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Relative Importance of Flow versus Pressure in Splanchnic Perfusion during Cardiopulmonary Bypass in Rabbits

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Background: Decreased gastrointestinal perfusion has been reported during cardiopulmonary bypass (CPB). Conflicting results have been published concerning thresholds of pressure and flow to avoid splanchnic ischemia during CPB. This study compared splanchnic perfusion during independent and randomized variations of CPB pump flow or arterial pressure.

Methods: Ten rabbits were studied during mild hypothermic (36°C) nonpulsatile CPB using neonatal oxygenators. Simultaneous measurements of tissue blood flow in four different splanchnic areas (gastric, jejunum, ileum, and liver) were performed by laser Doppler flowmetry (LDF) before CPB (T0) and during a 4-step factorial experimental block design. Pressure and flow were alternatively high or low in random order.

Results: Laser Doppler flowmetry was significantly lower than pre-CPB value but was better preserved (analysis of covariance) in all organs, except liver, when CPB flow was high, whatever the pressure. Splanchnic LDF values in the low- versus high-flow groups expressed as perfusion unit were (mean \pm SD): stomach, 94 ± 66 versus 137 ± 75 ; jejunum, $118 \pm$

78 versus 172 ± 75 ; ileum, 95 ± 72 versus 146 ± 83 ; and liver, 79 ± 72 versus 108 ± 118 . No significant difference of LDF was observed between the high- and low-pressure groups, whatever the flow, except for liver: stomach, 115 ± 64 versus 117 ± 83 ; jejunum, 141 ± 80 versus 148 ± 83 ; ileum, 127 ± 87 versus 114 ± 76 ; liver, 114 ± 88 versus 73 ± 70 .

Conclusion: Prevention of splanchnic ischemia during CPB should focus on preservation of high CPB blood flow rather than on high pressure. (Key words: Regional blood flow; splanchnic ischemia.)

LARGE variations in systemic arterial pressure are observed during cardiopulmonary bypass (CPB), requiring different therapeutic responses such as administration of vasopressors or vasodilators. Cardiac centers differ in their acceptable optimum level of CPB blood flow. This controversy is still debated¹ and is not confined to the CPB setting, as evidenced by a recent letter suggesting a review of the lower limit of autoregulation.² Most studies have been focused on cerebral, renal, or coronary vasculature during CPB, but few have addressed the splanchnic circulation.^{3,4} Human studies are difficult to perform because clinical assessment of splanchnic blood flow is difficult. Despite some controversies on methodologic problems, splanchnic blood flow is known to be altered during CPB. Splanchnic hypoperfusion could initiate bacterial translocation, inflammatory mediator release,^{5,6} and multiorgan dysfunction.⁷ A CPB model with small animals (rabbits) has been developed by some groups⁸⁻¹⁰ and has proved useful in pathophysiological studies. The present experimental trial using CPB in rabbits was designed to study the consequences of independent variations of arterial pressure and CPB blood flow on splanchnic tissue perfusion.

Materials and Methods

Surgical Preparation of the Animals

The study was performed in an authorized animal care laboratory according to the French health authority and was approved by the University research committee.

