Anesthesiology
80:1137–1147, 1994

Pulsatile Versus *Nonpulsatile Cardiopulmonary Bypass*

No Difference in Brain Blood Flow or Metabolism at 27°C

Bradley J. Hindman, M.D., Franklin Dexter, M.D., Ph.D.,† Keon Hee Ryu, M.D., Ph.D.,‡ Tom Smith, B.S.,§ Johann Cutkomp, B.S.§*

Background: **It is unclear whether nonpulsatile perfusion adversely affects the brain. This study compared cerebral blood flow (CBF) and cerebral metabolic rate for oxygen (CMR_{O_2}) between pulsatile and nonpulsatile cardiopulmonary bypass (CPB) in rabbits at 27°C.**

Methods: **In experiment A, 24 anesthetized New Zealand white rabbits underwent pulsatile CPB at 27°C, using α-stat acid-base management. Animals were randomized to three groups based upon the duration of the period of systolic ejection (100, 120, 140 ms) and were perfused for 20 min at each of three pulse rates (150, 200, 250 pulse/min), generating nine arterial pressure waveforms. Arterial pressure waveform, arterial and cerebral venous oxygen content, CBF (radiolabeled microspheres), and CMR_{O_2} (Fick) were measured at the end of each 20-min period. In experiment B, 16 anesthetized rabbits were randomized to pulsatile (120-ms ejection period, 250 pulse/min) or nonpulsatile CPB at 27°C. After 1 h, arterial pressure waveform, arterial and cerebral venous oxygen content, CBF and CMR_{O_2} were measured.**

Results: **In experiment A, CBF and CMR_{O_2} were independent of ejection period and pulse rate. Thus, all nine waveforms were physiologically equivalent. In experiment B, CBF did not differ between pulsatile and nonpulsatile bypass, 30 ± 4 *versus* 32 ± 5 ml · 100 g^{-1} · min^{-1}, respectively. CMR_{O_2} did not differ between pulsatile and nonpulsatile bypass, 1.7 ± 0.2 *versus* 1.6 ± 0.2 ml · 100 g^{-1} · min^{-1}, respectively.**

Conclusions: **During CPB in rabbits at 27°C, neither CBF nor CMR_{O_2} is affected by flow character. (Key words: Anesthesia: cardiovascular. Brain: blood flow; hypothermia; metabolism. Cardiopulmonary bypass: pulsatile flow. Temperature: hypothermia.)**

A long-standing question in cardiopulmonary bypass (CPB) management is whether conventional nonpulsatile flow may, in some way, compromise cerebral perfusion and contribute to neurologic injury occurring during cardiac surgery. Studies in normothermic dogs show that, compared with pulsatile perfusion, nonpulsatile perfusion results in: (1) cerebral capillary collapse, intravascular sludging, and venodilation[1]; (2) histopathology consistent with ischemia in arterial boundary zones[2]; and (3) an approximately 20% decrease in cerebral blood flow (CBF).[3,4] Collectively, these studies suggest brain blood flow and oxygenation might be better maintained with pulsatile CPB. On this basis, some cardiac surgery groups routinely employ pulsatile bypass[5] or use it when patients are considered to be at special risk of neurologic complications.[6]

Nevertheless, there remains to date no clinical evidence of better cerebral perfusion nor better neurologic outcome in patients undergoing cardiac surgery with pulsatile CPB. In a study of 312 patients undergoing coronary artery bypass grafting, Shaw *et al.* found no difference in neurologic outcome between patients undergoing pulsatile (n = 134) or nonpulsatile (n = 178) perfusion.[7] Likewise, in a study of patients undergoing coronary artery bypass grafting and randomized to either pulsatile (n = 8) or nonpulsatile (n = 14) perfusion, neither CBF nor cerebral metabolic rate for oxygen (CMR_{O_2}) during bypass nor postoperative neurologic outcome differed between groups.[8] Thus, the animal and the human literature are inconsistent as to whether pulsatile perfusion provides better brain

* Assistant Professor of Anesthesia, Cardiovascular Anesthesia Research Laboratory, Department of Anesthesia, College of Medicine, University of Iowa, Iowa City, Iowa.

† Resident in Anesthesia, Cardiovascular Anesthesia Research Laboratory, Department of Anesthesia, College of Medicine, University of Iowa, Iowa City, Iowa.

‡ Visiting Research Fellow, Department of Anesthesia, Catholic University Medical College, Seoul, Korea.

§ Research Assistant, Cardiovascular Anesthesia Research Laboratory, Department of Anesthesia, College of Medicine, University of Iowa, Iowa City, Iowa.

Received from the Cardiovascular Anesthesia Research Laboratory, Department of Anesthesia, College of Medicine, University of Iowa, Iowa City, Iowa. Accepted for publication January 26, 1994. Supported in part by National Institutes of Health Grant 1RO1HL47159 (BJH). Presented in abstract form at the Anesthesia and Cardiovascular Disease Symposium—'93, Milwaukee, Wisconsin, September 10–12, 1993.

blood flow and oxygenation and/or offers neurologic advantages.

Species differences, temperature differences, and differences in perfusion technology may offer a partial explanation for these inconsistencies. Inconsistencies also may relate to the issue of what constitutes "physiologically acceptable"[9] pulsatility and whether it is achieved in any given study. In other words, a fundamental issue in any study of pulsatile perfusion is whether the artificial pulsatile waveform adequately reproduces the essential physiologic aspects of native pulsatility.

Using our previously described animal model of CPB,[10] we sought to determine whether CBF and CMR_{O_2} differ between pulsatile and nonpulsatile perfusion during moderately hypothermic (27°C) CPB. Rabbits were chosen as the experimental species because: (1) unlike dogs, the rabbit brain is supplied exclusively by the internal carotid and vertebral arteries in a pattern highly analogous to humans[11]; and (2) arterial blood pressure and cerebrovascular responses to changes in arterial pressure (autoregulation)[12] and Pa_{CO_2}[13,14] closely approximate those of humans.

The experiment was conducted in two stages. In the first stage, we sought to define the dependence of CBF and CMR_{O_2} upon arterial pressure waveform characteristics. We did so to identify pulsatile arterial pressure waveforms that were "physiologically acceptable" to the cerebral circulation. Having established necessary pulse characteristics, we compared CBF and CMR_{O_2} between pulsatile and nonpulsatile CPB.

