CONTROLLED HYPOTENSION WITH ADENOSINE-TRIPHOSPHATE AND ITS INFLUENCE ON THE LIVER

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Since an increased incidence of traumatic shock in World War II, the problem of shock in the field of surgery has been remarkably clarified and the administration of fluid and blood against shock has been rationalized. Recent progress in anesthesiology with pre- and postoperative management has enabled surgeons to carry out difficult major operations with comparative safety. However, such operations can very frequently accompany massive and annoying hemorrhage, to which various countermeasures have been attempted.

One of them is artificial or controlled hypotension that means a method to lower the blood pressure when a massive bleeding is anticipated, for the purpose of minimizing hemorrhage from an operative field, facilitating the procedure of operation, shortening its time and saving the amount of blood transfusion.

Techniques utilized for this controlled hypotension were "arterial blood-letting" by Gardner[1], high spinal block by Griffiths[2] and autonomic ganglionic block introduced by Enderby[4]. Among the autonomic ganglion-blocking agents, pentamethonium (C_5) and hexamethonium (C_6) were the first drugs used for this technique but have been claimed to have certain difficulties in clinical application. A thiophanium derivative, "Arfonad", applied for surgical operation by Nicholson[9] etc. was proved to be superior to the drugs above in blood-pressure control.

Differing from these agents, the author noticed remarkable hypotensive and vasodilating effects of a free nucleotide in the living tissues, *i.e.*, adenosinetriphosphate (ATP), and succeeded in introducing this substance into the controlled hypotension method after various fundamental investigations. This device gave very satisfactory experimental and clinical results[15)-18)76)77)], and seem to have solved the difficult problems in previous techniques. The purpose of this paper is to present the controlled hypotension by ATP, its influence on the living body and interesting findings regarding the liver.

REVIEW OF THE LITERATURE

1) Controlled Hypotension

The prevention of hemorrhage during operation has been a big problem

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for surgeons. The late Prof. M. Saito of our department used to recommend a temporary ligation of the common carotid artery upon excising certain types of cerebral tumor. This was one of many devices, among which controlled hypotension has developed with the idea of lowering blood pressure to reduce bleeding.

Upon reviewing the literature concerning the controlled hypotension, Gardner[1] (1946) reported arterial bloodletting method by which a meningioma was safely excised with very minimal bleeding under hypotensive state induced by withdrawing 1600 ccm of arterial blood that was returned to the artery afterwards. Griffiths and Gillies[2] (1948) described the use of high spinal block induced by spinal anesthesia.

Paton and Zaimis[3] (1948) discovered the hypotensive action of pentamethonium and hexamethonium. Enderby[4,5] (1950) applied these agents to surgical operations with success. Then, they were utilized for pneumonectomy by Lewis[6] (1951) and for brain surgery by Vourch[7] with satisfactory results. Thereafter, these agents have been widely used in surgery, even in our country, as reported by Kuwabara[68], Sugawara[11,12], Uishi[13], Endo[14] and others. Another ganglion-blocking drug, a thiophanium derivative (RO-2222, Arfonad) described by Randall[8] (1949) was introduced to surgical operation by Nicholson[9] (1952) and Magill[10] (1953), and has been reported to be far superior to penta- and hexamethonium in control of blood pressure.

2) ATP and Its Hypotensive Action

ATP was purely isolated by Fiske and Subbarow[20] (1929) and Lohmann[19] (1931). It has been a principle substance in the recently advanced study of nucleic acids and nucleotides. Its chemical structure is, as shown in Fig. 1, adenyltriphosphoric acid or adenylpyrophosphoric acid; nemely two phosphate radicals (pyro-form) combine with adenylic acid, *i.e.*, adenosine monophosphate (AMP) which is made up of adenine (6-aminopurine), ribose and phosphoric acid (ester combination).

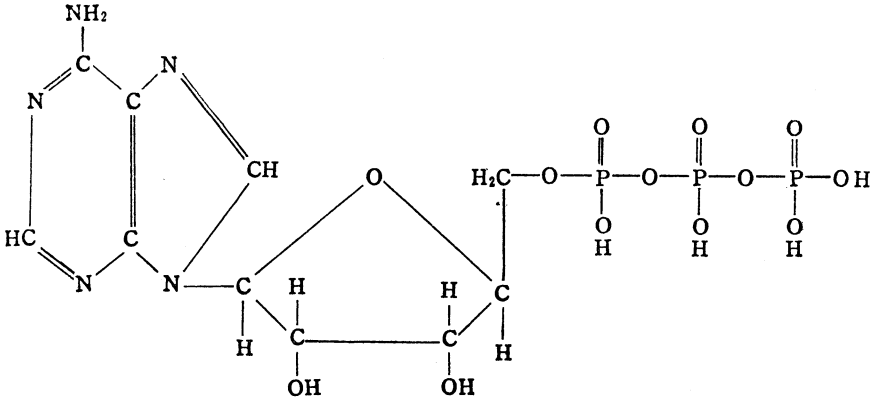

FIG. 1. The chemical structure of ATP (adenosinetriphosphate).

The role of ATP in a living body is to serve as carrier and transfer for high-energy phosphate radicals; namely the phosphate groups in ATP have two energy-rich bonds which produce important energy for all living phenomena upon hydrolysis of ATP to ADP and AMP. ATP is distributed throughout living tissues and has an essential relationship with the metabolisms of carbohydrate, fat and protein through various other coenzymes.

Despite of being such an important factor directly or indirectly to the function and metabolism of living body, ATP was not much utilized clinically in the past. The reasons for this fact are due to its instability as a product, different opinions and poor knowledge regarding its pharmacological action. Recent progress in pharmacology, however, has made these problems clear in considerable degree and accordingly the clinical application of ATP has extended.

Concerning the hypotensive function of adenosine compounds, Drury and Szent-Cyorgie[21] (1929) proved that adenosine and adenylic acid dilated the coronary vessels and reduced the arterial blood pressure in dogs and cats. Fleisch and Domenjoz[22] compared ATP and muscle adenylic acid as to their actions to the blood flow of the hind legs of dogs and reported that ATP had 70 times greater vasodilating action than muscle adenylic acid. Matsumoto[23] observed a fall in blood pressure by ATP in rabbits, and Ishii[72] concluded that this phenomenon occurred through the vagal nerve. Davies[24] reported that the intravenous injection of ATP caused dilatation of capillaries in the fingers and ears, and by the intraarterial injection of ATP, vessels were dilated in the extremity where the injection was performed. Kamiya[25] of our department microcinematographically observed the dilatation of capillaries and the slowing of blood flow in the mesentery of rats following the intravenous administration of ATP.

Regarding the mechanism of hypotension, Maekawa[26] stated that the intravenous injection of ATP was followed by ATP-ATPase reaction in serum, the amount of serum ATPase (adenosinetriphosphatase) was decreased and consequently the blood pressure was reduced. According to Funaki[27], the hypotension was due not only to vasodilation but also to a decrease in the volume of red cells. The author considered that the relaxation of vessel walls following I.V. ATP should directly cause the hypotension and also the resultant bradycardia mentioned below might promote this tendency.

Drury described that adenosine should act on the sinus node to cause bradycardia and atrioventricular block in guinea pigs. Wayne and Stoner stated that both ATP and adenosine reduced sinus rhythm by 30-40% and prolonged P-Q interval accompanying the occasional absence of QRS complex. Greene noticed the bradycardia due to AMP, ADP and ATP likewise.

3) Liver function

The liver is an organ to perform so various functions that the examination of only one sort of these functions may not give a proper imformation of this organ. Occasionally one functional deficiency can advance its grade without relating to other functions. Also, in several aspects of its functional activity,

the liver is intimately associated with other organs, so that it is difficult to delineate definitely the hepatic factor in investigating these functions. Moreover, it is important to note that the liver possesses a large functional reserve to maintain normal function even after the resection of as much as 85% of the entire liver. Upon considering these facts, the determination of the functional efficiency of the liver should be performed synthetically by adequately selected and carefully combined methods from numerous liver function tests.