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Ten New Zealand white rabbits of both sex (weighting 3.0–3.5 kg) were given midazolam 0.5 mg/kg body weight administered intramuscularly as premedication and were then anesthetized with ketamine HCl 75 mg/kg body weight administered intramuscularly (Imalgene; Rhone-Mérieux, Lyon, France). Adequate depth of anesthesia was ensured before any surgical procedures by the absence of pedal and palpebral reflexes. The marginal ear vein was cannulated (20-gauge cannula) for the administration of fluids (hetastarch, 3 ml · kg⁻¹ · h⁻¹) and drugs. The central ear artery was also cannulated (20-gauge cannula) and connected to a pressure transducer for measurement of systemic arterial pressure during surgery. All catheters were flushed with heparinized saline 10 IU/ml to prevent clotting during the experiment. A tracheotomy was performed (endotracheal tube size, 3.5 mm OD), and the lungs were ventilated mechanically using a neonatal apparatus (Dräger, Cicero, Lübeck, Germany) with 100% oxygen. Tidal volume was set at 15 ml/kg, and respiratory frequency was set at 35 breaths/min. Ventilation was adjusted to keep the partial pressure of carbon dioxide and pH in the physiologic range. End-tidal carbon dioxide concentrations were measured by integrated capnography. Body temperature was recorded using an electrical thermometer (Baxter, San Diego, CA) inserted orally into the esophagus, and temperature was maintained at 38.5–39.5°C before CPB by an electrical heating exchanger. Limb lead II of the electrocardiogram was continuously monitored by means of subcutaneous needle electrodes. Continuous anesthesia was maintained with ketamine 25 mg · kg⁻¹ · h⁻¹ and midazolam 0.125 mg · kg⁻¹ · h⁻¹ during all procedures. The left carotid artery was cannulated with a 20-gauge cannula and connected to a fluid-filled pressure transducer (Medex Medical SARL, Nantes, France). This catheter was used to take blood samples during the experiment and to measure mean nonpulsatile blood pressure during CPB.

A laparotomy was performed by a midline incision, and hemostasis was adjusted by diathermy. Systemic heparinization was performed (300 IU/kg body weight). The femoral arteries were then ligated for the CPB period, and the distal abdominal aorta was retrogradely cannulated with an 8-French-gauge arterial perfusion cannula (DLP; Medtronic, Grand Rapids, MI) approximately 10 mm above the femoral bifurcation. The aortic cannula was flushed with methylene blue after the end of the measurements to check the integrity and normality of the mesenteric arteries. This technique has been previously described.⁹ After checking the pulsatility of flow in

the arterial cannula, a sternotomy was performed. The right atrium was cannulated with a 16-French-gauge venous perfusion cannula (Stockert, Munich, Germany) *via* a purse string suture. Both aortic and venous cannulae were connected to the CPB circuit.

CPB

This technique of CPB involved the use of a small neonatal oxygenator (Microsafe; Polystan, Ballerup, Denmark) with a venous reservoir and heat exchanger, and connected with 7-mm tubing. Temperature was maintained by a thermostatic water pump adjusted to 38°C connected to the heat exchanger. Blood-gas concentrations were checked regularly, and 0.42% (wt/vol) sodium bicarbonate (10-ml bolus) was injected to maintain base excess > -5 mM and pH > 7.30 to avoid acidosis from femoral occlusion. Circuit priming consisted of 6.5% (w/v) hetastarch 300 ml, 0.42% sodium bicarbonate 20 ml, calcium chloride 250 mg, heparin 1,000 IU, and 100 ml fresh whole rabbit blood. One dose of antibiotic (cefazoline 1 g) was added to mimic clinical practice and prevent bacterial contamination. This priming fluid has been found to achieve a circulating hemoglobin concentration of 6–10 g/dl.¹⁰ Bypass was initiated at 100 ml · kg⁻¹ · min⁻¹ using a calibrated roller pump (Hospal BSM, Lyon, France) and then adjusted according to the experimental protocol. Oxygenation was ensured by continuous oxygen infusion (100 ml · kg⁻¹ · min⁻¹) through the oxygenator, and gas flow was adjusted to keep blood-gas parameters (arterial oxygen and carbon dioxide partial pressures, pH) in the physiologic range and particularly arterial carbon dioxide partial pressure between 4.7–6.0 kPa. After establishment of CPB, pulmonary ventilation was discontinued. The left ventricle was vented by a 16-gauge cannula inserted in the apex of the left ventricle to drain the blood in the venous circuit of the bypass. Pleural and mediastinal blood was scavenged and reinfused into the venous line.

Protocol

Baseline measurements (S0) were made before CPB. After steady state, CPB was instituted, and four sets of measurements were performed in random order, chosen in a permutation table: S1 = low pressure/low flow; S2 = low pressure/high flow; S3 = high pressure/low flow; and S4 = high pressure/high flow.

