioactive microsphere technique. Isotopes used included ^{46}Sc, ^{85}Sr, ^{95}Nb, ^{141}Ce (New England Nuclear, Boston, MA), although only two isotopes were used in each experiment. Stock microspheres (200 μl, ~0.9 million microspheres), vigorously mixed for 5 min before withdrawal, were diluted in 1.5 ml suspending solution (10% dextran-40 in normal saline with 0.5% (vol/vol) Tween-80) and mixed an additional 60 s. Microspheres were injected over 30 s into the arterial perfusion line approximately 25 cm proximal to the distal tip of the aortic cannula. Starting 15 s before microsphere injection and continuing 2 min thereafter, blood was simultaneously withdrawn from each brachial arterial catheter *via* a calibrated withdrawal pump (1.96 ml/min). After the experiment, the brain was removed and dissected into the following regions: right and left cerebral hemispheres, cerebellum, midbrain, and medulla. Fresh tissue samples were weighed, placed in counting tubes and, with reference blood samples, each counted for 5 min in a sodium iodide well-type γ counter (Minaxi γ Auto-Gamma 5000, Packard Instruments, Meriden, CT). Isotope separation, background, overlap corrections, and organ blood flow calculations (ml · 100 g^{-1} · min^{-1}) were performed by standard techniques.[12–14] Weight-averaged values for right and left cerebral hemispheric blood flow were used to calculate mean hemispheric CBF.

Oxygen content (ml O_2/dL) was calculated as (1.39 × percent saturation × hemoglobin concentration (g/dL)) + (Pa_{O_2} × 0.003). Cerebral oxygen extraction ratio (OER) was calculated as the arterial-cerebral venous oxygen content difference, divided by arterial oxygen content. CMR_{O_2} (ml O_2 · 100 g^{-1} · min^{-1}) was calculated as the product of mean hemispheric CBF (ml · 100 g^{-1} · min^{-1}) and the arterial-cerebral venous oxygen content difference.

Experiment A

The purpose of this experiment was to determine whether CBF or CMR_{O_2} depended on arterial pressure waveform configuration. We did this to ensure that, before comparing pulsatile *versus* nonpulsatile CPB (experiment B), artificial pulsatile waveforms adequately reproduced the essential features of native pressure waveforms.

Sixteen animals were anesthetized and prepared for CPB as described. For the first 30 min of CPB, all animals underwent pulsatile perfusion with an ejection period of 140 ms and a pulse rate of 250 pulse/min (pump stroke volume adjusted to maintain systemic flow at 100 ml · kg^{-1} · min^{-1}). Animals were randomly assigned to one of two groups: A1 (n = 8, 100-ms ejection period) and A2 (n = 8, 140-ms ejection period). In each animal, the ejection period of the pulsatile pump was adjusted according to assignment and kept constant for the remainder of the experiment. Thereafter, perfusion was maintained for 30 min at each of two different pulse rates: 150 and 250 pulse/min. The order of determination was randomized (150, 250 *vs.* 250, 150). In each instance, pump stroke volume was adjusted to maintain systemic flow at 100 ml · kg^{-1} · min^{-1}. Thus, four arterial pressure waveforms were created (two ejection periods × two pulse rates). At the end of each 30 min perfusion period (60 and

90 min of CPB), the following were recorded: 5 s of arterial pressure waveform (facial artery), arterial pressure from the brachial artery, central venous pressure, systemic flow rate, brain (epidural) temperature, and arterial hemoglobin concentration. Concurrent with these measurements, CBF determinations were made, and arterial and cerebral venous blood was collected for blood gas analysis and measurement of oxyhemoglobin saturation (OSM3, Radiometer).