From this aspect, the author selected the following techniques and investigated the condition of the liver under controlled hypotension.

1. Urine Urobilinogen Test: This is one of the most simple and useful tests for the liver function. However, it is doubtful, as emphasized by Magnus-Alsleben[29], that its intense reaction may indicate a high impairment in the liver. As to the genesis of urine urobilinogen, Müller's[30] enterohepatic circulation theory is generally approved at present. According to Osgood[31], this test is advantageous for examining a latent functional disturbance because the ability of the liver to reexcrete urobilinogen into the bile duct is so small that even its mild parenchymal damage may cause an increase in the amount of urobilinogen in urine.

2. Bilirubin Test: Concerning the relationship between bilirubin and liver cells, Minkowski and Naunyn[32] has stated that bilirubin is produced in the liver cells, but at the present time the reticuloendothelial system is generally believed to be the place of formation of bilirubin as McNee's opinion[33] and the function of liver cells is the removal of bilirubin from the blood stream and its excretion in the bile. Bollman[34] proved that even the resection of a large portion of the liver hardly resulted in an increase in serum bilirubin.

3. Millon's Test: This was devised by Millon (1948) but Imanaga's modified method[35] is widely used at present. The colored substances by this test are said to be tyrosine, indole[36], phenol[37], or tryptophan[39]. It has been reported by Imanaga[38], Yamazaki[37], Sato[39], Wowsi and Gelbird[40], Manke[41] and Furth and Scholl[42] that increased excretion of tyrosine, *i.e.*, positive Millon's test is noted in cases with liver impairment.

4. Sawada and So's Sublimate Test: This test is titrimetry of the serum with a solution of corrosive mercury chloride and is more sensitive than Takata's and Gross' tests. Hirayama[43] stated that this reaction is moderately accelerated by an increase in α and β globulins and markedly by γ globulin. According to Sato and Hashimoto[44], this test becomes positive if the sum of β and γ globulins exceeds 35-40% and the value of this sum is approximately parallel to the grade of positivity.

5. Thymol Turbidity Test: This test has been said to relate essentially with β and γ globulins and lipids in serum[45], and Hirayama proved that it was accelerated weakly by β-globulin and strongly by γ-globulin, but inhibited by serum albumin. Popper[46] reported that it intimately concerned with the

damage of hepatic parenchymal cells and also their regeneration.

Regarding the relationship between the liver and each fraction of serum proteins, it has been proved by various experiments[47) 48) 49) 73)] that serum albumin is decreased following experimental hepatectomy or artificial liver damage. Clinically, it is generally agreed that a decrease in albumin is noted in cases with hepatic parenchymal damage. Accordingly the albumin is believed to be made in the liver. On the other hand, globulin is frequently increased in cases with liver diseases[50)] and the formation of globulin is considered to be extrahepatic, namely, in the reticuloendothelial system[51)].

6. Cholesterol: Wacker and Hueck[52)] found the ratio of cholesterol and cholesterol esters to be almost constant in normal but vary in hepatic damage. This fact was utilized for the liver function determination by Hoagland[53)] and others. Sperry[54)] reported a decrease in the ratio of ester to total cholesterol (EQ) in cases with hepatic disease or damage. Tsukushi[55)] classified the degree of hepatic damage by EQ, since the value of EQ accorded with the results of other liver function tests. Tateishi[56)] reported that the action of cholesterol-esterase was diminished in hepatic damage, and an increase or decrease in this action was parallel with those in EQ.

7. Carbohydrate Metabolism: Liver glycogen was investigated by Carpenter[57)] and Hansen[58)]. Evans[59)], Murphy[60)] and Feiner[61)] have proved that it is diminished by ether or chloroform. There have been many works concerning blood sugar during anesthesia (Hugill[62)], Nagata[63)], Bass[64)] etc.) and also reports as to the relationship between blood sugar and invasion (Laborit[65)] and Saito[66)]).

Lactic and pyruvic acids are intermetabolites of carbohydrate and converted to glycogen by the liver or oxidized to CO_2 and H_2O. Oxygen deficiency or impaired hepatic function result in accumlation of excessive amounts of these acids in the blood. Accordingly, it is meaningful to measure these substances. Their relation with anesthesia was investigated by Koda[67)].

It is well known that the liver has an important role in carbohydrate metabolism. According to Mann and Magath[47)], galactose can enter the sphere of glucose-glycogen metabolism exclusively in the liver, whereas glucose can be utilized in the tissues without passing through the liver. Regarding blood sugar in hepatic damage, it is believed that the blood sugar rises at earlier stage and falls as the illness advances.

8. Bromsulphalein Test: Hemodynamics in the liver influences on its functional activity and reports concerning this test have been made by Lewis[69)], Sherlock[70)], Goodman[71)] and others.

RESULTS OF EXPERIMENTS

1) Methods of Experiments

Experiments were performed on adult dogs. Intravenous thiopentothal was used for intubation and induction of anesthesia which was maintained with ether and oxygen. The position of animal was horizontal.

a. Fundamental investigations

It was found that dog's arterial blood pressure fell very rapidly when ATP, extracted from the skeletal muscle of rabbit and dissolved in physiological saline solution, was injected intravenously to a dog.

In such cases, bradycardia and bradypnea appeared simultaneously with the hypotension. These manifestations, however, were only temporary and investigations revealed that blood pressure, respiration and pulse all returned to normal in 5-15 seconds when ATP less than 10 mg/kg body weight was used and in 30-40 seconds or 1-2 minutes at latest even when the dose was 10-20 mg/kg.

This hypotensive effect of ATP was noted following its intraaortic injection but the degree and duration of hypotension were far less than those following intravenous administration and bradycardia was hardly observed.

In order to investigate the vasodilating action, ATP was injected to frogs and examination of their webs revealed the distinct dilatation of capillaries.

b. Maintenance of hypotension

As stated above, the hypotensive effect of ATP is of short duration, so that a certain device is necessary to maintain hypotensive condition for a longer period. For this problem, the author adopted a continuous intravenous administration of ATP solution. Namely, 1% or 0.5% ATP in physiological saline solution is injected intravenously, while observing blood pressure and gradually increasing the rate of drip (gtt/min.) until expected hypotensive level is obtained (Fig. 2). Thereafter, this drip rate is kept for maintaining the constant level of hypotension for a period required. Discontinuation of the ATP administration can bring a quick recovery from this hypotensive state.

Apparatus for the continuous administration was carefully made for holding a constant and exact dripping rate regardless of the amount of solution left in a bottle.

Relationships between the administered amount of ATP solution and resultant blood pressure are indicated in Table 1, which were obtained from the average of 50 mongrel dogs. For example, by 1% solution it is necessary to use 0.002-0.004 g/kg body weight/min. for lowering blood pressure to 70-50

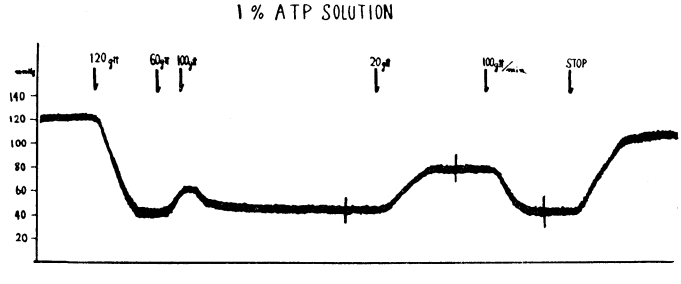

FIG. 2. A pressure curve of dog on intravenous drip administration of 1% ATP solution.

TABLE 1. Relationships between the Amount of ATP Solution Administered and Resultant Blood Pressure (Systolic)

1% ATP solution (g/kg of body weight/min.)	B.P.* (%)
0.002–0.004	70–50
0.005–0.014	45–30
0.015–0.024	35–25
0.5% ATP solution	
0.0015–0.0024	80–65
0.0025–0.0034	70–55
0.0035–0.0044	65–50
0.0045–0.0054	55–45

* % of the value prior to the ATP administration.