Each set of measurements included direct laser Doppler velocimetry (Perimed, Jarfalla, Sweden) in four different areas: stomach, ileum, jejunum, and liver with simultaneous measurements of two sites. After calibration

with a Perimed motility standard kit, one laser Doppler probe (Perimed P 424) was gently placed directly on the intestinal wall with a flexible holder and moved from site to site (with each site being marked by a thin superficial suture). Another similar probe, but including a small plastic suction disc allowing a more efficient and non-traumatic contact, was placed on the surface of the liver. These probes were connected to a 632-nm helium-neon laser tube and measured flow velocity to 1-mm depth.¹¹

High-flow CPB was defined as a pump flow of $100 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, and low-flow CPB was defined as $50 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. High pressure was defined as a mean arterial pressure of 90 mmHg, and low pressure was defined as 40 mmHg. At the end of the preparation, pump flow was turned down to 50 ml/min and then gradually increased by 50 ml/min every minute up to 500 ml/min. Continuous measurement of arterial pressure and LDF on gastric and ileum area were stored on computer to assess the relationship between tissue flow, perfusion pressure, and CPB flow.

Drugs

Drugs were administered as a bolus in the arterial line of the CPB, close to the animal to avoid biomaterial adsorption. Small amounts of noradrenaline (0.2-mg bolus) as a vasoconstrictor, or nicergoline (1-mg bolus) as an α_1 -antagonist vasodilator, were used as necessary to obtain low or high arterial pressure, whatever the CPB flow. We chose these two drugs to mimic our clinical practice in human CPB, when maintenance of pump flow is the primary goal. These drugs are characterized by a short half-life and a minimal action on venous return. Steady state was considered as a period with a stable LDF signal and adequate flow and arterial pressure levels.

Data Collection and Analysis

Laser Doppler flow data were collected using a multichannel monitor and two probes during steady-state periods of 10 min. Samples were computerized and stored by specially designed software (Perisoft, Jarfalla, Sweden). Curves were retrospectively analyzed, and mean values were calculated automatically by the software for each period.

Laser Doppler velocimetry flow data were expressed in perfusion units.

Statistics

Initial sample size was calculated from previous results validating the model to obtain α and β risk $> 50\%$ and a

power $> 50\%$, which are acceptable for this type of model. Values were expressed as mean \pm SD. Statistical analysis and graphs were performed using Systat version 7.0 for Windows, 1997 SPSS Inc statistical software, and Prism version 2.0 for Windows 1995 (Graphpad, Inc., San Diego, CA) statistical and graph software. Comparisons were made by two-way analysis of variance for randomized block design, followed by *post hoc* Scheffé test on the matrix of pairwise comparison probabilities. A control of the time effect was introduced in the analysis of covariance model as a "sequence order" cofactor, and the vasopressive drugs bolus effect was introduced as a "drug cofactor." Differences in means between groups were tested by Bonferroni-adjusted *t* test. Correlations were tested by parametric test (Pearson) or nonparametric test (Spearman). $P < 0.05$ was considered significant.

Results

All 10 animals successfully completed the experimental protocol. Descriptive data are summarized in table 1. LDF measurements were not standardized to increase the robustness of the statistics. LDF during high-flow CPB steps were significantly ($P < 0.05$) greater than during corresponding low-flow CPB, except for liver. Splanchnic LDF values in the low- versus high-flow groups expressed as perfusion unit were (mean \pm SD): stomach, 94 ± 66 versus 137 ± 75 ; jejunum, 118 ± 78 versus 172 ± 75 ; ileum, 95 ± 72 versus 146 ± 83 ; and liver, 79 ± 72 versus 108 ± 118 . No significant difference of LDF was observed between the high- and low-pressure groups, whatever the flow, except for liver (mean \pm SD): stomach, 115 ± 64 versus 117 ± 83 ; jejunum, 141 ± 80 versus 148 ± 83 ; ileum, 127 ± 87 versus 114 ± 76 ; and liver, 114 ± 88 versus 73 ± 70 . Two-way analysis of variance between all splanchnic LDF data, including flow and pressure factors, showed only CPB flow as a significant factor (F ratio = 3.93–6.40). No significant interaction was found between flow and pressure and between flow and sequence order. Statistics and differences of means between groups are summarized in table 2. A significant decrease of LDF was observed between high and low CPB flow for gastric (-31%), jejunum (-31%), and ileum (-34%) tissue. No significant difference was shown between low- and high-pressure levels in the different tissue beds studied. The observed difference for liver LDF was not significant for either pressure or flow factors (-27%).

