The Postpericardiotomy Syndrome and Antiheart Antibodies

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SUMMARY
In a prospective, double-blind study, heart-reactive antibody in high titer was detected, using an indirect immunofluorescent technique, in the serum of patients in whom the postpericardiotomy syndrome developed after intrapericardial surgery. The syndrome occurred in 26 of 56 consecutive longterm survivors of such surgery, an incidence of 30%. Presence of antibody correlated closely with the clinical syndrome. Demonstration of this antiheart antibody in high titer appears to offer laboratory confirmation of the syndrome.

Additional Indexing Words: Cardiac surgery, infants and children Heart-reactive antibody Intrapericardial surgery Postoperative complications Immunofluorescence Immunology

THE POSTPERICARDIOTOMY SYNDROME
is a common complication of surgery that involves entry into the pericardium. It occurs in approximately 30% of such patients, irrespective of whether the pericardium alone or a cardiac chamber, valve, or vessel is opened.1-6 A possible explanation for the occurrence beyond the first postoperative week of fever and both pericardial and pleural reactions, sometimes with effusions, is that the syndrome represents an immunologic response to damaged autologous tissue within the pericardium.1-2 To test this hypothesis, we undertook a prospective study to determine whether an antihete antibody developed in patients following intrapericardial surgery, and if so, whether its appearance bore any relation to the clinical syndrome.

Plan of Study
Patients
The study group consisted of a consecutive series of longterm survivors of intrapericardial surgery for congenital heart disease. Concurrent analyses were made on a double-blind basis of the serologic and clinical findings at prescribed intervals during the hospital course and on the first two visits after discharge. The investigators doing the immunologic studies had no contact with the patients and were unaware of the clinical course. Those responsible for evaluation and management of the patients did not know the results of the serologic studies while the patients were in the hospital. The results were compared periodically. The operative and postoperative management was standardized as much as possible. Antibiotics in the form of ampicillin and methicillin were administered for the first five days after surgery. Thereafter, antibiotics were given only for clear evidence of infection. No other medications were utilized except for digitalis and diuretics as indicated. Neither steroids nor salicylates were employed unless, under exceptional circumstances, it was the consensus of two of the investigators that they should be used. Ambulation was begun after the patients were afebrile for 48 hours. Patients were discharged if there was no appearance of clinical manifestations or worsening of the syndrome when they were ambulatory.

Controls
Fifteen patients undergoing either thoracic but noncardiac surgery or fracture surgery involving skeletal muscle disruption, or general surgery requiring large transfusions of blood served as controls. In addition, sera were analyzed from ten patients admitted with pericarditis of other causes: rheumatoid arthritis in two, virus in three, uremia in two, and unknown etiology in three others who had thalassemia major and hemochromatosis.

Clinical Evaluation
Judgment as to absence or presence of the syndrome, and its severity, was made by at least two cardiologists, based on daily examinations of the patients in the hospital and on laboratory evidence that included electrocardiograms and roentgenograms preoperatively.
and at least biweekly during the hospitalization.\textsuperscript{1-4, 7, 8} The same set of tests was made on the first two postoperative visits after release from the hospital and after that on indication. If the syndrome occurred, it was considered to be mild, moderate, or severe depending on the duration and intensity of the illness.

Previous experience with this syndrome had shown that it was difficult to make a distinction within the first postoperative week between surgical pericarditis and the postpericardiotomy syndrome. During the first few days after a pericardiotomy, a pericardial friction rub can be heard transiently, and ST segments are elevated in the electrocardiogram and then T waves become abnormal in many patients. Furthermore, in patients whose surgery involves use of the heart-lung machine and blood transfusions, fever is common in the first few days after surgery. Our earlier studies showed that these changes related to the surgery per se were gone by the end of the first postoperative week.\textsuperscript{1-4}

Patients were judged to have postpericardiotomy syndrome when there was either the persistence of, or appearance of, the following combination of findings beyond the first postoperative week: fever not otherwise explained, together with signs of pericardial reaction on physical examination and serially obtained electrocardiograms and roentgenograms. Pericardial effusion was evaluated by physical findings, including dämping of heart sounds and signs of tamponade when that occurred, and by serial radiologic studies as well as, in most instances, by echocardiography. Angiocardiography was used in one child for confirmation of marked effusion. Decrease in voltage in the electrocardiogram was not noted unless there was considerable pericardial effusion. Pleural involvement was indicated on physical examination by pleural rub and/or signs of effusion and by radiologic studies including films in decubitus position. Chest pain was not a prominent feature of young children with the syndrome, although older children did sometimes complain of pain. Neither arthralgia nor swelling of joints was seen in this syndrome in the pediatric age group, either during the course of this study to be reported, or in our previous cases. Elevation of white cell count and in polymorphonuclear cells was present during the syndrome.