Experiment B

Finding CBF and CMR_{O_2} to be equivalent among the four tested waveforms (see Results, Experiment A), the aim of the second experiment was to compare CBF and CMR_{O_2} between pulsatile and nonpulsatile normothermic CPB. Twenty-two additional animals were prepared for and underwent CPB as described. Animals were randomly assigned to one of two groups: B1 (n = 11, pulsatile perfusion) and B2 (n = 11, nonpulsatile perfusion). In the pulsatile group, CPB was maintained with a constant ejection period of 100 ms and pulse rate of 250 pulse/min. In animals undergoing nonpulsatile perfusion, CPB was maintained with a centrifugal pump. As in experiment A, no pharmacologic or mechanical means were used to influence arterial blood pressure.

At 30 and 60 min of CPB, the following were recorded in each animal: 5 s of arterial pressure waveform (facial artery), arterial pressure from the brachial artery, central venous pressure, systemic flow rate, brain (epidural) temperature, and arterial hemoglobin concentration. As before, CBF determinations made at this time, and arterial and cerebral venous blood was collected for blood gas analysis and measurement of oxyhemoglobin saturation.

Arterial Pressure Waveform Acquisition and Analysis

The main objective of waveform analysis was to provide a visual representation of arterial pressure waveforms, giving equal weight to each animal at a given combination of ejection period and pulse rate. In addition, we wished to provide numeric estimates of arterial pressure waveform characteristics (*e.g.,* maximal rate of change of pressure (dP/dt) and pulse pressure (difference between systolic and diastolic pressure)). Because these estimates were subject to large errors, no statistical analysis was undertaken. Analog outputs from the facial artery catheter (see above) were taken from the monitoring module (model 420, Camino), amplified, and digitized (model DT2801A, Data Translation, Marlboro, MA; 350 Hz, 12-bit resolution). The first complete trough-to-trough waveform in each animal was used to represent the entire 5-s sample. We estimated dP/dt for each pressure wave by visually selecting data points at the start and end of the pressure upstroke. Pulse pressure was calculated as the difference between peak systolic and trough diastolic pressures. Waveforms were grouped according to group assignment and either pulse rate (experiment A) or CPB duration (experiment B). Waveforms were visually phase aligned using the slope of the pressure wave at each data point. Waveforms were pressure-aligned by subtracting the mean value of the pressure wave from each data point, to create a "corrected waveform," with a mean of zero. A median waveform was generated by finding the median pressure at each time across all corrected waveforms. The median of the mean pressures was added to each data point of this waveform, creating an overall representative (median) waveform. To provide upper and lower boundaries about median waveforms, maximum and minimum values of corrected waveforms were added to the median of the mean pressures from appropriate data sets.

Statistics

Right and left microsphere counts appeared to be normally distributed, permitting linear regression analysis to test adequacy of microsphere mixing and distribution. In contrast, box and whisker plots suggested that many physiologic variables were not normally distributed. Consequently, all physiologic variables were summarized using their median ± quartile deviation, the latter equaling half the difference between the first and third quartiles. Changes in physiologic variables were assessed qualitatively to preserve statistical power to detect differences in CBF and CMR_{O_2}.

Analyses were performed using Systat statistical software.[15] CBF appeared to follow a normal distribution, whereas CMR_{O_2} appeared normally distributed after log transformation. Thus, CMR_{O_2} data were log-transformed before analysis. In experiment A, CBF and CMR_{O_2} were compared between ejection period groups and pulse rates using univariate repeated measures analysis of variance. In experiment B, CBF and CMR_{O_2} were compared between groups and over time using univariate repeated measures analysis of variance. No interaction terms were statistically significant ($P > 0.15$). *Post hoc* power to detect differences between groups was esti-