Central esophageal temperature was kept constant

Table 1. Descriptive Data

	S0	S1	S3	S2	S4
		LP/LF	HP/LF	LP/HF	HP/HF
Gastric LDF	474 ± 143	82 ± 28	86 ± 63	126 ± 57	148 ± 91
Jejunum LDF	430 ± 132	105 ± 42	130 ± 104	177 ± 94	166 ± 55
Ileum LDF	379 ± 194	97 ± 66	94 ± 82	158 ± 98	135 ± 69
Liver LDF	359 ± 177	98 ± 89	59 ± 47	130 ± 144	86 ± 88
CPB flow (ml · kg ⁻¹ · min ⁻¹)		50	50	100	100
Mean arterial pressure (mmHg)	74.9 ± 15.2	33.6 ± 5.1	98.2 ± 15.1	41.9 ± 9.6	95 ± 14
Temperature (°C)	38.9 ± 0.8	36.1 ± 1.2	36 ± 1.5	36.5 ± 1.5	35.8 ± 1.3

Data expressed as mean ± SD for n = 10 experiments.

CPB = cardiopulmonary bypass; CPB Flow = pump flow; HF = high flow; HP = high pressure; LDF = absolute value of splanchnic laser Doppler flowmetry at steady state (perfusion unit); LF = low flow; LP = low pressure; S0 = before CPB.

Table 2. Statistics

LDF	Statistics Grouped by Pressure Level			Statistics Grouped by Flow Level		
	Mean	SD	95% CI	Mean	SD	95% CI
Gastric						
Low pressure	115	64	—	Low flow	94.9	66
High pressure	117.6	83	—	High flow	137.6	75
Difference	-2.6	—	-44 to 39	Difference	-42.7*	-88 to 2.7
Jejunum						
Low pressure	141.6	80	—	Low flow	118.1	78
High pressure	148.6	83	—	High flow	172.0	75
Difference	-7.0	—	-57 to 43	Difference	-53.9*	-103 to -4.5
Ileum						
Low pressure	127.7	87	—	Low flow	95.6	72
High pressure	114.6	76	—	High flow	146.6	83
Difference	13.1	—	-23 to 49	Difference	-50.9*	-101 to -0.7
Liver						
Low pressure	114.3	88	—	Low flow	79.1	72
High pressure	73.3	70	—	High flow	108.6	118
Difference	41	—	-18 to 100	Difference	-29.5	-92 to 33

Measurements are the LDF in perfusion unit of different splanchnic tissue. The mean is calculated within groups depending on the carotid arterial pressure and on the CPB blood flow.

* Bonferroni-adjusted $P < 0.05$.

CI = confidence interval; CPB = cardiopulmonary bypass; LDF = laser Doppler flowmetry.

during CPB. It remained mildly hypothermic from 38.9°C (normal rabbit temperature, approximately 39°C) before CPB to 35.8–36.5°C during CPB. No significant difference of temperature between sequences was observed.

Analysis of variance was performed between all LDF measurements after coding for drugs (no drug, vasodilator or vasopressor bolus) and pump flow level. This analysis of variance introducing vasoactive agents as a cofactor was not significant ($F = 1.02$ – 1.8) and did not

alter the main results concerning arterial pressure level in a clinical point of view.

