0031-3998/84/1804-0365$02.00/0
PEDIATRIC RESEARCH

Vol. 18, No. 4, 1984
Printed in U.S.A.

Hyperimmunoglobulin-E-Associated Recurrent Infection Syndrome Accompanied by Chemotactic Inhibition of Polymorphonuclear Leukocytes and Monocytes

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Summary

An 8-yr-old girl with a history of severe recurrent infections including perinephritic, pulmonary, and hepatic abscesses had elevated serum IgE levels. Her serum inhibited chemotaxis of polymorphonuclear leukocytes (PMN) and monocytes. Exchange blood transfusion or plasma exchange at the time of severe infection resulted in normalization of chemotactic activity of PMN shown by the skin window method. Although this effect became negative 1 wk after the treatment, the procedures improved her clinical course. The patient's serum, obtained by exchange blood transfusion, *1)* inhibited normal PMN chemotaxis toward cultured supernatant of *E. coli*, zymosan-activated serum, and formyl methionyl-leucyl-phenylalanine (f·Met-Leu-Phe), a synthetic chemotactic peptide; *2)* inhibited monocyte chemotaxis, *3)* showed an absence of digestive activity of f·Met-Leu-Phe, *4)* was heat stable at 56°C for 30 min and *5)* showed an absence of antigenicity of IgE in a partial purified inhibitor with a molecular weight of 30,000–40,000. The inhibitory effect seemed to be reversible.

Abbreviations

f·Met-Leu-Phe, formyl methionyl-leucyl-phenylalanine
HIE, hyperimmunoglobulin E recurrent infection syndrome
IgE, immunoglobin E
PMN, polymorphonuclear leukocytes

HIE is defined as having several clinical features: recurrent infection caused by *Staphylococcus aureus* and *Hemophilus influenzae*, recurrent eczematoid rashes and mucocutaneous candidiasis, moderate eosinophilia, and hyperimmunoglobulin E (1, 3, 5, 10, 11, 18, and 21). The infections are often remarkable for their paucity of surrounding inflammation, causing so-called "cold" abscesses. The studies so far have revealed that impaired chemotactic movement of PMN may be the primary pathogenesis of repeated infections. The basis of the impaired PMN movement, however, is a matter of current controversy. It has been generally accepted that the cause of impaired PMN chemotaxis existed in the patient's own PMN (1, 5, 10, 11, 18, 21), but, recently an inhibitor of chemotactic movement of normal PMN was demonstrated in the serum of some patients with the disease (7, 15). In the present paper, we describe a case of HIE accompanied by inhibition of PMN and monocyte chemotaxis. Several characteristics of the inhibitor were also studied.