Materials and Methods

Experimental protocols were approved by the Animal Care and Use Committee of the University of Iowa.

Experiment A

The aim of this experiment was to determine whether CBF and/or CMR_{O_2} varied with arterial pressure pulse wave contour. Anesthesia was induced in 24 New Zealand white rabbits (weight 4.1–4.8 kg) by intravenous administration of 2 mg/kg diazepam and 10–15 μg/kg fentanyl *via* 22-G ear vein catheter. After local infiltration with 1% lidocaine, a tracheotomy was performed and the trachea intubated with a 3.0 cuffed tracheal tube. Thereafter, the animals' lungs were mechanically ventilated to achieve normocarbia, and anesthesia was maintained with 1.5–2.0% isoflurane in oxygen for the remainder of prebypass 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-French solid-state pressure transducer (model 110-4G, Camino, 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 drive. Both brachial arteries were cannulated (saline-filled PE-160 tubing) for microsphere reference blood samples. The left brachial arterial catheter also was used for blood pressure monitoring and collection of arterial blood.

A midline abdominal incision was made. The viscera were covered with a transparent plastic sheet (SaranWrap, Dow Brands, Indianapolis, IN) and the distal abdominal aorta isolated from surrounding tissue. The sternum was divided in midline, the thymus retracted, and a Teflon-pledgeted 4-0 silk purse-string suture placed in the right atrium. After systemic heparinization (300 U/kg, intravenously), the distal aorta was ligated and cannulated in retrograde fashion with a 10-French pediatric arterial perfusion cannula (Biomedicus, Eden Prairie, MN) 7–10 mm superior to the distal aortic bifurcation. A 21-French venous cannula

(Polystan, Ballerup, Denmark) was placed in the right atrium. The aortic and right atrial cannulas were connected to the perfusion circuit, and 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).

The bypass circuit consisted of a venous reservoir, a pulsatile perfusion system (Medical Engineering Consultants, Los Angeles, CA), a membrane oxygenator/heat exchanger (Capiox 308, Terumo, Piscataway, NJ), and a variable-temperature water pump (VWR Scientific, San Francisco, CA). The pulsatile pump has two pumping chambers in series, powered by a synchronous external hydraulic drive system. Each chamber has an inlet and outlet tricuspid valve to ensure unidirectional flow. The first chamber received blood from the venous reservoir and pumped it through the oxygenator. The second chamber received blood from the oxygenator and pumped it to the arterial cannula. The duration of systolic ejection (ms), pulse rate (pulse/min), and stroke volume (ml) were varied independently. Circuit priming fluid consisted of 300 ml 6% (weight/volume) hydroxyethyl starch in normal saline (Hetastarch, Du Pont, Bannockburn, IL), 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 rabbit packed erythrocytes, achieving a priming hemoglobin concentration of 7.5–12.8 g/dL (OSM3, Radiometer, Copenhagen, Denmark).‖ CPB was initiated and maintained throughout the experiment at a systemic flow rate of 80 $ml \cdot kg^{-1} \cdot min^{-1}$, monitored with a calibrated in-line electromagnetic flow meter (TX-40P, Biomedicus). The pulmonary artery was clamped to ensure complete venous outflow to the bypass 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. For the first 5 min of bypass, no active heating or cooling measures were taken. Thereafter, systemic cooling was initiated with a water pump temperature of 27°C. α-Stat acid-base management was used.[15] 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 37°C (IL1304, Instrumentation Laboratory, Lexington, MA). Sodium bicarbonate was given to maintain a base excess greater than −4 mEq/l, calculated at 37°C (median 1.3 $mEq \cdot kg^{-1} \cdot h^{-1}$). Rabbit erythrocytes were given to maintain hemoglobin concentration between 7 and 9 g/dL. No pharmacologic or mechanical means were used to control systemic arterial pressure.

For the first 30 min of CPB (cooling phase), 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 80 $ml \cdot kg^{-1} \cdot min^{-1}$). Animals were then randomly assigned to one of three groups: A1 (n = 8, 100-ms ejection period), A2 (n = 8, 120-ms ejection period), or A3 (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 20 min at each of three pulse rates: 150, 200, and 250 pulse/min.# The order of determination was randomized (*e.g.*, 150, 200, 250 *vs.* 150, 250, 200), and in each instance, pump stroke volume was adjusted to maintain systemic flow constant at 80 $ml \cdot kg^{-1} \cdot min^{-1}$. Thus, nine arterial pressure waveforms were created. At the end of each of the three 20-min perfusion periods, the following were recorded: 5 s of arterial pressure waveform (facial artery), arterial pressure from the brachial artery, central venous pressure, bypass flow rate, brain (epidural) temperature, arterial hemoglobin concentration, and arterial blood gases (measured at 37°C). Concurrent with these measurements, CBF determinations were made (see below), and arterial and cerebral venous blood was collected for blood gas analysis and measurement of oxyhemoglobin saturation (OSM3, Radiometer). At experiment completion, animals were killed by discontinuation of bypass and intracardiac administration of saturated KCl solution.

CBF was measured by the radioactive microsphere technique. Isotopes used included ^{46}Sc, ^{85}Sr, ^{95}Nb, ^{141}Ce, and ^{153}Gd (New England Nuclear, Boston, MA), although only three isotopes were used in each experiment. Stock microspheres (400 μl, ~1.8 million microspheres), vigorously mixed for 5 min before with-

‖Absorption coefficients for rabbit hemoglobin were used.

#The spontaneous heart rate of a normothermic (37°C) rabbit is 250 beats/min, decreasing to approximately 150 beats/min at 27°C.

drawal, were diluted in 1.5 ml suspending solution (10% dextran-40 in normal saline with 0.5% (vol/vol) Tween-80) and mixed for an additional 60 s. Microspheres were injected over 30 s into the arterial perfusion line approximately 25 cm proximal to 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* 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, counted for 5 min in a sodium iodide well-type gamma counter. Isotope separation, background, and overlap corrections and organ blood flow calculations (ml · 100 $g^{-1} \cdot min^{-1}$) were performed by standard techniques.[16-18] 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 × % saturation × hemoglobin concentration (g/dL)) + (Pa_{O_2} × 0.003). Cerebral oxygen extraction ratio was calculated as the arterial-cerebral venous oxygen content difference divided by arterial oxygen content. CMR_{O_2} (ml $O_2 \cdot 100\ g^{-1} \cdot min^{-1}$) was calculated as the product of mean hemispheric CBF (ml · 100 $g^{-1} \cdot min^{-1}$) and the arterial-cerebral venous oxygen content difference.