Table 1. Systemic Variables: Experiment A

Variable	Group	Pulse Rate (pulse/min) 150	250
Systolic arterial pressure (mmHg)	A1	104 (9)	91 (9)
	A2	107 (11)	99 (11)
Diastolic arterial pressure (mmHg)	A1	61 (7)	66 (3)
	A2	60 (10)	66 (11)
Mean arterial pressure (mmHg)	A1	75 (8)	76 (4)
	A2	78 (11)	81 (11)
Pulse pressure (mmHg)	A1	43 (7)	30 (7)
	A2	44 (5)	28 (5)
dP/dt (mmHg/s)	A1	1,810 (560)	1,360 (280)
	A2	1,040 (240)	880 (170)
Systemic flow ($ml \cdot kg^{-1} \cdot min^{-1}$)	A1	100 (5)	101 (5)
	A2	97 (3)	100 (3)
Central venous pressure (mmHg)	A1	3 (1)	3 (1)
	A2	3 (1)	3 (1)
Bypass duration (min)	A1	72 (15)	72 (15)
	A2	71 (15)	74 (15)
*p*H	A1	7.35 (0.01)	7.37 (0.02)
	A2	7.37 (0.01)	7.37 (0.02)
Pa_{CO_2} (mmHg)	A1	41 (1)	40 (2)
	A2	41 (1)	41 (2)
Pa_{O_2} (mmHg)	A1	244 (22)	266 (25)
	A2	262 (30)	265 (33)
Hemoglobin (g/dl)	A1	7.8 (0.3)	8.0 (0.3)
	A2	7.6 (0.1)	7.9 (0.3)
Arterial oxygen content (ml O_2/dl)	A1	11.2 (0.3)	11.4 (0.4)
	A2	11.1 (0.1)	11.5 (0.5)

Values are median and quartile deviation (parentheses): group A1 (n = 8); group A2 (n = 8).

mated using the mean of the two measurements in each animal. The estimate of the pooled variance between groups used to calculate power[16] incorporated linear correlation between the two measurements.[17]

Results

Experiment A (Pressure Wave Configuration)

Microsphere Validation. Paired right and left microsphere reference counts were well matched (r^2 = 0.995, slope = 1.02, intercept (−37 cpm) not significantly different than zero), indicating adequate microsphere mixing and uniform distribution. There were no right-left CBF asymmetries between the cerebral hemispheres.

Systemic Variables. Systemic physiologic variables during CPB for groups A1 and A2 are summarized in table 1. Figure 1 shows the corresponding representative (median) arterial pressure waveforms and the upper and lower boundaries about the medians (*i.e.*, the worst cases). Figure 2 shows a native (non-CPB) rabbit facial arterial pressure waveform for comparison to artificial waveforms. There were no differences between or within groups A1 and A2 with respect to the following: mean arterial pressure, systemic flow, central venous pressure, CPB duration, arterial *p*H, P_{CO_2}, P_{O_2}, hemoglobin concentration, or oxygen content. Although mean arterial pressure did not differ between groups (~78 mmHg), as expected, arterial systolic pressure decreased and diastolic pressure increased with increasing pulse rate. Consequently, pulse pressure decreased with increasing pulse rate. Likewise, dP/dt decreased with increasing pulse rate. Mean arterial pressures recorded from the facial artery were 8 ± 4 mmHg (median ± quartile deviation) less than those recorded from the brachial artery.

Cerebral Physiology. Cerebral physiologic variables are summarized in table 2. There were no differences between or within ejection period groups with respect to the following: brain temperature, cerebral venous oxygen content, arterial-cerebral venous oxygen content difference, and cerebral oxygen extraction ratio. Hemispheric CBF (~85 $ml \cdot 100\ g^{-1} \cdot min^{-1}$) was independent of both ejection period group ($P = 0.92$) and pulse rate ($P = 0.56$). Similarly, CMR_{O_2} (~4.3 ml $O_2 \cdot 100\ g^{-1} \cdot min^{-1}$) was independent of both ejection period group ($P = 0.36$) and pulse rate ($P = 0.99$).

