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HEMODYNAMIC STUDIES ON EXTRACORPOREAL CIRCULATION WITH PULSATILE AND NON-PULSATILE BLOOD FLOWS

By

AKIRA NONOYAMA

From the 2nd Surgical Division, Kyoto University, Medical School
(Director : Prof. Dr. YASUMASA AOYAGI)
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INTRODUCTION

It is of prime importance that pulsation of blood flow should be maintained during total by-pass. Never-the-less, there are few papers concerning this problem except WESOLOWSKI, who experimentally proved that the pulsatile blood flow was quite unnecessary to maintain the good physiological state of the animals. GIBEON[52] and KANTROWITZ[24] experimentally succeeded extracorporeal circulation in 1950, and in 1951 DENNIS[9] successfully repaired atrial septal defect using the artery pump with low amplitude pulsation. Since then, the artery pumps of metal-finger and DEBAKEY types which produce low amplitude pulsation are now in wide clinical use.

Recently, however, it has been noticed that[16)18)32)33)] during the prolonged extracorporeal circulation various unfavorable phenomenon, such as an unexpected fall in arterial blood pressure or a development of metabolic acidosis were often experienced even with a relatively high blood flow. The causes of these unpleasant phenomenon have not yet been sufficiently clearified, but the unphysiologic condition of the blood stream, namely diminution or disappearance of pulsation in arterial blood stream during extracorporeal circulation seemed to be one of the important causative factors of these phenomenon.

The present investigation, therefore, was attempted to solve the significance of pulsatile blood flow during extracorporeal circulation using the artery pump constructed by Dr. GORO KAMIMOTO, Professor of the Faculty of Technology, Kyoto University. Although the survival rate after total by-pass was used as a basis of decisions in the experiments of WESOLOWSKI and others,[60] the present author paid special attentions to pathologic physiology during heart-lung by-pass in this experiment.

Chapter I. Studies on the Artificial Heart-Lung Apparatus

Section 1. Studies on the mechanical pump

All the mechanical pumps in current use for artificial circulation to replace the heart have been divided into two categories those of high amplitude pulsation and those of low amplitude pulsation. We constructed, as already reported[35)46)], an

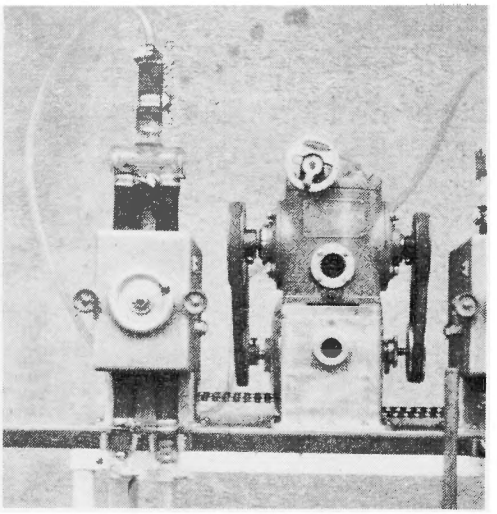


Fig. 1 a Close up photograph of the artery pump. No. 1 type.

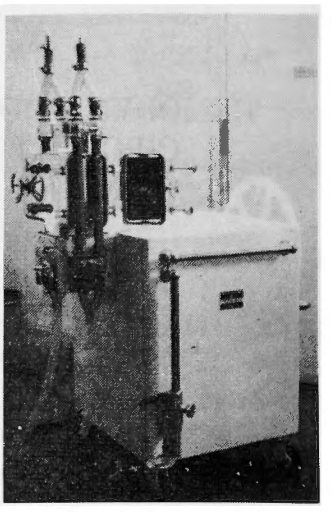


Fig. 1 b Photograph of the artery pump. No. 2 type.

artery pump with high amplitude pulsation; type-1 is illustrated in Fig. 1a, and type-2 is showed in Fig. 1b. An emergency handle is attached to type-2 for power supply in case of stoppage of electric current. In this pump a moving plate compresses against two silicone rubber tubes, and squeezes blood out in a pulsatile manner. Stainless ball valves are used to prevent regurgitation of the blood stream.

Experimental Results

(1) Output

The pump has a capacity of 5,000 cc per minute over a range of 40 to 140 strokes per minute; the stroke volume is easily maintained from 0 and 50cc and its adjustment is very simple. The figure shows a pressure-flow relation (Fig. 2). As the output is not influenced by change of pulse rate in this pump, it is possible to use any optimal pulse rate without changing flow.

(2) Pulsation

The pressure curve of this pump recorded by electromanometer in model-experiment is quite similar to that of the living organism (Fig. 3). This is the main advantage of this pump. The pressure pattern of the DeBakey pump recorded with the same pulse rate shows a decreased pulse pressure.

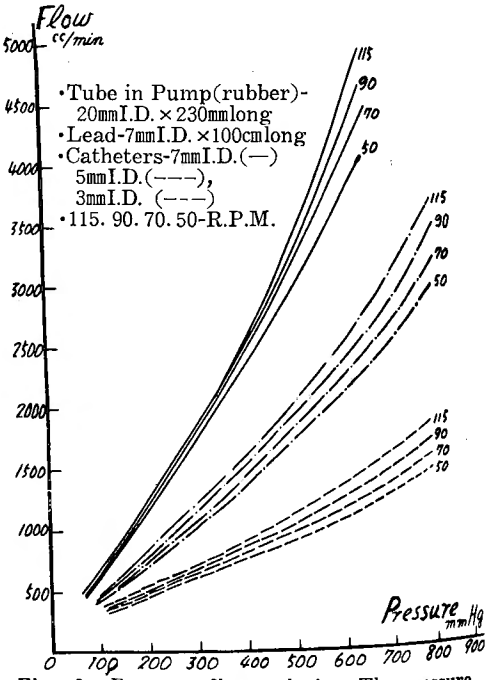


Fig. 2 Pressure-flow relation. The pressure is a systolic pressure in the artery pump.

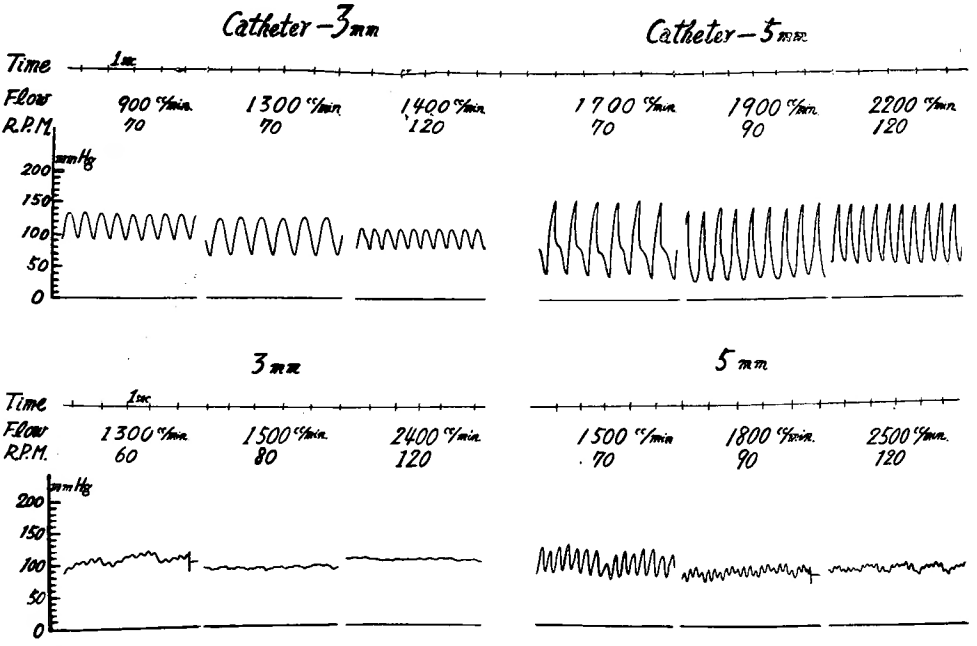


Fig. 3 Pulse wave tracings recorded with an electromanometer in model-experiment. Above in the figure is shown the pressure pattern of the artery pump. Below is shown the pressure pattern of the DeBakey pump recorded with the same pulse frequency

The changes in pulse pressure studied in model-experiment using the arterial cannulas of 3mm. and 5mm. in caliber are illustrated in Figure 4. The increase in pulse rate is accompanied by the decrease in pulse pressure.