Postoperative complications with which the postpericardiotomy syndrome can be confused were specifically investigated and excluded: infection, including possible bacteremia or endocarditis; postperfusion syndrome with fever, hepatosplenomegalgy and atypical lymphocytes; atelectasis; and cardiac failure.

**Serologic Studies**

Serum samples were collected preoperatively and two or three times weekly during the hospital stay, as well as on the first two postoperative visits. In the operating room samples of pericardium and myocardium were obtained and quick-frozen in liquid nitrogen at -76°C for use as substrate.

An indirect immunofluorescent technique\textsuperscript{9, 10} was utilized for demonstration of antibody. Serum samples in 1:5 dilution were layered onto frozen, cut sections of autologous pericardium, myocardium, and cadaver heart, fixed to glass slides. After 30 min, the sections were washed twice in 0.05 M phosphate-buffered saline at a pH of 7.5. They were then counterstained with fluorescein-labeled goat antihuman IgG for 30 min. They were again washed and were mounted in 50% glycerol for viewing, using a Zeiss ultramicroscope. Intensity of fluorescent staining was judged on a scale of 0 to 4+ by two experienced observers (J.C.M. and J.Z.), who read the slides independently and agreed upon the results.

To study organ and species specificity of the antibody, positive sera were absorbed by various human and animal tissues, including human skeletal muscle, thymus, kidney, and liver as well as canine cardiac and skeletal muscle. Absorption by streptococcal membrane was also tested. One milliliter of serum was combined for 60 min with 40 mg of lyophilized tissue, and the supernate was used as described above for determination of immunofluorescence. Frozen sections of these organs were also substituted for heart and pericardium in the immunofluorescence system.

**Results**

**Clinical Investigation**

In the first 18 months of this study, 26 patients out of 86 survivors of intrapericardial surgery had the postpericardiotomy syndrome (PPS), an incidence of 30%. This has been the usual incidence each year at this institution. The syndrome was judged to be mild in seven, who had fever, pericardial friction rub, and continuing electrocardiographic evidence of pericardial abnormality beyond the first postoperative week but only slight pericardial or pleural effusion radiographically. Four had severe signs of illness: fever for longer than two weeks and with marked pericardial and moderate pleural effusion; three of these required one or more pericardiocenteses for cardiac tamponade. Fifteen had PPS in moderate form with definite but not large pericardial effusion and often with pleural effusion.

Duration of hospitalization was one criterion of severity, since the patients remained in the hospital until there was no evidence that signs or symptoms worsened when the patients were ambulatory. The length of hospital stay was more reliable in this regard than was duration of illness, for some of the signs (particularly the electrocardiographic abnormalities) tended to persist, and the patients after discharge were not examined sufficiently frequently to note the day of resolution of the last abnormality. The average stay in the hospital was 12 days for those with no syndrome, 15 for those with mild PPS, 23 for those with moderate involvement, and 35 days for those with the severe form of the complication.
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The kinds of malformations for which the patients underwent cardiac surgery were the usual range for pediatric cardiology patients. Most operations involved cardiopulmonary bypass, but ten did not, as for example, when the surgery was a palliative procedure to perform an aortico-pulmonary anastomosis or to create an atrial septal defect. The syndrome occurred in one child with a patent ductus arteriosus whose pericardium was entered to facilitate cardiac massage during a period of cardiac slowing and hypotension when there was bleeding from the aortic end of the ductus (see below, fig. 4). The only operation following which there was no evidence of PPS was the Mustard procedure for complete transposition of the great arteries. None of nine babies and children whose pericardium was to a large extent removed in order to construct an intra-atrial baffle developed the syndrome.