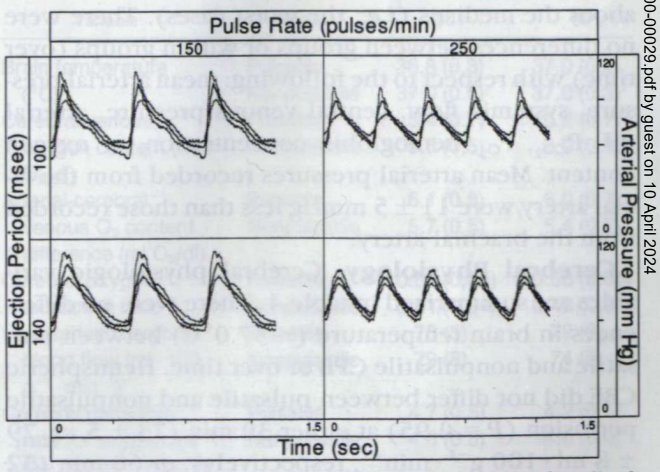

Fig. 1. Experiment A. Solid lines = representative (median) facial artery pressure waveforms during cardiopulmonary bypass at each combination of group assignment (ejection period) and pulse rate. Dotted lines = maximum and minimum boundaries about the medians. In each ejection period group, n = 8.

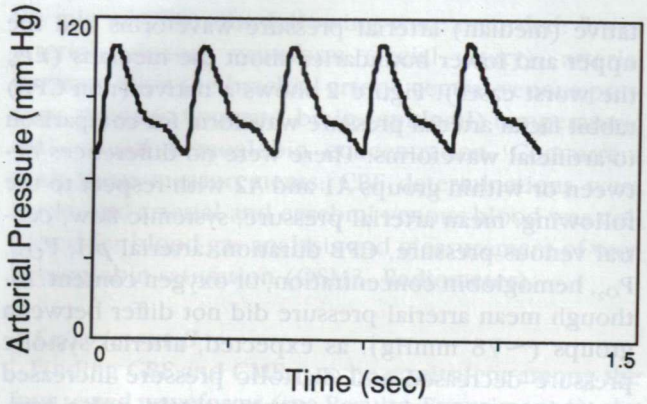

Fig. 2. Native (noncardiopulmonary bypass) facial artery pressure waveform from a single animal. Arterial pressure is 112/69, mean arterial pressure 88 mmHg, pulse rate 250/min, and dP/dt 1,699 mmHg/s.

Experiment B (Pulsatile Vs. *Nonpulsatile CPB)*

Microsphere Validation. Paired right and left microsphere reference counts were well matched (r^2 = 0.99, slope = 1.04, intercept (163 cpm) not significantly different than zero), indicating adequate microsphere mixing and uniform distribution. There were no right-left CBF asymmetries between the cerebral hemispheres.

Systemic Variables. Systemic physiologic variables for groups B1 (pulsatile CPB) and B2 (nonpulsatile CPB) are summarized in table 3. Figure 3 shows the corresponding representative (median) arterial pressure waveforms and the upper and lower boundaries about the medians (*i.e.,* the worst cases). There were no differences between groups or within groups (over time) with respect to the following: mean arterial pressure, systemic flow, central venous pressure, arterial *p*H, P_{CO_2}, P_{O_2}, hemoglobin concentration, or oxygen content. Mean arterial pressures recorded from the facial artery were 11 ± 5 mmHg less than those recorded from the brachial artery.

Cerebral Physiology. Cerebral physiologic variables are summarized in table 4. There were no differences in brain temperature (~37.0°C) between pulsatile and nonpulsatile CPB or over time. Hemispheric CBF did not differ between pulsatile and nonpulsatile perfusion (P = 0.95) at either 30 min (73 ± 5 *vs.* 79 ± 8 ml · 100 g^{-1} · min^{-1}, respectively), or 60 min (72 ± 8 *vs.* 74 ± 9 ml · 100 g^{-1} · min^{-1}, respectively). There was no significant change in hemispheric CBF in the 30-min interval between measurements (P = 0.08). CMR_{O_2} did not differ between pulsatile and nonpulsatile CPB (P = 0.33) at either 30 min (4.7 ± 0.5 *vs.* 4.3 ± 0.5 ml O_2 · 100 g^{-1} · min^{-1}, respectively) or 60 min (4.2 ± 0.6 *vs.* 4.0 ± 0.6 ml O_2 · 100 g^{-1} · min^{-1}, respectively). There was a significant (P = 0.014) decrease in CMR_{O_2} between measurements (0.4 ± 0.4 ml O_2 · 100 g^{-1} · min^{-1}).