%, and by 0.5% solution, 0.0025-0.0034 g/kg/min. for 70-55% of blood pressure. These values are, of course, only standard, and hence for practical use one should obtain and keep optional hypotensive condition by regulating the rate of ATP drip while observing the state of bleeding in an operative field and examining blood pressure.

c. Side effects

In order to investigate the lethal dose of ATP, its physiological saline solution was injected to 50 mice through the tail vein. LD_{50} was 360 mg/kg by single intravenous administration. The mouse to be died showed agony and spasm during or following the injection. This result, however, is based upon the data by single and rapid intravenous injection under no anesthesia. Therefore, it is doubtful whether this value can be applied to a case with drip intravenous administration under general anesthesia.

Clinically, when an intravenous drip ATP administration was performed to non-anesthetized patients and the blood pressure fell to about 70% of the previous value, they developed pallor, agony and sometimes shock state, which disappeared immediately after discontinuation of the administration. On the other hand, when ATP was similarly administered under general anesthesia, no untoward effect was noted even by employing a considerably large amount of ATP.

In other words, so far as a careful and sufficient anesthesia is administered, ATP of practical dosage for controlled hypotension does not cause any side effect and is entirely safe even though its total amount becomes very large throughout an operative course.

2) Influences on the Liver

The liver performs various important functions and is considered to be the most reactive organ against foreign invasions and also a good indicator for operative prognosis[28]. For discussing the excellency of the controlled hypotension with ATP, it is reasonable to investigate its influences on the liver. As stated previously, the author selected the following techniques and

synthetically examined the condition the liver: urine urobilinogen test, bilirubin test, Millon's test, Sawada and So's sublimate test, thymol turbidity test, cholesterol, blood sugar, lactic and pyruvic acids, liver glycogen, BSP test, and histological examination.

1. Urine urobilinogen and urobilin tests

Urine urobilinogen (Ehrlich's method) and urobilin (Schlesinger's method) were investigated on 5 mongrel dogs weighing 8–10 kg. Their blood pressure ranged from 170 to 140 mmHg and was lowered to 90–60 mmHg for about one hour by the ATP controlled hypotension method. Urine specimens were taken before, during and after the controlled hypotension as shown in Table 2 which indicated normal urobilin and urobilinogen throughout this investigation.

TABLE 2. Urine Urobilin and Urobilinogen in Dogs under the Controlled Hypotension by ATP

No.	Sex	Body weight (kg)	Blood pressure systolic (mmHg)		Tests	Before	During Cont. Hypotension		After					
			before	during			30′	60′	30′	60′	2	3	6	24 hrs.
101	M	10	150	90	Urobilin	−	−	−	−	−	−	−	−	−
					Urobilinogen	+	+	+	+	+	+	+	+	+
102	F	9	170	60	Urobilin	−	−	−	−	−	−	−	−	−
					Urobilinogen	+	+	+	+	+	+	+	+	+
103	M	12	160	90	Urobilin	−	−	−	−	−	−	−	−	−
					Urobilinogen	+	+	+	+	+	+	+	+	+
104	M	8	140	80	Urobilin	−	−	−	−	−	−	−	−	−
					Urobilinogen	+	+	+	+	+	+	+	+	+
105	F	9.5	160	80	Urobilin	−	−	−	−	−	−	−	−	−
					Urobilinogen	+	+	+	+	+	+	+	+	+

2. Bilirubin test

Serum bilirubin was investigated by Hijmans van den Bergh's direct and indirect reactions, and by Meulengracht's icterus index, employing the same animals as in the above examination. The times of blood aspiration were also same. Hijmans v.d. Bergh's qualitative reaction revealed no abnormality (Table 3), and Meulengracht's quantitative measurement, *i.e.*, icterus index indicated almost normal values throughout procedures (Table 4), for instance 2.0–3.5 during controlled hypotension and 1.5–3.0 3 hours after.

Urine bilirubin was examined by Gmelin's test, employing 3 mongrel dogs weighing 8.5–12 kg. B.P. which was 150–160 mmHg was lowered by ATP drip administration and kept at 80–60 mmHg for 1 hour. The results were all negative as shown in Table 5.

3. Millon's test

Imanaga's modified method was utilized. The urine specimens of 5 dogs

TABLE 3. Serum Bilirubin in Dogs under the Controlled Hypotension by ATP (Hijmans van den Bergh's qualitative reaction)

No.	Sex	Body weight (kg)	Blood pressure systolic (mmHg)		Before	During Control. Hypotension		After					
			Before	During		30′	60′	30′	60′	2	3	6	24 hrs.
101	M	10	150	90	—	—	—	—	—	—	—	—	—
102	F	9	170	60	—	—	—	—	—	—	—	—	—
103	M	12	160	90	—	—	—	—	—	—	—	—	—
104	M	8	140	80	—	—	—	—	—	—	—	—	—
105	F	9.5	160	80	—	—	—	—	—	—	—	—	—

TABLE 4. Serum Bilirubin in Dogs under the Controlled Hypotension by ATP (Meulengracht's icterus index)

No.	Sex	Body weight (kg)	Blood pressure systolic (mmHg)		Before	During Control. Hypotension		After					
			Before	During		30′	60′	30′	60′	2	3	6	24 hrs.
101	M	10	150	90	2.0	2.5	2.5	2.5	2.0	2.0	2.0	2.0	1.5
102	F	9	170	60	1.5	1.5	2.0	2.0	1.5	1.5	1.5	2.0	1.5
103	M	12	160	90	3.0	3.5	3.5	3.5	3.5	3.0	3.0	2.5	2.5
104	M	8	140	80	2.0	2.0	2.0	1.5	2.0	1.5	1.5	2.0	2.0
105	F	9.5	160	80	2.5	2.5	2.0	2.5	2.5	2.0	1.5	1.5	1.5

TABLE 5. Urine Bilirubin in Dogs under the Controlled Hypotension by ATP (Gmelin's method)

No.	Sex	Body weight (kg)	Blood pressure systolic (mmHg)		Before	During contr. Hypotension	After			
			Before	During		60′	60′	3	6	24 hrs.
107	F	8.5	160	80	—	—	—	—	—	—
109	F	12	150	60	—	—	—	—	—	—
110	F	10	150	60	—	—	—	—	—	—

TABLE 6. Urine Millon's Test in Dogs under the Controlled Hypotension by ATP (Imanaga's modification: mg/dl)

No.	Sex	Body weight (kg)	Blood pressure systolic (mmHg)		Before	During contr. Hypotension	After			
			Before	During		60′	60′	3	6	24 hrs.
106	M	9	140	70	6.0	8.0	8.0	7.0	7.0	7.0
107	F	8.5	160	80	5.0	4.5	6.0	3.5	3.5	4.5
108	M	11	170	80	8.0	10.0	15.0	10.0	10.0	8.0
109	F	12	150	60	8.0	8.0	7.5	8.0	8.0	8.0
110	F	10	150	60	6.0	5.5	8.5	6.5	9.5	7.0

weighing 8.5–12 kg were examined before, during and after (1, 3, 6 and 24 hours) ATP administration. The results are as shown in Table 6, 5.0–8.0 mg/dl (before), 4.5–10.0 mg/dl (during), 6.0-15.0 mg/dl (1 hour after) and 4.5-8.0 mg/dl (24 hours after). In a dog, No. 108, blood pressure was lowered to

80 from 170 mmHg for one hour when the value of Millon' test became approximately doubled (15 mg/dl vs. 8 mg/dl) and returned to 8 mg/dl in 24 hours. In other dogs, Nos. 109 and 110, hypotension of similar degree was maintained for one hour but their values showed only mild changes of within 3.5 mg/dl. Mochida stated that the range of variety in normal dogs was 20 mg/dl. All of the results by this test can be regarded as normal although one case (No. 108) showed a marked increase.