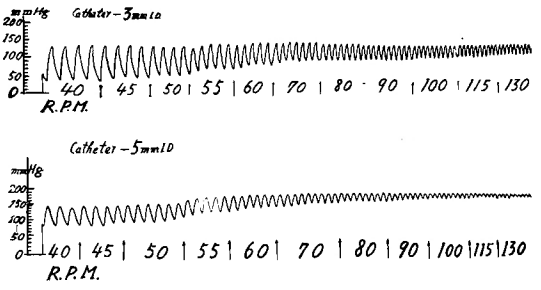
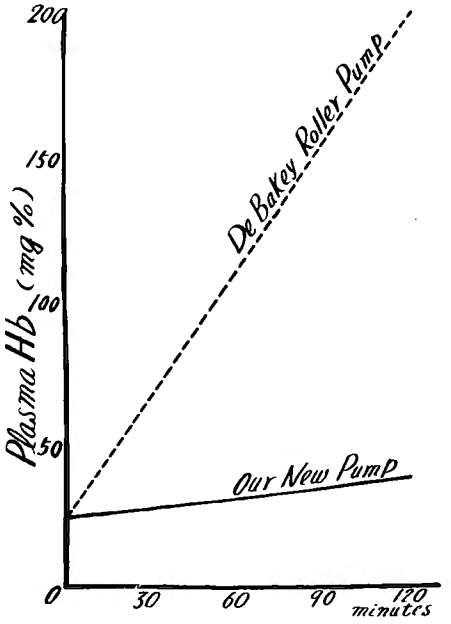


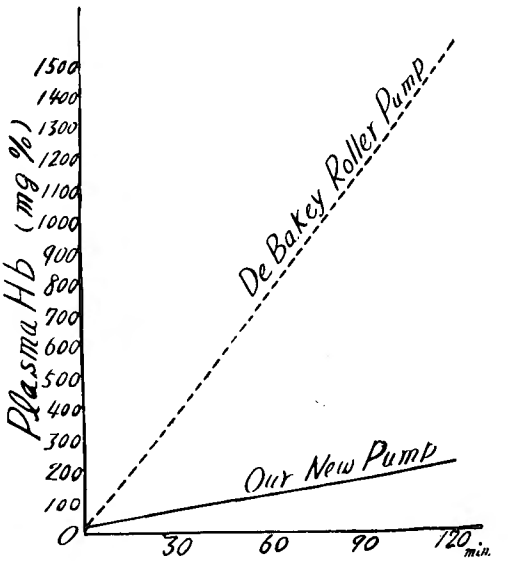
Fig. 4 The changes in pulse pressure in model-experiment using arterial cannulas of 3 mm. and 5 mm. caliber.

(3) Damage to blood cells

This pump causes little hemolysis. In this pump a rubber tube is not entirely closed even in the case of the maximum output. Such a construction of the pump seems to minimize injuries to the blood cells. As a matter of fact, when hemolysis or plasma hemoglobin determination[50] was used for an index of blood damage,[9)15)21)26)27)] the hemolysis caused by this pump was quite negligible, compared with that caused by the DeBakey pump (Fig. 5 a, b). Plasma hemoglobin during total body perfusion increased mildly (Fig. 6). Its content was 15.8-55.1mg% (average 35.8 mg %) at the termination of one hour perfusion. Comparing with the results formerly reported by others,[11)46)60)] this present results, is far below the renal threshold,[17)30)] and is regarded as very excellent. No definite relationship was established between hemolysis and flow. However, as Lillehei[11)] reported, hemolysis increased mildly in



a. Increase of Plasma Hb with time (at 2 Liters per Minute)



b. Increase of Plasma Hb with time (at 5 Liters per Minute)

Fig. 5 The hemolysis caused by this arterial pump is quite negligible, compared with that caused by the DeBakey pump.

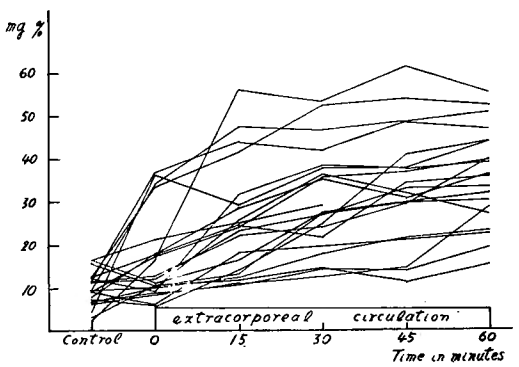


Fig. 6 Hemolysis during extracorporeal circulation.

Fig. 7 Photograph of author's oxygenator. (a) gas distributor. (b) blood manifold. A layer of blood-oxygen foam is created by passing oxygen through blood. Venous blood is trickled through the foam.

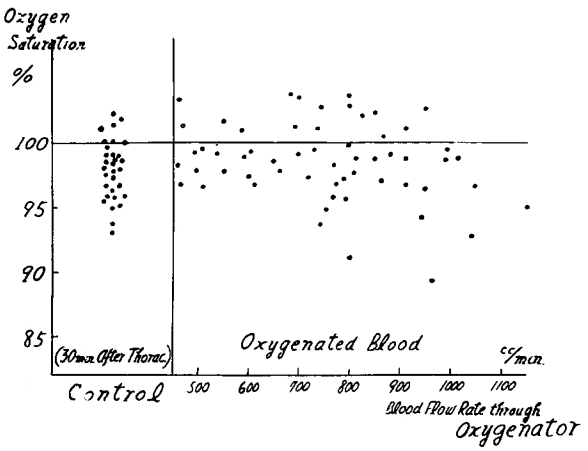


Fig. 8 Arterial oxygen saturation by this oxygenator.

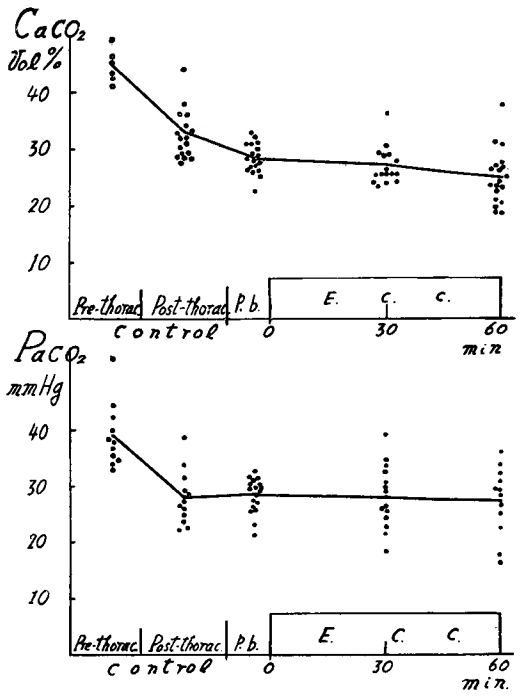


Fig. 9 Carbon dioxide content and carbon dioxide tension in the arterial blood during total body perfusion.
$Caco_2$: arterial carbon dioxide content.
$Paco_2$: arterial carbon dioxide tension.
p. b. : priming blood.

proportion to the duration of extracorporeal circulation.

Section 2. Studies on the oxygenator

We improved various oxygenators and eventually modified and employed a foam oxygenator of WAUD-SALISBURY type[45)46)57)] (Fig. 7). In this oxygenator, oxygen is blown into the blood from the gas distributor in the lower part of the oxygenator, and the blood is sprayed onto the blood foams uniformly from the above. The priming blood volume of this oxygenator is 300cc. Pure oxygen was used in a ratio of nearly 1 : 1 to blood, and usually the amount of oxygen needed was very small.

Experimental Results

(1) Oxygenation of venous blood

The arterial oxygen saturation by this oxygenator is excellent, and when the blood flow is less than 1.1 1/min., it usually shows the value of 95-100% saturation (Fig. 8).

(2) Elimination of carbon dioxide

The oxygen flow through this oxygenator is very small, but the carbon dioxide content and Pco_2 in the arterial blood after passage through this oxygenator somewhat decreases (Fig. 9). The use of pure oxygen is said to wash out carbon dioxide in excess,[14)15)20)29)32)34)] and oxygen containing CO_2 in 2-5 vol. % is usually used to prevent the decrease in Pco_2.[8)15)]

[33)49)] As GIBBON[18] described, Pco_2 should be maintained over 25mm. Hg. at the lowest.

Chapter II. The Role of the Pulse in Extracorporeal Circulation

Methods and Materials

Fifty healthy adult mongrel dogs, weighing 7 to 12 kilograms were anesthetized with intravenous pentobarbital sodium (25 to 30 milligrams per kilogram of body weight). Respiration was maintained with intermittent positive pressure with pure oxygen. The chest was opened by an incision through right fourth and left third intercostal spaces. The azygos vein was ligated and sling ligatures were placed around both venae cavae. Three milligrams of heparin per kilogram of body weight was given intravenously after all dissection had been completed. For arterial blood delivery a metal cannula of 3mm. in diameter was inserted through the left carotid artery into the aorta, and for venous cannulation two vinyl tubes of 5mm. in caliber were passed through the right atrium and one was placed into the superior and the other into the inferior venae cavae. Venous blood was sucked by gravity at a negative pressure of about 30cm. H_2O and was collected in the reservoir. A large amount of normal saline solution was pumped through the circuit, and the heart-lung apparatus was filled with heparinized blood. The amount of blood necessary to fill the apparatus was approximately 1500cc. Operations were performed with clean but not sterile and all dogs were subsequently sacrificed for pathohistologic examination.

The flow rate was accurately determined with the electromagnetic flowmeter or rotameter. The arterial pressure was recorded from the femoral artery, and the venous pressure from the inferior vena cava. Throughout the experiment the pulse rate was set at 70 to 80 per minute, and when a non-pulsatile flow was required pulsation was removed by an air chamber (Fig. 10) interposed in the delivery tube.

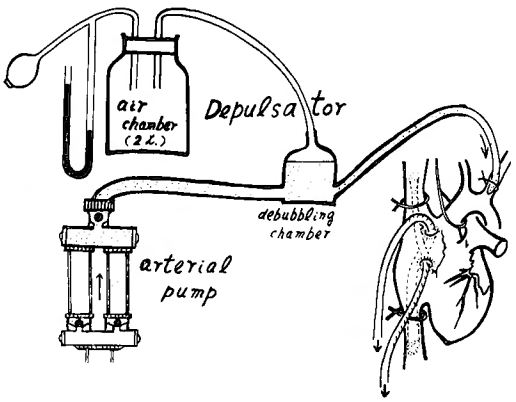


Fig. 10 Diagram of the depulsator. When a non-pulsatile flow is required pulsation is removed by an air chamber.