Discussion

We found no significant difference in either CBF or CMR_{O_2} between pulsatile and nonpulsatile CPB at normothermia. The rabbit was chosen as the experimental species because, like humans but unlike dogs, cats, sheep, and pigs, rabbits do not possess rete mirabilae—internal/external carotid arterial communications. The rabbit brain is supplied exclusively by paired internal carotid and vertebral arteries, with a fully developed circle of Willis.[18] Also, many physiologic characteristics of rabbits closely approximate those of humans, including: (1) arterial blood pressure, (2) cerebrovascular responses to changing Pa_{CO_2}[19] and blood pressure (autoregulation),[20] and (3) resting CBF and CMR_{O_2}.[21] Besides species differences, this study differs from prior animal studies of pulsatile CPB because, in addition to CBF, CMR_{O_2} was measured. Combined CBF and CMR_{O_2} measurements provide for a better assessment of the relationship between cerebral oxygen supply and demand than CBF measurements alone.

A criticism sometimes made of studies that find no difference between pulsatile and nonpulsatile CPB is that the artificial pressure waveform may not have ad-

Table 2. Cerebral Variables: Experiment A

Variable	Group	Pulse Rate (pulse/min) 150	250
Brain temperature (°C)	A1	36.6 (0.2)	36.7 (0.2)
	A2	36.9 (0.3)	36.7 (0.2)
Cerebral venous oxygen content (ml O_2/dl)	A1	6.2 (1.0)	6.2 (0.9)
	A2	6.2 (0.7)	6.0 (0.9)
Cerebral arterial-venous O_2 content difference (ml O_2/dl)	A1	5.3 (1.4)	5.2 (0.8)
	A2	4.9 (0.5)	5.3 (0.5)
Cerebral oxygen extraction ratio	A1	0.48 (0.11)	0.46 (0.08)
	A2	0.45 (0.05)	0.47 (0.07)
Hemispheric cerebral blood flow (ml · 100 g^{-1} · min^{-1})	A1	85 (19)	87 (14)
	A2	86 (9)	86 (9)
Cerebral metabolic rate for oxygen (ml O_2 · 100 g^{-1} · min^{-1})	A1	4.2 (0.5)	4.3 (0.4)
	A2	4.4 (0.2)	4.2 (0.2)

Values are median and quartile deviation (parentheses): group A1 (n = 8); group A2 (n = 8).

Table 3. Systemic Variables: Experiment B

Variable	Group	Bypass Duration (min) 30	60
Systolic arterial pressure (mmHg)	Pulsatile	101 (8)	98 (9)
	Nonpulsatile	—	—
Diastolic arterial pressure (mmHg)	Pulsatile	64 (7)	67 (7)
	Nonpulsatile	—	—
Mean arterial pressure (mmHg)	Pulsatile	79 (7)	82 (8)
	Nonpulsatile	75 (9)	75 (6)
Pulse pressure (mmHg)	Pulsatile	37 (4)	32 (5)
	Nonpulsatile	—	—
dP/dt (mmHg/s)	Pulsatile	1,540 (230)	1,120 (190)
	Nonpulsatile	—	—
Systemic flow ($ml \cdot kg^{-1} \cdot min^{-1}$)	Pulsatile	104 (4)	104 (4)
	Nonpulsatile	98 (3)	100 (4)
Central venous pressure (mmHg)	Pulsatile	3 (1)	3 (1)
	Nonpulsatile	2 (1)	2 (1)
pH_a	Pulsatile	7.37 (0.02)	7.35 (0.02)
	Nonpulsatile	7.38 (0.01)	7.37 (0.01)
Pa_{CO_2} (mmHg)	Pulsatile	39 (1)	41 (1)
	Nonpulsatile	39 (2)	40 (1)
Pa_{O_2} (mmHg)	Pulsatile	255 (38)	249 (25)
	Nonpulsatile	261 (24)	272 (19)
Hemoglobin (g/dl)	Pulsatile	7.8 (0.3)	7.7 (0.3)
	Nonpulsatile	8.0 (0.3)	7.7 (0.3)
Arterial oxygen content (ml O_2/dl)	Pulsatile	11.4 (0.3)	11.1 (0.4)
	Nonpulsatile	11.6 (0.4)	11.1 (0.3)

