The Effects of Nonpulsatile Perfusion on the Renal Energy Metabolism

NOBUYOSHI DAITOH

The 2nd Department of Surgery, Faculty of Medicine,Kyoto University
(Director : Prof. Dr. YORINORI HIKASA)

Introduction

This study was designed to compare the physiologic effects of pulsatile and nonpulsatile perfusion on organs. The importance of delivering pulsatile flow rather than nonpulsatile flow during extracorporeal perfusion has not been completely established. Daily use of the nonpulsatile roller pump for open heart surgery has demonstrated that, for short periods at least, nonpulsatile perfusion is sufficient to maintain biological needs. In spite of the adequate flow rates and the mean arterial pressures during nonpulsatile perfusion, however, profound disturbances in physiologic function are seen which severely limit the length of time for safe perfusion.

The physiologic consequences of nonpulsatile blood flow have interested many investigators who concluded that nonpulsatile flow increases systemic vascular resistance, alters the distribution of blood flow, affects blood flow in the microcirculation, decreases oxygen consumption and cellular metabolism, reduces lymph flow, decreases renal function, and reduces the safe duration of cardiopulmonary bypass. Other investigators have challenged neary all of these conclusions; thus, the role of the pulse pressure in circulatory homeostasis remains unsettled. Few data describe the special effects of pulsatile flow on the metabolism of any organ.

In the present study, energy charge was employed as the primary indicator for comparing the effects of pulsatile and nonpulsatile blood flow on energy metabolism in the canine kidney. The "energy charge" of the adenylate system, defined as $(ATP + 1/2ADP)/(ATP + ADP + AMP)$, was proposed as a fundamental metabolic control parameter by D. E. ATKINSON in 1967.

The reasons why the kidney was chosen as the objective organ were ;
1) it is possible to compare the difference when one kidney is perfused with pulsatile flow and the other is perfused with nonpulsatile flow, 2) it seems to be a critical organ which is most sensitive under abnormal conditions of hemodynamics such as shock, 3) clinicaly,
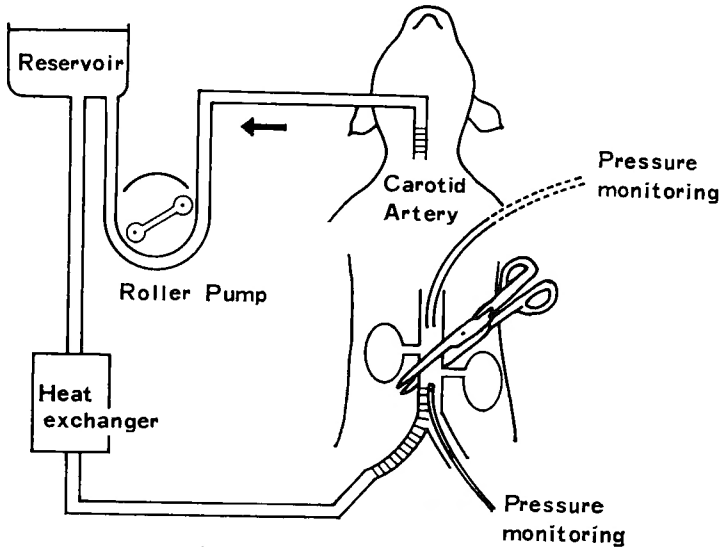
Fig. 1

acute renal insufficiency is one of the most serious complications in open heart surgery, 4) evaluation of the function in the kidney in experiments using animals is rather easy in contrast with the other important organs such as the brain or the liver.

Methods

Experimental preparation

Twenty seven mongrel dogs weighing from 15 to 30 kilograms were anesthetized wtih intravenous pentobarbital sodium (25 mg per kilogram), intubated, and ventilated on room air with a Harvard respirator.

In preveous studies on nonpulsatile perfusion of the kindly by some investigators, it was often pointed out that clamping of the renal artery which was necessary for insertion of the arterial cannula to get nonpulsatile flow might cause some changes in renal function. Unilateral depulsation without transient ischemia was attained through the following experimental preparations in the present study. It is possible to interrupt the abdominal aorta by clamping it between the ostia of the renal arteries because, in dogs, the two ostia are generally found to be 1 to 2 cm apart, cephalad in the right and caudad in left renal artery. (In only one case among the 27 dogs studied, was the left ostium located cephalad.)

Pulsatile blood flow from the beating of the dog's own heart (pulse pressure 40 to 50 mmHg) was run into the right kidney as a control. On the other hand, the arterial blood flow via the carotid cannula was led into a reservoir 1.8 m above by a roller pump and a completely pulseless flow was delivered via a heat exchanger into the femoral artery, and to the left kidney.