In this study the incidence of the syndrome varied with the age of the patients (fig. 1). Although about half of the subjects were aged five years or less, only one-fifth of the instances of the syndrome were in this young age group. ($\chi^2 = 11.3; df = 1; P < 0.001$). None of the eleven babies operated on in the first year of life had the complication, whereas all but two of the 12 children aged 11–15 years had PPS. The four patients with severe illness were over 11 years of age.

Fourteen patients had undergone a previous intrapericardial operation, usually for palliation in infancy. None had the syndrome after the first operation, but seven of them did develop the complication at subsequent surgery during the course of this study.

Steroids were administered to only one patient for treatment of a severe form of the syndrome. Following an aortico-pulmonary (Waterston) anastomosis, he developed high fever and two episodes of pericardial tamponade requiring pericardiocentesis. Signs of the illness promptly abated when administration of prednisolone was instituted. Therapy was tapered and then terminated after three weeks (fig. 6). Steroids in therapeutic doses were used for a boy with tetralogy of Fallot just prior to and for the first 17 days following operation. The medication was employed to correct a previously demonstrated hemorrhagic diathesis due to vascular fragility. He did not bleed unduly, but the treatment did not prevent occurrence of a moderate form of severe PPS.

Salicylates were given to one patient with severe syndrome from the ninth postoperative day for a month. She promptly became afebrile; the signs of large pericardial and pleural effusions resolved more slowly.

Immunologic Studies

All preoperative sera and the sera from control patients were nonreactive for antiheart antibodies. During the postoperative course of some of the cardiac patients, however, heart-reactive antibodies were demonstrated by the indirect immunofluorescent technique as staining in the region of the sarcolemmal membrane. The greater the intensity of staining and the greater the degree of positivity, the more diffuse was the staining. In some with high titer, the staining was still present in a 1:80 dilution.

The antiheart antibody was demonstrated on absorption studies to bind to heterologous as well as to autologous heart tissue and to be specific for muscle, skeletal as well as cardiac. It bound to a lesser degree to smooth muscle but did not bind to other organs such as liver, kidney, spleen, lung. It was not absorbed by streptococcal membrane. The immunologic data on the first 60 patients in the ongoing, prospective study are reported separately in greater detail.\textsuperscript{10}

Serial serologic testing in the postoperative patients revealed three patterns of response of antiheart antibody. In figure 2 the findings are represented as three conceptualized curves based on a composite of data points from the subjects in each group. In 13 cases there was no rise at all. This Group 1 was considered negative. In 23 cases there
was elevation to greater than 2+, beginning near the end of the first week and declining in the second month. This group was considered positive (Group III). A larger, intermediate group of 50 patients had a rise in heart-reactive antibody beginning at the same time, but the level did not exceed 2+, and it dropped away by the end of the first month.

**Correlation of Clinical and Immunologic Data**

When the results of the clinical and serologic studies, obtained on a double-blind basis, were compared, a close correlation was found between the manifestation of PPS and presence of antihert antibody in high titer (fig. 3). None of the 13 cases in Group I with negative antibody response had the syndrome, while all 23 cases in Group III with high antihert antibody had PPS that was severe in four and moderate in 15. Of the intermediate Group II consisting of 50 cases, three had a mild episode of the syndrome.

A close correlation was observed between rise of antibody and appearance of the syndrome not only collectively but also in each patient individually. Resolution of the clinical signs was followed later by a fall in antibody titer (figs. 4-6). Fever due to the complication usually merged with the early postoperative fever, and the rise and fall of the white blood cell count followed that of the temperature curve. Friction rub, pleural and pericardial reaction, electrocardiographic abnormalities, and elevation of heart-reactive antibody to 2+ or higher were present by the end of the first week.

**Figure 2**
Conceptualized curves from multiple data points show three patterns of response of heart-reactive antibody titer: negative (13 cases in Group I), intermediate and less than 2+ with decline by one month (50 cases in Group II), and positive in high titer and of duration more than one month (23 cases of Group III).

**Figure 3**
Correlation of antibody response with presence or absence of PPS. None with negative antibody response but all with positive antibody had the syndrome. Three of the 50 with intermediate elevation had a mild form of the syndrome.

Clinical and radiologic signs of improvement usually occurred before the electrocardiographic abnormalities disappeared, and the elevated anti-
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manifestations of illness responded within a few days, but the heart-reactive antibody titer was still elevated significantly into the second postoperative month. It was normal in the third month (fig. 6). In the patient who received salicylates because of severe syndrome, heart-reactive antibody remained elevated greater than 2+ for more than a month longer, but clinical improvement was evident within a week.