The animals were divided into two groups, i. e., the pulsatile and non-pulsatile, and observations were made on each group with either pulsatile or non-pulsatile flow under the same flow rate from 50 to 120 cc/kg/min. for a period of sixty to ninety minutes of extracorporeal circulation. Care was taken to keep the rectal temperature above 36°C. during the procedure. Arterial and venous blood samples drawn simultaneously in oiled syringes during perfusion were analyzed by the VAN SLYKE and NEILLE technique[54)] for oxygen content, oxygen capacity[48)] and carbon dioxide content. The pH was measured by the Shimadzu glass electrode at 37°C. Pco_2 and HCO_3 were calculated from the VAN-SLYKE and SENDROY's nomogram,[55)]

and buffer base from the SINGER and HASTINGS' nomogram[51]. Serum sodium and potassium levels were measured with the flame photometer (RANGE) and venous hematocrit values were determined by the volume method.

Experimental Results

(1) Arterial blood pressure

The pressure curve of the organism recorded during extracorporeal circulation with the pulsating artery pump was quite similar to that recorded before extracorporeal circulation (Fig. 11). This pressure curve was taken from femoral artery after the clamping of the aorta.

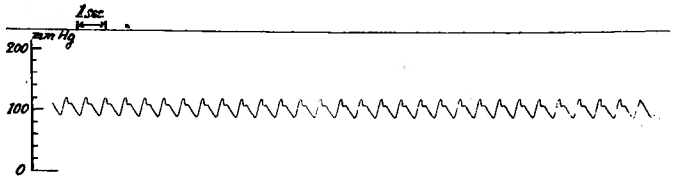


Fig. 11 Electromanometric pulse wave traces taken within the femoral artery.

The arterial pressure was easily maintained in the pulsatile group, i. e., under the same flow rate the arterial pressure in the pulsatile group was kept approximately 15mm. Hg. higher than in the non-pulsatile group (Fig. 12).

In both groups a linear relationship was noted between arterial pressure and flow rate, but in the pulsatile group the increase in flow rate did not cause a proportional rise of the arterial pressure when flow rate was more than 90cc/kg/min., and the pressure-flow relation came to lie horizontally.

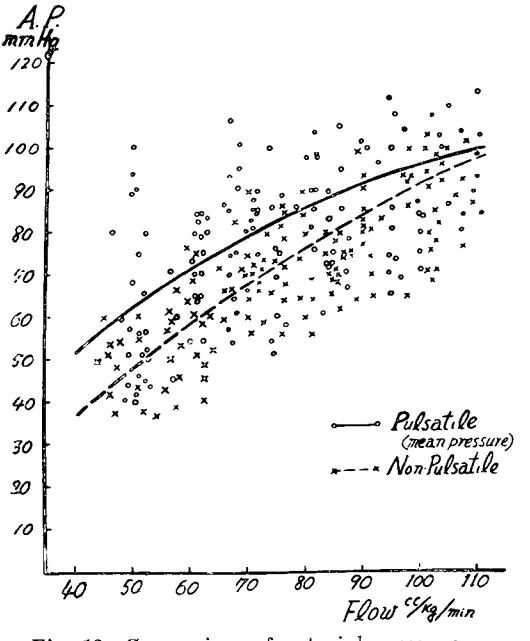


Fig. 12 Comparison of arterial pressure between pulsatile and non-pulsatile flow under the same flow rate.

In the non-pulsatile group the arterial pressure was maintained in a relatively good condition within 15 to 20 minutes after beginning of total body perfusion, but 30 minutes later the arterial pressure began gradually to fall in many cases (Fig. 13). This hypotension seemed to be irreversible and was neither normalized by increasing flow rate, nor by using the vasopressors.

(2) Peripheral vascular resistance

Peripheral vascular resistance was calculated from the formula:

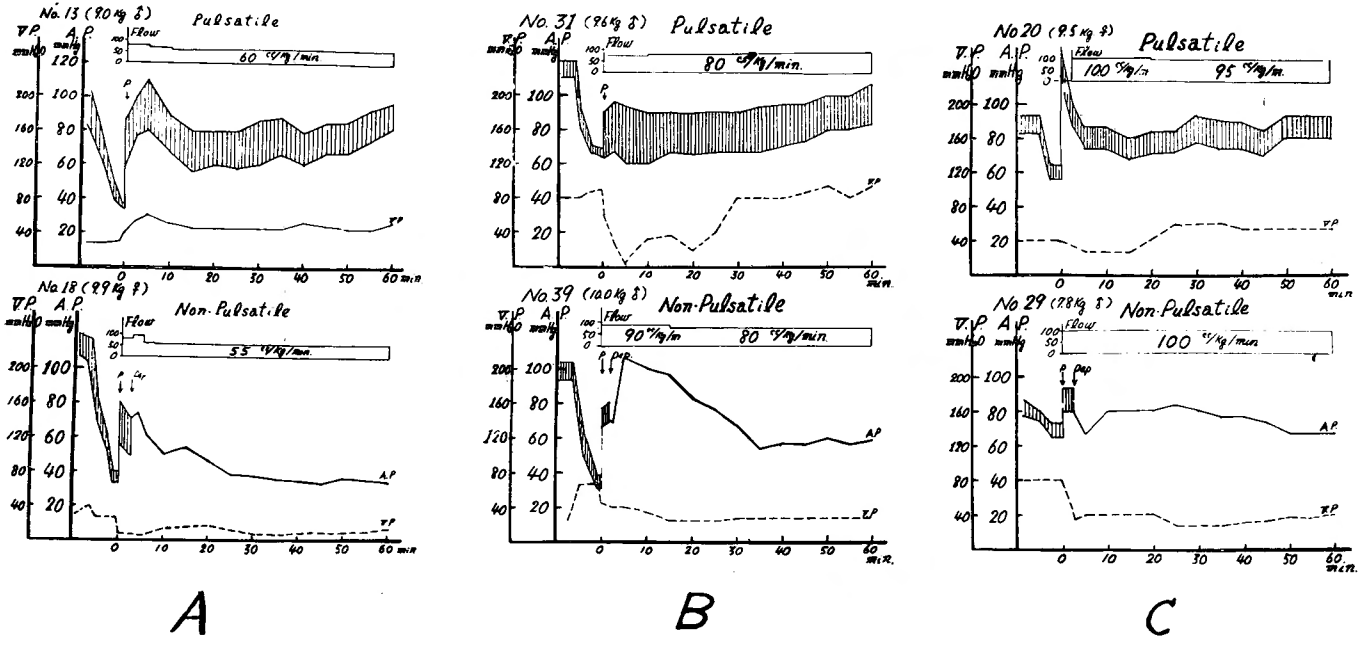


Fig. 13 illustrates arterial pressure during extracorporeal circulation between pulsatile (top row) and non-pulsatile flow (bottom row).

A. Flow rate, 55～60 cc/kg/min. B. Flow rate, 80cc/kg/min. C. Flow rate, 95～100 cc/kg/min.

$$\frac{\text{arterial blood pressure-venous pressure (mm. Hg.)}}{\text{flow in cc/kg/min.}}$$

In both groups, peripheral resistance increased above normal immediately after onset of perfusion, but just as in the case of arterial pressure, it gradually fell in the course of perfusion in the non-pulsatile group. On the other hand, in the pulsatile group it usually remained constant throughout the period of extracorporeal circulation, and the tonus of the peripheral blood vessel was seemed to be in good condition (Fig. 14).

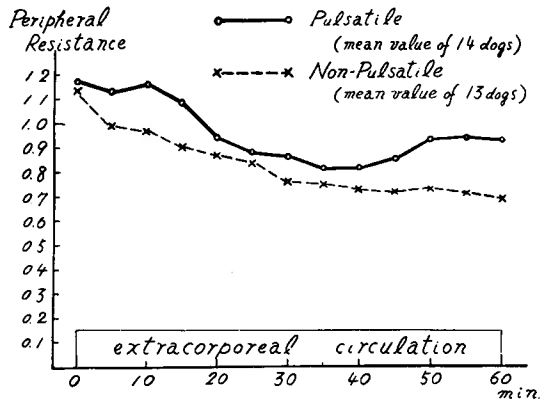


Fig. 14 Peripheral vascular resistance not only lowered but was liable to show a further decrease in the course of time in the non-pulsatile group, whereas in the pulsatile group it was adequately maintained throughout the period of perfusion.

As to the relationship between peripheral resistance and flow rate (Fig. 15), the peripheral resistance increased with decrease in the flow rate so as to maintain the arterial pressure in the pulsatile group, whereas in the non-pulsatile group a linear relationship was noted between the both; that is, decrease in flow rate was accompanied by decrease in peripheral resistance.

(3) Central venous pressure

No remarkable difference was noted between both groups. Almost all cases showed below 10cm. H_2O during total body perfusion (Fig. 16). The diameter of a venous cannula and

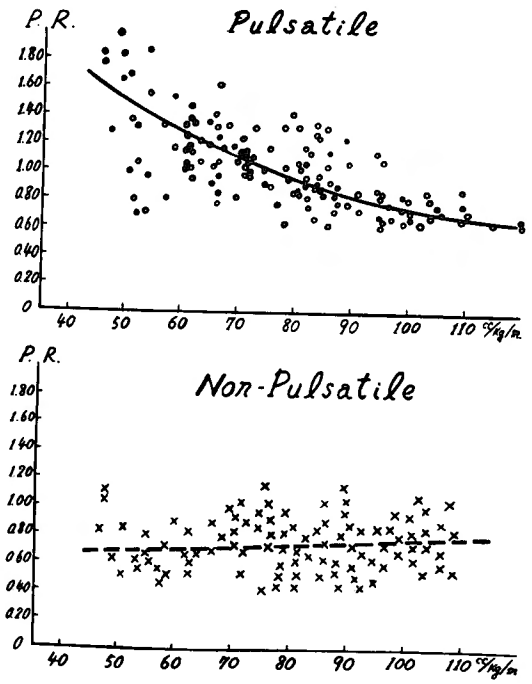


Fig. 15 Relationship between peripheral resistance and flow rate.