The blood pressure was continuously monitored by strain gauge transducers via two catheters inserted, one through the left subclavian artery and the other through the

femoral artery so that its tip lay in the abdominal aorta near the ostium of the renal artery, respectively. The reservoir and the circuit for depulsation was primed with the fresh blood drawn from a donor dog. The abdominal aorta was interrupted after starting the extra-corporeal circulation. The desired blood pressure level was obtained by controling the blood volume in the reservoir and afterwards the pressure of the bilateral renal arteries was carefully maintained at a set level under the control of the roller pump and the screw clamp.

Procedure 1.

This study was divided into two groups: Group 1-A with a normal mean pressure at 100 to 120 mmHg and Group 1-B with a low mean pressure at 60 to 70 mmHg.

After a given period of the experimental perfusion with pulsatile flow to the right kidney and nonpulsatile to the left, the lower poles of the both kidneys were clamped with stainless tongs precooled in liquid nitrogen and the specimens were immersed in it for the assay of adenine nucleotides. Every experiment was terminated at the point of this sampling because of the damage to the kidneys.

Procedure 2.

After 2 hours of the perfusion as described above, the cross-clamp on the abdominal aorta was released and the extracorporeal circulation was discontinued. Afterwards both kidneys were supplied with the same pulsatile flow.

In the normal pressure group (Group 2-A), the mean arterial pressure was maintained spontaneously at approximately the same level as before and after declamping. In the low pressure group (Group 2-B), the blood of the reservoir was rapidly transfused just prior to declamping untill it showed a recovery of the pressure level to 100 to 120 mmHg similar to the procedure of weaning from the heart-lung bypass in clinical open heart surgery.

After 30 minutes of declamping, sampling from both kidneys was made with the method described in Procedure 1.

Biochemical assay of adenine nucleotides[5]

The frozen renal tissues were powdered with a motor and pestle in a liquid nitrogen bath. The powdered tissue was weighed and homogenized in 3 volumes of cold 5% of perchloric acid at 0°C. The extract was centrifuged at 10,000 r.p.m. for 15 minutes at 0°C. The supernatant was adjusted to PH 6.0 with cold 60% K_2CO_3 and recentrifuged at 10,000 r.p.m. for 5 minutes. The amounts of ATP, ADP and AMP were spectrophotometrically determined at a wavelength of 340 nm and the energy charge was calculated from the formula $(ATP + 1/2ADP)/(ATP + ADP + AMP)$.

Urine was collected via the same-sized catheters inserted into the bilateral ureters and checked every half hour. Renal blood flow was monitored in 6 dogs which weighed over 20 kg in Procedure 1. by the electromagnetic flow probes around the renal arteries (Statham SP1400). Lactated Ringer solution was infused intravenously and the central venous pressure

was maintained at 4 to 6 cmH$_2$O during the experiment. Blood PH was kept between 7.35 and 7.45 using sodium bicarbonate as needed and hematocrit values above 30% were maintained by blood transfusion. Blood gases were determined with a Corning 165 gas analyzer. No drugs were used except Heparin sodium (3mg/kg) and sodium bicarbonate.

Results

Table 1 and 2, and Figure 2-6 summarize the mean values and standard deviations of the energy charge, total adenine nucleotide concentrations, urine volume, creatinine clearance and renal blood flow. Statistical analysis, for significant differences between the pulsatile and nonpulsatile perfusion, was performed by means of the paired-sample Student t-test. Significant differences with a value of P=0.05 are noted by (*), and P=0.01 by (**).

Energy charge
Procedure 1.

In every paired sample of both the normal pressure Group 1-A and the low pressure Group 1-B, the energy charge of the kidney perfused with pulsatile flow was higher than that on the other side in any instance. These findings were so even in a small number of the experimental cases in which the urine output was less in the pulsatile perfusion. The

Table 1.   Changes in Energy Charge of the bilateral kidneys following pulsatile and nonpulsatile perfusion

	normal control	0.891±0.006	

Procedure 1.
Group 1 – A (mean Pressure 100-120 mm Hg)

	1 hr	2 hr	3 hr	4 hr
Pulsatile	0.880±0.011	0.864±0.011	0.852±0.010	0.842±0.010
nonpulsatile	0.833±0.008	0.823±0.016	0.806±0.009	0.805±0.009
paired-sample t-test		(*)	(**)	(**)

Group 1 – B (mean Pressure 60 – 70 mm Hg)

	1 hr	2 hr	3 hr
Pulsatile	0.851±0.012	0.823±0.012	0.774±0.026
nonpulsatile	0.807±0.016	0.754±0.015	0.652±0.024
Paired-sample t-test	(**)	(**)	

Results shown are mean values ± SD （n=3）
Significant differences with a value of P=0.05 are
noteel by (*), and P=0.01 by (**)

Table 2. Changes in total Adenine Nucleotides

control　　1.90±0.11 μmole/g

Procedure 1.