Discussion

This study demonstrated that heart-reactive antibody in high titer appeared in the serum of patients in whom the postpericardiotomy syndrome developed after intrapericardial surgery and that the presence of the antiheter antibody correlated with the clinical manifestations of the syndrome.

The findings of heart-reactive antibody by immunofluorescent technique in patients with the syndrome confirm the observations of Van der Geld, who used nonhuman myocardium in testing. Robinson and Brigden, utilizing the tanned red cell technique and nonhuman myocardium, demonstrated antibodies in five patients with the syndrome after mitral valvotomy. Still earlier, Gery, Davis, and Ehrenfeld obtained, by passive agglutination techniques with human heart extract, a positive reaction in a patient with the syndrome and a negative reaction on recovery. They considered that they had demonstrated a heart-specific antibody. It seems quite likely that antiheter antibody identified in the foregoing and in the present study plays a role in pathogenesis of the syndrome. Kaplan and Frengly, Fowler, as well as Roberts and Lessof, have suggested a similar possibility in recent reviews of the subject. We believe that detection of heart-reactive antibody in high titer offers confirmation of the presence of the syndrome. We detected no such elevation of circulating heart-reactive antibody in the sera of ten children with pericarditis of other etiologies or in the other patients who served as controls. In children with acute rheumatic fever, Zabriskie found heart-reactive antibody to be present but elevated only to intermediate levels, none greater than 2+. The sera of a few patients thus far studied with the clinically similar syndrome following myocardial infarction exhibited a degree of elevation of antiheter antibody similar to that of the patients with postpericardiotomy syndrome. Thus a laboratory test appears to be available to supplement clinical findings in making the diagnosis of this condition.

Figure 5

Course of seven-year old girl L.P., with moderately severe PPS after open repair of tetralogy of Fallot, with right ventriculotomy, excision of infundibular pulmonic stenosis, and closure with a teflon patch of ventricular septal defect. Note the rise in heart-reactive antibody when clinical manifestations appeared, and the decline of elevated antibody following resolution of clinical features.

heart antibody was the last finding to become normal.

In the boy with tricuspid atresia and a Waterston anastomosis, who was treated with prednisolone because of the severity of his syndrome, the clinical

Figure 6

Severe PPS in 13-year-old boy, G.O.B., with tricuspid atresia and pulmonic stenosis who underwent a Waterston operation with anastomosis of the ascending aorta and right pulmonary artery. After the second pericardial tap because of cardiac tamponade, prednisolone treatment was begun. All manifestations subsided immediately. When steroids were tapered, fever recurred briefly. Heart-reactive antibody continued to be significantly elevated after steroids were discontinued and the patient was discharged from the hospital.

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The antibody requires further characterization, and its role in pathogenesis of the syndrome needs to be defined. Whether it acts alone or in combination with another agent such as a virus is unknown.

At the present time we can only speculate on the role of the demonstrated antibody. It may simply be a spectator, but it is tempting to think that this is not so because of the consistency of its presence in high titer in those with the syndrome but not in the postoperative patients without PPS, nor in the other forms of pericarditis studied. The antibody is unlike that found in rheumatic fever because of the lower titer of longer duration in that condition and the binding to Streptococcal membrane in rheumatic fever but not in PPS. The antibody may be directly cytotoxic. Possibly the effect of the antibody is on the sensitized lymphocyte which might either enhance or block further tissue damage. These and other questions are under current investigation by the authors.

Our hypothesis at the present time is that the antibody appears in the serum of a certain number of individuals who by reason of their age and previous immunologic experience react to the epicardial injury incurred at pericardiotomy, and to the trapping of blood within the pericardial sac. The immunologically-determined response is in the epicardial layer of myocardium, which responds by inflammation and by outpouring of fluid in varying amounts into the pericardial sac. The pleural reaction, sometimes with unilateral or bilateral effusions, is viewed as a "neighborhood" response of adjacent tissue, since in the PPS there is no involvement of more distant serous surfaces, such as synovia or peritoneum.

Through understanding of pathogenesis may come improvement in management beyond the present empiric treatment for signs and symptoms. Understanding etiology might even lead to prevention of the postpericardiotomy syndrome.

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