Values are median and quartile deviation (parentheses): pulsatile (B1, n = 11); nonpulsatile (B2, n = 11).

equately reproduced the essential features of the native waveform.[22] This criticism is easy to make and difficult to refute because the critical features of pulsatile flow (*e.g.*, dP/dt, pulse rate, pulse pressure, systolic/diastolic ratio) are not known. We addressed this issue in experiment A, by first determining whether CBF or CMR_{O_2} depended on arterial pressure waveform configuration. By altering pump ejection period and pulse rate, four different arterial pressure waveforms were created. Within the range of waveforms tested, we found neither CBF nor CMR_{O_2} depended on arterial pressure waveform configuration. Thus, all four pulsatile waveforms were physiologically equivalent with respect to CBF and CMR_{O_2} and apparently adequately represented a "true" pulsatile waveform.

We selected one of the four waveforms to serve as our test waveform in the subsequent experiment. In experiment B, we found no difference in CBF between pulsatile and nonpulsatile CPB. This is in contrast to the work of Dernevik *et al.*[3] and Tranmer *et al.*,[4] in which, in normothermic dogs, pulsatile CPB

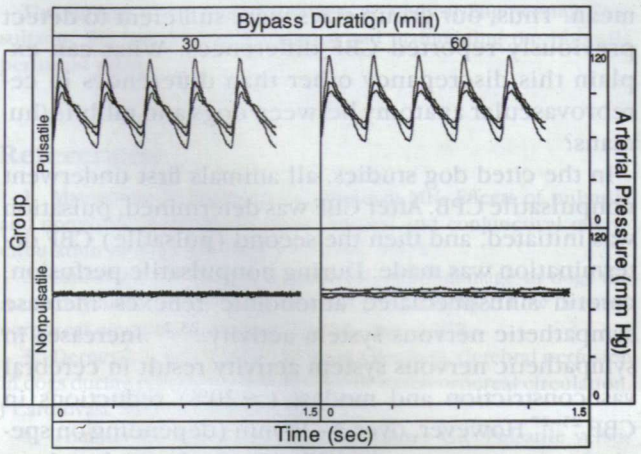

Fig. 3. Experiment B. Solid lines = representative (median) facial artery pressure waveforms during cardiopulmonary bypass. Dotted lines = maximum and minimum boundaries about the medians. In each group, n = 11.

increased CBF to values 16–19% greater than achieved during nonpulsatile CPB. *Post hoc* analysis indicates we had sufficient power ($\alpha = 0.05$, $\beta = 0.80$) to detect hemispheric CBF differences between pulsatile and nonpulsatile CPB of 20% of the overall

Table 4. Cerebral Variables: Experiment B

Variable	Group	Bypass Duration (min) 30	60
Brain temperature (°C)	Pulsatile	36.8 (0.3)	37.0 (0.2)
	Nonpulsatile	37.0 (0.5)	37.0 (0.3)
Cerebral venous oxygen content (ml O_2/dl)	Pulsatile	5.4 (0.7)	5.2 (0.7)
	Nonpulsatile	5.6 (0.5)	6.0 (0.3)
Arterial-cerebral venous O_2 content difference (ml O_2/dl)	Pulsatile	6.1 (0.6)	6.0 (0.7)
	Nonpulsatile	5.7 (0.5)	5.4 (0.2)
Cerebral oxygen extraction ratio	Pulsatile	0.51 (0.05)	0.56 (0.05)
	Nonpulsatile	0.51 (0.04)	0.48 (0.01)
Hemispheric cerebral blood flow ($ml \cdot 100\ g^{-1} \cdot min^{-1}$)*	Pulsatile	73 (5)	72 (8)
	Nonpulsatile	79 (8)	74 (9)
Cerebral metabolic rate for oxygen ($ml\ O_2 \cdot 100\ g^{-1} \cdot min^{-1}$)†	Pulsatile	4.7 (0.5)	4.2 (0.6)
	Nonpulsatile	4.3 (0.5)	4.0 (0.6)

Values are median and quartile deviation (parentheses): pulsatile (B1, n = 11); nonpulsatile (B2, n = 11).