4. Sawada and So's sublimate test

Under the conditions similar to the preceding paragraph, blood was examined by titration with corrosive sublimate solution. The blood pressure was 170-140 mmHg and was kept at 80-60 mmHg for one hour by ATP. In the results (Table 7), the amount of sublimate solution used was 0.6-0.48 ccm before hypotension and 0.62-0.46 ccm 1 hour after recovery.

TABLE 7. Sawada and So's Sublimate Test in Dogs under Controlled Hypotension by ATP (unit: ccm of corrosive sublimate solution)

No.	Sex	Body weight (kg)	Blood pressure systolic (mmHg)		Before	During contr. Hypotension	After			
			Before	During		60′	60′	2	3	24 hrs.
106	M	9	140	70	0.54	0.52	0.50	0.50	0.54	0.48
107	F	8.5	160	80	0.6	0.6	0.62	0.58	0.60	0.60
108	M	11	170	80	0.52	0.52	0.46	0.48	0.52	0.52
109	F	12	150	60	0.58	0.46	0.48	0.52	0.60	0.62
110	F	10	150	60	0.48	0.46	0.48	0.50	0.52	0.50

5. Thymol turbidity test (Maclagun)

According to Gornall and Bardawill, the normal value of dog in this test is 0.2-1.2 Maclagan unit (0.5 in avarage). Experiments were performed on 5 dogs as shown in Table 8 and the results were 0.4-1.2 unit before, 0.5-1.2 unit during and 0.6-1.0 unit 3 hours after ATP administration.

TABLE 8. Thymol Turbidity Test in Dogs under the Controlled Hypotension by ATP (Maclagan's unit)

No.	Sex	Body weight (kg)	Blood pressure systolic (mmHg)		Before	During contr. Hypotension		After		
			Before	During		30′	60′	60′	3	6 hrs.
112	F	9.5	160	80	0.6	0.5	0.5	0.4	0.6	0.6
113	F	8.0	150	60	0.8	1.0	1.2	0.8	1.0	0.8
115	M	7.8	160	70	0.4	0.5	0.8	0.8	0.6	0.6
116	M	10	170	90	1.2	1.0	0.8	1.0	0.8	0.8
118	F	9.0	150	70	0.8	1.2	1.2	1.2	1.0	1.0

6. Cholesterol

Quantitative measurement of cholesterol, free and total, was performed with Sperry's method based upon Yoshikawa's description. In this method, a

variation in EQ (cholesterol ester/total cholesterol × 100) indicates the grade of liver disturbance. Experiments were performed on 5 dogs as seen in Table 9. As the results, EQ was 73.90–69% before, 76.69–66.26% at 30 minutes during, 76.6–60.12% at 60 minutes during and 84.89–68.31% 2 hours after ATP administration. An attention must be made on No. 107 which shows aggravation (60.12% from 72.32%) at the end of one hour's hypotension, but returns to 73.68% 1 hour later.

TABLE 9. Cholesterol under the Controlled Hypotension by ATP
(Quantitative measurement by Sperry's method)

No.	Sex	Body weight (kg)	Blood pressure systolic (mmHg) Before	Blood pressure systolic (mmHg) During	Cholesterol (mg/dl)	Before	During contr. Hypotension 30′	During contr. Hypotension 60′	After 1	After 2	After 3	After 6 hrs.
101	M	10	150	90	Total	215.5	163.0	145.0		203.5		
					Free	67.0	55.0	41.0		64.5		
					Ester	148.5	108.0	104.0		139.0		
					E.Q. (%)	69.0	66.3	71.7		68.3		
103	M	12	160	90	Total	174.0	125.5	117.5		115.5		135.0
					Free	48.0	33.5	27.5		26.5		34.5
					Ester	126.0	92.0	90.0		89.0		100.5
					E.Q. (%)	72.4	73.3	76.6		77.1		74.4
105	F	9.5	160	80	Total	147.5	102.0	115.0	115.0		96.0	
					Free	38.5	30.5	35.5	31.5		27.0	
					Ester	109.0	71.5	79.5	83.5		69.0	
					E.Q. (%)	73.9	70.1	69.1	72.6		71.9	
106	M	9	140	70	Total	108.0	81.5		93.0	92.0	100.0	108.0
					Free	31.5	18.0		15.0	14.0	25.5	22.0
					Ester	76.5	63.5		78.0	78.0	75.5	86.0
					E.Q. (%)	70.8	76.7		83.9	84.9	75.5	79.6
107	F	8.5	160	80	Total	112.0	98.0	84.0	95.0		101.0	
					Free	31.0	26.0	33.5	25.0		32.0	
					Ester	81.0	72.0	50.5	70.0		69.0	
					E.Q. (%)	72.3	73.5	60.1	73.7		68.3	

7. Liver glycogen

The amount of liver glycogen may be affected by diet given for several days prior to the examination. Consequently the dogs used in this experiment were kept in fasting state for about 15 hours.

Under local anesthesia, a small incision was made on the abdomen and a piece of the liver (100–200 mg) was excised. Then, general anesthesia was started to perform the procedure of controlled hypotension of one hour's duration. The biopsy was made before, immediately after, 30 min. and 60 min. after ATP administration. Each specimen was placed in pure alcohol solution

and measured by Boettiger's method. The location of biopsy on the liver was non-selective.

The results are shown in Table 10. If regarding the influence of difference in anesthesia as minimum, it can be said that the liver glycogen tends to decrease during ATP administration and to increase 30-60 min. after that. However, according to Fisher's direct probability calculation, it becomes $\alpha = 0.175$ and one may not make an assertion from such a small number of cases like this but at least the aforementioned tendency can not be denied.

TABLE 10. The Amount of Glycogen in the Liver under Controlled Hypotension by ATP on Dogs* (Boettiger's method)

No.	Sex	Body weight (kg)	Specimen taken	Blood pressure (mm Hg)	Liver glycogen (%)
51	M	8.5	Before anesthesia	150	6.78
			Before ATP injection	150	4.75
			During injection (60')	80	3.71
			60 min. after injection	140	3.49
52	M	9	Before ATP injection	120	1.74
			During (60 min.)	60	3.72
			30 min. after	120	1.59
			60 min. after injection	120	2.19
54	F	7	During ATP injection (60')	70	7.15
			30 min. after	130	6.0
			60 min. after injection	120	6.75
55	M	6.5	Before ATP injection	140	9.30
			During (45 min.)	80	2.28
			60 min. after	140	9.50
57	M	7	Before ATP injection	140	8.6
			During (60 min.)	80	2.6
			30 min. after	130	1.05
			60 min. after injection	140	1.20
58	M	7	Before anesthesia	140	3.86
			Before ATP injection	140	2.94
			During (60 min.)	70	2.74
			30 min. after	130	2.21
			60 min. after injection	130	2.14
59	F	8	Before ATP injection	160	10.0
			During (60 min.)	90	8.1
			30 min. after	150	6.5

* All cases were anesthetized with pentothal and ether intratracheal general anesthesia.

8. Blood sugar, lactic and pyruvic acids

On 4 dogs following 15 hour's fasting, ATP hypotension was carried out under ether anesthesia. Blood specimens were taken before, during, immediately, 30 min. and 60 min. after ATP administration, from the femoral artery and also through a catheter having been fluoroscopically inserted to the hepatic vein. Blood sugar was measured with Hagedorn-Jensen's method, lactic acid

with Barker and Summerson's dihydroxy diphenyl method and pyruvic acid with Friedmann's dinitrophenyhydrazine method.

Blood sugar (Table 11) generally decreases but there is no case showing a marked hypoglycemia. Hepatic arterio-venous sugar difference indicates the tendency of "releasing" of sugar from the liver during ATP administration, namely, venous blood sugar increases relatively against arterial blood sugar. After the administration, it becomes a mild "releasing", approaching a normal fasting state.