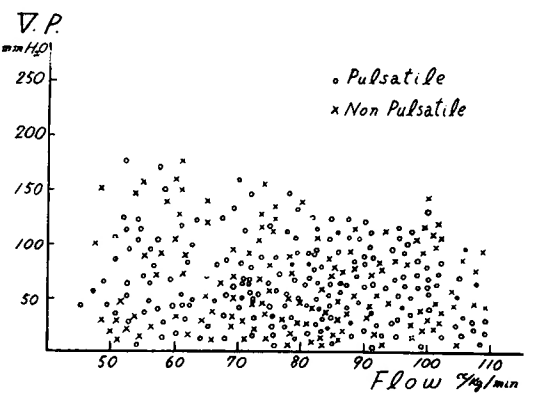


Fig. 16 There was no remarkable difference in venous pressure between both groups.

distance of reservoir level seem to be two chief factors that determine the venous pressure, and a poor suction may cause a rise in the venous pressure. The use of a smaller venous cannula not only caused an abnormal rise in this pressure, but also decreased the venous return as well.

Besides the above findings, in some cases of the non-pulsatile group, it was noted that the venous return gradually decreased during perfusion under comparatively low venous pressure, or that the gradual rise in the venous pressure with lowering arterial pressure.

These phenomenon were never noted in the pulsatile group.

(4) Body weight and venous hematocrit value

To ascertain a state of blood balance, pre- and post-experimental body weight was measured (Fig. 17). As thoracotomy, laparatomy and intravenous drip of normal saline solution were performed before extracorporeal circulation, some degree of post-experimental increase in body weight was noted, but the rate of increase was greater in the non-pulsatile group. This increase in body weight in the non-pulsatile group seemed to be eventually attributable to blood pooling in peripheral tissues.

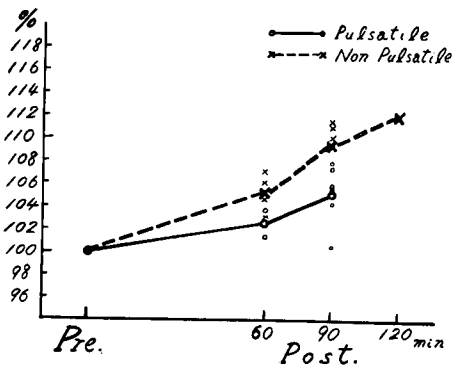


Fig. 17 Changes of body weight immediately after perfusion.

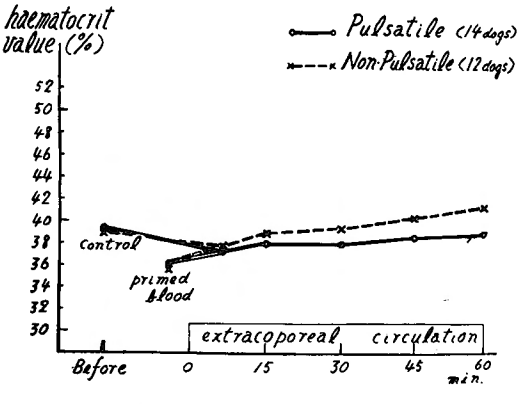


Fig. 18 Changes in hematocrit values during extracorporeal circulation.

No direct relationship was noted between the rate of increase in body weight, and the arterial or venous pressures during extracorporeal circulation, but the body weight showed a tendency to increase with the duration of total body perfusion. There was, however, no appreciable post-experimental increase in body weight in some cases of the non-pulsatile group, which had shown marked hypotension in early stage of perfusion.

In the non-pulsatile group the hematocrit values tended gradually to rise with the duration of perfusion (Fig. 18).

(5) Oxygen consumption

The oxygen content, saturation and consumption of the arterial and venous blood before and during extracoporeal circulation are presented in Table 1. Oxygen consumption was calculated from the formula: the arterio-venous oxygen difference

Table 1 Oxygen content, saturation and consumption of arterial and venous blood before and during perfusion.

Group	No.	body weight (kg)	control (30min. after thoracotomy)					perfusion 30 min.							perfusion 60 min.						
			$A.-O_2$ cont. Vol %	$A.-O_2$ satur. %	$V.-O_2$ cont. Vol %	$V.-O_2$ satur. %	$A.\cdot V.\ O_2$ diff. Vol %	flow cc/kg/m.	$A.-O_2$ cont. Vol %	$A.-O_2$ satur. %	$V.-O_2$ cont. Vol %	$V.-O_2$ satur. %	$A.\cdot V.\ O_2$ diff. Vol %	O_2-Cons. cc/kg/m.	flow cc/kg/m.	$A.-O_2$ cont. Vol %	$A.-O_2$ satur. %	$V.-O_2$ cont. Vol %	$V.-O_2$ satur. %	$A.\cdot V.\ O_2$ diff. Vol %	O_2-Cons. cc/kg/m.
pulsatile	13	9.0	19.1	95.2	14.4	72.0	4.7	61	17.5	97.8	10.5	59.0	7.0	4.27	61	17.6	99.1	6.4	35.8	11.2	6.83
	17	11.7	16.6	95.9	7.6	43.8	9.0	86	13.6	89.2	6.2	40.9	7.4	6.36	82	15.3	101.1	7.1	47.0	8.2	6.72
	20	9.5	15.8	93.8	12.2	72.5	3.6	105	16.2	98.8	10.6	61.3	5.6	5.88	100	16.6	102.7	8.5	52.4	8.1	8.10
	21	10.5	27.4	102.3	19.7	73.5	7.7	71	22.6	104.8	10.1	46.9	12.5	8.87	71	21.4	101.1	11.8	56.1	9.6	6.82
	31	9.6	14.5	99.1	8.3	57.0	6.2	81	13.4	98.3	4.7	34.7	8.7	7.03	81	10.4	95.9	3.4	31.3	7.0	5.68
	33	8.4	17.0	100.1	13.4	80.4	3.6	96	13.9	102.9	8.7	64.3	5.2	5.02	96	14.0	103.8	7.9	58.6	6.1	5.84
	35	8.8	14.2	96.3	4.2	28.4	10.0	91	11.0	97.7	4.6	40.6	6.4	5.83	97	10.7	98.9	5.1	50.1	5.6	5.47
	36	9.1	24.6	101.9	13.4	55.6	11.1	126	11.4	95.1	7.3	61.2	4.1	5.12	115	11.0	92.9	5.2	44.0	5.8	6.65
	42	8.7	14.8	98.7	9.2	61.4	5.6	52	13.0	96.8	5.8	43.5	7.2	3.73	52	14.8	101.4	9.3	63.9	5.5	2.84
	43	8.6	15.2	100.1	8.6	56.7	6.6	76	12.5	98.6	6.0	47.7	6.5	4.89	76	12.1	97.9	7.0	56.8	5.1	3.86
	47	8.9	14.5	96.7	6.6	44.0	7.9	68	12.7	97.4	5.3	40.7	7.4	4.99	68	11.2	96.8	3.5	30.2	7.7	5.17
	49	8.6	17.7	93.1	11.6	61.0	6.1	94	18.2	98.9	11.0	59.7	7.2	6.74	91	17.4	96.9	9.7	54.0	7.7	7.07
Non-pulsatile	15	10.5	16.8	97.4	9.2	53.5	7.6	90	16.0	96.5	12.6	76.2	3.4	3.06	85	17.0	100.5	12.8	75.6	4.2	3.59
	16	9.8	18.2	98.4	8.4	46.0	9.8	103	16.2	98.9	11.0	67.4	5.2	5.36	101	16.3	99.6	10.8	65.6	5.5	5.55
	18	9.9	20.8	98.5	10.5	49.5	10.3	55	14.9	101.7	8.6	58.7	6.3	3.47	59	14.8	101.0	9.7	66.2	5.1	3.01
	22	11.2	18.2	99.7	7.4	40.4	10.8	63	16.5	104.6	8.7	55.3	7.8	4.91	63	14.9	103.8	9.7	67.3	5.2	3.28
	25	10.5	19.8	98.9	11.4	57.4	8.4	72	13.5	94.9	6.3	44.1	7.2	5.18	43	14.7	103.2	4.5	31.8	10.2	4.38
	29	7.8	16.4	99.1	8.2	49.8	8.2	103	13.2	95.7	9.2	67.1	4.0	4.11	103	13.1	97.2	8.3	61.7	4.8	4.98
	32	11.8	18.3	101.8	7.3	40.5	11.0	72	15.9	102.4	8.2	52.9	7.7	5.53	70	15.8	102.1	8.8	57.1	7.0	4.86
	37	10.3	17.2	100.2	10.3	59.8	6.9	70	14.7	97.4	9.4	62.1	5.3	3.73	73	13.6	93.8	8.8	60.9	4.8	3.47
	38	11.0	12.1	98.1	5.7	46.2	6.4	86	11.8	94.3	7.0	56.3	4.8	4.09	95	9.2	96.9	5.7	61.6	3.5	3.36
	39	10.0	17.0	98.7	10.9	63.1	6.1	80	11.9	91.1	6.8	52.4	5.1	4.08	80	13.2	99.9	4.1	53.6	6.1	4.91
	40	7.7	15.8	96.2	8.4	50.9	7.4	95	10.0	99.5	6.4	63.1	3.6	3.44	90	9.8	101.2	5.4	56.3	4.4	3.90
	50	7.8	16.8	95.9	10.3	59.0	6.5	58	11.1	98.2	5.2	46.2	5.9	3.42	58	11.9	99.1	5.9	49.0	6.0	3.48

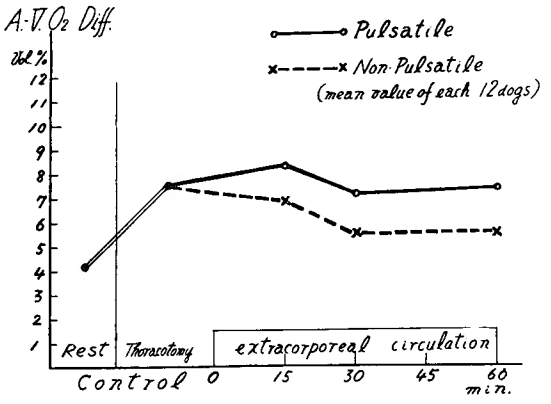


Fig. 19 Arterio-venous oxygen difference tended to decrease in the course of perfusion in the non-pulsatile group.