Group 1-A (pressure 100-120 mmHg)

	1 hr.	2 hr.	3 hr.	4 hr.
Pulsatile	1.68±0.35	1.61±0.31	1.56±0.30	1.46±0.42
nonpulsatile	1.37±0.33	1.31±0.29	1.25±0.44	1.00±0.39

Group 1-B (pressure 60-70 mmHg)

	1 hr.	2 hr.	3 hr.
Pulsatile	1.48±0.31	1.29±0.38	0.86±0.37
nonpulsatile	1.33±0.36	1.18±0.41	0.87±0.43

Procedure 2.

Group 2-A (pressure 100-120 mmHg)

Pulsatile → pulsatile	1.58±0.34
nonpulsatile → pulsatile	1.28±0.31

Group 2-B (pressure 60-70 mmHg → 100-120 mmHg)

Pulsatile → pulsatile	1.28±0.40
nonpulsatile → pulsatile	1.19±0.37

Results show are mean value ± S.D. , n=3

Paired-sample t-test : non significant

mean energy charge values for Group 1-A remained above 0.80 over 4 hours of perfusion in either type of blood flow. Statistical differences became significant as the perfusion time increased ; 2 hours $P<0.05$, 3 and 4 hours $P<0.01$. In the low pressure Group 1-B, on the contrary, the first 2 hours perfusion made significant differences for the value of energy charge ($P<0.01$), while it was not significant after 3 hours of perfusion, that is, both of the kidneys subsided in poor state.

Procedure 2.

Thirty minutes natural pulsation after 2 hours of depulsated perfusion showed that recovery of the energy charge in the normal pressure Group 2-A was complete, while in Group 2-B it remained depressed in spite of restoration of the arterial pressure by blood transfusion ($P<0.05$).

Total adenine nucleotide concentration

Procedure 1.

The tendency similar to the changes in the energy change was observed. The total adenine nucleotides decreased as the perfusion time went by and the mean values in the kidney with the pulsatile perfusion were greater than in the others, but were statistically not significant.
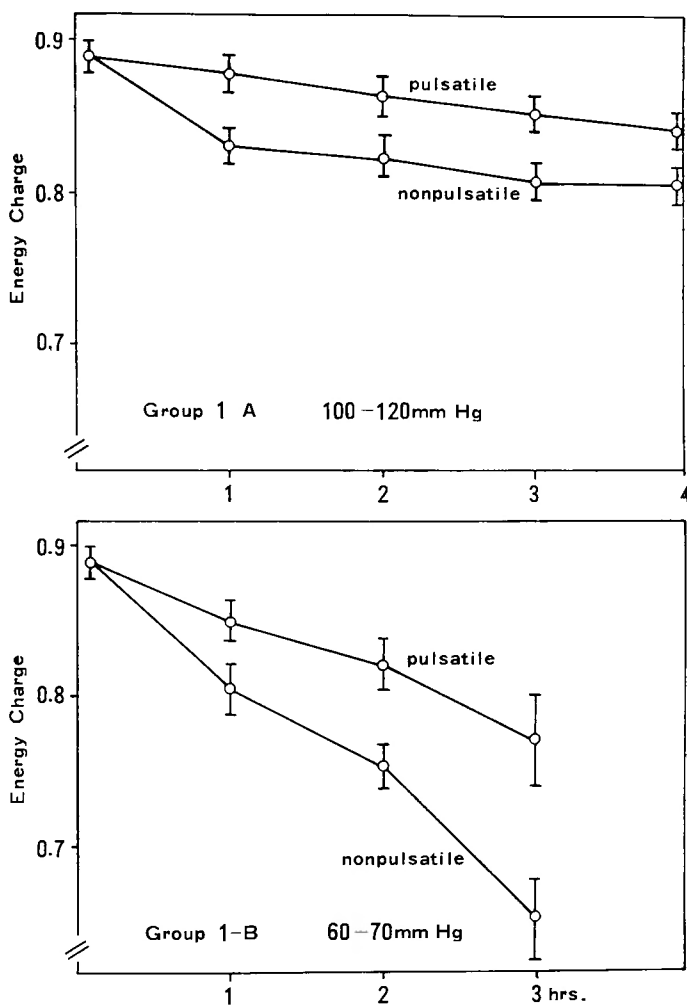
Fig. 2 Effect of pulsatile and nonpulsatile flow(n=3)

Procedure 2.

The adenine nucleotide concentrations in the nonpulsatile perfusion of Group 2-A did not recover at the point of 30 minutes after declamping to the level of pulsatile perfusion. In the Group 2-B the values remained low in both kidneys.

Urine volume
Procedure 1.