CASE REPORT

The patient, an 8-yr-old Japanese girl, was the product of a normal full-term pregnancy and delivery. Both parents and a sibling, a 10-yr-old sister, are in good health. Her paternal grandfather and grandmother are first cousins. No one in the family had a history of increased susceptibility to severe infection. She had eczematoid rash 1 wk after the delivery, which was intractable to treatment. At 6 mo of age, she had a surgical operation on a perinephritic abscess caused by *E. coli*. Severe post-operative complications of pneumonia and meningitis caused by candida followed for the next 4 mo. Pulmonary abscesses caused by *Staphylococcus aureus*, *Hemophilus parainfluenzae*, and *Hemophilus influenzae* were diagnosed at 4 2/12 yr, 5 7/12 yr, and 6 4/12 yr of age, respectively. During this period, skin abscesses and otitis media caused by *Staphylococcus aureus* and a nail infection with candida were noted repeatedly. At 8 6/12 yr of age, she was again admitted to our hospital because of high fever and abdominal pain. The diagnosis of hepatic and intra-abdominal abscesses were made on her physical examination (a round swelling with 3 cm in diameter at right lower abdomen), on roentgenography (an elevation of diaphragma at right side) and CT scanning (multiple round area with low density in the liver, and a round mass in the abdominal cavity). Loss of bone density with thinning of vertebrae was noticed by a roentgenogram of the spine. The laboratory findings on admission were as follows: leukocyte count, 17,700/mm^3 (neutrophil 75%, lymphocyte 21%, monocyte 2%, and eosinophil 2%); total protein, 6.8 g/dl (albumin, 32.8%; α_1-globulin, 6.2%; α_2-globulin, 1.3%; β-globulin, 8.6; γ-globulin, 34.0%); CRP, 4+; rheumatoid factor, 2+; anti-DNA titer 1:320; IgG, 1429 mg/dl; IgA, 73 mg/dl; IgM, 570 mg/dl; IgE, 26,000 U/ml; CH50, 33.8 U/ml; C_3 145 mg/dl; C_4, 20.0 mg/dl; T cell, 72%; B cell, 19.4%; serum Zn, 102 μg/dl; Cu, 150 μg/dl; and histamine, 5.4 ng/ml. Thymidine uptake of lymphocyte stimulated by phytohemagglutinin and concanavalin A was normal. A strong positive skin reaction against eggs and cow's milk was noted. Our screening tests for PMN function revealed the following: positive myeloperoxidase of PMN, positive nitrobule tetrazolium dye reduction test (8), reduced mobilization of PMN by skin window test (900 cells toward patient's serum, 4500 cells toward control serum, and 3050 cells toward phosphate buffered saline (9). Further studies on phagocytosis (19), bactericidal properties (19), and chemotaxis of normal PMN in the presence of patient's serum were carried out. The first two functions of the patient's PMN were similar to those of control, whereas the patient's serum clearly inhibited normal PMN chemotaxis (1/4 of control). Based on these results, to

prevent post-operative infections because the patient had had severe complications from the previous operation of the perinephritic abscess, an exchange blood transfusion was performed immediately after the surgical operation of hepatic and intraabdominal abscesses. A pathologic study showed that these abscesses were caused by *Staphylococcus aureus* and around them small amounts of PMN had infiltrated.

As shown in Figure 1, the chemotactic movement of the patient's PMN apparently improved within 48 h after the exchange blood transfusion by the skin window method (9). The effect, however, disappeared 1 wk after the transfusion. The almost identical result was obtained at repeated exchange blood transfusions and plasma exchange (Fig. 1). The clinical course of the patient after the operation was without further complications. The blood obtained at exchange blood transfusion was used for further studies.

The presence of chemotactic inhibitors was detected in the patient's serum by the same technique at ages of 9 9/12 yr and 11 yr, when a pulmonary abscess recurred.

MATERIALS AND METHODS

Preparations of PMN and monocytes. Heparinized blood was obtained from the patient and the normal volunteers. Fractions of mononuclear cells and PMN were separated on Ficoll-Conray (specific gravity, 1.078) gradient as described earlier (2). The first fraction contained almost all parts of monocytes, but was contaminated with 70–80% lymphocyte. Further purification was not performed because the presence of lymphocyte had no influence on monocyte chemotaxis (20). The second fraction consisted of more than 95% of PMN. Each fraction was washed two times with buffered saline (pH 7.4) and resuspended in RPMI 1640 (Gibco Lab., NY) containing 5% fetal calf serum at a density 2×10^5 cell/ml in monocytes and 5×10^5 cell/ml in PMN.

Measurement of cyclic AMP and cyclic GMP in PMN. Cyclic AMP and cyclic GMP were measured using commercially available kit (Yamasa Shoyu Co., Tokyo).

Preparation of chemoattractant. Culture filtrate of *E. coli* was prepared by the method of Ward *et al.* (22). *E. coli* was grown at 37°C for 24 h in medium TC-199. The culture medium was centrifuged at 10,000 rev/min for 30 min and passed through 0.45-μm Millipore filter. Zymosan-activated serum was prepared by the method of Cates *et al.* (4). Serum obtained from normal volunteers was pooled, incubated with zymosan (25 mg/ml) (Sigma Chemical Co., St Louis, MO) at 37°C for 30 min and centrifuged at 500 *g* for 10 min. The supernatant was heated at 56°C for 30 min. Both *E. coli* culture filtrate and zymosan-activated serum were stored at −70°C and used after dilution in an appropriate concentration.

