REGIONAL BLOOD FLOW IN THE LIVER, PANCREAS AND KIDNEY DURING PULSATILE AND NONPULSATILE PERFUSION UNDER PROFOUND HYPOTHERMIA

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Regional blood flow in the liver, pancreas and kidney was measured under conditions of profound hypothermia associated with total circulatory arrest, to determine whether cardiopulmonary bypass with pulsatile flow would improve the blood flow in these visceral organs in comparison with nonpulsatile flow.

Using 56 adult mongrel dogs, total cardiopulmonary bypass was carried out to induce hypothermia and 40 min of total circulatory arrest was performed at 20°C. After total arrest, the temperature was raised to 35°C.

With pulsatile flow, a decrease of the regional blood flow in the liver, pancreas and kidney was prevented during cooling, especially at 20°C before total circulatory arrest. Moreover, regional renal blood flow recovered rapidly with pulsatile flow after total arrest at 20°C, while after arrest with nonpulsatile flow blood flow in the kidney could not be measured in the cortex and was significantly lower in the medulla.

In summary, pulsatile flow improves the hepatic, pancreatic and renal blood flow and, referring to our previous experiments, protects the function of these organs during cardiopulmonary bypass associated with profound hypothermia and total circulatory arrest.

IN the past, we have advocated investigations into profound hypothermia and circulatory arrest with limited cardiopulmonary bypass to improve on the operative results of cardiac repair in neonates and infants.^{1,2} However, surface cooling involved in this hypothermia technique requires careful, intensive monitoring, and, in some cases, cannot be applied due to severe preoperative cardiac failure. A number of

cardiac surgeons³⁻⁵ have recently employed rapid cooling with conventional nonpulsatile bypass in preference to surface cooling because non-physiological deviations in blood flow distribution in the visceral organs and induced metabolic acidosis may be reduced by virtue of innovative improvements in operative techniques and associated procedures. In spite of the technical refinements of these specialists, basic disadvantages in the use of non-physiological cardiopulmonary bypass still remain.

Previously, we have suggested that pulsatile perfusion can be useful from the metabolic point of view for cardiac surgery under hypothermia.⁶⁻⁹ In conjunction with these former

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Fig.1. Simultaneous tracings of electrocardiogram, blood pressure in the aortic arch and blood flow in the ascending aorta at 20°C during fibrillation.

Legend: ECG = electrocardiogram; B.P. = blood pressure; PAD = pulsatile assist device; B. Flow = blood flow.

investigations, the present work was aimed at examining the advantages of pulsatile perfusion under profound hypothermia by measuring the regional blood flow in the visceral organs such as the liver, pancreas and kidney. The influence of pulsatile flow on regional blood flow in the visceral organs under profound hypothermia with total circulatory arrest has never previously been reported in the English literature.

MATERIALS AND METHODS

Fifty-six adult mongrel dogs, weighing 8 to 12 kg, were anesthetized with intravenous sodium pentobarbital, 25 mg per kilogram, and maintained with intermittent small doses of intravenous pentobarbital. Total cardiopulmonary bypass was carried out for cooling, and 40 min of total circulatory arrest was performed at a brain temperature of 20°C. Cardiac arrest was obtained with an administration of Young's solution¹⁰ (2 ml/kg) into the coronary arteries through the aortic root after aortic cross-clamping. After 40 min of total circulatory arrest, the brain temperature was raised to 35°C with core rewarming using total cardiopulmonary bypass. The dogs were then sacrificed.

During total bypass, ordinary nonpulsatile blood flow was used in one group (27 dogs) and pulsatile flow, using a pulsatile assist device (PAD), Datascope System 42, was employed in another group (29 dogs). PAD was driven manually and the pulse frequency was changed depending on the brain temperature (40 beats/min between 20°C and 22.5°C, 60 between 22.5°C and 25°C, and 80 above 25°C).

The inflation and deflation of the PAD were adjusted to afford the highest possible pulse

Fig.2. Illustration of cardiopulmonary bypass circuit including pulsatile assist device (PAD).

Legend: Oxy = oxygenator; HE = heart exchanger; P = pump; R = reservoir.

pressure at all times. On average, 40 to 50 mmHg of the arterial pulse width were obtained when the PAD was driven (Fig. 1).