TABLE 11. Blood Sugar under the Controlled Hypotension by ATP on Dogs (Hagedorn-Jensen's method)

No.	Sex	Body weight (kg)	Stage	Blood pressure (mm Hg)	Arterial blood sugar (mg/dl)	Arteriovenous difference (mg/dl)
51	M	8.5	Before ATP injection	150	133	−29
			During (30 min.)	80	128	− 6
			During (60 min.)	80	99	−56
			After (30 min.)	150	95	− 5
			After (60 min.)	140	60	+18
52	M	9	Before	120	108	+42
			During (60 min.)	60	63	+27
			After (30 min.)	120	79	+67
			After (60 min.)	120	107	+51
53	F	8	Before	140	142	+ 68
			During (60 min.)	70	147	+136
			After (30 min.)	140	170	
55	M	6.5	Before	140	197	−80
			During (45 min.)	80	150	−16
			After (30 min.)	140	111	− 5
			After (60 min.)	140	98	− 2

TABLE 12. Lactic Acid under the Controlled Hypotension by ATP on Dogs

No.	Sex	Body weight (kg)	Stage	Blood pressure (mm Hg)	Lactic acid in arterial blood (mg/dl)	Arteriovenous difference (mg/dl)
56	F	8	Before	130	45	−18
			During (60′)	70	27	+ 5
			After (30′)	130	35	−10
58	M	7	Before	140	16	− 1
			During (30′)	70	18	− 8
			During (60′)	70	14	+ 1
			After (30′)	130	20	− 4
			After (60′)	130	23	+ 8.5
59	F	8	Before	160	45	+ 8
			During (30′)	90	80	+ 1
			After (30′)	150	61	+ 7
60	M	9	Before	130	23	−13
			After (30′)	130	27	− 1.5
			After (60′)	130	32	− 2

TABLE 13. Pyruvic Acid under the Controlled Hypotension by ATP on Dogs

No.	Sex	Body weight (kg)	Stage	Blood pressure systolic (mm Hg)	Pyruvic acid in arterial blood (mg/dl)	Arteriovenous difference (mg/dl)
56	F	8	Before	130	0.4	+1.15
			During (60')	70	1.9	−0.35
			After (30')	130	1.15	−0.45
58	M	7	Before	140	2.4	−0.7
			During (30')	70	1.9	−1.2
			During (60')	70	2.1	−0.9
			After (30')	130	2.0	−0.55
			After (60')	130	2.5	−0.7
59	F	8	Before	160	3.7	+1.9
			During (30')	90	3.5	+0.45
			After (30')	150	3.2	+0.05
60	M	9	During (60')	70	1.1	−0.25
			After (30')	130	1.2	−0.05
			After (60')	130	1.6	+0.05

Lactic acid (Table 12) tends to increase mildly one hour after the administration. Regarding its hepatic arterio-venous difference, a trend of "taking in" is noted after the administretion. Pyruvic acid (Table 13) shows little change throughout. Hepatic arterio-venous difference indicates a slight "taking in" tendency. After all, it is probable that the changes in either lactic or pyruvic acids are not remarkale.

9. Bromsulphalein test

Bromsulphalein test was performed on 3 dogs weighing 7–8 kg by Goodman's single method at the stages before, during and after ATP administration. An estimation from the results (Table 14) of this BSP clearance test disclosed that the hepatic blood flow during ATP hypotension was not altered from that prior to ATP injection. Consequently, it is certain that the controlled hypotension by ATP would not lower the hepatic blood flow.

TABLE 14. Bromsulphalein Test under the Controlled Hypotension by ATP on Dogs (Goodman's single method)

No.	Sex	Body weight (kg)	Stage	Clearance (ccm/min./kg)	Blood pressure systolic (mmHg)
81	M	7	Before	9.9	150
			During (30')	10.9	60
			After (60')	5.0	120
82	M	8	Before	12.2	140
			During (30')	11.2	50
			After (60')	7.3	120
84	F	8	Before	15.4	150
			After (60')	10.8	150

10. Histological studies

For investigating the influence of ATP hypotension upon the liver tissue, biopsies were performed before, 5, 10, 20, 30 and 45 min. during ATP administration, and 15 and 30 min. after its cessation. The specimens were stained with hematoxylin-eosin and PAS but there was no abnormal finding noted in the liver tissue, nor significant difference in PAS positivity. One example is shown in Table 15.

TABLE 15. Histopathological Findings in the Liver under Controlled Hypotension with ATP (Dogs)

Blood pressure (systolic)	ATP administration						After	
	before	5	10	20	30	45 min.	15	30 min.
	120	70	60	60	60	60	100	100
Cords of liver cells disordered	+	±	±	+	±	+	+	−
Sinusoids distended	±	+	+	−	+	±	−	±
Liver cells vacuolated	+	±	±	±	±	±	−	−
Liver cells destroyed	−	−	−	+	+	±	−	−
Capsule thickened	−	−	−	−	−	−	−	−
Cellular infiltration of Glisson's sheath	−	−	−	−	−	−	±	−
Hydrops of Glisson's sheath	−	−	+	+	+	+	+	−
Portal branches destroyed	−	−	?	+	±	±	±	−
Thickened intima of hepatic artery	−	±	±	+	+	+	−	±
Biliary epithelium abrased	−	−	±	−	−	+	−	−
Bile thrombi	−	−	−	−	−	−	−	−
Cellular infiltration around hepatic ducts	−	−	−	−	−	−	−	−
Kupffer cells swollen	−	−	±	±	−	±	±	±
Central veins dilated	±	±	±	−	+	±	−	−
Fat droplet	−	−	−	−	−	−	−	−

3) Influences on Electrocardiogram

Electrocardiographic changes by ATP were investigated with 3 methods, *i.e.*, continuous intravenous drip. single rapid injection into the external jugular vein, and into the common carotid artery.

Blood pressure was automatically recorded with an electromanometer connected to a catheter inserted through the femoral artery to the thoracic aorta. The grade of fall in blood pressure was most strongly observed by injection through the ext. jugular vein (50% fall in 10 seconds) and most weakly through the common carotid artery. In the case of continuous intravenous drip administration (120 gtt/min.), B.P. fell to about 50% in 50 sec. From these examinations, it was confirmed that B.P. decreased rapidly by the intravascular injection of ATP regardless of the region injected and also that the drip administration was favorable in the aspects of rapidity and easier regulation.

Electrocardiograms on the intravenous drip administration of ATP (Fig. 3) indicated that there was no marked change in ST segment, and PQ interval was slightly prolonged during the administration although within normal limit. R-R interval was 0.28 sec. before, then prolonged to 0.48 sec. 15 sec. after

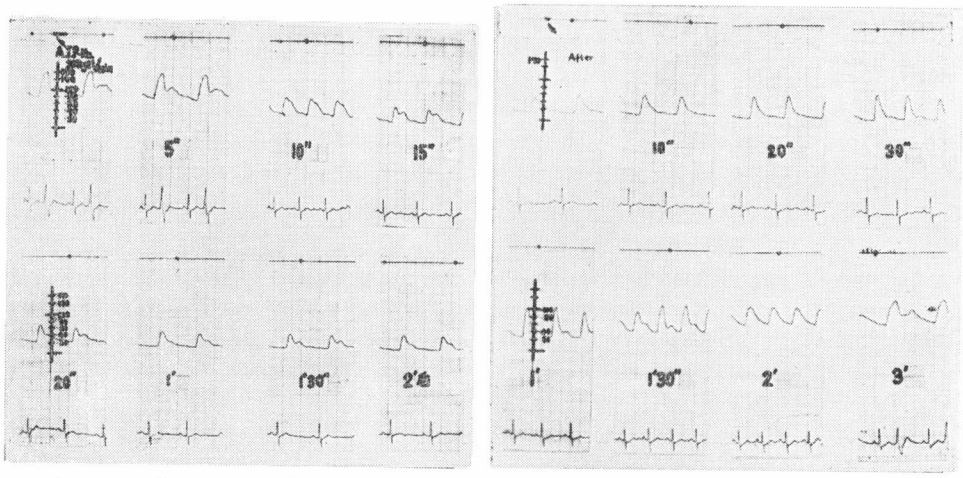

FIG. 3. Electrocardiograms and pressure curves of dog on the intravenous drip administration of ATP (1% solution 120 gtt/min.). The administration was continued for 10 min. and stopped at the point indicated by an arrow sign.

starting the injection, 0.52 sec. at 1 min. and 0.57 sec. at 1 min. 30 sec. and this value continued until the cessation of I.V. ATP, after when it changed as 0.55 at 10 sec., 0.45 at 20 sec., 0.43 at 30 sec., 0.37 at 1 min. and 0.3 at 1 min. 30 sec. indicating a recovery to its previous value. It seems that R-R interval shows almost the same process of time change as regards prolongation and shortening.