Descriptive data of arterial pressure and ileum LDF computerized at the end of the experimental design during progressive stepwise increase of CPB flow are represented in figure 1. They showed an acceptable variability of the model and a linear relationship between ileal LDF measurements and CPB flow. Linear regression between gastric and ileum LDF and CPB blood flow or arterial pressure are presented in figure 2. Dispersion

PRESSURE- VERSUS FLOW-INDUCED SPLANCHNIC ISCHEMIA DURING CPB

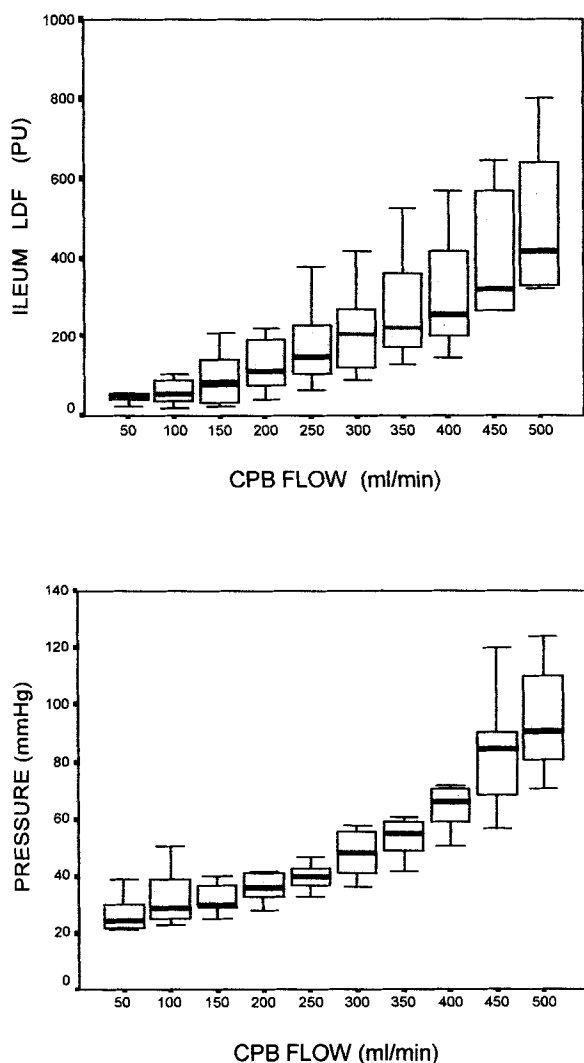


Fig. 1. Variability of splanchnic laser Doppler flow (LDF) and arterial pressure measurements during progressive increase of cardiopulmonary bypass flow. Data are presented as box plots (median, 25–75% of distribution, and extreme values).

was more important for the pressure data. A significant correlation ($P < 0.001$) using a parametric or nonparametric test has been shown between CPB blood flow and gastric LDF ($R = 0.69$; $\rho = 0.70$; $R^2 = 0.48$), ileum LDF ($R = 0.74$; $\rho = 0.80$; $R^2 = 0.55$), and arterial pressure ($R = 0.79$; $\rho = 0.84$; $R^2 = 0.62$). The correlation between pressure and gastric LDF ($R = 0.48$; $\rho = 0.51$; $R^2 = 0.23$) or ileum LDF ($R = 0.47$; $\rho = 0.56$; $R^2 = 0.22$) was also significant, but the fraction of total variance explained by the variation of pressure expressed by R^2 was low.