Synthesized chemotactic peptide f·Met-Leu-Phe was purchased from Protein Research Foundation, Osaka, Japan.

PMN chemotaxis. Chemotaxis using the Boyden chamber was studied according to the method of Horwitz and Garrett (13), using polycarbonate filter (Nuclepore filter; General Electric Co., NY) 2-μm pore size. The upper chamber was filled with 5×10^5 cells suspended in RPMI 1640 containing 5% fetal calf serum and the lower chamber was filled with 1.0 ml of medium containing chemoattractant. Chemotactic activity was displayed with the number of migrated granulocytes. In order to test an inhibitory activity of the patient's serum and partial purified factor, these were added to the lower chamber. This method was practical and convenient, and the results obtained were similar to each other when these were added to the upper or the lower chamber. The percentage inhibition of PMN was calculated by the formula: 100 × (1 − number of migrated PMN in the presence of patient's serum/number of migrated PMN in the presence of control serum).

Random mobility. Random mobility was tested using the Boyden chamber with buffered saline without chemoattractant in the lower chamber.

Monocyte chemotaxis. Monocyte chemotaxis was studied by the Boyden chamber using 5-μm pore polycarbonate filter (12). The upper chamber was filled with 2×10^5 cells and the lower chamber with 1.0 ml of medium containing zymosan-activated serum (10%) and test sample.

Digestive activity of synthetic peptide. f·Met-Leu-[^{3}H]Phe (specific activity, 46.4 Ci/mol) was purchased from New England Nuclear Corp., purified on Dowex 50 W X 2 with 0.01 N HCl, stored at 4°C, and used after neutralizing with 0.1 N NaOH as described (17). The 0.05 μCi of labeled peptide (10^{-9} M) was incubated with 20 μl of either the patient's or control's serum at 37°C for 2 h. After incubation the medium was deproteinized with acetone and lyophilized. In order to detect f·Met-Leu-[^{3}H] Phe and its digested products, ascending paperchromatography was used with a solvent system of *n*-butanol:acetic acid:H_2O, 3:1:1 (16). After development, the chromatograms were cut into 1-cm strips, which were placed in vials and counted by liquid scintillation counter (Pakard, TRI-CARB, B 2450) in a ACS II (Amersham).

Gel filtration. A Sephadex G-200 column, 2.9 × 90 cm was equilibrated with 0.04 M, pH 7.4 phosphate buffered saline at 4°C. The column was calibrated with standard molecular weight marker proteins. Three milliliters of the control or patient's serum was layered on the gel and eluated with phosphate buffered saline. The eluate was fractionated and assayed for chemotactic inhibitory activity. The percentage inhibition was calculated by the formula described above, where each corresponding fraction was used as a control and a test sample. IgE content in these fractions was measured by enzyme immunoassay method using commercially available kit (Kainos Laboratories, Inc., Tokyo).

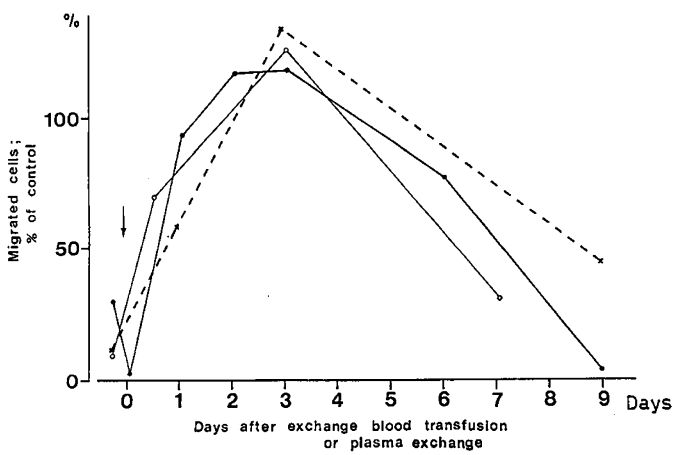

Fig. 1. Effect of exchange blood transfusion of plasma exchange on polymorphonuclear leukocyte chemotaxis shown by skin window method (8). After 7 h, the number of leukocytes that migrated into the skin window chamber, which was filled with the patient's or control serum at the test time, was counted, and the percentage of the former number to the latter number was calculated. (●——●), the first exchange blood transfusion; (○——○), the second exchange blood transfusion; and (×-----×), plasma exchange.