As an interesting phenomenon, it was frequently experienced that a bigeminy probably due to anesthetic influence disappeared instantly by starting ATP administration and again appeared after its discontinuance. This problem is considered to need further investigation

Electrocardiograms on the single rapid injection into the external jugular vein (Fig. 4) showed ST segment with no marked change and PQ interval of normal limit. R-R interval was 0.28 sec. before the injection, then 0.29 at 2 sec., 0.35 at 5 sec., 0.64 at 20 sec. (highest), 0.55 at 30 sec., 0.40 at 1 min. and 0.28 sec. at 2 min., suggesting a steady recovery.

In the case of single rapid injection into the common carotid artery (Fig. 5), notwithstanding that B.P. did not fall so much as in the aforementioned 2 cases, R-R interval became its highest value (0.60 sec.) at 10 sec. and then returned to its previous value at 2 min.

Also a massive injection of ATP into the coronary artery made the heart beat completely stopped. This discovery has been applied for the artificial cardiac arrest in open-heart surgery as reported by Sakakibara,[75] my co-worker, but its detailed description is omitted in this paper.

At any rate, the electrocardiographic change on controlled hypotension by ATP is only bradycardia, and shows no abnormality in the myocardium or conducting system.

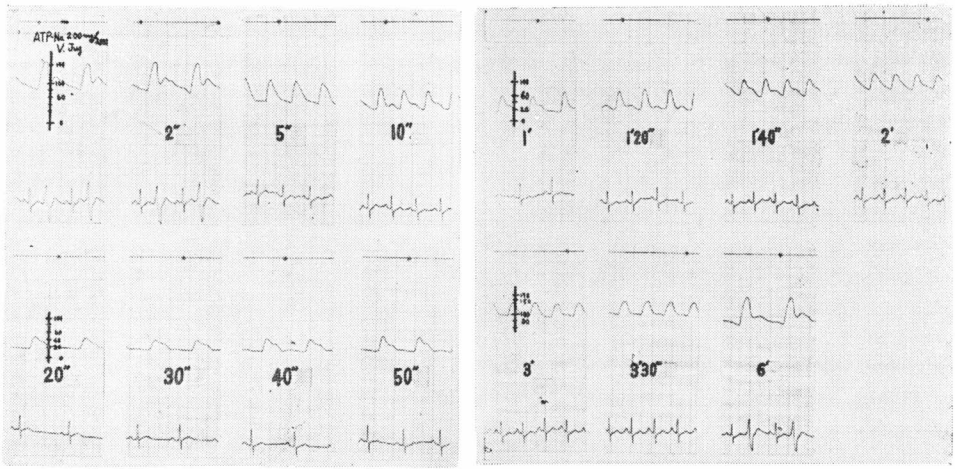

FIG. 4. Electrocardiograms and pressure curves of dog following the rapid injection of ATP into the external jugular vein (200 mg ATP in 20 ccm solution injected in 2 sec.).

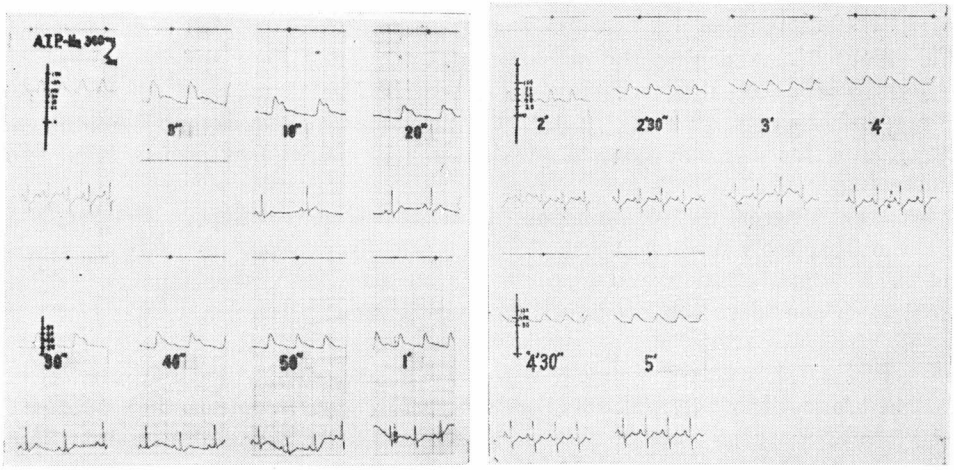

FIG. 5. Electrocardiograms and pressure curves of dog following the rapid injection of ATP to the common carotid artery (300 mg ATP in 20 ccm solution injected in 2 sec.).

CLINICAL RESULTS

From the experimental results, the controlled hypotension by ATP was proved to have an excellent pressure-controllability with no untoward effect on the living body. Generally, major surgical operations on the brain, lung and heart ought to accompany massive hemorrhage which needs a large amount of blood transfusion. The author believes that no matter how the knowledge and technique of blood transfusion be advanced, the transfusion

itself would still give some stress to a subject. This controlled hypotension would, of course, exert a certain harmful influence on the living body but it should fully compensate those by blood loss and transfusion. In these aspects, its clinical applications have been performed for the following operations.

A. Brain Surgery

Thirteen patients with skull fracturs, intracranial hematoma or brain tumor (Table 16) were operated on under the controlled hypotension by ATP. Their age ranged from 16 to 72. Anesthesia used was either potentiated (cocktail lytique plus general anesthesia) or local anesthesia with pharmacological hibernation.

The amount of ATP administered depended upon the duration and difficulty of operation. As a rule, there was expected a comparatively large amount of bleeding on skin incision, bone excision and tumor extirpation. For such stages, hypotension was induced selectively, while in the rest of operative course the administration of ATP was interrupted to maintain normal blood pressure, so as to keep the harmful influence of hypotension per se as minimal as possible (Fig. 6).

The level of hypotension needed to inhibit bleeding is variable by different investigators' reports. In this technique, an almost perfectly dry field could be obtained at between 90-65 mmHg (systolic) by regulating the drip rate of ATP while observing the operative procedure. In the course of operation, hemostasis was assured easily by discontinuing ATP administration.

Blood was transfused correspondingly to the amount of bleeding and immediately after operation the blood pressure returned to its preoperative

TABLE 16. Brain Surgery under ATP-Controlled Hypotension

No.	Sex	Age	Disease	Anesthesia	ATP used (g)	Blood pressure (mmHg)			Blood loss	Blood transfused (ccm)
						before	during (systolic)	after		
1	F	16	Intracranial hematoma	Hibernation + local	4	126/88	75–70	120/90	430	400
2	M	20	Brain tumor	〃	4	120/60	80–70	110/86	270	400
3	M	17	〃	Potentiated general	4	118/76	80–70	110/70	620	600
4	M	21	Ventricular cyst	Hibernation + local	4	130/80	90–80	120/74	550	600
5	M	43	Brain tumor	Potentiated general	1	108/40	80–75	110/60	400	400
6	M	31	Skull fracture	〃	1	100/64	80–75	105/60	350	400
7	F	72	Brain tumor	〃	1	150/100	90–85	136/80	510	600
8	F	32	〃	〃	2	120/74	75–70	110/68	700	600
9	M	21	Intracranial hematoma	Hibernation + local	1	110/60	75–70	120/80	500	300
10	M	19	Brain tumor	Potentiated general	3	135/80	80–70	110/70	380	400
11	F	55	〃	〃	4	135/85	80–70	110/75	470	400
12	M	49	〃	〃	2	120/70	70–65	115/78	410	400
13	M	32	〃	〃	2	108/62	70–60	100/70	380	400

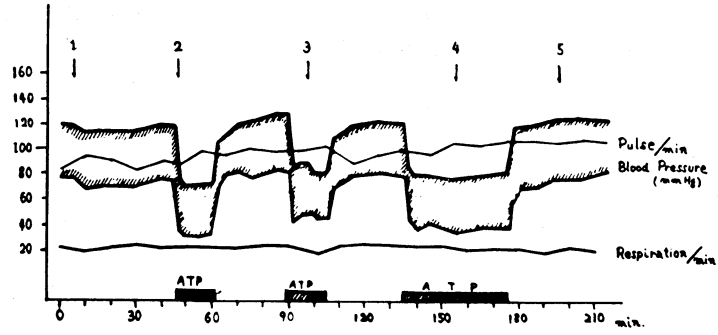

FIG. 6. A case with brain tumor operated upon under the controlled hypotension by ATP.