Experiment B

The aim of the second experiment was to compare CBF and CMR_{O_2} between pulsatile and nonpulsatile bypass. Sixteen additional animals (weight 4.1–4.9 kg) were prepared for and underwent CPB as described above, with the following modifications.

In experiment B, a slightly higher systemic flow rate was used than in experiment A, to be methodologically consistent with prior nonpulsatile bypass studies from our laboratory.[10] CPB was maintained in all animals at 100 ml · $kg^{-1} \cdot min^{-1}$ for the duration of bypass. Animals were randomly assigned to one of two perfusion modes: B1 (n = 8, pulsatile perfusion) or B2 (n = 8, nonpulsatile perfusion). In the pulsatile group, CPB was maintained with the pulsatile perfusion system described above with a constant ejection period of 120 ms and pulse rate of 250 pulse/min. In animals undergoing nonpulsatile perfusion, CPB was maintained with a centrifugal CPB pump (BP-50, Biomedicus). Animals were cooled to 27°C, and CPB was maintained for 60 min. As in experiment A, no pharmacologic or mechanical means were used to influence systemic arterial blood pressure.

We were concerned about potential differences in drug pharmacokinetics between pulsatile and nonpulsatile perfusion,[19,**] which could lead to differing anesthetic drug levels between groups. Differing anesthetic levels could influence both CBF and CMR_{O_2}, confounding interpretation of pulsatility effects. To avoid this possibility, anesthesia was maintained with isoflurane rather than with fentanyl/diazepam. Isoflurane vapor was added to oxygenator inflow gases *via* a calibrated vaporizer. Isoflurane concentration in oxygenator inflow and exhaust gas was monitored by a calibrated agent analyzer (Datex, Puritan-Bennett, Helsinki, Finland). Inspired isoflurane concentration was set at 2% at the initiation of bypass and was decreased to 1% once a brain temperature of ~27°C was achieved.

After 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, bypass flow rate, brain (epidural) temperature, arterial hemoglobin concentration, arterial blood gases (measured at 37°C), and inspired and expired isoflurane concentration. As before, CBF determinations were 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 objective of our 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)) that would allow qualitative comparisons among waveforms in this study and those of other studies. Because these estimates are highly subject to error, no statistical analysis was

**Howie MB, Mortimer W, Philip J, Dumond DA, McSweeney TD: Elimination of postbypass secondary peaks of fentanyl by pulsatile cardiopulmonary bypass (abstract). ANESTHESIOLOGY 69:A60, 1988.

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, at each of the three pulse rates, 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 the end of the pressure upstroke. Pulse pressure was calculated as the difference between peak systolic and trough diastolic pressures. Pressure waveforms in each of the nine ejection period/pulse rate combinations 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, creating nine sets of "corrected waveforms." At each combination of group assignment (ejection period) and pulse rate, a median waveform was generated across all corrected waveforms, and the median of the mean pressures was added to each data point of this waveform to create the 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 many physiologic variables were not normally distributed. Consequently, physiologic variables are summarized using their median ± quartile deviation, the latter equaling half the difference between the first and third quartiles.

Analyses were performed using Systat statistical software.[20] 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 among ejection-period groups and pulse rates using repeated measures analysis of variance. Huynh-Feldt $\epsilon = 1.00$ in all cases.[21] In experiment B, CBF and CMR_{O_2} were compared between groups using Student's *t* test.

Results

Experiment A

Microsphere Validation. Paired right and left microsphere reference counts were well matched ($r^2 = 0.995$, slope = 1.05, intercept (−228 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 A1, A2, and A3 are summarized in table 1. Figure 1 shows representative (median) arterial pressure waveforms and the upper and lower boundaries about the medians. There were no differences among or within groups with respect to the following: bypass duration, mean arterial pressure, central venous pressure, systemic flow, arterial *p*H, P_{CO_2}, P_{O_2}, hemoglobin concentration, and oxygen content. Although mean arterial pressure did not differ among groups, both arterial systolic pressure and pulse pressure decreased with increasing pulse rate. Likewise, dP/dt decreased with increasing pulse rate. Mean arterial pressures recorded from the facial artery were 9 ± 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 among groups (A1, A2, and A3) or within groups with respect to the following: brain temperature, cerebral venous P_{O_2}, cerebral venous oxygen content, arterial-cerebral venous oxygen content difference, and cerebral oxygen extraction ratio. Hemispheric CBF (~ 30 ml · 100 g^{-1} · min^{-1}) was independent of both group ($P = 0.94$) and pulse rate ($P = 0.17$). Similarly, CMR_{O_2} (~ 1.8 ml O_2 · 100 g^{-1} · min^{-1}) was independent of both group ($P = 0.51$) and pulse rate ($P = 0.73$).

Experiment B

Microsphere Validation. Paired right and left microsphere reference counts were well matched (r^2 0.84, slope = 0.99, intercept (−315 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 bypass) and B2 (nonpulsatile bypass) are summarized in table 3. There were no differences between groups with respect to the following:

Table 1. Systemic Variables: Experiment A

Variable	Group	Pulse Rate (pulse/min) 150	200	250
Systolic arterial pressure (mmHg)	A1	98 (7)	84 (3)	79 (8)
	A2	92 (9)	78 (9)	77 (10)
	A3	92 (11)	90 (7)	84 (7)
Diastolic arterial pressure (mmHg)	A1	54 (5)	52 (7)	51 (7)
	A2	56 (6)	51 (5)	53 (4)
	A3	53 (9)	56 (4)	56 (9)
Mean arterial pressure (mmHg)	A1	66 (6)	64 (5)	61 (7)
	A2	66 (6)	61 (4)	63 (4)
	A3	66 (8)	70 (5)	68 (9)
Pulse pressure (mmHg)	A1	38 (4)	33 (5)	27 (4)
	A2	39 (6)	30 (5)	24 (5)
	A3	39 (3)	32 (2)	24 (3)
dP/dt (mmHg/s)	A1	930 (230)	700 (140)	460 (80)
	A2	590 (220)	420 (110)	320 (150)
	A3	550 (160)	400 (80)	260 (80)
Systemic flow ($ml \cdot kg^{-1} \cdot min^{-1}$)	A1	80 (3)	80 (3)	80 (3)
	A2	80 (3)	80 (3)	80 (3)
	A3	79 (3)	80 (2)	80 (2)
Central venous pressure (mmHg)	A1	2 (1)	2 (1)	2 (1)
	A2	2 (1)	3 (1)	2 (1)
	A3	3 (1)	3 (2)	3 (1)
Bypass duration (min)	A1	67 (15)	66 (20)	66 (15)
	A2	67 (20)	57 (10)	77 (10)
	A3	66 (10)	76 (21)	68 (18)
*p*H	A1	7.38 (0.03)	7.38 (0.02)	7.37 (0.01)
	A2	7.39 (0.03)	7.38 (0.02)	7.37 (0.02)
	A3	7.35 (0.03)	7.37 (0.02)	7.39 (0.03)
Pa_{CO_2} (mmHg)	A1	39 (2)	42 (2)	39 (1)
	A2	40 (2)	40 (2)	40 (2)
	A3	40 (2)	41 (2)	40 (2)
Pa_{O_2} (mmHg)	A1	263 (6)	255 (4)	259 (5)
	A2	266 (15)	257 (15)	260 (19)
	A3	244 (17)	255 (5)	245 (12)
Hemoglobin (g/dL)	A1	7.8 (0.3)	7.9 (0.5)	7.9 (0.2)
	A2	7.8 (0.4)	8.2 (0.4)	8.0 (0.4)
	A3	7.9 (0.3)	8.0 (0.3)	7.9 (0.4)
Arterial oxygen content (ml O_2/dL)	A1	11.3 (0.3)	11.3 (0.2)	11.4 (0.3)
	A2	11.4 (0.5)	11.9 (0.5)	11.5 (0.1)
	A3	11.4 (0.5)	11.7 (0.5)	11.4 (0.5)

Values are median and quartile deviation (parentheses); group A1, n = 8; group A2, n = 8; group A3, n = 8.

mean arterial pressure, central venous pressure, systemic flow, arterial *p*H, P_{CO_2}, P_{O_2}, hemoglobin concentration, or oxygen content, oxygenator inflow or exhaust isoflurane concentration. Figure 2 shows representative (median) arterial pressure waveforms and the upper and lower boundaries about the medians. Mean arterial pressure recorded from the solid-state transducer in the facial artery was 5 ± 2 mmHg less than that recorded from brachial arterial catheter.

Cerebral Physiology. Cerebral physiologic variables are summarized in table 4. There were no differences between groups (B1 and B2) with respect to the following: brain temperature, cerebral venous P_{O_2}, cerebral venous oxygen content, arterial-cerebral venous oxygen content difference, and cerebral oxygen extraction ratio. Hemispheric CBF did not differ between pulsatile and nonpulsatile perfusion (30 ± 4 *vs.* 32 ± 5 $ml \cdot 100\ g^{-1} \cdot min^{-1}$, respectively; $P = 0.41$). Simi-

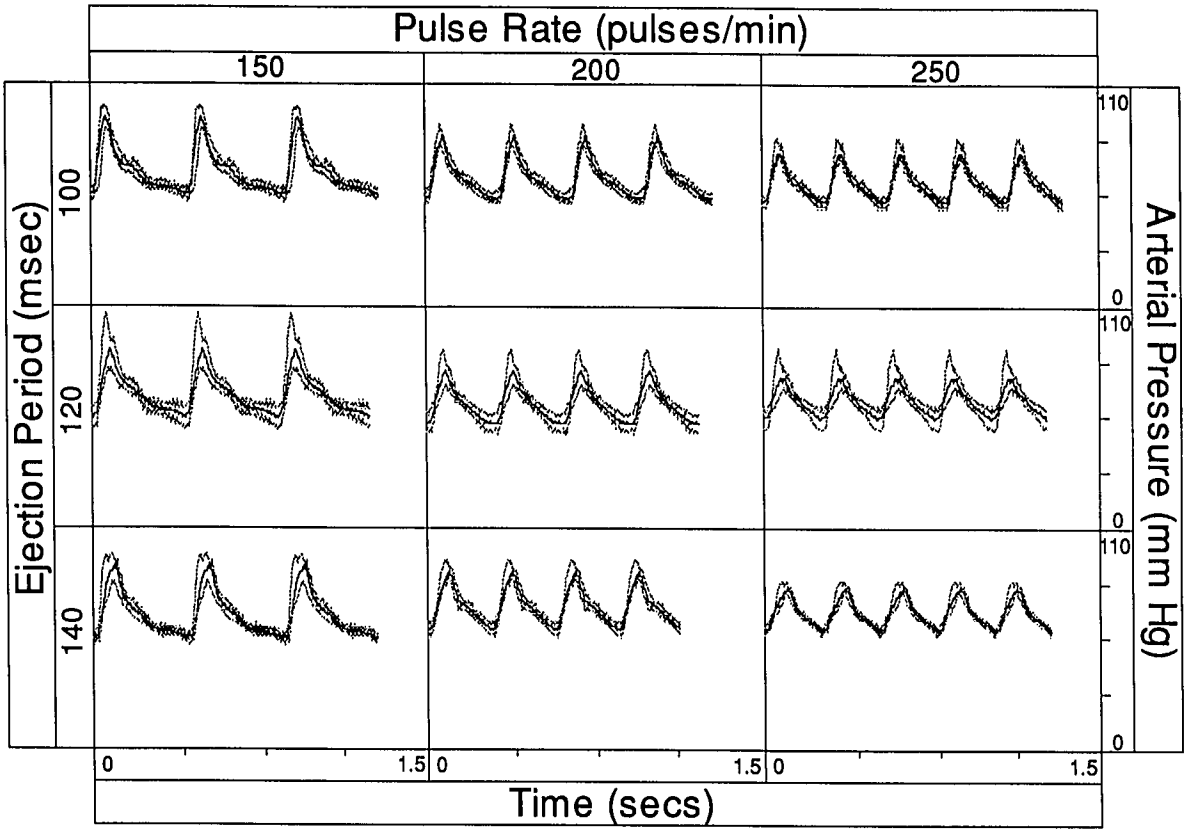

Fig. 1. Experiment A. Solid lines = representative (median) arterial pressure waveform from the facial artery at each combination of group assignment (ejection period) and pulse rate. Dotted lines = maximum and minimum boundaries about the median line. In each ejection period group, n = 8.

larly, CMR_{O_2} did not differ between pulsatile and nonpulsatile CPB (1.7 ± 0.2 *vs.* 1.6 ± 0.2 ml $O_2 \cdot 100\ g^{-1} \cdot min^{-1}$, respectively; $P = 0.60$).