A hollow-fibre oxygenator containing a heat exchanger (CAPIOX II, TERUMO, JAPAN) was used for the bypass. The venous return cannulae were placed in the right atrium (Fig. 2). Arterial blood was returned to the aortic root through a right-angled aortic cannula (No. 49-12305, Sarns International Inc., 3.8 mm in diameter). Total bypass was assured by venting the left ventricle (via the left atrial appendage) and occluding the main pulmonary artery. PAD was interposed in the arterial line, as close as possible to the arterial cannula.

The bypass circuit was primed with fresh heparinized whole blood obtained on the morning of the experiment from a single donor dog and diluted with low molecular weight dextran. During total bypass, packed cell volume was maintained between 20 and 25%, and the arterial flow rate was changed according to the brain temperature (100 ml/kg/min above 30°C, 80 ml/kg/min between 30 and 25°C, 60 ml/kg/min between 25 and 20°C). The temperature difference between the arterial blood and brain tissue was kept below 8°C during both cooling and rewarming. Carbon dioxide gas mixed with oxygen was used in the hollow-fibre oxygenator and sodium bicarbonate was administered to maintain PaO₂ above 100 mmHg, PaCO₂ between 30 and 50 mmHg and the pH between 7.3 and 7.5. Arterial blood gas analysis data were corrected to the temperature of the blood when samples were taken. Before the initiation of

TABLE I REGIONAL BLOOD FLOW IN THE LIVER, PANCREAS AND KIDNEY

Organ	Pul. or Nonpul.	No. of dogs	Cooling period (°C)				Rewarming period (°C)			
			35	30	25	20	20	25	30	35
Liver	P	8	65.0 ± 5.3	53.7 ± 6.6	54.0 ± 9.5	51.4 ± 4.8*	51.8 ± 8.3	30.5 ± 9.4	42.8 ± 4.7	53.5 ± 6.6
	N	6	70.3 ± 9.7	56.8 ± 9.1	42.8 ± 2.9	30.0 ± 5.7	41.5 ± 5.3	37.5 ± 4.9	35.3 ± 4.9	50.5 ± 4.1
Pancreas	P	7	58.0 ± 9.7	40.3 ± 3.6	54.5 ± 13.9	67.6 ± 7.1*	39.3 ± 7.3	35.0 ± 7.3	44.0 ± 8.0	40.3 ± 6.0
	N	9	42.5 ± 7.0	49.0 ± 6.2	45.8 ± 8.5	27.5 ± 4.7	25.0 ± 4.9	33.0 ± 7.3	45.8 ± 8.4	48.3 ± 12.8
Kidney (Cortex)	P	6	169.7 ± 12.9*	132.9 ± 9.4*	102.7 ± 11.5	71.4 ± 8.5*	68.5 ± 4.4*	60.2 ± 11.5	78.8 ± 17.2	119.0 ± 7.7*
	N	6	81.8 ± 4.2	80.5 ± 7.9	78.5 ± 16.8	45.8 ± 5.1	0	52.3 ± 26.0	63.5 ± 8.4	88.9 ± 11.7
Kidney (Medulla)	P	8	101.4 ± 17.7	80.1 ± 15.7*	46.6 ± 8.3	43.0 ± 12.2	24.1 ± 10.2*	18.6 ± 5.6	51.1 ± 14.7	75.6 ± 13.0
	N	6	88.8 ± 16.7	43.3 ± 7.8	50.3 ± 5.1	27.9 ± 9.2	0.82 ± 0.82	12.6 ± 4.3	40.4 ± 14.1	57.2 ± 11.5

(mean ± SEM ml/min/100g)

Legend: * = $p < 0.05$; N = Nonpulsatile group; P = Pulsatile group.