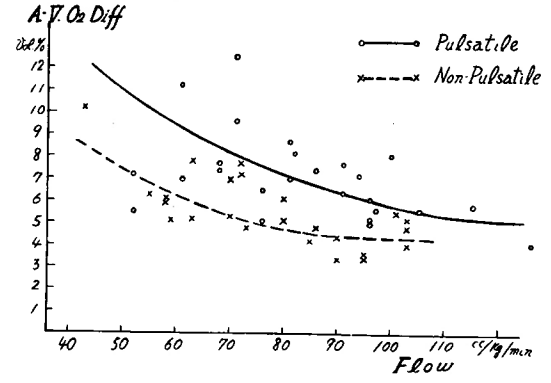


Fig. 20 Relationship between arterio-venous oxygen difference and flow rate. In the pulsatile group arterio-venous oxygen difference was nearly the same as that of control.

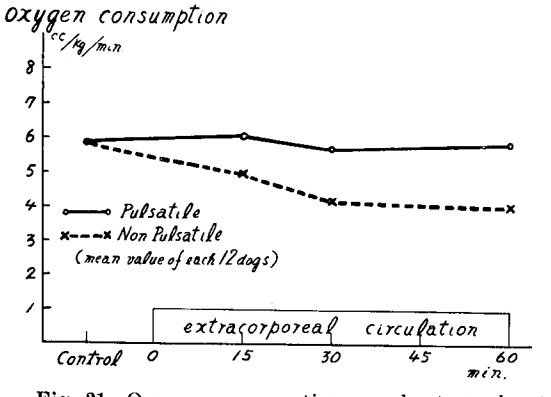


Fig. 21 Oxygen consumption was kept nearly at a constant as well as adequate level in the pulsatile group, while in the non-pulsatile group it fell off by degrees in the course of time.

× flow rate.

Although the arterial oxygen saturation was kept above 90%, mostly between 98 and 100%, in all cases, the venous oxygen saturation and arterio-venous difference differed greatly in the two groups; in the pulsatile group the venous oxygen saturation markedly decreased and the arterio-venous oxygen difference remained the same as, or larger than that of the normal level, while in the non-pulsatile group the venous oxygen saturation was high and the arterio-venous oxygen difference gradually decreased in the course of perfusion and became smaller than that of the control level (Fig. 19).

This condition was clearly seen in the relationship between the arterio-venous oxygen difference and flow rate (Fig. 20). In the pulsatile group the arterio-venous oxygen difference was nearly the same as that of the control, whereas in the non-pulsatile group much smaller.

The comparison in oxygen consumption between both groups also gave the same results. In the pulsatile group the oxygen consumption was kept nearly at a constant as well as adequate level, a value near 6cc/kg/min. of control, while in the non-pulsatile group it fell down with the passage of perfusion time, and after 60 minutes it showed a value of 4 cc/kg/min. on average (Fig. 21).

As to the relationship between oxygen consumption and flow rate (Fig. 22), the increase in flow rate was accompanied by the increase in oxygen consumption in both groups, but there was a marked difference of

more than 1-1.5 cc/kg/min. between the two groups. It was interesting to note that normal oxygen consumption was obtained usually with a flow rate of 75cc/kg/min. in the pulsatile group, but it did not reach a normal level even with such a high flow as more than 100 cc/kg/min. in the non-pulsatile group. This fact was related to high oxygen saturation of the venous blood in the non-pulsatile group, and it is more likely that the organism perfused with non-pulsatile flow is forced to put in a situation that it may not be able to take up adequate amount of oxygen.

Changes in the arterio-venous carbon dioxide difference (Fig. 23) and in the carbon dioxide output (Fig. 24), as well as the relation between carbon dioxide output and flow rate (Fig. 25), were further investigated. Nearly the same results were obtained as in the cases of oxygen, but the difference between the two groups were not so conspicuous at this point.

(6) Acid-base balance

The results of pH, buffer base and bicarbonate during extracorporeal circulation are given in the table (Table 2 a. b). As shown in the table, while only a slight fall in pH (Fig. 26), and mild changes in buffer base and bicarbonate (Fig. 27) were observed in the pulsatile group, pH fell to 7.10 (7.21-7.00) at 60 minutes after commencement of extracorporeal circulation, and buffer base and bicarbonate markedly decreased in the non-pulsatile group.

As the carbon dioxide tension of the venous blood ($Pvco_2$) remained within normal limit in the two groups,

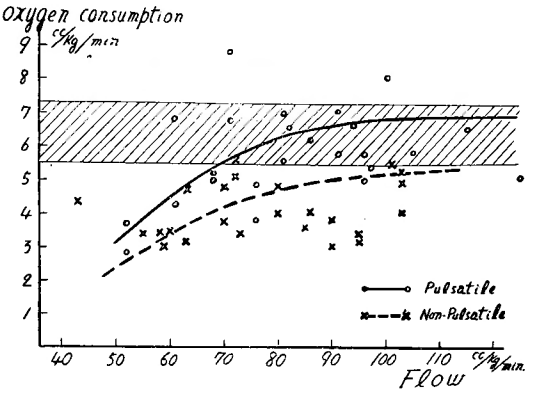


Fig. 22 Relationship between oxygen consumption and flow rate. Oxygen consumption did not reach a normal level even with such a high flow as more than 100cc/kg/min. in the non-pulsatile group.

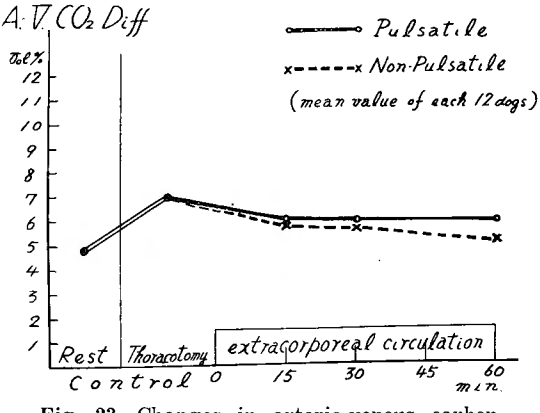


Fig. 23 Changes in arterio-venous carbon dioxide difference during perfusion.

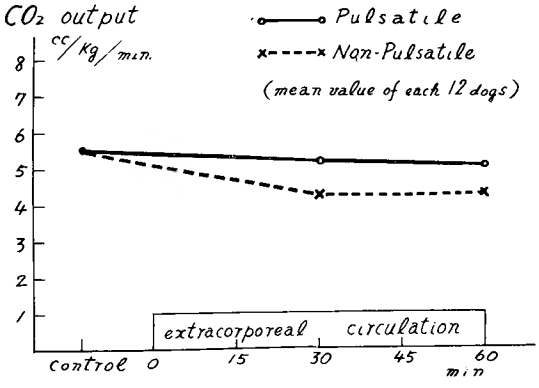


Fig. 24 Changes in carbon dioxide output during perfusion.

Table 2 (a) Changes in pH, buffer base and bicarbonate in the pulsatile group.

No.	Time (min.)	Flow (cc/kg/m.)	venous blood Ht(%)	pH	CO_2cont. (mM/L.)	HCO_3^- (mM/L.)	HCO_3^--corrected to a pHof 7.4 (mM/L.)	buffer base (mEq/L.)	P_{CO_2} (mmHg)
10	control*		30	7.42	16.2	17.7	18.2	39.4	28.0
	30	63	35	7.35	13.7	15.0	13.9	36.2	27.0
13	control		39	7.42	16.7	19.0	19.5	41.1	30.0
	30	61	38	7.31	13.4	15.0	12.7	36.0	29.4
	60	61	39	7.24	12.1	13.4	9.3	33.4	31.4
17	control		38	7.38	15.4	17.1	16.6	39.8	29.8
	30	86	42	7.22	12.8	13.9	9.8	34.4	34.9
	60	82	40	7.22	11.8	12.7	8.7	33.1	32.0
31	control		49	7.34	18.6	20.9	19.5	41.6	40.8
	30	81	37	7.30	13.4	14.8	12.6	35.7	30.0
	60	81	36	7.26	11.8	12.9	10.2	33.2	28.8
33	control		37	7.38	14.6	16.3	15.8	39.1	28.0
	30	96	35	7.33	13.1	14.2	12.5	36.0	27.1
	60	96	36	7.32	12.2	13.4	11.5	34.7	26.2
35	control		37	7.42	18.5	20.4	20.9	42.1	32.8
	30	91	26	7.37	15.9	17.0	16.4	37.4	29.7
	60	97	21	7.32	14.4	14.3	12.7	33.7	28.8
36	control		43	7.39	15.2	17.2	17.5	40.8	28.7
	30	126	32	7.30	13.8	14.7	12.7	35.4	30.6
	60	115	30	7.32	14.7	15.6	11.0	36.0	31.1
42	control		42	7.48	13.8	16.3	18.2	41.8	22.2
	30	52	44	7.20	13.1	11.2	9.8	34.1	37.8
	60	52	43	7.14	14.0	15.0	9.2	32.6	44.8
	90	50	42	7.09	13.5	14.2	7.4	31.0	48.0
44	control		38	7.42	17.8	20.0	20.5	42.7	32.0
	30	84	35	7.25	14.0	14.7	11.7	34.2	34.7
	60	84	33	7.19	12.9	13.8	9.8	32.5	36.9
47	control		40	7.35	17.7	19.3	18.1	41.7	37.0
	30	68	39	7.28	17.0	18.4	15.9	38.9	40.9
	60	68	37	7.21	17.4	18.3	14.4	37.5	47.9
49	control		43	7.37	15.3	17.4	16.7	41.0	31.0
	30	94	43	7.25	16.5	18.0	11.1	37.6	43.2
	60	91	45	7.24	16.5	18.2	11.2	38.0	44.0

Table 2 (b) Changes in pH, buffer base and bicarbonate in the non-pulsatile group.