Discussion

This study indicates that at moderate hypothermia (27°C), nonpulsatile CPB does not appear disadvantageous in terms of either brain blood flow or oxygen metabolism.

There are several theories as to how pulsatile perfusion might produce different circulatory effects as compared to equivalent mean flow achieved with nonpulsatile perfusion. The extent to which these mechanisms apply to the cerebral circulation, *if at all,* is unknown. Some authors propose that the greater peak hydraulic power of pulsatile flow recruits capillary beds that would otherwise be closed under nonpulsatile conditions.[22,23] By so doing, pulsatile perfusion is thought to decrease vascular resistance,[22-25] increase the uniformity of tissue perfusion,[26] decrease oxygen diffusion distances, and improve tissue oxygenation.[22,24,27] The greater peak sheer stress of pulsatile flow also may inhibit erythrocyte aggregation and flow stagnation[1] and/or promote release of endothelial-derived vasodilators such as prostacyclin[28] and nitric oxide.[29] Yet another proposal is that baroreceptor reflexes, which depend on arterial pulse rate, pulse pressure, and dP/dt,[30-32] play an important role in blood flow regulation. In the absence of pulsatile flow, reflex mechanisms mediated *via* the carotid sinus, brainstem cardiovascular centers, and the autonomic nervous system[32] increase arterial and venous smooth muscle tone.[32-34] In this way, vascular resistance, and perhaps blood flow distribution, can be influenced by pulsatility.

Despite these theoretical differences, numerous studies do not find systemic hemodynamic[35-39] blood

Table 2. Cerebral Variables: Experiment A

Variable	Group	Pulse Rate (pulse/min) 150	200	250
Brain temperature (°C)	A1	26.9 (0.4)	27.1 (0.3)	27.0 (0.3)
	A2	27.2 (0.2)	27.3 (0.2)	27.2 (0.1)
	A3	27.0 (0.3)	27.2 (0.5)	27.2 (0.2)
Cerebral venous P_{O_2} (mmHg)	A1	34 (2)	35 (3)	34 (3)
	A2	34 (2)	34 (3)	35 (3)
	A3	34 (3)	33 (2)	33 (3)
Cerebral venous oxygen content (ml O_2/dL)	A1	5.6 (0.2)	5.7 (0.4)	6.0 (0.4)
	A2	5.5 (0.3)	5.5 (0.3)	5.5 (0.7)
	A3	5.2 (0.6)	5.8 (0.4)	5.5 (0.6)
Cerebral arteriovenous oxygen content difference (ml O_2/dL)	A1	5.6 (0.4)	5.9 (0.5)	5.4 (0.7)
	A2	5.9 (0.3)	5.6 (0.7)	6.0 (0.4)
	A3	6.1 (0.4)	6.0 (0.4)	6.0 (0.6)
Cerebral oxygen extraction ratio	A1	0.50 (0.03)	0.50 (0.03)	0.48 (0.05)
	A2	0.52 (0.04)	0.50 (0.06)	0.52 (0.05)
	A3	0.52 (0.03)	0.51 (0.04)	0.53 (0.06)
Hemispheric cerebral blood flow ($ml \cdot 100\ g^{-1} \cdot min^{-1}$)	A1	29 (4)	30 (3)	28 (4)
	A2	30 (3)	30 (3)	29 (3)
	A3	29 (3)	29 (3)	31 (2)
Cerebral metabolic rate for oxygen ($ml\ O_2 \cdot 100\ g^{-1} \cdot min^{-1}$)	A1	1.8 (0.2)	1.7 (0.2)	1.7 (0.1)
	A2	1.8 (0.1)	1.8 (0.1)	1.8 (0.1)
	A3	1.7 (0.3)	1.8 (0.2)	1.8 (0.1)

Values are median and quartile deviation (parentheses): group A1, n = 8; group A2, n = 8; group A3, n = 8.

flow or metabolic[35,36,40,41] differences between pulsatile and nonpulsatile perfusion. Studies finding differences between pulsatile and nonpulsatile flow may have achieved arterial pressure/flow characteristics necessary to produce "physiologically acceptable" pulsatility, whereas negative studies, perhaps, did not. Thus, in any study of pulsatile perfusion, it appears necessary to determine whether pulse characteristics adequately represent pulsatile perfusion in the system being tested. However, because the essential characteristics and mechanisms distinguishing pulsatile from nonpulsatile perfusion are largely unknown, choice of any descriptor of arterial pressure waveform characteristics (*e.g.*, pulse pressure, dP/dt, systolic/diastolic ratio) is arbitrary. Some authors advocate use of energy indexes to quantitate pulsatile perfusion.[22,42] These indexes require measurement of arterial *flow* waveforms, as opposed to, or in addition to, pressure waveforms. We saw no advantage to that approach. First, energy indexes do not always distinguish pulsatile from nonpulsatile flow.[22] Second, arterial *pressure,* not flow, is monitored clinically. Third, as Grossi *et al.* observed, pulse shape and pulse rate distinguish pulsatile and nonpulsatile flow, not energy indexes *per se.*[42]