RESULTS

Cyclic AMP and cyclic GMP in the patient's PMN. Cyclic AMP and cyclic GMP in the patient's PMN were 4.0 pmol/10^7 cells (control, 3.9 ± 1.6) and 0.2 pmol/10^7 cells (control, 0.18 ± 0.01), respectively.

Chemotaxis of patient and control PMN. Random mobility and chemotactic movement of the patient's and control's PMN were similar when these were washed two times with buffered saline (Table 1). Similar observations were made when washing was done, after the incubation with patient's serum at 37°C for 30 min (the data was not shown); however, in the presence of

Table 1. *Polymorphonuclear leukocyte (PMN) chemotaxis*

Chemoattractant	Patient PMN	Control PMN
Buffer, phosphate buffered saline	8*	4*
Medium, RPMI 1640	12	21
Chemotactic peptide†		
10^{-8} M	128	104
10^{-7} M	167	153
E. coli supernatant (10%)	92	101
Zymosan-treated serum (5%)	179	137

* The number of migrating cells in five microscopic fields.
† *N*-formyl methionyl-leucyl-phenylalanine.

Table 2. *Effect of serum inhibitor on the movement of polymorphonuclear leukocyte*

Chemoattractant	Control serum*	Patient serum*
Chemotactic peptide† (10^{-7} M)	268 ± 22‡	45 ± 2‡
E. coli supernatant (10%)	336 ± 13	116 ± 23
Zymosan-treated serum (5%)	923 ± 84	358 ± 41

* 10%.
† *N*-formyl methionyl-leucyl-phenylalanine.
‡ The number of migrating cells in five microscopic fields.

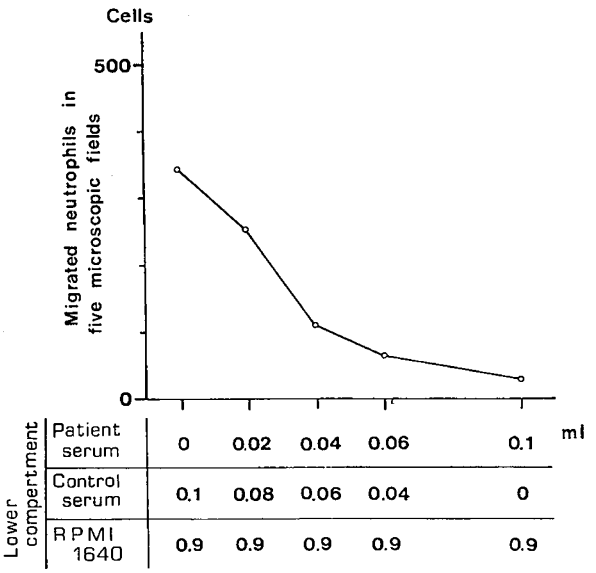

Fig. 2. Inhibitory effect of the patient's serum on chemotaxis of normal polymorphonuclear leukocytes, shown by replacing control serum with the patient's serum gradually.

patient's serum (10%), chemotaxis of normal PMN was impaired toward all of three chemoattractants tested (Table 2). Using five different normal donors, this observation was confirmed. The degree of inhibitory effect of patient's serum was dose-dependent as shown in Figure 2 where, as the amount of control serum was replaced with increasing amounts of the patient's serum, the number of mobile PMN toward synthetic peptide was reduced. Figure 3 displays the chemotaxis of PMN at varying concentrations of f·Met-Leu-Phe (1×10^{-8} to 6×10^{-7} M). The peptide concentration to obtain the maximum chemotaxis was identical, amounting to 8×10^{-8} M in the presence of both the control and the patient's serum (5%), but the maximum number of cell movements was clearly reduced in the latter situation.