Although the mean values of the hourly urine volume for the pulsatile group were greater than the other group, in neither instance were the differences between the two groups statistically significant. In a small number of instances, moreover, the urine output was less in the pulsatile group. It was the arterial pressure level that exerted greater influence
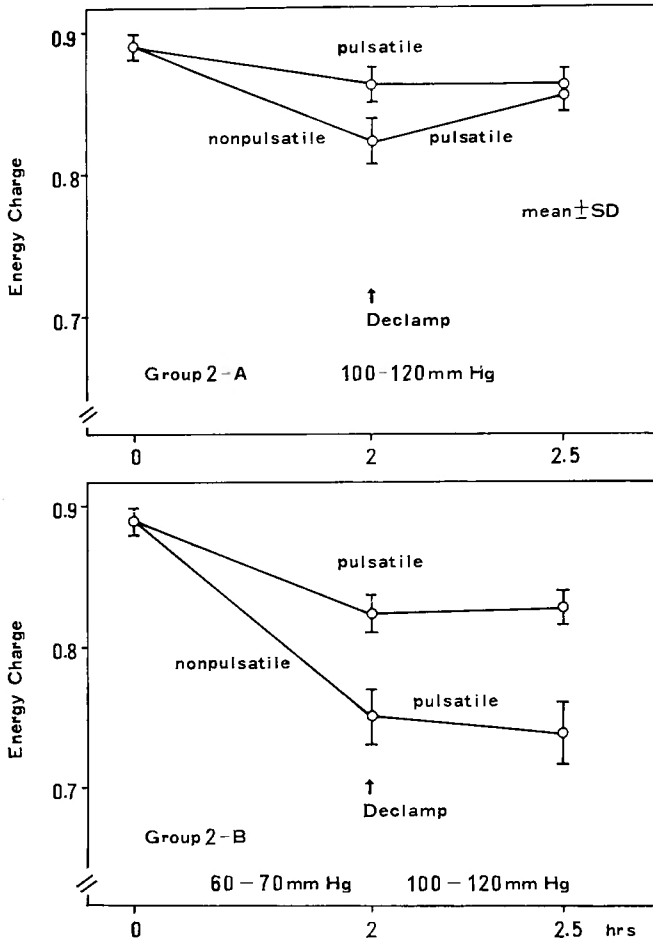
Fig. 3 Changes from Nonpulsatile to Pulsatile flow (n=3)

upon the urine volume rather than the presence of pulsation.

Endogeneous creatinine clearance

Data were obtained only from the experiments of Group 2-A. No significant differnce was found in any instance in these experiments, although, the mean creatinine clearance values dropped during depulsation.

Renal blood flow

The data of renal blood flow were expressed as percent changes compared with that of the starting point of the perfusion, shown as Fig. 6. It was rather difficult to measure the blood flow of the small-siged vessel such as the renal artery of the experimental animal during long period without impairment of blood supply, and the measurement of the blood flow was performed for 2 hours.
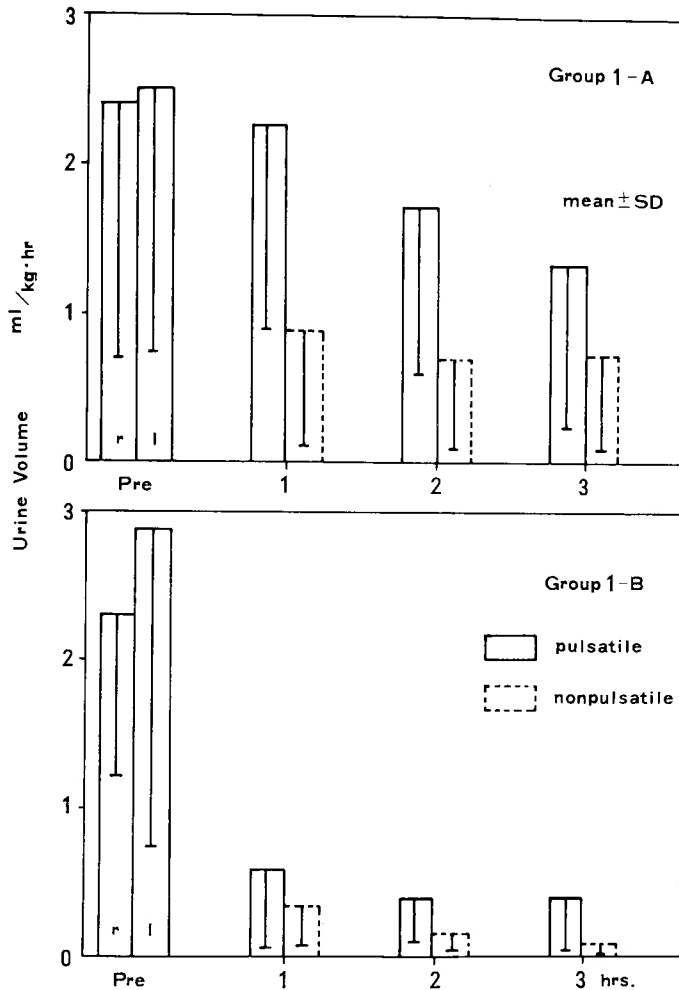
Fig. 4 Changes in Urine Volume (n=5)