Experiment A was performed to determine whether CBF and/or CMR_{O_2} depended upon the pulsatile arterial pressure waveform. Pulse rate was varied over a physiologically relevant range (for the rabbit) and pump ejection period was varied among groups to produce a range of pulse pressures, dP/dt, and systolic/diastolic time ratios (fig. 1). The carotid sinuses and aortic arch were undisturbed to preserve any autonomic reflexes. At one end of the spectrum, we produced the best arterial pressure waveform technically possible (ejection period 100 ms, 150 pulse/min), one appearing indistinguishable from a normal rabbit arterial pressure waveform. At the other end of the spectrum, we produced an arterial pressure waveform that, although pulsatile, had relatively small pulse pressure, small dP/dt, and a less "physiologic" appearance (ejection period 140 ms, 250 pulse/min). We found CBF and CMR_{O_2} were independent of arterial pressure waveform configuration within the range tested. We concluded that all nine pulsatile waveforms were physiologically

Table 3. Systemic Variables: Experiment B

Variable	Group	
	Pulsatile (B1)	Nonpulsatile (B2)
Systolic arterial pressure (mmHg)	87 (8)	—
Diastolic arterial pressure (mmHg)	54 (4)	—
Mean arterial pressure (mmHg)	67 (3)	66 (5)
Pulse pressure (mmHg)	32 (5)	—
dP/dt (mmHg/s)	760 (250)	—
Systemic flow ($ml \cdot kg^{-1} \cdot min^{-1}$)	101 (4)	102 (4)
Central venous pressure (mmHg)	2 (2)	2 (2)
Isoflurane (%)		
Inspired	1.0 (0.0)	1.0 (0.0)
Expired	0.7 (0.1)	0.8 (0.1)
*p*H	7.38 (0.03)	7.39 (0.02)
Pa_{CO_2} (mmHg)	39 (1)	40 (1)
Pa_{O_2} (mmHg)	274 (21)	267 (11)
Hemoglobin (g/dL)	8.0 (0.3)	8.4 (0.4)
Arterial oxygen content (ml O_2/dL)	11.7 (0.4)	12.0 (0.5)

Values are median and quartile deviation (parentheses): group B1, n = 8; group B2, n = 8.

Table 4. Cerebral Variables: Experiment B

Variable	Group	
	Pulsatile (B1)	Nonpulsatile (B2)
Brain temperature (°C)	26.8 (0.1)	26.9 (0.1)
Cerebral venous P_{O_2} (mmHg)	36 (5)	39 (3)
Cerebral venous oxygen content (ml O_2/dL)	5.7 (0.6)	6.5 (0.3)
Cerebral arteriovenous oxygen content difference (ml O_2/dL)	5.7 (0.6)	5.6 (0.8)
Cerebral oxygen extraction ratio	0.50 (0.05)	0.47 (0.05)
Hemispheric cerebral blood flow ($ml \cdot 100\ g^{-1} \cdot min^{-1}$)	30 (4)	32 (5)
Cerebral metabolic rate for oxygen ($ml\ O_2 \cdot 100\ g^{-1} \cdot min^{-1}$)	1.7 (0.2)	1.6 (0.2)

Values are median and quartile deviation (parentheses): group B1, n = 8; group B2, n = 8.

equivalent, and thus, any combination of ejection period (100–140 ms) and pulse rate (150–250 pulse/min) would provide an equivalent and probably adequate test of pulsatile perfusion during CPB at 27°C.

In experiment B, we compared CBF and CMR_{O_2} between pulsatile (ejection period 120 ms, 250 pulse/min) and nonpulsatile bypass at 27°C. We found pulsatility to have no effect on brain blood flow or oxygen metabolism. In experiment A, anesthesia was maintained with fentanyl and diazepam. However, in experiment B we wished to avoid any potential differences in the metabolism of these agents between pulsatile and nonpulsatile perfusion.[19,43,**] Were they present, differences in fentanyl and diazepam concentrations between groups could have confounded interpretation of CBF and CMR_{O_2} findings. To avoid this possibility, anesthesia was maintained with isoflurane during CPB. We recognize that the cerebral vasodilatory properties of isoflurane might obscure CBF differences between pulsatile and nonpulsatile perfusion. However, inspection of tables 2 and 4 shows both CBF and CMR_{O_2} to be indistinguishable between groups anesthetized with fentanyl/diazepam and those anesthetized with isoflurane. Hence, it does not appear anesthetic choice had any effect upon either CBF or CMR_{O_2} at 27°C, nor that it is likely to have obscured CBF or CMR_{O_2} differences between pulsatile and nonpulsatile perfusion.

Our finding of equivalent CBF and CMR_{O_2} with pulsatile and nonpulsatile perfusion during moderately hypothermic bypass is consistent with the only human

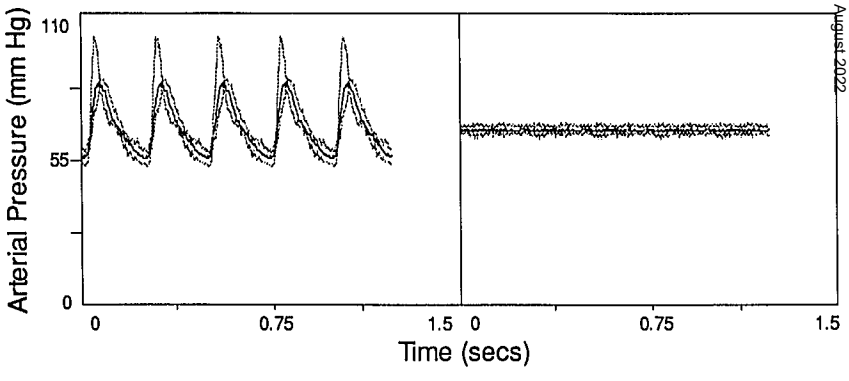

Fig. 2. Experiment B. Solid lines = representative (median) arterial pressure waveform from the facial artery. Dotted lines = maximum and minimum boundaries about the median line. (*Left*) Group B1 (n = 8), pulsatile (ejection period 120 ms, 250 pulse/min). (*Right*) Group B2 (n = 8), nonpulsatile.

study to make a similar comparison.[8] Why might pulsatility be unimportant to CBF and CMR_{O_2} at 27°C? First, baroreceptor responses are likely to be highly attenuated and/or eliminated by the combined effects of anesthesia[44-46] and hypothermia. Furthermore, it appears that, even at normothermia, baroreceptor responses and sympathetic nervous system activity have little sustained effect upon CBF and CMR_{O_2}.[47] Second, recent evidence indicates cerebrovascular smooth muscle tone and responsiveness to vasoregulators is altered by hypothermia. Using an isolated rat cerebral arteriole preparation, Ogura *et al.* found hypothermia decreased (30°C) or eliminated (20°C) vasoconstrictive and vasodilatory responses to acute changes in *p*H, as well as vasoconstrictive responses to $PGF_{2\alpha}$.[48] Thus, during CPB at reduced temperatures, CBF may be determined progressively less by "normal" regulators of cerebrovascular tone and more by the direct and/or indirect effects of hypothermia upon cerebrovascular smooth muscle. Finally, the synthesis of many vasoregulators thought to be influenced by arterial pulsation (*e.g.,* nitric oxide) also may be inhibited by hypothermia.