Chemotaxis of patient's and control monocyte. Random mobility and chemotactic movement of patient's and control monocytes were similar. In the presence of patient serum, chemotaxis of normal monocytes was impaired toward zymosan-activated serum (Fig. 4).

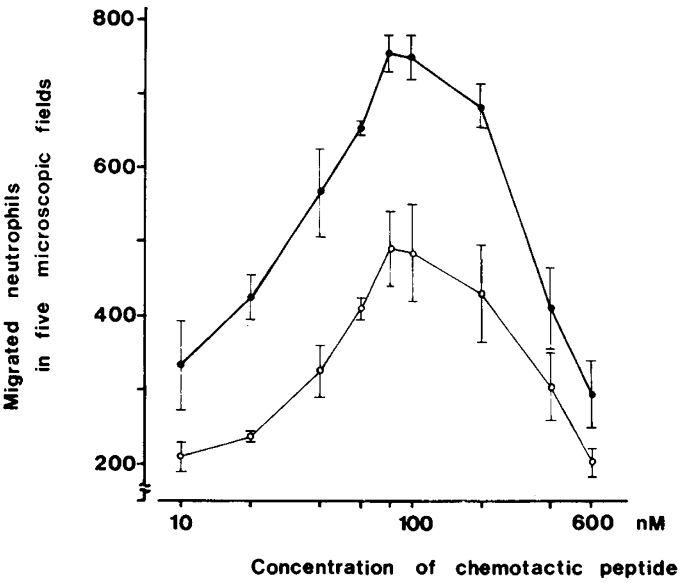

Fig. 3. Chemotaxis of normal polymorphonuclear leukocytes by increasing concentration of chemotactic peptide (f·Met-Leu-Phe) in the presence of the patient's serum (5%) and in the presence of control serum (5%). (O——O), patient's serum and (●——●), control serum.

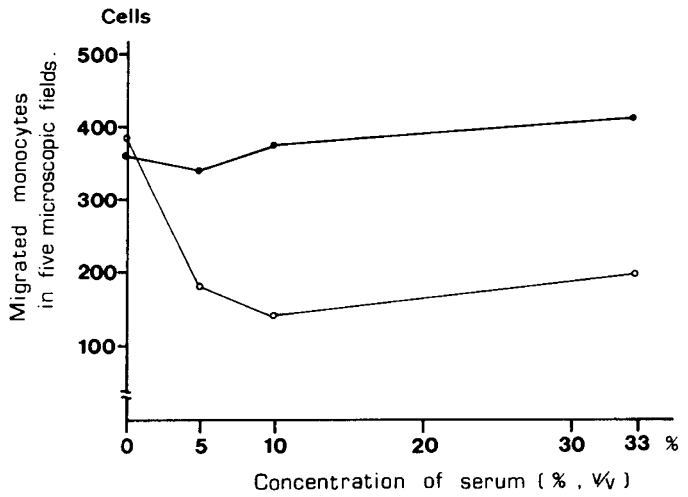

Fig. 4. Inhibition of normal monocyte migration toward zymosan-activated serum by increasing concentration of the patient's serum. (O——O), patient's serum and (●——●), control serum.

Digestive activity on labeled synthetic peptide. The radioactivities of the incubated samples containing patient's and control serum, appeared in a peak of f·Met-Leu-Phe with a different Rf value of presumed products of Met-Leu-Phe, Leu-Phe, and Phe. So neither the patient's nor the control serum had any activity of f·Met-Leu-Phe digestion.

Partial purification. Chemotactic inhibitory activity of the patient's serum was stable when incubated at 56°C for 30 min. As shown in Figure 5, two peaks of percentage inhibition were observed in the fractionated samples of patient's serum. The first peak corresponded to an approximately 30,000–40,000 dalton molecular weight and the second peak was probably that of the one absorbed with Sephadex G-200. Neither of them had IgE antigenicity. IgE peak was found in at the respected site of the fraction.