Discussion

The main result from this study is that low splanchnic tissue perfusion during CPB is primarily dependent on CPB output (blood flow) rather than on perfusion pressure. This result may seem to conflict with an early study using microspheres to measure flow,⁴ which did not find such a decrease in the splanchnic area, or partially with more recent study that also used microspheres.³ This difference is an example of the variation between macrocirculatory and microcirculatory studies. Microsphere techniques are validated to measure volume blood flow¹²; laser Doppler velocimetry is sensitive to erythrocyte (RBC) velocity (V_{RBC}) and number of RBCs passing through the sample volume per unit time (N_{RBC}). The product of V_{RBC} and N_{RBC} expressed as perfusion unit is indicative of the tissue perfusion and seems more correlated to capillary partial pressure of oxygen than volume flow.¹³ A similar discrepancy between visceral perfusion and tissue perfusion has been described when the measurements are made at a tissue level with different techniques such as laser Doppler or gastric tonometry.¹⁴ LDF measurements were validated in various situations such as *in vitro* gut segment preparation,¹¹ assessment of rectal mucosal perfusion in neonates,¹⁵ and gastric perfusion measurement during CPB.^{16–18} These measurements were reproducible.¹⁹ In an experimental model using pigs, Tao *et al.*²⁰ showed that CPB increased the superior mesenteric blood flow, whereas ileal mucosal blood flow assessed by laser Doppler decreased consistently with the occurrence of a gut acidosis, confirming a tissue level injury and the special interest of LDF monitoring.

An experimental crossover study²¹ similar to ours has been performed comparing high or low perfusion pressure during CPB with or without dopamine. However, in this study, the high-pressure state was obtained by increasing pump output. Another study, the most similar to the present one, used the microspheres technique in a three-step trial³ comparing low flow with or without phenylephrine to normal flow. Despite the different design, the results are comparable to ours, except that the high-flow/low-pressure state was not obtained. This situation is important in clinical practice and occurs often, mostly at the onset of CPB. It is also difficult to draw conclusions about the effect of low flow or phenylephrine alone. Unlike LDF measurements, the radioactive method does not permit continuous measurement of tissue perfusion and cannot be used to investigate splanchnic autoregulation.

The local autoregulatory control of splanchnic tissue per-

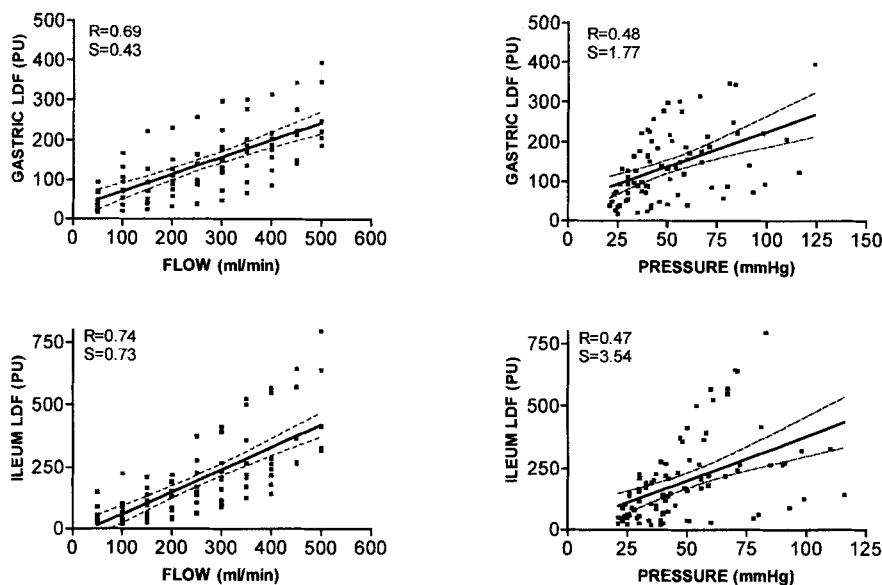


Fig. 2. Relationship between gastric or ileum laser Doppler flow (expressed in perfusion unit) and arterial pressure or cardiopulmonary bypass flow. Data are presented as linear regression (solid straight line) graph and 95% confidence interval (dotted lines). R = coefficient of correlation; S = slope.