TABLE II CHANGES IN REGIONAL BLOOD FLOW IN THE LIVER, PANCREAS AND KIDNEY WHEN BLOOD FLOW AT 35°C DURING COOLING WAS ASSUMED TO BE 100

Organ	Pul. or Nonpul.	No. of dogs	Cooling period (°C)				Rewarming period (°C)			
			35	30	25	20	20	25	30	35
Liver	P	8	100 ± 0	84.9 ± 7.2	87.9 ± 9.0	84.0 ± 7.9*	79.0 ± 10.0	61.6 ± 18.7	69.6 ± 10.5	91.8 ± 12.2
	N	6	100 ± 0	76.4 ± 11.3	76.6 ± 11.1	54.0 ± 9.3	74.1 ± 18.0	65.2 ± 15.7	56.6 ± 11.7	80.6 ± 12.9
Pancreas	P	7	100 ± 0	76.8 ± 8.2	81.1 ± 8.8	91.9 ± 5.4*	51.2 ± 12.8	51.9 ± 5.3	111.7 ± 25.9	79.7 ± 17.5
	N	9	100 ± 0	78.1 ± 11.5	92.1 ± 6.4	66.6 ± 3.9	30.4 ± 2.7	60.4 ± 5.5	77.1 ± 6.5	103.4 ± 4.0
Kidney (Cortex)	P	6	100 ± 0	80.2 ± 4.4	62.1 ± 8.6	48.8 ± 6.6	41.6 ± 4.6*	38.9 ± 10.0	54.5 ± 14.5	71.8 ± 7.5
	N	6	100 ± 0	94.8 ± 16.4	69.1 ± 9.1	56.7 ± 7.3	0	35.5 ± 8.8	69.9 ± 9.6	77.9 ± 3.6
Kidney (Medulla)	P	8	100 ± 0	79.6 ± 9.6*	44.6 ± 3.4	35.8 ± 5.8	21.2 ± 9.2*	16.1 ± 4.9	43.6 ± 7.0	61.4 ± 5.8
	N	6	100 ± 0	48.7 ± 4.2	51.9 ± 4.7	33.7 ± 7.0	1.58 ± 1.58	15.7 ± 3.1	39.6 ± 10.2	65.7 ± 5.4

(mean ± SEM %)

Legend: * = $p < 0.05$; N = Nonpulsatile group; P = Pulsatile group

Fig.3. Regional blood flow in the liver.

(A) Actual value of regional blood flow.
 (B) Changes in regional blood flow are shown, when blood flow at 35°C during cooling was assumed to be 100.

Fig.4. Regional blood flow in the pancreas.

Abbreviations are the same as in Fig. 3.

bypass, a section of skull from the parietal region was removed, and the brain temperature was measured using a needle thermometer probe inserted vertically 1.0 cm into the brain tissue.

Regional hepatic, pancreatic and renal tissue blood flows were measured by polarographic recording of hydrogen gas desaturation with needle-shaped platinum electrodes (TYPE M UHE-100 UNIQUE MEDICAL, JAPAN). The electrodes were 5 cm in length, 300 μ in diameter and 1 mm of the tip of each electrode was coated with platinum. An indifferent electrode was inserted into the subcutaneous tissue at the inguinal region. An amplifier, (MHG-DI, UNIQUE MEDICAL, JAPAN) and recorder, (SERVOCORDER, SR-6312, GRAPHTEC CORP., JAPAN) were used for the measurements.

Hydrogen gas was delivered into the oxygenator of the bypass circuit for 10 sec, giving a concentration 10 times that of oxygen. Even during delivery of the hydrogen, blood gas analysis did not indicate a decrease of PaO_2 below 100 mmHg. Blood flow in ml/min/100g of tissue was calculated from the slope of the desaturation curves plotted on semilogarithmic paper according to the formula: $F/W = 69.3/T_{1/2}$, where F/W is blood flow (ml) in 100g of tissue

and $T_{1/2}$ is the half-time (minutes) of hydrogen gas desaturation. To measure regional blood flow in the liver, renal cortex and renal medulla, active electrode tips were placed 15 mm below the surface of the liver, and 3 mm and 10 mm below the surface of the kidney respectively. Since the pancreas was quite thin, the platinum electrode was simply inserted into the pancreatic tissue. Regional blood flow measurements were performed at 35°C, 30°C, 25°C and 20°C in periods of both cooling and rewarming. In addition to the actual value of blood flow in the tissue, the increase or decrease in the measured values after the start of core cooling were expressed as a percentage under the assumption that these values at a brain temperature of 35°C were 100. Statistical analyses were performed by means of Student's t-test and values were considered significant if the probability value was less than or equal to 0.05. The exact number of experiments in each organ and in each corresponding group are shown in Table I and Table II.