Discussion

1. Experimental preparation

Many previous studies have demonstrated the possible profound physiologic disturbances which accompany nonpulsatile extracorporeal circulation in open heart surgery. The suggestions that pulsatile flow might be advantageous have been disregarded for two reasons in daily use. First, the conventional roller pump has an inherent safety and simplicity hard to duplicate with any of the other pumping mechanisms. Unfortunately available pulsatile pumps were not satisfactory for clinical use because of excessive hemolysis, low output capacity, the hazard of air or hydraulic fluid embolus, or mechanical complexity and unreliability. Second, early investigators of extracorporeal perfusion dismissed the importance
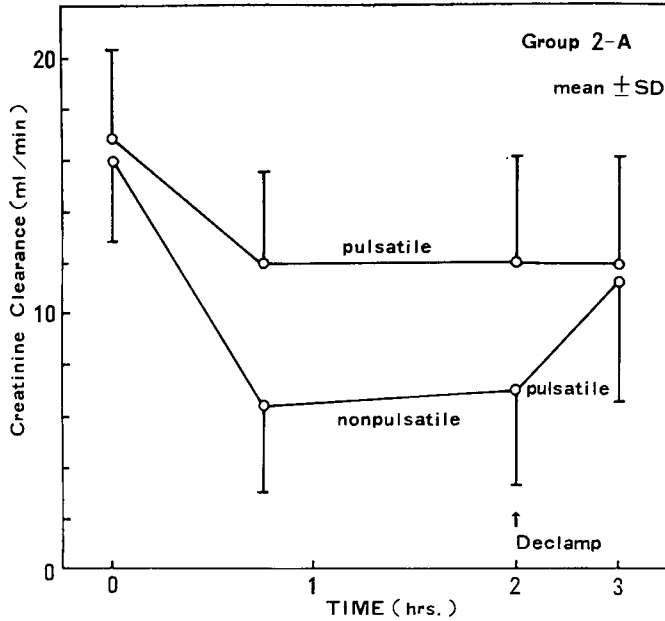
Fig. 5　Renal　function　in　Group 2 -A　（n=3）

of the pulsatile nature of normal blood flow. This dismissal was based mainly on the results of perfusion conducted by WESOLOWSKI[41] and on the work of GOODYER and GLENN[15] who used a depulsing mechanism to deliver the nonpulsatile flow to the kidney for periods of 20 to 30 minutes. During this time, they were unable to demonstrate a variation in urine output, glomerular filtration rate, or renal plasma flow. It is believed that these periods are too short to be applied to the present practical problems.

A renewed interest in the physiologic effects of pulsatile and nonpulsatile flow has been stimulated by the desire to support the circulation for prolonged periods with extracorporeal devices in cases of assisted circulation, transplantation of an artificial heart and conservation of isolated organs for transplantation.

The experimental model in the present studies has several characteristics. First, this model allows the study of the effect of nonpulsatile flow on one kidney while the contralateral normal kidney serves as a control. Almost all of the preveous works were performed in the manner of alternate sequence with pulsatile and nonplsatile flow or in different individuals. For this reason, the statistical analysis was done by the paired-sample t-test in the present study. Second, the unilateral depulsation was obtained without transient ischemia by cannulation or anastomosis. This procedure is important for the assay of tissue or cellular metabolism. Third, the carotid sinus and the aortic arch were naturally pulsated during the entire time of the perfusion. Absence of pulsation to the barocepters permits the sympatheticotonic state which affects peripheral vascular resistance[11][24][31].
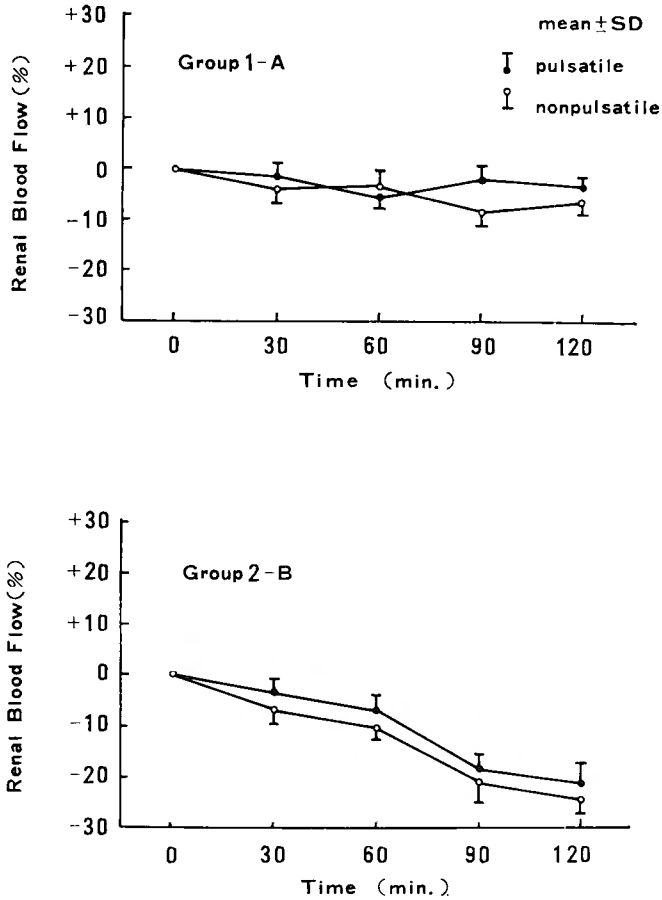
Fig. 6 Changes in Renal Blood Flow.