K.S. 20-year-old male Anesthesia: cocktail lytique, pentothal and N_2O

1. Intubated and anesthesia began. 2. Skin incised. 3. Skull opened. 4. Removal of a tumor. 5. Operation ended.

value. There was no case requiring any drugs for pressure elevation. In these operations, the duration of craniotomy reached 1 to 4 hours but no case developed cerebral edema.

B. Pulmonary Surgery

The lung with pleural adhesion always accompanies a considerable amount of bleeding on lysing the adhesion, although not much bleeding is seen in operation of lung without it. Eight difficult cases such as having had history of pleuritis, artificial pneumothorax or long duration of present illness were selected for the ATP hypotension. The results were, as shown in Table 17, that the blood loss remained within 100–280 ccm and accordingly the amount of blood transfusion required was small.

In the pulmonary surgery, as same as in the cardiac surgery mentioned below, various intrathoracic procedures cause alteration of blood pressure, so that it was difficult to maintain as stable hypotensive state as in the brain

TABLE 17. Pulmonary Surgery under ATP-Controlled Hypotension

No.	Sex	Age	Region of lung resected	Anesthesia	ATP used (g)	Blood pressure (mm Hg)			Blood loss (ccm)	Blood transfused (ccm)
						before	during (systolic)	after		
1	M	32	rt. upper	Ether gen.	3	132/86	80–70	123/70	187	200
2	M	28	〃	〃	3	126/66	85–70	108/60	153	200
3	F	38	rt. upper segmental	〃	2	128/60	75–70	120/70	100	100
4	M	21	rt. upper	〃	3	108/72	80–65	112/74	158	200
5	F	26	lt. upper segmental	〃	4	120/68	80–70	110/60	220	200
6	M	45	rt. lower	〃	5	135/90	75–65	104/80	200	200
7	F	36	lt. upper	〃	2	125/70	70–50	120/75	230	300
8	F	35	rt. upper	〃	3	128/78	60–55	120/75	280	300

surgery, but approximately 80–60 mmHg (systolic) could be kept to minimize the blood loss. It was also able to prevent postoperative intrathoracic hemorrhage by returning the blood pressure to its normal level for assuring hemostasis occasionally when necessary and before closing the chest wound.

C. Cardiac Surgery

ATP has been found to affect favorably on the heart, as described previously, and therefore the application of ATP is considered advantageous for a cardiac operation if the controlled hypotension should be indicated for its operative procedure.

For the operation of patent ductus arteriosus, the controlled hypotension makes the procedure of closing the ductus easier and also minimizes the blood loss and transfusion. In this operation, since the systemic circulation increases after the closure of ductus, the amount of blood transfusion must be as minimal as possible. Hence, this operation is believed to be a good indication of the controlled hypotension. When children develop tachycardia after anesthetized or opening the chest, as frequently so, the bradycardiac effect of ATP becomes more meaningful.

Three cases with patent ductus arteriosus were operated on under the controlled hypotension with success as indicated in Table 18, and one of them is shown in Fig. 7 in detail.

Upon making a shunt for the operation of Fallot's tetralogy, there is usually no reason to regard this method as its indication. Adult cases, however, sometimes show severe pleural adhesion with development of small collateral vessels which is presumed to be a compensatory mechanism for increasing the pulmonary circulation. For such cases, the controlled hypotension should be utilized because of hemorrhage during the lysis of adhesion. Since extreme hypotension may cause a thrombosis, it must be careful not to make blood pressure lower than 80 mmHg on expecting too much hemostatic effect.

TABLE 18. Cardiac Operations under ATP-Controlled Hypotension

No.	Sex	Age	Disease	Anesthesia	ATP used (g)	Blood pressure (mmHg)			Blood loss (ccm)	Blood transfused (ccm)
						before	during (systolic)	after		
1	F	4	Patent Ductus Arteriosus	Pentothal + N_2O	0.8	118/65	90–80	110/60	160	150
2	M	9	〃	〃	0.5	106/40	85–75	98/60	180	200
3	F	9	〃	〃	1.0	110/48	80–75	100/70	110	100
4	M	28	Fallot's tetralogy	Ether	1.0	124/90	90–80	112/50	143	200
5	M	21	〃	〃	2.0	114/75	90–80	104/64	158	200
6	F	23	〃	〃	1.0	120/80	85–80	110/65	120	200
7	M	21	Mitral stenosis	Pentothal + N_2O	0.8	125/90	90–80	110/70	180	200
8	F	23	〃	〃	0.6	110/74	85–80	112/74	140	160
9	F	22	〃	〃	1.0	122/68	85–80	120/80	150	180
10	F	29	〃	〃	1.0	114/74	90–80	106/70	220	200
11	F	28	〃	〃	0.6	120/80	80–75	108/60	310	300

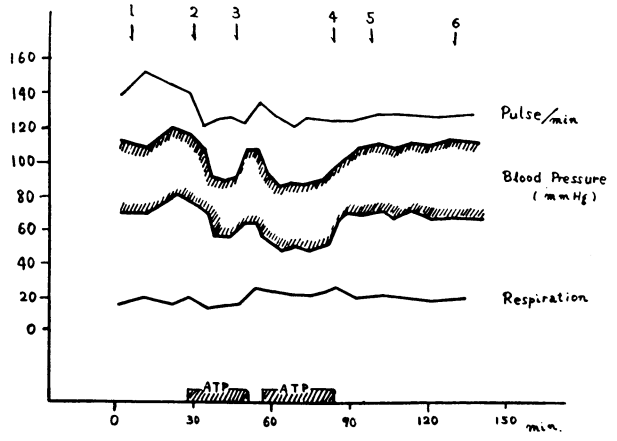

FIG. 7. A case with patent ductus arteriosus operated on under controlled hypotension with ATP.

T.T. 4-year-old female Anesthesia: Pentothal and N_2O

1. Intubated. 2. Skin incised. 3. Thorax opened. 4. Ductus cut. 5. Thorax closed. 6. Operation ended.

In mitral stenosis, there may be marked pathological changes in the lungs due to pulmonary congestion and dangerous complications such as pulmonary edema can be developed frequently by even slight alteration in hemodynamics. It is, therefore, useful to utilize the ATP-hypotension method for diminishing the volume of circulation and cardiac output so as to lighten a burden upon the pulmonary circulation, and moreover for saving the amount of blood transfusion to avoid a strain to the right heart. In the operation of valvulotomy, this method was performed on 5 cases with satisfactory results (Table 18).

Besides these, we have succeeded in applying ATP for artificial cardiac arrest on experimental open-heart surgery,[75][78] namely, injecting ATP into the coronary artery to make the heart beat stop electively, and this device is about to be in clinical use.

D. Application for the treatment of pulmonary edema

As a preventive measure for pulmonary edema in the operation of mitral stenosis, the utilization of ATP-controlled hypotension was already explained, but it has been experienced that this method can be an excellent emergency therapy for a postoperative pulmonary edema.