RESULTS

Regional blood flow measured in the liver, pancreas and kidney (cortex and medulla) are

Fig.5. Regional blood flow in the cortex of the kidney.
Abbreviations are the same as in Fig. 3.

shown in Table I during both cooling and rewarming. In Table II, the changes in the regional blood flow are shown when the blood flow at 35°C during the cooling period was assumed to be 100. In Figs 3–6, actual values of regional blood flow and changes of the values in percentages in each organ are shown.

Regional blood flow in the liver decreased gradually during the course of the cooling period in both groups (Fig. 3). However, the decrease of the blood flow was more remarkable in the nonpulsatile group than the pulsatile group, and a statistically significant difference between the 2 groups was observed at 20°C before the total circulatory arrest. That is, hepatic blood flow at 20°C during the cooling period was 30.0 ± 5.7 ml/min/100g ($54.0 \pm 9.3\%$ of control value) in the nonpulsatile group in contrast to 51.4 ± 4.8 ml/min/100g ($84.0 \pm 7.9\%$) in the pulsatile group. During the rewarming period, there was no significant difference between the 2 groups.

Regional pancreatic blood flow in the pulsatile group decreased at 30°C after the initiation of cooling (Fig. 4). However, in this group, blood flow in the pancreas increased gradually during the cooling period after 30°C in spite of a de-

Fig.6. Regional blood flow in the medullary layer of the kidney.
Abbreviations are the same as in Fig. 3.

crease in the arterial flow rate. On the other hand, pancreatic blood flow in the nonpulsatile group decreased after 30°C during cooling and at 20°C, a statistically significant difference was found between the pulsatile group (67.6 ± 7.1 ml/min/100g, $91.9 \pm 5.4\%$), and the nonpulsatile group (27.5 ± 4.7 ml/min/100g, $66.6 \pm 3.9\%$). Namely, a decrease of the pancreatic blood flow during core cooling could be suppressed with pulsatile perfusion. During the rewarming period, pancreatic blood flow increased in both groups according to a rise in the brain temperature, and there was no significant difference between the 2 groups.

Regional blood flow in the cortex of the kidney decreased significantly in the nonpulsatile group from the beginning of the cooling period, in contrast to the blood flow in the pulsatile group (Fig. 5). The blood flow in the renal cortex during the cooling period was always higher in the pulsatile group than in the nonpulsatile group, and statistically significant differences between the 2 groups were found at 35°C, 30°C and 20°C. During the rewarming period, the renal cortical blood flow could not be measured in the experimental cases in the non-

pulsatile group at 20°C just after the initiation of bypass for rewarming. However, blood flow could be measured at 20°C in the pulsatile group, at which point a statistically significant difference was found between the 2 groups. During the rewarming period, blood flow was always higher in the pulsatile group than in the nonpulsatile group, and there was a statistically significant difference between the two groups at 35°C (119.0 ± 7.7 ml/min/100g in the pulsatile group and 88.9 ± 11.7 ml/min/100g in the nonpulsatile group).

Regional blood flow in the medullary layer of the kidney was always higher in the pulsatile group than in the nonpulsatile group except for one period at 25°C during the cooling period and a significant difference was found at 30°C (80.1 ± 15.7 ml/min/100g in the pulsatile group and 43.3 ± 7.8 ml/min/100g in the nonpulsatile group) (Fig. 6). Renal medullary blood flow in the nonpulsatile group was significantly lower than that in the pulsatile group at 20°C just after the initiation of bypass for rewarming, and a significant difference was found at this period. At the other periods during rewarming, the renal medullary blood flow was always higher in the pulsatile group than the nonpulsatile group, but no significant difference could be found between the 2 groups.