In summary, this study indicates that at moderate hypothermia (27°C) with α-stat management, nonpulsatile CPB does not appear disadvantageous to the rabbit brain in terms of blood flow or oxygen metabolism. Nevertheless, measurement of bulk CBF and CMR_{O_2} cannot adequately assess microcirculatory status or regional neuronal viability. Intravascular sludging, capillary collapse, or ischemic boundary zones in animals undergoing nonpulsatile perfusion, as seen by other investigators[1,2] cannot be ruled out. Additional studies of brain histology and/or neurologic outcome are needed before the neurologic benefits of pulsatile CPB can be confidently confirmed or refuted.

The authors wish to thank Michelle Elkins of Medical Engineering Consultants for her help in setting up and maintaining the pulsatile perfusion pump.

References

1. Matsumoto T, Wolferth CC, Perlman MH: Effects of pulsatile and nonpulsatile perfusion upon cerebral and conjunctival microcirculation in dogs. Am Surg 37:61–64, 1971

2. Sanderson JM, Wright G, Sims FW: Brain damage in dogs immediately following pulsatile and non-pulsatile blood flow in extracorporeal circulation. Thorax 27:275–286, 1972

3. Dernevik L, Arvidsson S, William-Olsson G: Cerebral perfusion in dogs during pulsatile and nonpulsatile extracorporeal circulation. J Cardiovasc Surg 26:32–35, 1985

4. Tranmer BI, Gross CE, Kindt GW, Adey GR: Pulsatile versus nonpulsatile blood flow in the treatment of acute cerebral ischemia. Neurosurgery 19:724–731, 1986

5. Smith PLC, Newman SP, Ell PJ, Treasure T, Joseph P, Schneidau A, Harrision MJG: Cerebral consequences of cardiopulmonary bypass. Lancet 1:823–825, 1986

6. Kuroda Y, Uchimoto R, Kaieda R, Shinkura R, Shinohara K, Miyamoto S, Oshita S, Takeshita H: Central nervous system complications after cardiac surgery: A comparison between coronary artery bypass grafting and valve surgery. Anesth Analg 76:222–227, 1993

7. Shaw PJ, Bates D, Cartlidge NEF, French JM, Heaviside D, Julian DG, Shaw DA: An analysis of factors predisposing to neurological injury in patients undergoing coronary bypass operations. Q J Med 72:633–646, 1989

8. Henze T, Stephan H, Sonntag H: Cerebral dysfunction following extracorporeal circulation for aortocoronary bypass surgery: No differences in neuropsychological outcome after pulsatile versus nonpulsatile flow. Thorac Cardiovasc Surg 38:65–68, 1990

9. Taylor KM, Bain WH, Davidson KG, Turner MA: Comparative clinical study of pulsatile and non-pulsatile perfusion in 350 consecutive patients. Thorax 37:324–330, 1982

10. Hindman BJ, Dexter F, Cutkomp J, Smith T, Tinker JH: Hypothermic acid-base management does not affect cerebral metabolic rate for oxygen at 27°C: A study during cardiopulmonary bypass in rabbits. ANESTHESIOLOGY 79:580–587, 1993

11. Scremin OU, Sonnenschein RR, Rubinstein EH: Cerebrovascular anatomy and blood flow measurements in the rabbit. J Cereb Blood Flow Metab 2:55–66, 1982

12. Tuor UI, Farrar JK: Pial vessel caliber and cerebral blood flow during hemorrhage and hypercapnia in the rabbit. Am J Physiol 247: H40–H51, 1984

13. Orr JA, DeSoignie RC, Wagerle LC, Fraser DB: Regional cerebral blood flow during hypercapnia in the anesthetized rabbit. Stroke 14: 802–807, 1983

14. Pearce WJ, Scremin OU, Sonnenschein RR, Rubinstein EH: The electroencephalogram, blood flow, and oxygen uptake in rabbit cerebrum. J Cereb Blood Flow Metab 1:419–428, 1981

15. Hickey PR, Andersen NP: Deep hypothermic circulatory arrest: A review of pathophysiology and clinical experiences as a basis for anesthetic management. J Cardiothorac Anesth 1:137–155, 1987

16. Buckberg GD, Luck JC, Payne DB, Hoffman JIE, Archie JP, Fixler DE: Some sources of error in measuring regional blood flow with radioactive microspheres. J Appl Physiol 31:598–604, 1971

17. Heymann MA, Payne BD, Hoffman JIE, Rudolph AM: Blood flow measurements with radionuclide-labeled particles. Prog Cardiovasc Dis 20:55–79, 1977

18. Marcus ML, Bischof CJ, Heistad DD: Comparison of microsphere and xenon-133 clearance method in measuring skeletal muscle and cerebral blood flow. Circ Res 48:748–761, 1981

19. Hynynen M, Olkkola KT, Näveri E, Palojoki R, Neuvonen PJ, Heinonen J: Thiopentone pharmacokinetics during cardiopulmonary bypass with a nonpulsatile or pulsatile flow. Acta Anaesthesiol Scand 33:554–560, 1989

20. Wilkinson L: Systat: The System for Statistics. Evanston, Systat, 1990

21. Crowder MJ, Hand DJ: Analysis of repeated measures. London, Chapman and Hall, 1990, p 55

22. Shepard RB, Kirklin JW: Relation of pulsatile flow to oxygen consumption and other variables during cardiopulmonary bypass. J Thorac Cardiovasc Surg 58:694–702, 1969

23. Raj JU, Kaapa P, Anderson J: Effect of pulsatile flow on microvascular resistance in adult rabbit lungs. J Appl Physiol 72:73–81, 1992