2. Energy charge

Few data describe the effect of pulse pressure on the cellular metabolism. The increased level of serum lactic acid and lowered PH value are the prominent findings in the nonpulsatile perfusion of the whole body as described by TRINKLE[10], JACOBS[21], and GERMAN[13], and in the isolated kidney of the dog as reported by PAQUET[35]. In the experiment during a 2 hour coronary perfusion with ventricular fibrillation, greater lactate extraction was shown in the pulsatile flow[16]. SHEPARD and KIRKLIN[12], however, have reported less obvious difference between the two types of perfusion.

Oxygen consumption is another indicator that describes cellular metabolism. Although HALLEY[17] and SHEPARD[38] demonstrated quantatively greater oxygen uptake in the pulsatile whole body perfusion, several investigators denied the significant difference between the two groups[6][16][18].

What is the essential indicator for disclosing more subtle changes in the metabolic state of organs or tissues ?

It has been suggested that the concentrations of ATP, ADP and AMP change in shock or circulatory failure[4][12] and that the total adenine nucleotide concentrations fall remarkably in the irreversible cellular derangements that are ultimately lethal to the vital organs[36]. The adenine nucleotides are not only substrates and products of energy couples, but play an important role as regulatory effectors.

In view of the many metabolic reactions in which ATP, ADP and AMP participate as modulators, D. E. ATKINSON has pointed out that the energy status of the cell may be expressed by what he calls the Energy Charge of the cell, i. e. the extent to which the ATP-ADP-AMP system is "filled" with high-energy phosphate groups. If all the adenine nucleotide in the cell is ATP, the adenylate system is completely filled and is considered to have an energy charge of 1.0. At the other extreme, if all the adenine nucleotide is present as AMP, the system is empty of high-energy phosphate groups and has an energy charge of 0. If all the adenine nucleotide is ADP or as an equimolar mixture of ATP and AMP, it is only half-full of high-energy groups and has an energy charge of 0.5. The energy charge of the ATP-ADP-AMP system can be calculated for any given set of concentrations of ATP, ADP and AMP by the equation :

$$\text{Energy Charge} = \frac{1}{2}\left(\frac{2\text{ATP}+\text{ADP}}{\text{ATP}+\text{ADP}+\text{AMP}}\right)$$

ATKINSON has suggested that the energy charge is a major factor in the regulation of pathways that produce and utilize high-energy phosphate groups. The curves in the figure show the relationship of the rates of ATP-generating and ATP-utilizing metabolic processes as a function of the energy charge. The metabolic steady state in which ATP production is equal to ATP utilization is given by the intersection of the two curves, corresponding to an energy charge of about 0.85[2][3][8][25][26].

If these response patterns observed in vitro reflect the behavior of the enezymes in
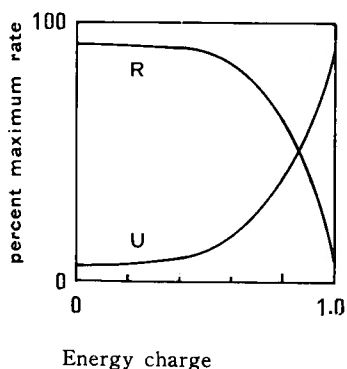
Energy charge

Generalized response to the energy charge
of enzymes involved in regulation of ATP-
regenerating(R) and ATP-utilizing(U) sequences.

vivo, the energy charge in a living cell must be rather strongly stabilized in a range near 0.85, since any tendency for the charge to fall would be resisted by the consequent increase in the rate of regeneration of ATP and decrease in the rates of sequences in which it is used.

Since that proposal the energy charge of various states of many kinds of spieces from the vegitative bacterial cells to the mammalian tissues has been calculated. The report about the energy charge in *Escherichia coli* during growth and starvation[7] suggested that growth could occur only at the energy charge values above 0.8, that viability was maintained at values between 0.8 and 0.5, and that cells died at values below 0.5.