DISCUSSION

Changes in the blood flow distribution in various visceral organs during extracorporeal circulation with pulsatile and nonpulsatile flow have been studied by many investigators. Notably, comparison of the blood flow in the kidney with pulsatile and nonpulsatile cardiopulmonary bypass has been reported by many workers.¹¹⁻²⁰ However, only a few researchers have measured regional blood flow in the liver, and in the pancreas in particular during bypass.^{11,12,17} Moreover, changes in the regional blood flow in the visceral organs under profound hypothermia combined with total circulatory arrest have rarely been investigated. Total corrections of complicated cardiac anomalies in infancy have been performed under profound hypothermia with or without total circulatory arrest with reasonable results.^{1-5,21,22} In addition, open heart surgery necessitating long duration of aortic cross-clamping has usually been undertaken under moderate or profound hypothermia. As physiologically abnormal situations during cardiopul-

monary bypass must be corrected in these critical cases, the effectiveness of pulsatile flow under hypothermia on the regional blood flow in the visceral organs was considered most worthy of investigation.

Regarding the actual measurement of the blood flow, at present, the radioactive microsphere method is considered the most reliable and accurate means to determine the regional blood flow in tissue. However, in 1964, Aukland and co-workers²³ first reported the hydrogen clearance method for blood flow measurement in the myocardium, renal cortex and skeletal muscle. Also, in 1975 LaMorgese and colleagues²⁴ examined the statistical correlation between the polarographic and microsphere methods to measure cerebral blood flow rates in the cat. We have already compared these methods while measuring the myocardial blood flow²⁵ and both experiments proved that a statistically significant positive correlation exists between the two methods. Therefore, as regional blood flow measurements should be performed repeatedly at the same region during both cooling and rewarming, the hydrogen gas clearance method was employed in this study.

Concerning experimental protocol, most of the studies carried out until now to determine the regional blood flow, especially in the kidney during pulsatile perfusion, have been performed either under normothermia,^{12,16-19} or by maintaining a constant mean arterial pressure with various flow rates.²⁰ In contrast, in the present investigation the perfusion flow rate and the pulse frequency produced by PAD were varied according to the cerebral temperature, since oxygen consumption decreases when the body temperature falls. Also, an excessively high flow rate compared to the body temperature causes interstitial edema in the visceral organs. On one occasion, a high arterial blood flow of 100 ml/kg/min was maintained during the entire period of hypothermia, but this high flow perfusion under hypothermia resulted in severe swelling of the liver, especially during rewarming, and a significant decrease in regional hepatic blood flow.

In this study, mongrel dogs were used, making it highly probable that the regional blood flow in the visceral organs would be affected by their unique inherent hemodynamic responses to the cardiopulmonary bypass. In order to exclude individual variations of regional blood flow in each organ, the increase or decrease in the

measured values was expressed as a percentage, as well as the actual values measured, assuming the value at 35°C to be 100. It was thought that the changes in the regional blood flow in each organ during hypothermia, and the differences between pulsatile and nonpulsatile groups, would become clearer and easier to comprehend using this method.

Regional blood flow in the kidney and liver during pulsatile and nonpulsatile perfusion has been measured with different results by various investigators. Some of them,^{12,13,17,18,20} observed no difference in blood flow to the renal arterial beds between the pulsatile and nonpulsatile bypass and found no advantage of pulsatile flow over nonpulsatile flow. On the other hand, others^{11,19} have noted a slightly higher blood flow in the kidney with pulsatile cardiopulmonary bypass compared to nonpulsatile, and have demonstrated a significant redistribution of renal cortical blood flow to the juxtamedullary cortex with nonpulsatile flow due to greater vasoconstriction in the outer cortex. The discrepancy among various authors may be related to the duration of perfusion, perfusion temperature, perfusion flow rate, pulse frequency, and the physical properties of the created pulse pressure contour. As for the duration of perfusion, Sink and associates,²⁰ compared renal cortical blood flow in only 10 min of stable nonpulsatile and pulsatile perfusion. As pulsations seem to act as a physiological stimulus regulating the hemodynamics in the system, longer pulsatile perfusion time is necessary to observe the changes in regional blood flow between the 2 groups, as already pointed out by Nakayama et al.¹¹ The efficacy of pulsatile flow can also vary depending on the perfusion temperature. Under a low body temperature, poor capillary flow is easily caused by increased blood viscosity due to the hemoconcentration.^{26,27} Also, a reduced perfusion temperature may interfere with autoregulation and alter vascular resistance. Thus, perfusion temperature plays an important part when comparing the effectiveness of pulsatile and nonpulsatile flow.