fusion assumes a constant tissue perfusion inside an arterial pressure range or volume blood flow.²² The mechanisms involve a release of vasoactive mediators, capillary recruitment, and autonomic feedback. This study is not designed to argue for a precise mechanism. Nevertheless, the linear relationship between arterial blood flow mechanically induced by CPB and tissue laser Doppler velocimetry could be interpreted as a disturbance of autoregulation, with a complete dependency between tissue perfusion and CPB flow. This requires confirmation with comparable human studies. Autoregulation of splanchnic perfusion includes a myogenic response^{11,23} such as renal autoregulation, occurring < 5 min after a decrease in arterial pressure. Therefore, the present trial design with a 10-min step to be appropriate. Furthermore, some of the initial physiologic studies of oxygen uptake and blood flow regulation have used very high levels of blood flow²⁴ to obtain a steady state of autoregulation. In conclusion, splanchnic autoregulation at normal CPB pump flow level has never been assessed. The relation between flow and resistance can be described by the hemodynamic version of Ohm's law: $Q = (P_a - P_v)/R$, where Q is the mesenteric blood flow, P is the hydrostatic pressure in the artery and vein, and R is the vascular resistance.²² Because venous pressure stays constant (and low) during regular CPB, splanchnic blood flow can be linearly correlated to CPB output. The Doppler technique could be a valuable method to test regional vascular resistance during CPB and vasodilators. This point has been discussed¹² in relation to the discrepancy between LDF and other blood flow measurements, especially during use of vasoactive drugs. Nevertheless, cardiac out-

puts of animals in this study¹² could be considered to be very low, and blood volume uncontrolled, implying an acceptable conclusion only in the low-flow/low-volume state. This is not the case during CPB, where these parameters are controlled: volume flow by the priming solution and CPB pump output, venous portal pressure by the right atrial cannula that vented all caval blood, and RBC number constant after reinfusion.

The absence of a significant relationship between hepatic LDF and CPB output or arterial pressure could be explained by the physiologic balance in perfusion between arterial and venous hepatic flow. Unfortunately, venous portal blood flow could not be measured in this study. No differences in hepatic perfusion were found between pulsatile and nonpulsatile CPB²⁵ if blood flow is maintained in the high range, but total blood flow seems better preserved by high CPB flow. Hepatic disturbance in inflammatory disease may be more related to endothelial permeability and macrophage activation than hypoperfusion.²⁶

Mild hypothermia does not seem to be a major factor in splanchnic hypoperfusion^{27,28} but can reduce metabolic demand so that perturbations in pressure-dependent flow could be tolerated without ischemia. Surface temperature can influence tissue perfusion, but this phenomena is probably attenuated by the direct infusion of CPB thermostat-temperature-controlled blood.

Hemodilution by the pump prime in small animal models has been accepted in other studies⁹; hematocrit is kept constant throughout because all intravenous and

extravascular blood is reinfused. Moreover, gastric mucosal acidosis is not worsened by hemodilution.²⁹

Limitation of the Study

One limitation in transposing our results to the medical practice is the presence of atherosclerosis, which seems to be more relevant than age.¹ Non-CPB animal models are necessary to confirm the CPB action on autoregulation.

Ketamine used to maintain anesthesia does not act on intestinal motility.³⁰ Animals were allowed to eat and drink freely until the beginning of experiments to prevent stress and intestinal mucosal injury. This does not occur in human clinical guidelines. Furthermore, potential effects from laparotomy on visceral vascular resistance could not be excluded.

In this study using small animals, Doppler signals were approximately 1 mm deep from the surface, including global mucosal and muscularis tissue flow measurements. A comprehensive approach of flow redistribution between mucosa and muscularis or tissue heterogeneity was not permitted in our model. *In situ* experiments with needle probes to differentiate the two intestinal layers is not possible because of bleeding during CPB. Caution must therefore be exercised in extrapolating these results from the present animal model to the human clinical situation.

Conclusion

Splanchnic perfusion is altered during CPB and could not be assumed by monitoring only arterial pressure. Flow is more important than pressure in maintaining splanchnic perfusion. During CPB, splanchnic autoregulation seems to be altered in this animal model, and a linear relation between tissue perfusion assessed by LDF and CPB blood flow was found. Nevertheless, differences in behavior between hepatic, gastric, and ileal tissue perfusion have been demonstrated.

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