In the present studies, under the normal arterial pressure (Group 1-A), the energy charges of the kidneys were maintained in the physiologically normal level above 0.8 over 4 hours with either flow patterns and the difference between pulsatile and nonpulsatile flow groups got gradually significant after 2 hours of perfusion. At the lower pressure Group 1-B, on the contrary, the pulsatile group showed an advantage over the other for the first 2 hours and after that the difference disappeared.

The findings indicate that the primary factor that affects the energy charge level of the renal tissue is the mean arterial pressure and that the difference between the two groups is brought under the following two occasions; the one, after 2 hours perfusion at a normal arterial pressure level and the other, during the early period before the impairment of the organ progresses under the lower pressure perfusion.

In Procedure 2, the energy charge of kidney in Group 2-A perfused with nonpulsatile flow for 2 hours was restored to near the control level after 30 minutes pulsatile perfusion at the normal pressure, while the level in Group 2-B remained urrecovered in spite of 30 minutes normal pressure perfusion. The total adenine nucleotide concentration did not recover the control value even after 30 minutes pulsatile perfusion with either Group 2-A or 2-B.

OZAWA and his associates[31] reported that, in the livers of rats with hemorrhagic shock, the shed blood reinfusion restored the fallen energy charge to the normal values immediately when the shock was reversible, while it did not recover to the normal level when irreversible. They also observed that the energy charge responded more rapidly to the changes of tissue perfusion and oxygen supply than to the total adenine nucleotide concentrations.

3. Effects of pulse pressure on vascular tone and microcirculation

There is abundant evidence available concerning physiologic disturbances of the nonpulsatile perfusion in the kidney[9,20,21,22,29,31,33,35,37]. The present experiments have indicated that the energy charge level was significantly different between pulsatile and nonpulsatile perfusion, although the urine output and creatinine clearance were less obviously different.

Where does the difference of the effect on the cellular metabolism come from concerning the presence of pulse pressure ?

Renal blood flow in the normal pressure group did not decrease during 2 hours of

perfusion, whether it is pulsatile or not. This finding is in accord with several preveous observations. MANDELBAUM[27] reported that average renal blood flow during pulsatile perfusion was 14 cc/kg/min or 13.5% of the pump output, and in the nonpulsatile one hour perfusion, it avaraged 14.4 cc/kg/min or 13.8% of output. GOODMAN[14] also noted similar findings through measurement by a electromagnetic flow probe. BOUCHER and co-workers[6] observed no changes on renal blood flow with nonpulsatile perfusion by the technique using microspheres.

One harmful effect attributed to nonpulsatile perfusion may be related to increased production of renin. As early as 1940, KOHLSTAEDT and PAGE[23] suggested that decreased pulse pressure, as well as decreased mean arterial pressure, was responsible for increased release of renin, and this suggestion was supported by a number of investigators[19][39]. In 1968, MANY and co-workers[28] produced pulseless renal blood flow by attaching a depulsing chamber between the descending aorta and renal vessels, and they demonstrated 27% increase in levels of renin in the renal vein. In another series of experiments[29], they demonstrated redistribution of renal cortical blood flow angiographycally, with a greater amount of contrast meterial appearing in the juxtamedullary region in the pulseless animals. According to GOODMAN[14], using the microsphere technique, there was a progressive decrease in the percent of flow perfusing the outer cortex with the constant renal flow in the nonpulsatile circulation. They also suggested a close correlation between secretion of renin and distribution of blood flow within the kidney from the findings of unequal distribution of renin in the juxtaglomerular apparatus in the outer cortical layer and progressively lower levels in the subsequent layers.

Another possible effect of the nonpuslatile perfusion is the impairment of lymphflow. The lymphatic system has the specific function of removing from the interstitial fluid the substances that cannot gain entry into the capillaries. The first to demonstrate a relation between the arterial pulse and the flow of the interstitial fluid and lymph in animal experiments were Parsons and McMASTER[30], who perfused rabbit ears with alternative pulsatile and nonpulsatile flow. They noted that there was almost no lymph flow if the pulsation was absent and showed that pulsatile perfusion of rabbit ears greatly increased the rate of diffusion of dye introduced into the subcutaneous tissue. PAQUET[35] demonstrated by the isolated kidney perfusion that the weight of the organ increased much more in the nonpulsatile group.

That the arterial pulse might exercise an influence upon the rate of fluid exchange between the extracellular compartment is supported by the evidence that the cerebrospinal fluid is propelled by similar mechanisms[43]. It has been known that the cerebrospinal fluid pulsates synchronously with the heart beat. The hypothesis that the pulse pressure might be a factor of importance for the metabolism of the central nervous system was supported by the finding of HALLEY, REEMTSMA and CREECH[17] that the oxygen consumption in the brain during nonpulsatile perfusion was decreased despite a normal rate of blood flow and unaltered cerebrovascular resistance. A similar role of the pulse pressure in the

circulation of the aqueous humor has been suggested by DUKE-ELDER[10].