Continuing on to the specific visceral organs studied, hepatic blood flow is supplied by 2 sources, the hepatic artery and portal vein. The hydrogen gas clearance curve we obtained therefore consisted of 2 components, namely, the hepatic arterial and the portal venous curves. In the present study, the latter half of the clearance curve was used for the regional hepatic blood

flow measurements as Kurosawa and associates²⁸ have already reported that the blood flow calculated with the latter half of the clearance curve is highly correlated with the hepatic arterial blood flow.

In this study, regional renal cortical blood flow decreased remarkably from the beginning of cardiopulmonary bypass for cooling in the nonpulsatile group at 35°C in comparison with the pulsatile group. The initial drop in the systemic blood pressure at the beginning of bypass caused by the imbalance of the arterial flow and venous drainage was avoided as far as possible, and the same bypass technique was employed in both the nonpulsatile and the pulsatile group. It has also been reported that nonpulsatile flow caused a rather higher systemic blood pressure than pulsatile flow in vagotomized cats with intact carotid sinuses.²⁹ Therefore, it is apparent that the significant difference in the regional renal cortical blood flow at 35°C during cooling between the two groups was derived from the existence or nonexistence of the pulse wave.

We determined that the renal cortical blood flow in the nonpulsatile groups could not be measured by the hydrogen gas clearance method at 20°C just after the reperfusion for rewarming, while in the pulsatile group clearance curves were obtained and calculation of blood flow was possible at the same region. Also, blood flow in the renal medulla was significantly lower in the nonpulsatile group than in the pulsatile group at 20°C during the rewarming period. Ames³⁰ and Kloner,³¹ have already demonstrated the no reflow phenomenon in the brain and myocardium, i.e. failure to achieve uniform reperfusion after the temporary disruption of the blood supply. Kloner and associates,³¹ considered that this failure of reflow resulted from extensive capillary damage and myocardial cell swelling. Ames and colleagues,³⁰ concluded that the circulatory defect resulted from a shift of ions and water from plasma to perivascular cells, which led to a narrowing of the vascular lumen and an increase in the viscosity of the blood. It can be considered that the no reflow phenomenon also occurred in the present experiment in the kidney, which is more sensitive to ischemia than the liver and pancreas. The data obtained in this study pertaining to the regional renal blood flow may illustrate that the oscillatory energy of the pulsatile flow maintains the arterioles open in comparison with nonpulsatile flow as has been reported by Shepard and co-workers.^{32,33}

Turning to past biochemical studies on the liver and pancreas with pulsatile perfusion during hypothermia, our clinical and experimental studies⁷⁻⁹ revealed that plasma triglyceride levels were significantly higher in the pulsatile group than in the nonpulsatile group. Pulsatile flow also attenuated the catecholamine stress response to cardiopulmonary bypass. Although low temperature itself reduces beta cell function in the pancreas,³⁴ low plasma insulin levels with concomitant hyperglycemia, characteristic phenomena under hypothermia,^{35,36} were significantly modified in cases of pulsatile flow. The significant increase in the plasma levels of triglyceride in the pulsatile group may indicate an acceleration of very low density lipoprotein synthesis in the liver in the pulsatile group, rather than the oxidation of free fatty acids, which means more favorable lipid metabolism in the liver. Higher plasma insulin and lower glucose levels in the pulsatile rather than the nonpulsatile group mean minimized hyperglycemia and a better utilization of glucose during pulsatile perfusion under hypothermia.

In addition, the present study revealed improved hepatic, pancreatic and renal blood flow during the cooling period and better renal blood flow at 20°C during rewarming in the pulsatile group than in the nonpulsatile group. Thus, it can be considered that the application of pulsatile cardiopulmonary bypass for profound hypothermia possesses many advantages over conventional nonpulsatile perfusion, and presumably protects the function of those organs studied in this experiment. It can be noted that core cooling with nonpulsatile perfusion and 40 min total circulatory arrest at 20°C has been clinically used with reasonable operative results.⁵ However, this present data suggest that not only complicated cardiac anomalies in infancy but also acquired cardiac diseases necessitating hypothermia can be repaired more safely with pulsatile perfusion under hypothermia and with circulatory arrest when needed.

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