No.	Time (min.)	Flow (cc/kg/m.)	venous blood Ht(%)	pH	CO_2cont. (mM/L.)	HCO_3^- (mM/L.)	HCO_3^- corrected to a pHof 7.4 (mM/L.)	buffer base (mEq/L.)	PCO_2 (mmHg)
15	control		38	7.39	14.7	16.1	15.9	39.9	27.6
	30	90	36	7.14	11.1	11.5	5.0	29.7	35.6
	60	85	38	7.12	10.1	10.4	3.4	27.6	33.0
16	control		35	7.37	14.5	16.0	15.2	38.3	28.0
	30	103	30	7.20	13.2	13.6	8.6	32.1	35.6
	60	101	32	7.14	12.8	13.0	6.5	30.2	39.1
18	control		48	7.30	14.9	17.0	15.1	39.9	36.4
	30	55	44	7.26	14.0	15.3	12.1	36.8	35.6
	60	59	46	7.16	14.8	15.2	9.8	34.1	45.6
25	control		44	7.37	16.2	18.7	17.9	42.0	33.0
	30	72	44	7.12	14.4	15.1	8.8	33.4	48.6
	60	43	46	7.08	13.4	14.0	6.8	30.7	48.0
29	control		40	7.37	14.3	15.9	15.2	38.5	28.2
	30	103	41	7.17	11.4	12.1	7.1	31.4	33.6
	60	103	43	7.06	9.2	9.6	2.2	26.6	34.0
32	control		39	7.48	14.4	16.5	18.6	41.3	22.8
	30	72	40	7.20	14.6	15.1	10.4	35.0	41.0
	60	70	41	7.21	14.0	14.9	10.4	34.7	38.2
38	control		35	7.33	19.7	20.1	18.7	39.1	38.2
	30	86	33	7.04	15.5	11.3	3.7	30.3	43.4
	60	95	38	7.00	14.3	10.5	3.1	28.9	43.8
39	control		36	7.48	15.6	17.6	19.6	40.3	24.5
	30	80	38	7.21	15.0	15.9	11.9	33.4	40.7
	60	80	39	7.09	14.7	15.2	8.5	31.1	49.6
	90	80	37	7.03	13.3	13.7	6.0	28.3	51.7
40	control		26	7.30	15.4	16.0	13.6	35.7	35.5
	30	95	28	7.04	11.6	11.3	4.7	26.1	41.4
	60	90	30	7.09	10.8	10.6	5.0	26.6	35.3
48	control		40	7.35	13.4	14.9	13.9	37.6	27.8
	30	93	40	7.19	14.1	15.2	10.5	33.9	40.6
	60	93	39	7.14	12.5	13.2	7.5	31.1	39.6
50	control		38	7.38	17.8	19.6	19.1	41.3	34.1
	30	58	34	7.11	14.3	14.7	8.9	31.1	47.1
	60	58	36	7.04	13.0	13.1	5.8	28.3	48.6

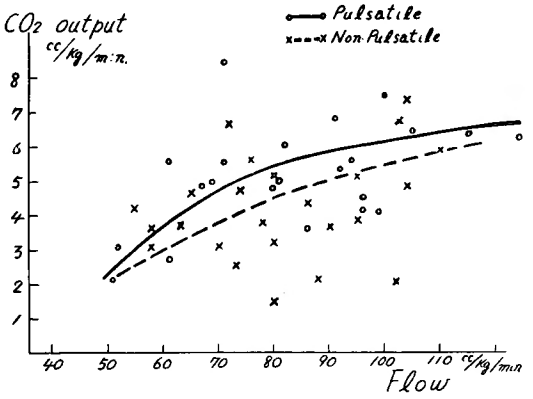


Fig. 25 Relationship between carbon dioxide output and flow rate.

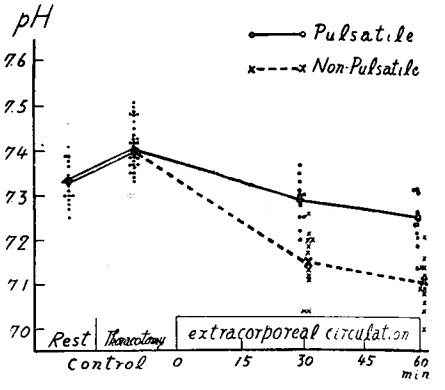


Fig. 26 The pH fell to 7.10 at 60 minutes after onset of perfusion and resulted in metabolic acidosis in the non-pulsatile group.

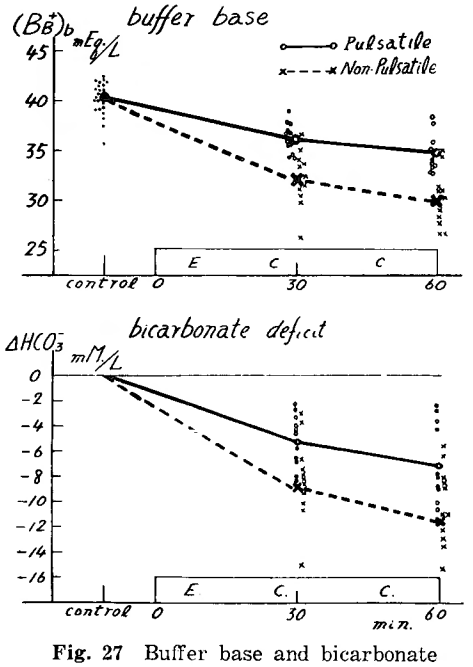


Fig. 27 Buffer base and bicarbonate markedly decreased in the non-pulsatile group.

the fall in pH noted in the non-pulsatile group might be due to the occurrence of metabolic acidosis. This metabolic acidosis became more and more pronounced with the passage of perfusion time.

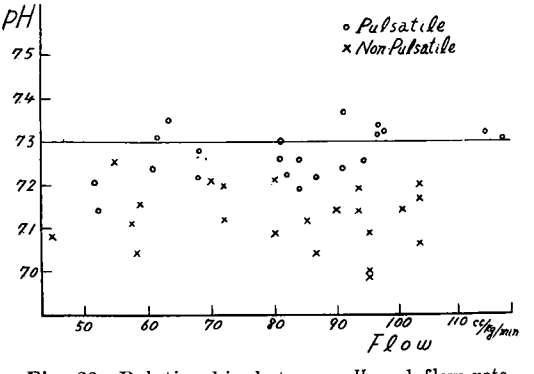


Fig. 28 Relationship between pH and flow rate. No direct correlationship was noted excepting a slight improvement of pH caused by increase of flow rate in the pulsatile group.

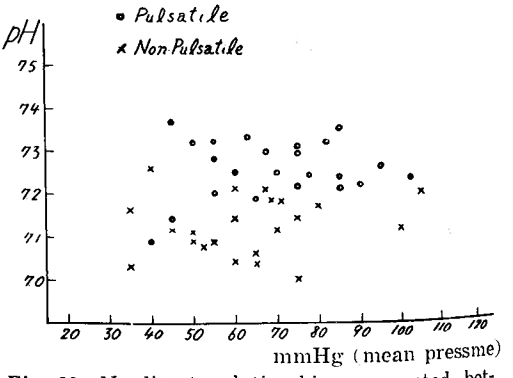


Fig. 29 No direct relationship was noted between pH and arterial pressure in both groups.

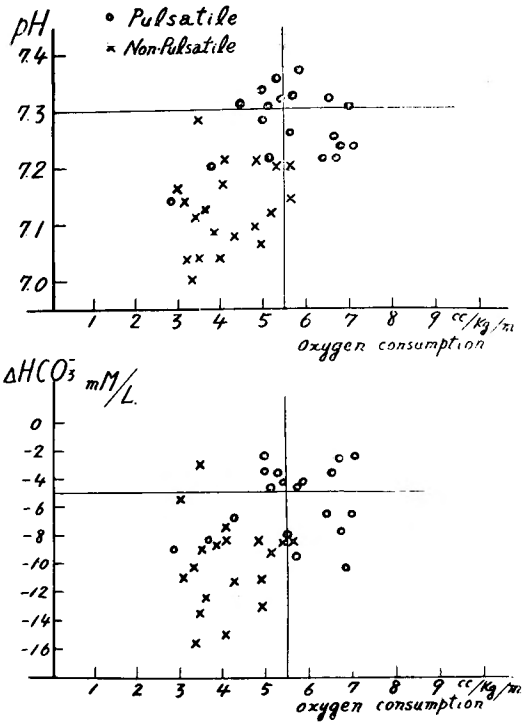


Fig. 30 There was linear relationship between oxygen consumption and pH and bicarbonate deficit in both groups.