A 46-year-old male patient developed pulmonary edema postoperatively following extirpation of a mediastinal tumor (Fig. 8). Cyanosis, agony and dyspnea were with moist rales throughout the lung fields. B.P. was 160 over 85 mmHg and pulse 190. There was a large amount of foamy blood sputum found upon inserting an intratracheal tube. ATP was started by drip I.V. administration and his pulse, respiration and B.P. (90/50 mmHg) returned to

normal level in 30 min. He was recovered completely by 5 hours' ATP administration.

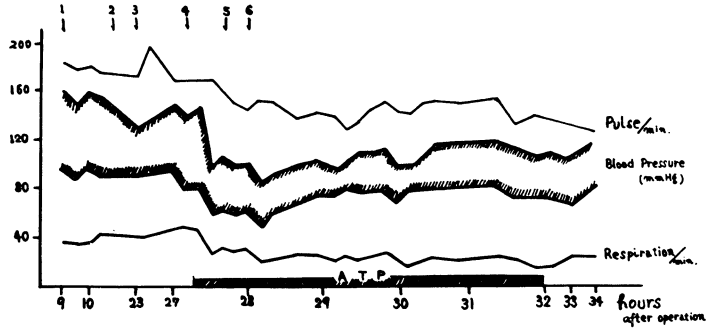

FIG. 8. A case of postoperative pulmonary edema developed following extirpation of a mediastinal tumor and treated by ATP drip administration.

M.N. 46-year-old male Mediastinal fibrosarcoma

1. Marked perspiration. Weak breathing sounds over the right lung. 2. Expectration difficult. 3. Dyspneic and cyanotic. 4. Moist rales throughout the lungs. 5. Rales diminished. 6. Rales disappeared.

TABLE 19. Liver Function Tests in Clinical Cases Operated on under the Controlled Hypotension by ATP

Age	Sex	Disease	Anesthesia	ATP used (g)	Bilirubin urine*		Urobilinogen in urine		Icterus Index		Takata's Reaction		Millon's test (mg/dl)		BSP at 30′ (%)	
					pre	post	pre	post	pre	post	pre	post	pre	post	pre	post
16	F	Intracranial hematoma	Hibernation +local anesthsia	4	−	−	+	+	4.0	5.0	−	−	8	7	5	5
20	M	Brain tumor	Potentiated N_2O general	4	+	+	+	+	8.0	6.0	+	−	12	10	10	5
21	M	Ventricular cyst	Hibernation +local	4	−	−	+	+	5.0	4.0	−	−	6	7	5	5
31	M	Skull fructure	Potentiated N_2O general	1	−	−	+	+	3.0	4.0	−	−	6	6	5	5
32	F	Brain tumor	〃	2	−	−	+	+	5.0	5.0	−	−	10	12	5	5
21	M	Imtracranial hematoma	Hibernation +local	1	−	−	+	+	6.0	5.0	−	−	9	8	5	5
28	M	Pulmonary tuberculosis	Ether general	3	−	−	+	+	4.0	4.0	+	+	14	16	10	10
26	F	〃	〃	4	−	−	+	+	4.0	3.0	−	−	9	7	5	5
35	F	〃	〃	3	−	−	+	+	3.0	3.0	−	−	4	6	5	5
4	F	Patent ductus arteriosus	Pentothal N_2O	0.8	−	−	+	+	3.0	4.0	−	−	6	5	5	5
28	M	Tetralogy of Fallot	Ether general	1	−	−	+	+	5.0	4.0	−	−	4	4	5	5
22	F	Mitral stenosis	Pentothal N_2O general	1	−	−	+	+	4.0	3.0	−	−	6	6	5	5

* Examinations were performed preoperatively and 1 week postoperatively in all cases.

E. Liver function in clinical cases

In each clinical case, liver function was investigated preoperatively and one week postoperatively with urine bilirubin test, urine urobilinogen test, Meulengracht's icterus index, Takata's reaction, Millon's test and BSP test (Table 19). Although it was anticipated that the influence of operation, anesthesia, blood transfusion and this method might accumulatively disturb the hepatic function, there appeared no particular change on these 6 tests. Also serum protein, albumin and globulin were proved to return to each preoperative level 3 days after operation. After all, it can be said that this controlled hypotension by ATP gives no harmful influence upon the hepatic function.

DISCUSSION

In order to approach a surgeon's dream "non-bleeding operation", various devices have been attempted. Controlled hypotension is one of those attempts and the author has established a new method utilizing ATP, of which superiority and advantage have been described. In this chapter, the important points will be discussed.

Controllability of blood pressure: The largest disadvantage of previous hypotensive methods is an inefficiency in controlling blood pressure. In the method with autonomic ganglion-blocking agent such as C_6, an individual difference in reactivity for the drug is so strong that it is difficult to foreknow its hypotensive effect and accordingly to decide its dosage for each individual case preoperatively. In general, excessive hypotension gives too much influence on a living body, while if the grade of hypotension is insufficient, the original purpose, *i.e.*, reducing hemorrhage can be hardly achieved and further it is difficult to calculate the dose to be added. Also this method requires to change patient's posture frequently during operation for regulating the level of blood pressure and may disturb the operative procedure. These problems are considered to derive from the deficiency in pressure-control. Arfonad is more quick acting, in comparison with C_6 and its action is of shorter duration and therefore permits greater control, but it is not easily obtainable in this country and, by the reports of various investigators, its controllability seems not entirely satisfactory.

The method with drip intravenous ATP has a perfect pressure controllability, namely, regardless of anesthesia used, posture or individual difference in reactivity to the drug, an adequate hypotensive level of desired duration can be obtained at any time only by regulating its dripping rate.

Generally, it is never necessary to keep a hypotensive condition throughout a full operative course. Moreover, if the hypotension lasts for a long period, it produces harmful effects on the living body, and ultimately an irreversible hypotensive state would be taken place. By this method, the duration of hypotension can be shortened as possible, because the effect of drug appears instantly after commencing its drip administration and can be maintained for a desired period at the level least necessary enough to inhibit bleeding, and a

discontinuance of the drip can quickly raise the blood pressure when bleeding is not anticipated during operation. In addition, it makes easy to find bleeding points and assure hemostasis and therefore does not leave the fear of postoperative hemorrhage.

Influences on the liver

Bromage[74] (1952) has reported that, under the hypotension by C_6, the liver shows a hypoxic state while there is no macroscopic change noted in other organs. In animal experiments performed by the author, the hypotension with C_6 of too low level or long duration (more than 3 hours) caused disturbances on the liver function, revealed by Millon's test, thymol turbidity test and Sawada-So's test, although there was no marked finding in other functional examinations. The changes which appeared in the tests mostly recovered to normal limit by the 3rd day. In the method with ATP, there was shown no functional disturbance or damage on the liver under the hypotensive influence of one hour's duration.

At the clinical application, the controlled hypotension by ATP exerted no influence on the liver, but when C_6 was employed to the patients with hepatic failure, the grade of dysfunction was intensified. This point can be essential for evaluating the method for controlled hypotension.

CONCLUSIONS

A new method of controlled hypotension was established.

1) As a drug, ATP (adenosine triphosphate), an important substance in energy metabolism was used.

2) By regulating the drip rate of its intravenous administration, a desired hypotensive level could be obtained at any time and for any duration.

3) This method could minimize blood loss and ensure hemostasis during operation with no danger of postoperative bleeding.

4) Electrocardiographic studies revealed that there was no change in the myocardium or conducting system.

5) Liver function was not influenced by this method and even its application to the patient with hepatic disturbance did not aggravate its grade.

6) This method could confine the duration of hypotensive state to the minimum of necessity and otherwise the operation could be performed under normotension. Therefore, the harmful influence of prolonged hypotension might be prevented.

7) Because of free pressure-controllability, no antagonistic drug was necessary.

8) No side effect of ATP was encountered under sufficient anesthesia.

From these points, it can be said that the controlled hypotension utilizing ATP is superior method, being entierly different from the other techniques for artificial hypotension.

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