* $P = 0.95$ between groups, $P = 0.08$ over time.

† $P = 0.33$ between groups, $P = 0.014$ over time.

mean. Thus, our group sizes were sufficient to detect previously reported CBF differences. What can explain this discrepancy other than differences in cerebrovascular anatomy between dogs and rabbits/humans?

In the cited dog studies, all animals first underwent nonpulsatile CPB. After CBF was determined, pulsation was initiated, and then the second (pulsatile) CBF determination was made. During nonpulsatile perfusion, carotid sinus-mediated autonomic reflexes increase sympathetic nervous system activity.[23,24] Increases in sympathetic nervous system activity result in cerebral vasoconstriction and modest (~20%) reductions in CBF.[25–27] However, over 3–20 min (depending on species), compensatory vasodilation in the pial and parenchymal vasculature[25,28,29] restores CBF to baseline.[25,29,30] When changing from nonpulsatile to pulsatile CPB (as was done in the cited dog studies), sympathetic nervous system activity should decrease, at least transiently. This acute decrease in sympathetic tone should result in a modest temporary decrease in cerebrovascular resistance[25] and a transient increase (~20%) in CBF. Again, however, this change in sympathetic nervous system activity will not have sustained effects on CBF because of counter-regulatory mechanisms. Thus, it seems possible that, when going from one mode to another, temporary CBF differences, mediated by alterations in sympathetic tone, could exist between pulsatile and nonpulsatile CPB. However, when CPB techniques are maintained at steady-state, as they were in this experiment, CBF differences between pulsatile and nonpulsatile CPB are negligible.

The absence of CBF differences in this study suggests other mechanisms, thought to distinguish pulsatile from nonpulsatile flow, may not influence CBF during CPB. Nitric oxide is a potent cerebral vasodilator[31,32] and plays a major role in maintaining basal cerebrovascular tone.[33] Both Hecker *et al.*[34] and Lamontagne *et al.*[35] have shown nitric oxide release increases with increasing endothelial shear stress. Likewise, Pohl *et al.*[36] and Rubanyi *et al.*[37] found endothelial nitric oxide release increased when flow was changed from a nonpulsatile to a pulsatile mode. Therefore, one might expect pulsatile CPB to have resulted in greater endothelial nitric oxide release and, consequently, greater CBF as compared to nonpulsatile CPB. However, it has been shown that nitric oxide exerts negative feedback regulation of its own synthesis.[38] Were nonpulsatile flow to decrease nitric oxide release, a feedback-mediated increase of nitric oxide synthesis might restore cerebrovascular tone to baseline. In such a circumstance, sustained CBF differences between pulsatile and nonpulsatile CPB would not exist. Yet another explanation for the lack of an effect of pulsation upon CBF in this experiment may relate to hemodilution. Todd *et al.* found hemodilution to a hematocrit of ~14% completely eliminated CBF responses to nitric oxide synthase inhibition, *i.e.*, no decrease in CBF.‖ Although a much less profound degree of hemodilution was used in the current experiment (hematocrit ~24%), perhaps the hemodilution of CPB decreases basal endothelial nitric oxide release. In such a circumstance, pulse-mediated effects on nitric oxide release and CBF could be rendered inconsequential.