Under these circumstances, that is, because of pooling of the interstitial fluid and, in the kidney, because of the secretion of renin, edema might appear in the interstitial space[32)44]. Maintenance of cationic gradients between cells and their sorroundings is vital for the function of the tissue, in this case the renal tubules. Edema will cause impaired oxygen transport, and a decrease of the energy containing compound ATP leads to damage of the energy dependent potassium-sodium pump, which expels sodium ion from the cell and accumulates potassium ion. Impaired ATPase system will bring intracellular sodium accumulation, i. e., cell swelling. And a vicious cycle might start to occur[42].

Renal Arterial Pressure. (mmHg)
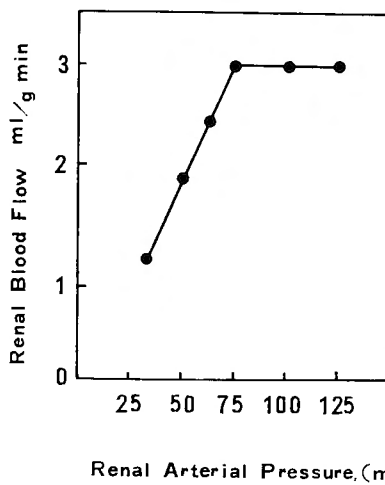
Diagrammatic presentation of renal Blood floow.

Fig. 8

In the low pressure Group 1-B, the renal blood flow decreased from the starting point of perfusion. The diagrammatic presentation of renal blood flow in relation to the arterial pressure was obtained from the works by ABE[1], which showed that the critical arterial pressure was 75 mmHg. Afferent inpulses from the barorecepters leads to constriction of the vessels of the whole body and increased renin secretion in the kidney. Cellular metabolism would be disturbed in a short period of perfusion.

Summary

The effects of pulsatile and nonpulsatile blood flow on renal energy metabolism were studied. The unilateral depulsation without the transient ischemia was attained by the abdominal aorta interruption between the ostia of the renal arteries and depulsated blood flow was led to the left renal artery through the fomoral artery. The following results and conclusions were obtained.

1. The energy charge was the good indicator which described the changes in the energy metabolism of the renal tissue. Its changes were more sensitive than that of the

total adenine nucleotides.

2. The primary factor that affected the energy charge level of the renal tissue was the mean arterial pressure to the kidney.

3. The predominance of pulsatile perfusion was shown under the following two occasions: the one, after 2 hours perfusion at the normal arterial pressure level and, the other, during the early period before the impairment of the tissue progressed under the low pressure perfusion.

4. Urine output and creatinine clearance were not necessarily the excellent indicators to show the difference between pulsatile and nonpulsatile perfusion.

From the results of the present study, it is concluded that, in spite of the mechanical complexity, pulsatile perfusion should be adopted in open heart surgery or in the field of extracorporeal circulation with high flow rate when the perfusion time will be prolonged or the patient is under the circulatory failure.

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和文抄録

非拍動流体外循環の影響について

——腎臓エネルギー代謝の検討を中心として——

京都大学医学部外科学教室第2講座（主任：日笠頼則教授）

大　頭　信　義

　非拍動流体外循環の生理的影響については，開心術が開始された当初より関心がもたれ，幾多の研究がなされてきたが，拍動流血液ポンプの機構の複雑さ，及び血液成分の損傷の問題とともに議論の余地の多い所である．今回，非拍動流循環の影響を腎臓エネルギー代謝の面から検討した．

　腹部大動脈を左右腎動脈分岐部間においてクロスクランプして，右腎臓には拍動流を，左腎臓には非拍動流を，一時的な血流遮断をすることなく導いた．細胞内エネルギー代謝の分析のためには，急速凍結した腎組織より Adenine Nucleotide を定量して，D. E. Atkinson が提唱して以来，諸組織のエネルギー平衡の指標として評価されている Energy Charge（ATP+½ADP）／（ATP＋ADP＋AMP）を算出して，両者の比較検討を行なった．

　1) energy charge は，腎組織のエネルギー代謝を検討するのに優れた指標であり，Adenine Nucleotide 総量よりも鋭敏に反応した．

　2) 腎組織の energy charge に最も大きな影響を与える因子は腎動脈圧であった．

　3) 拍動流循環の優位性は次の2つの場合において認められた．それは正常血圧下では2時間以上の長時間灌流を行なった場合であり，低血圧（60～70mmHg）下では，未だ循環障害の顕著でない初期においてであった．

　4) 尿量及びクレアチニン・クリアランスでは統計学的に有意な差は認められなかった．