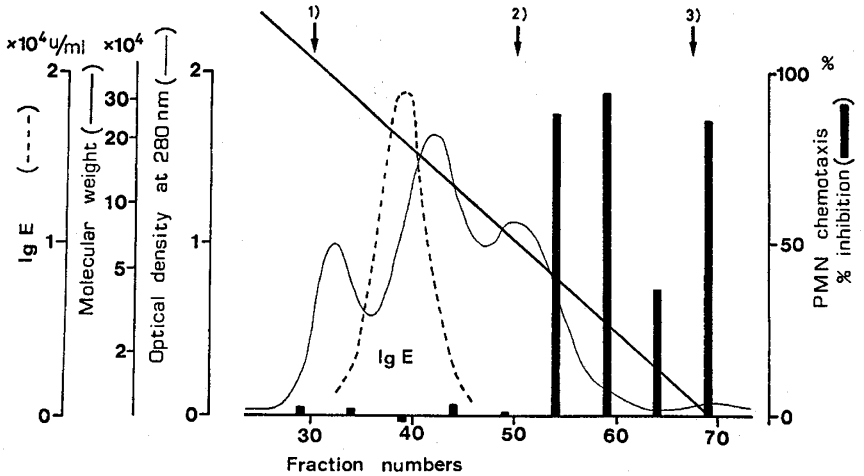

Fig. 5. Chromatography of patient's serum on Sephadex G 200. Alternate tubes was assayed for chemotactic inhibitory factor by the Boyden chamber method. *1)* blue dextran; *2)* albumin; and *3)* cytochrom C.

DISCUSSION

Our clinical and laboratory observations include *1)* severe recurrent infection caused by *Staphlococcus aureus* and *Hemophilus influenzae*, accompanied by allergic rash and candidiasis, *2)* elevated serum concentration of IgE and *3)* impaired PMN chemotactic movement by skin window method. These observations indicate that the patient was suffering from HIE (1, 3, 5, 10, 11, 17, 21). Her other defense mechanisms against infection, including cellular and humoral immunity and phagocytosis and bactericidal capacity of PMN, were normal. Defective chemotaxis, as found in other patients with HIE (1, 5, 10, 11, 17, and 21), appeared to be a major factor responsible for the recurrent infection.

In our patient, PMN functions were normal. Cyclic AMP and cyclic GMP concentration in the patient's PMN were within normal limits. *In vivo* movement of the patient's PMN was impaired and defective PMN chemotaxis was normalized within 48 h after exchange blood transfusion or plasma exchange by the *in vivo* study using the skin window method. The study of the patient's serum, obtained by exchange blood transfusion, revealed that the patient's serum caused an impaired chemotactic movement of normal PMN (Table 1), the degree of impairment being dose-dependent of patient's serum (Fig. 2). After washing the patient's and control's PMN, which were incubated with patient's serum in advance, the PMN chemotactic movement returned to normal. In addition, the patient's serum had no digestive activity of f·Met-Leu-Phe peptide. These results demonstrate that there is an inhibitor of chemotaxis or an inactivator of chemotactic factor in her serum, and the effect of such substance seems to be reversible. The patient's serum inhibited chemotaxis of normal PMN toward three different factors as shown in Table 2.

These observations suggest that the impaired chemotactic movement is attributable to an inhibitor of chemotaxis but not an inactivator of chemotactic factor. Another possible interpretation may be that the mechanism of inhibitory chemotaxis in the patient could be involved in the postreceptor site of PMN movement. This possibility was supported by our observation that the concentration of f·Met-Leu-Phe needed to obtain the maximum chemotactic movement of PMN was 8×10^{-8} M in the presence of both control and patient's serum. In other words, the maximum movement did not shift to a lower concentration of the chemotactic peptide (14).