24. Jacobs LA, Klopp EH, Seamone W, Topaz SR, Gott VL: Improved organ function during cardiac bypass with a roller pump modified to deliver pulsatile flow. J Thorac Cardiovasc Surg 58:703–712, 1969

25. Minami K, Korner MM, Vyska K, Kleesiek K, Knobl H, Korfer R: Effects of pulsatile perfusion on plasma catecholamine levels and hemodynamics during and after cardiac operations with cardiopulmonary bypass. J Thorac Cardiovasc Surg 99:82–91, 1990

26. Williams GD, Seifen AB, Lawson NW, Norton JB, Readinger RI, Dungan TW, Callaway JK, Campbell GS: Pulsatile perfusion versus conventional high-flow nonpulsatile perfusion for rapid core cooling and rewarming of infants for circulatory arrest in cardiac operation. J Thorac Cardiovasc Surg 78:667–677, 1979

27. Dunn J, Kirsh MM, Harness J, Carroll M, Straker J, Solan H: Hemodynamic, metabolic, and hematologic effects of pulsatile cardiopulmonary bypass. J Thorac Cardiovasc Surg 68:138–147, 1974

28. Watkins WD, Peterson MB, Kong DL, Kono K, Buckley MJ, Levine FH, Philbin DM: Thromboxane and prostacyclin changes during cardiopulmonary bypass with and without pulsatile flow. J Thorac Cardiovasc Surg 84:250–256, 1982

29. Hutcheson IR, Griffith TM: Release of endothelium-derived relaxing factor is modulated both by frequency and amplitude of pulsatile flow. Am J Physiol 261:H257–H262, 1991

30. Angell James JE: The effects of altering mean pressure, pulse pressure and pulse frequency on the impulse activity in baroreceptor fibres from the aortic arch and right subclavian artery in the rabbit. J Physiol (Lond) 214:65–88, 1971

31. Chapleau MW, Abboud FM: Determinants of sensitization of carotid baroreceptors by pulsatile pressure in dogs. Circ Res 65: 566–577, 1989

32. Chapleau MW, Hajduczok G, Abboud FM: Pulsatile activation of baroreceptors causes central facilitation of baroreflex. Am J Physiol 256:H1735–H1741, 1989

33. Minami K, Vyska K, Korfer R: Role of the carotid sinus in response of integrated venous system to pulsatile and nonpulsatile perfusion. J Thorac Cardiovasc Surg 104:1639–1646, 1992

34. Nakayama K, Tamiya T, Yamamoto K, Izumi T, Akimoto S, Hashizume S, Iimori T, Odaka M, Yazawa C: High-amplitude pulsatile pump in extracorporeal circulation with particular reference to hemodynamics. Surgery 54:798–809, 1963

35. Louagie YA, Gonzalez M, Collard E, Mayne A, Gruslin A, Jamart J, Buche M, Schoevaerdts JC: Does flow character of cardiopulmonary bypass make a difference? J Thorac Cardiovasc Surg 104:1628–1638, 1992

36. Dapper F, Neppl H, Wozniak G, Strube I, Zickmann B, Herlein FW, Neuhof H: Effects of pulsatile and nonpulsatile perfusion mode during extracorporeal circulation: A comparative clinical study. Thorac Cardiovasc Surg 40:345–351, 1992

37. Kono K, Philbin DM, Coggins CH, Slater EE, Triantafillou A, Levine FH, Buckley MJ: Adrenocortical hormone levels during cardiopulmonary bypass with and without pulsatile flow. J Thorac Cardiovasc Surg 85:129–133, 1983

38. Frater RWM, Wakayama S, Oka Y, Beckere RM, Desai P, Oyama T, Blaufox MD: Pulsatile cardiopulmonary bypass: Failure to influence hemodynamics or hormones. Circulation 62(suppl I):I19–I25, 1980

39. Alston RP, Murray L, McLaren AD: Changes in hemodynamic variables during hypothermic cardiopulmonary bypass: Effects of flow rate, flow character, and arterial pH. J Thorac Cardiovasc Surg 100: 134–144, 1990

40. Driessen JJ, Fransen G, Rondelez L, Schelstraete E, Gevaert L: Comparison of the standard roller pump and a pulsatile centrifugal pump for extracorporeal circulation during routine coronary artery bypass grafting. Perfusion 6:303–311, 1991

41. Alston RP, Singh M, McLaren AD: Systemic oxygen uptake during hypothermic cardiopulmonary bypass: Effects of flow rate, flow character, and arterial pH. J Thorac Cardiovasc Surg 98:757–768, 1989

42. Grossi EA, Connolly MW, Krieger KH, Nathan IM, Hunter CE, Colvin SB, Baumann FG, Spencer FC: Quantification of pulsatile flow during cardiopulmonary bypass to permit direct comparison of the effectiveness of various types of "pulsatile" and "nonpulsatile" flow. Surgery 98:547–554, 1985

43. Mathie RT: Hepatic blood flow during cardiopulmonary bypass. Crit Care Med 21(suppl):S72–S76, 1993

44. McCallum JB, Stekiel TA, Bosnjak ZJ, Kampine JP: Does isoflurane alter mesenteric venous capacitance in the intact rabbit? Anesth Analg 76:1095–1105, 1993

45. Taneyama C, Goto H, Kohno N, Benson KT, Sasao J, Arakawa K: Effects of fentanyl, diazepam, and the combination of both on arterial baroflex and sympathetic nerve activity in intact and baro-denervated dogs. Anesth Analg 77:44–48, 1993

46. Ohsumi H, Sakamoto, Yamazaki T, Okumura F: Effects of fentanyl on carotid sinus baroreflex control of circulation in rabbits. Am J Physiol 256:R625–R631, 1989

47. Heistad DD, Kontos HA: Cerebral circulation, Handbook of Physiology: Section 2. The Cardiovascular System. Volume 3. Peripheral Circulation and Organ Blood Flow: Part 1. Edited by Shepherd JT, Abboud FM. Bethesda, American Physiological Society, 1983, pp 137–182

48. Ogura K, Takayasu M, Dacey RG: Effects of hypothermia and hyperthermia on the reactivity of rat intracerebral arterioles *in vitro*. J Neurosurg 75:433–439, 1991