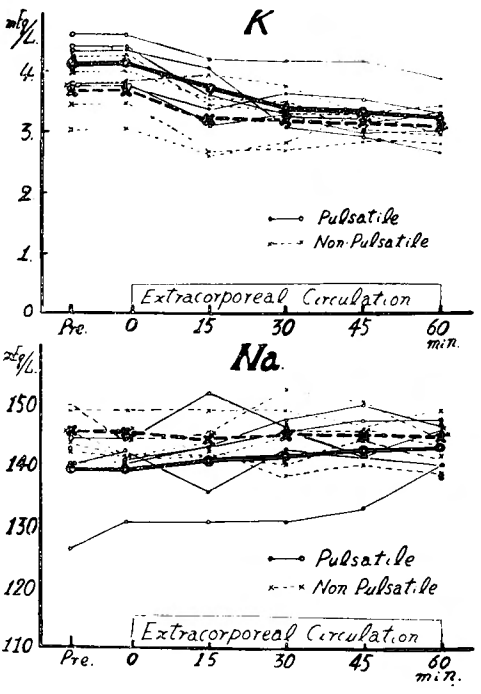


Fig. 31 Serum sodium and potassium levels between both groups.

Table 3 Serum sodium and potassium levels during total body perfusion.

Group	No.	body weight (kg)	Potassium (mEq/L.) Control	priming blood	perfusion 15 min.	30 min.	45 min.	60 min.	Sodium (mEq/L.) Control	priming blood	perfusion 15 min.	30 min.	45 min.	60 min.
Pulsatile	28	10.5	3.69	2.75	3.16	3.31	3.13	3.28	145	145	152.5	145	142.5	145
	31	9.6	4.41	4.05	4.05	3.09	2.83	2.64	126	130.5	130.5	130.5	133	140
	33	8.4	3.65	3.38	3.65	3.27	2.98	3.08	143	140	143	146	147.5	147.5
	35	8.8	4.62	3.28	4.20	4.23	4.14	3.81	140	141	143.5	147.5	150	147
	36	9.1	4.42	3.32	3.47	3.11	3.56	3.32	140	142.5	135.5	142.5	142.5	138
	average		4.16	3.36	3.71	3.40	3.33	3.23	139	140	141	142	143	143.5
Non-Pulsatile	29	7.8	4.18	3.36	3.44	3.36	3.36	3.42	150	140	145	152.5	150	145
	32	11.8	3.47	3.24	2.64	2.69	2.80	2.77	149	149	149	149	145	149
	37	10.3	3.70	3.28	3.96	3.75	3.20	3.05	142.5	145	145	138	140	138
	39	10.0	4.00	3.38	3.53	3.45	3.01	3.01	146	144	142	140	146	146
	40	7.7	3.01	2.50	2.60	2.81	3.25	3.01	144	140	140	146	146	142
	average		3.67	3.15	3.23	3.21	3.12	3.05	143	143.5	144	145	145.5	144

As to the relationship between pH, flow rate (Fig. 28) and arterial pressure (Fig. 29), any direct correlationship was noted neither between pH and flow rate, nor between pH and arterial pressure excepting a slight improvement of pH caused by increase in flow rate in the pulsatile group. There was, however, a linear relationship between oxygen consumption and pH or bicarbonate deficit (Fig. 30) in the two groups.

(7) Electrolytes (sodium and potassium)

In the two groups serum sodium level remained nearly constant during extracorporeal circulation, while serum potassium slightly decreased (Fig. 31, Table 3).

DISCUSSION

Relatively few studies had been reported on the role of pulsatile blood flow in the arterial system of the organism. GOODYER and GLENN[19] demonstrated that excretion of water and electrolytes, and clearance of inulin and para-aminohippurate were unchangeable when arterial pulsation in the renal circulation was almost eliminated without change in the mean arterial pressure. SELKURT[47] and RITTER[40] also observed that reduced amplitude pulsatile flow with normal mean pressure had no influence on renal functions and concluded that pulsation had no obvious role in renal hemodynamics. Further, RANDALL[41] examined pulsatile and steady pressure-flow relations in the vascular bed of the hind leg of the dog and demonstrated no difference between pulsatile and non-pulsatile flow relations. GIBBON[52] concluded that a pulsatile flow was not necessary for extracorporeal circulation for a period of at least 46 minutes on the bases of his own experiments and also on the fact that functions of the abdominal vital organs was within normal range in the patients with coarctation of the aorta. KANTROWITZ[24] reported that essentially non-pulsatile flow was adequate for short period of time of total body perfusion. JONGBLOED[23] pointed out, however, that a pulsatile flow had an important role for the adequate perfusions of organs. DODRILL,[13] Peirce[40] and SOUTHWORTH[40] also stated that pulsating delivery was desirable to maintain vascular tone.

WESOLOWSKI[58] also demonstrated in 1952 that the pulse had a definite physiologic role in the maintenance of peripheral vasomotor tone and, therefore, of arterial pressure. However, he and his associates[59][60] concluded in 1955 that arterial pressure and peripheral vascular resistance were stable during the non-pulsatile perfusion for a period of three hours, and that the pulse was essentially not necessary to maintain peripheral vascular tone during by-pass.

At present KIRKLIN[27] pointed out that the better perfusion might possibly be obtained by the use of a pulsatile flow, while SENNING[1][49] and SWAN[1] noted that a pulsatile flow would be desirable for adequate perfusion of organs. Under such circumstances the indispensability of pulsatile flow has recently been gradually recognized.

Results of the present investigation showed that with the same flow rate the pulsatile flow could maintain the arterial pressure more effectively, and frequent episodes of hypotension were encountered in the non-pulsatile group. DONALD[16] pointed

out that even the use of a flow rate nearly as cardiac output was unable to maintain the arterial pressure at a normal level. CLOWES[6] also reported the hypotension which resembled to normovolemic shock, and MENDELSOHN[32] thought that this hypotension might be due to the peripheral vasodilatation.

Concerning the peripheral vascular resistance, READ,[42] DONALD[33] and others stated that during extracorporeal circulation peripheral vascular resistance was higher than that of normal, and DIETTERT[12] also pointed out that this might be resulted from peripheral vasoconstriction during perfusion. In the present investigations, a rise of peripheral resistance and, therefore, peripheral vasoconstriction occurred immediately after onset of perfusion in both groups, but in the course of time the arterial pressure and peripheral resistance began to fall in the non-pulsatile group, and 20-30 minutes later marked peripheral vasodilatation seemed to occur.

As to the relation between changes in hemodynamics and flow rate; it was ascertained that in the pulsatile group peripheral resistance increased with the decrease in flow rate, and the vasoconstriction might occur to prevent from lowering of arterial pressure. However, a linear relationship noted in the non-pulsatile group was quite similar to that observed in the denervated individual.

The venous pressure did not differ markedly in both groups, but when total body perfusion in the non-pulsatile group was continued over 30 minutes, there was a decrease in venous return, though no change was observed in the venous pressure. Probably, this should be resulted from pooling due to peripheral vasodilatation. The development of blood pooling, however, may be followed by a rise in venous pressure, which in turn leads to dilatation of peripheral blood vessels at which point vicious circle ensues as READ[43] pointed out, and causes decrease in peripheral resistance and hypotension. KIREY and GIANELLI[25] also noted that there occurred changes in vascular resistance and venous return when extracorporeal circulation was prolonged over 30 minutes, although neither hemorrhage nor changes in the venous pressure had been demonstrated.

The increase in body weight noted in the non-pulsatile group might be the result of blood pooling. According to MCMASTER[31] and PARSON,[39] non-pulsatile flow prompted the formation of edema. As being mentioned later, non-pulsatile flow also caused tissue hypoxia, and HENDLEY[22] stated that hypoxia prompted the tendence of edema formation, decreased vascular resistance and increased permeability of capillary. Therefore, it may well be considered that the changes not only in vascular tone and in hydrostatic pressure of capillary, but also in permeability have contributed to the development of blood pooling in the non-pulsatile group.

The extravascular leakage of blood elements resulted from increased permeability may explain the difference in venous hematocrit values between both groups. It was generally noted that hematocrit values usually showed mild increase during extracorporeal circulation.

KIRKLIN,[26] DONALD,[33] DIETTERT[12] and many others asserted that the venous oxygen saturation indicated the state of oxygen uptake at the tissues and lowering of the venous oxygen content reflected the tissue hypoxia. In the opinion of the

present author, however, oxygen consumption could really reveal the degree of hypoxia and the venous oxygen content or saturation could not always reflect the degree of oxygen utilization. TAKEDA[35)36)] noted, in vital microscopic study of the peripheral vascular bed, that in the non-pulsatile group the blood flow gradually slowed down in the true capillaries 10 to 15 minutes after onset of perfusion and finally came almost to stasis. Such an impairment of the blood flow in the true capillaries should lead to hypoxia in peripheral tissues, and then to accumulation of waste substance, causing lowering of vasomotor tone with dilatation of arterioles and complete hemostasis in the true capillaries. SWAN[1)] and DONALD[33)] also reported that the reduction of oxygen consumption might be the result of insufficient supply of blood to the tissue.

Hypoxia reduces pH value and causes metabolic acidosis. CRAFOORD,[1)8)] ANDERSEN[2)] and SENNING,[49)] KIRKLIN,[26)] DEWALL[10)] and LILLEHEI,[37)] GIBBON,[18)] DENNIS,[53)] MENDELSOHN[32)] and LITWIN[1)28)] reported that hypoxia would probably lead to disturbance of cellular metabolism in the peripheral tissue, and then to the accumulation of lactate by anerobic glycolytic process producing metabolic acidosis. The marked metabolic acidosis noted in the non-pulsatile group was clearly a result of hypoxia. The fact that no improvement of pH and buffer base were obtained by the increasing flow rate in the non-pulsatile group seems to be connected with the fact that in the non-pulsatile group the oxygen consumption does not reach normal level even when the flow rate of over 100 cc/kg/min. is employed.