In earlier studies of HIE, it was reported that the cause of defective chemotactic movement existed in patient's PMN (1, 5, 10, 11, 17, 21). On the other hand, Friedenberg *et al.* (7), Matsumoto *et al.* (15), and Donabedian *et al.* (6) found a chemotactic inhibitor in their patient's serum or cultured medium of patient's mononuclear cells. A more likely identity of our patient's chemotatic inhibitor is the factor identified by Donabedian because heat stability and the ability to inhibit monocyte chemotaxis as well as PMN chemotaxis are identical in this factor.

In their assay system, the incubated PMN with HIE chemotactic inhibitor was washed with buffered saline before placing them in the Boyden chamber, and, therefore, the inhibitory effect of their factor seemed to be irreversible. On the other hand, the effect of our patient's inhibitor was reversible, as discussed above. Molecular weight of both factors appeared to be different and further study is necessary. Because the partially purified inhibitor in the present case had no antigenicity toward IgE, a relationship between elevation of serum IgE and the inhibitory factor is still obscure. Further characterization, origin, and functioning point of our patient's inhibitor should be studied in the future.

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24. Received for publication December 29, 1982.
25. Accepted for publication July 5, 1983.

0031-3998/84/1804-0369$02.00/0
PEDIATRIC RESEARCH

Vol. 18, No. 4, 1984
Printed in U.S.A.

Cardiac Function and Myocardial Metabolism during Tachycardia Induced by Atrial and Ventricular Pacing

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Summary

We studied atrial and ventricular pacing-elicited tachycardia in mongrel adult dogs to evaluate ensuing changes in cardiac function and myocardial metabolism. The aortic pressure, left ventricular pressure, and left ventricular end diastolic pressure were measured under anesthesia. Using an electromagnetic flowmeter, coronary blood flow and aortic blood flow were recorded simultaneously with the recording of ECG. Atrial and ventricular pacing (1.5 times the basic heart beat) were performed using a catheter introduced via the jugular vein and positioned in the coronary venous sinus.

Aortic blood and coronary venous blood were sampled for determination of blood oxygen concentrations and lactic acid concentrations. The results showed that oxygen extraction changed little compared with the control study on atrial pacing (AP) and ventricular pacing (VP) whereas the lactate uptake showed little change in the AP control study but decreased slightly in the VP study. It appears that aerobic metabolism occurs during both AP and VP when the pacing rate is not more than 1.5 times the basic heart beat.

Abbreviations

ABF, aortic blood flow
AP, atrial pacing
CBF, coronary blood flow
HR, heart rate
LVEDV, left ventricular end diastolic volume
PAO, aortic pressure
PLV, left ventricular pressure
PLVED, left ventricular end diastolic pressure
VP, ventricular pacing

Along with the advances in the treatment and diagnosis of heart diseases, there has been progress in artificial pacemakers. The pacemaker is now used frequently for the treatment and prevention of arrhythmia in both children and adults. Although previous studies have shown clearly that AP is more physiologic and desirable than VP, there are some cases which necessitate the use of VP because of the condition of the illness (1, 4, 6). There is little opportunity to investigate clinically a tachycardiac state that is maintained by AP or VP for an adequate length of time. An attempt to learn to what extent tachycardia can be maintained by AP or VP, even though nonphysiologic, is by no means useless. From such a viewpoint, we induced experimentally tachycardia by AP and VP in mongrel adult dogs and studied changes in cardiac function and myocardial metabolism.

SUBJECTS AND METHODS

Ten mongrel dogs weighing 14–24 kg were anesthetized by intravenous injection of pentobarbital (30 mg/kg). After intratracheal intubation, a ventilator was used to achieve a constant pH and PO_2 in arterial blood.

With the animals fixed in a supine position, a median incision was made. The pericardial membrane was cut widely from the center to the apex. As shown in Figure 1, a catheter was introduced from the femoral artery and positioned in the arch of the aorta and left ventricle. The catheter was to a Statham $P_{23}D_b$ transducer for measuring the P_{AO}, P_{LV}, and P_{LVED}.