To our knowledge, this is the first study to assess whether CMR_{O_2} differs between pulsatile and nonpulsatile CPB at normothermia. We found no significant difference. *Post hoc* analysis indicates we had sufficient power ($\alpha = 0.05$, $\beta = 0.80$) to detect CMR_{O_2} differences between pulsatile and nonpulsatile CPB of ~25% of the overall mean. Therefore, CMR_{O_2} differences less than 25% could have gone undetected. Some elements of our data suggest there might be a small CMR_{O_2} difference between pulsatile and nonpulsatile CPB. The OER was ~10% greater with pulsatile CPB (table 4). Analysis of the OER data (repeated-measures analysis of variance) suggests OER might have been greater in the pulsatile group ($P = 0.03$). Given CBF equivalence under pulsatile and nonpulsatile conditions, this implies CMR_{O_2} should be ~10% greater with pulsatile flow. Inspection of table 4 shows median CMR_{O_2} values were ~10% greater in the pulsatile group. However, several considerations must be kept in mind. First, inspection of table 4 shows OER differences between pulsatile and nonpulsatile CPB were neither large nor uniformly present and, given the number of statistical comparisons made, a P value of 0.03 cannot be considered significant. Second, unlike all other comparisons made in this study, OER data violated several assumptions inherent in the statistical methodology. Third, one should not perform independent analyses of CMR_{O_2} and OER because they share common factors in their calculation. Fourth, power analysis indicates, given our CMR_{O_2} variance, that more than 70 animals per group would be required to demonstrate a

‖ Todd MM, Wu B, Warner DS: The roles of adenosine and nitric oxide in the cerebral blood flow effects of hypoxia and hemodilution (abstract). Soc Neurosci Abstr 19:1225, 1993.

CMR_{O_2} difference of 10% between groups. Finally, in a study of normothermic CPB in dogs, there was no difference in systemic OER between pulsatile and nonpulsatile flow, even under conditions of markedly reduced perfusion.[39] Thus, greater oxygen extraction with pulsatile flow has not been demonstrated in any other system. Therefore, if CMR_{O_2} differences do exist between steady-state pulsatile and nonpulsatile CPB (and we emphasize that our data do not indicate they do), they are exceedingly small and would require an unacceptably large number of animals to demonstrate.

In a prior study with this preparation, we did not detect a change in either CBF or CMR_{O_2} during 60 min of normothermic nonpulsatile CPB.[11] Consequently, we were surprised to find that, in the current experiment, CMR_{O_2} decreased slightly over the 30-min measurement interval and that CBF may have done the same. In our prior study, power analysis indicated we had sufficient power to detect a change in CBF of 19 $ml \cdot 100\ g^{-1} \cdot min^{-1}$ and CMR_{O_2} of 1.4 $ml \cdot 100\ g^{-1} \cdot min^{-1}$.[11] Thus, the decreases in CBF and CMR_{O_2} observed in the current experiment (4 ± 3 $ml \cdot 100\ g^{-1} \cdot min^{-1}$ and 0.4 ± 0.4 ml $O_2 \cdot 100\ g^{-1} \cdot min^{-1}$, respectively) are quite small and were well below the limits of resolution of our prior study. In the current experiment, OER remained constant over time. This finding indicates changes in CBF and CMR_{O_2}, whatever their cause, were coupled. Although the current experiment cannot provide insight into the mechanisms responsible for decreases in CMR_{O_2} and CBF during CPB, one thing is clear. Because decreases in CMR_{O_2} and CBF were equivalent during both pulsatile and nonpulsatile CPB, lack of pulsatile flow *per se* was not responsible for the observed changes. Other factors, such as cerebral embolization, must be responsible.

In summary, this study indicates that, at normothermia, nonpulsatile CPB does not appear disadvantageous to the rabbit brain in terms of either bulk blood flow or oxygen metabolism. Although CMR_{O_2} decreased slightly over time during CPB, lack of arterial pulsation did not appear to be the factor responsible for these changes. This study cannot address potential differences in regional CBF, microvascular perfusion, or cerebrovascular responses to ischemia between pulsatile and nonpulsatile CPB. Therefore, additional studies will be necessary before the impact of pulsatile CPB upon neurologic outcome after cardiac surgery can be definitively established.

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