Table 4 Priming blood used in present investigation. A slight lowering of pH and oxygen content was noted.

No.	room temper. (°C)	Ht(%)	oxygen content (Vol %)	oxygen saturat. (%)	CO_2 content (mM/L.)	pH	buffer base (mEq/L.)	Pco_2 (mmHg)
13	17.5	38	18.8	96.2	11.9	7.26	32.4	28.5
15	16.5	23	16.0	96.3	14.0	7.30	33.7	30.0
16	17.5	28	12.2	97.5	11.5	7.28	31.8	26.0
17	20.0	38	13.3	96.8	10.2	7.17	30.2	29.9
18	21.5	40	16.9	98.7	14.1	7.29	36.2	33.0
25	24.0	40	15.5	100.0	12.7	7.36	37.6	25.8
29	29.0	38	14.5	93.7	12.4	7.24	34.4	31.3
31	26.0	38	14.7	97.4	13.6	7.28	35.6	31.8
32	28.0	38	15.6	95.8	12.9	7.27	35.4	30.9
33	29.0	30	15.3	98.1	11.8	7.37	34.9	21.6
39	20.0	38	14.8	98.7	12.9	7.26	34.0	31.4
41	18.0	30	13.9	97.9	13.4	7.30	34.3	29.5
42	20.0	37	14.6	97.3	12.1	7.38	36.8	23.4
43	18.0	30	13.2	96.1	12.2	7.29	31.5	26.0
46	20.0	36	13.7	97.9	13.9	7.35	36.8	27.8
48	19.0	37	14.1	99.1	14.6	7.37	38.4	27.4
49	20.0	39	14.4	98.2	14.8	7.34	38.3	30.6
50	23.0	33	12.5	97.8	12.0	7.25	33.4	30.0
av.		35	14.7	97.4	12.8	7.30	34.8	28.6

As regard to the occurrence of metabolic acidosis during extracorporeal circulation, the changes in priming blood, as LILLEHEI,[56] MENDELSOHN,[32] DIETTERT,[12] BEER[3] and ZENKER[61] pointed out, should be taken into consideration besides hypoxia. The priming blood was left usually at room temperature for a certain length of time untill the total by-pass was settled, and some kind of changes might happen, such as a slight lowering of pH and oxygen content (Table 4).

Respiratory alkalosis due to hyperventilation should also be taken into consideration as one of the cause of acidosis. According to the recent studies, LITWIN,[28] MAGOVERN,[29] PAPADOPOULOS[38] and others reported that hyperventilation might probably stimulate the production of lactic acid, and thus exert an accelerating influence upon the development of metabolic acidosis. The arterial carbon dioxide tension measured before the commencement of extracorporeal circulation was noted less than 30 mm. Hg. in this experiment.

SUMMARY

In the pulsatile group the arterial pressure is maintained above 80mm. Hg. with a flow rate of 80 cc/kg/min., and oxygen consumption and pH, too, are kept nearly within normal limits, while in the non-pulsatile group the animal can not be maintained in a good condition even with high flow of 110 cc/kg/min. The pulsatile flow may be indispensable not only for a prolonged perfusion, but also for a short-term extracorporeal circulation in order to establish a better prognosis.

Moreover, in the present investigation the arterial cannula of 3mm. in caliber was inserted through the left carotid artery of the dog, but more effective pulsatile flow should be obtained by inserting larger cannula directly into the aorta.

CONCLUSION

The effectiveness of a pulsatile and non-pulsatile blood flow in extracorporeal circulation was experimentally studied and the following results were obtained.

(1) In each group either pulsatile or non-pulsatile flow was used for a period of sixty to ninety minutes of total body perfusion ;

(a) Arterial pressure was easily maintained in the pulsatile group, and was kept about 15mm. Hg. higher on the average than that of the non-pulsatile group under the same flow rate. Consequently, if the arterial pressure of over 80mm. Hg. was desired, the pulsatile group needed a flow rate of 70 cc/kg/min., while a flow rate as much as 90 cc/kg/min. was necessary in the non-pulsatile group.

(b) Peripheral resistance also, just as in the case of the arterial pressure, began to decrease from 20 minutes later after the commencement of extracorporeal circulation, and gradually fell in the course of perfusion in the non-pulsatile group.

(c) Central venous pressure did not differ markedly in both groups, but from the results of changes in body weight and venous hematocrit value, the blood pooling seemed to occur during perfusion in the non-pulsatile group.

(d) In the pulsatile group oxygen consumption showed almost normal level throughout total by-pass, while in the non-pulsatile group it fell gradually in the

course of perfusion.

(e) In the non-pulsatile group pH fell to 7.10 at 60 minutes after onset of perfusion, and marked metabolic acidosis was noted. In both groups, any direct correlationship was noted neither between pH and flow rate nor between pH and arterial pressure, but a linear relationship was observed between pH and oxygen consumption.

(2) From the above mentioned results, it would be safely concluded that the perfusion with pulsatile flow should be safer procedure when the blood flow is below 100 cc/kg/min. as commonly adopted at present, and particulary when the extracorporeal circulation is continued over 30 minutes.

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和 文 抄 録

人工心肺装置及び体外循環の実験的研究，特に生体に及ぼす脈動の有無の影響について

京都大学医学部外科学教室第2講座（指導：青柳安誠教授）
野々山　明

人工心肺装置を用いて体外循環を行う際には，生体の血流は動脈ポンプによつて支配される．而も現在広く臨床に応用されている Metalfinger 型或いは De Bakey 型の動脈ポンプでは，生体に送られた血液はほとんど脈動を持たない所謂定常流に近い流れになつている．ところで，かかる非生理的な血流で生体を灌流しても悪影響がないであろうかという疑問は，人工心肺装置を取扱う者が誰しも当初から抱いたことであつたが，Wesolowski が肺循環，大循環に於ける脈動の役割を実験的に検討して，その結果無脈動流で長時間灌流してもほとんど支障のないことを確かめて以来，この問題は一応解決されたかのように思われた．しかし最近，体外循環が長時間に及ぶ場合には比較的大流量を用いても，動脈圧の低下，代謝性アチドージスの発生等種々の不愉快な現象の発生することが注目されるようになり，而も，その原因については充分解明されていない状態である．併し，われわれは，かかる現象のおこる原因の一つとして，体外循環に切り換えた際の脈動の減少乃至消失という非生理的な血流状態が大きい役割を演じているのではないかと考えた．そこで，この脈動流及び無脈動流の問題を解明するために，さきに Wesolowski が術後生存率を主な判定基準とした報告とは別に，主として体外循環中の病態生理を追求した．即ち，体重7～12kgの成熟雑犬を用い，京大工学部神元教授の御指導によつて作製した独自の脈動式動脈ポンプを使用し，脈動数70～80の脈動流を流した群と，air chamber を応用した Depulsator でほゞ完全に脈動式ポンプの脈動を消失して定常流を流した群の2群について，夫々流量50～120cc/kg/min. で1乃至1時間半の完全体外循環を行つて，次の結果をえた．

(1) 脈動流では動脈圧の維持が容易であり，同一流量の無脈動流群との間に約15mm Hgの差を認めた．従つて，80mmHg の動脈圧を維持する為には，脈動流ならば 70cc/kg/min. の流量で充分であるが，無脈動流では 90cc/kg/min. の流量を必要とした．

(2) 末梢血管抵抗も動脈圧の場合と同様に，無脈動流群では，体外循環開始後20分頃から減少し始め，その後，時間の経過と共に低下するのを認めた．また，脈動流では低流量になるにつれて末梢血管抵抗は増加し，出来るだけ動脈圧を維持しようと働いているのに反して，無脈動流群では，末梢血管抵抗と流量とは直線関係を示し，流量が少なくなれば末梢血管抵抗もそれだけ減少した．

(3) 中心静脈圧は両群の間に著明な差を認めなかつたが，無脈動流群では，体外循環時間の経過と共に体重は増加し，ヘマトクリツト値は次第に上昇する傾向にあり，この結果から，無脈動流群では体外循環中に pooling がおこつていることが推測された．

(4) 酸素消費量は，脈動流群では体外循環中ほぼ一定で正常の 6 cc/kg/min. に近い値であつたのに対し，無脈動流群では体外循環時間の経過と共に次第に減少

して，体外循環60分では平均 4 cc/kg/min. に低下していた．酸素消費量と流量との関係をみても，両群の間には約1.5cc/kg/min. の著明な差が存在し，脈動流群では流量 75cc/kg/min. で既に正常値に達するのに反して，無脈動流群では 100cc/kg/min. を越える大流量の場合でもなお正常値に及ばなかつた．無脈動流群では，動・静脈血酸素較差が少なく，従つて，静脈血酸素飽和度も高い値であつたが，酸素消費量は低下し，hypoxiaの存在が認められた．

(5) 脈動流群では，pHは僅かに低下し，buffer base, bicarbonateは共に軽度の変動を生ずるのみであつたが，無脈動流群では体外循環60分で pH は 7.10 に低下し，bicarbonate deficitも－12mM/L. となり，著明な代謝性アチドージスが認められた，両群共にpHは動脈圧，流量との間に直接の相関関係はなかつたが，pH及び bicarbonate deficit と酸素消費量との間には直線関係が認められ，無脈動流群にみられた顕著な代謝性アチドージスは hypoxia の結果による酸素欠乏性アチドージスであることが明らかにされた．

(6) 以上の結果から，体外循環とくに30分以上に及ぶ長時間の灌流には脈動流を保有することが必要である．