Viral Illness and the Postpericardiotomy Syndrome

A Prospective Study in Children

MARY ALLEN ENGLE, M.D., JOHN B. ZABRISKIE, M.D., LAURENCE B. SENTERFIT, PH.D., WILLIAM A. GAY, JR., M.D., JOHN E. O'Loughlin, JR., M.D., AND KATHRYN H. EHLERS, M.D.

SUMMARY Postoperative fever and pericardial-pleural reaction, designated postpericardiotomy syndrome (PPS), is a common complication of cardiac surgery involving entry into the pericardium. To determine whether the etiology of PPS is viral or immunologic, we undertook a prospective, triple-blind study of consecutive long-term survivors of intrapericardial surgery in the pediatric age group. We evaluated clinical evidence of syndrome and concurrent appearance of antihuman antibody (AHA) by indirect immunofluorescence and antiviral antibody (AVA) by complement fixation in sera preoperatively and serially postoperatively. Incidence of PPS was 27% overall in 400 subjects, but only 3.5% in infants younger than 2 years of age. AHA in high titer appeared in all patients with PPS. A fourfold or greater rise in titer to AVA was found in 70% of these but in only 5% of those with negative AHA and no PPS. AVA rise, tested in 280 consecutive patients, was to no single one of the eight viruses studied (adenovirus, cytomegalovirus, and Cox-sackievirus B 1–6). Instead, the rise and fall, consistent with antiviral response to a recent infection, was exhibited usually to one but occasionally to two or more viruses, and the viral prevalence changed from year to year, as did that in the community. The study suggests that concurrent fresh or reactivated viral illness plays a role in triggering the immunologic response that characterizes the PPS.

THE POSTPERICARDIOTOMY syndrome (PPS) is a frequent cause of postoperative fever and discomfort after cardiac surgery in which the pericardium is entered.\textsuperscript{1,2} It is characterized by the persistence, or by the appearance beyond the first postoperative week of fever with signs of pericardial and often pleural reaction, frequently with effusions. PPS occurs after wide opening of the pericardium,\textsuperscript{1,2} but the mechanisms involved have not been fully clarified.

To test the hypothesis that an immunologic response was a component of the syndrome, we undertook a prospective study to determine whether a heart-reactive antibody appeared in the serum of patients undergoing intrapericardial surgery, and if so, whether its appearance was related to the clinical syndrome. Antihuman antibody (AHA) was determined by an indirect immunofluorescent technique.\textsuperscript{4} In that study, double-blinded for serologic and clinical findings, we demonstrated that heart-reactive antibody did appear in high titer in patients with clinical evidence of PPS.\textsuperscript{6} After we confirmed these results in 120 consecutive infants and children who were long-term survivors of intrapericardial surgery, we tested the hypothesis that viral illness might be involved in PPS. We did this by measuring antiviral antibody (AVA) and AHA concurrently. AVA was measured in a different laboratory by complement fixation technique. The prospective study became triple-blinded. In the next 137 children so studied, we found a high order of association between clinical syndrome, appearance of AHA in high titer, and a significant rise in AVA to one or more of the viral agents tested.\textsuperscript{6,7} The present report extends those studies and provides additional evidence for the contribution of viral illness to the immunologically determined response that characterizes PPS.

Materials and Methods

In a consecutive series of infants and children who were all long-term survivors of intrapericardial sur-
surgery, we sampled blood preoperatively, 7-10 days postoperatively, 2-3 weeks postoperatively and, in those with clinical PPS, 2-3 months postoperatively. One portion of serum was analyzed for heart-reactive antibody by indirect immunofluorescence and was graded 0 to 4+, while the other was analyzed for complement-fixing antibody to a battery of eight common viruses (adenovirus, coxsackievirus B 1-6 and cytomegalovirus) as well as to Mycoplasma pneumoniae.\textsuperscript{6, 7} Patients were examined daily in the hospital and on postoperative visits by two pediatric cardiologists. Diagnosis of PPS was based on the presence, beyond the first postoperative week, of fever, signs of pericardial friction rub or effusion, laboratory evidence of pericardial reaction by leukocytosis greater than 10,000 leukocytes/mm\textsuperscript{3} and electrocardiographic evidence of serial T-wave changes of evolving pericardial reaction. Pleural and pericardial effusions were determined radiographically, and the latter was confirmed by M-mode echocardiography.\textsuperscript{8, 9} Some young children were "cranky;" most of the older children noted precordial pain that was localized or that radiated on deep inspiration to the left shoulder and was worse when supine. Signs of tamponade developed in some with severe PPS. Surgical techniques and perioperative care were standardized insofar as possible. Two surgeons performed all but a few of the operations. Antibiotics were given for the first 5 days, and neither steroidal nor non-steroidal anti-inflammatory agents were used unless specifically ordered for severe PPS. In the first 100 patients, ambulation was not permitted until the child became afebrile, but early ambulation as tolerated was allowed for the next 300 subjects.

Results

Postpericardiotomy Syndrome

One hundred eight of 400 consecutive long-term survivors had PPS clinically. This incidence of 27% is consistent with that observed at this institution for the past 2 decades.\textsuperscript{1-8, 10} The syndrome was usually evident by the second postoperative week, but occasionally in the third week after discharge from the hospital. No patient had onset of PPS more than 1 month postoperatively, although there was a late recurrence of mild PPS in three children who had already recovered from PPS in the first weeks after surgery.

Antiheart Antibody

Heart-reactive antibody was negative in all patients preoperatively and it remained so in 173 patients (43.2%) postoperatively (negative group). In the other patients, heart-reactive antibody usually began to appear by 7-10 days postoperatively. In 103 patients (25.8%) it rose to 2+ or greater and declined in the second month (positive group). In the intermediate group of 124 patients (31%), the titer did not reach 2+ and declined sooner, disappearing about 1 month postoperatively. When the clinical data on 400 patients were combined with data from serologic measurement of AHA (fig. 1), we found consistently as the study progressed that none of the patients with negative AHA had PPS, whereas all of those with positive response did (p < 0.001). The syndrome was severe in 27, moderate in 36 and mild in 40 patients. Of the 124 patients with intermediate AHA response, five patients (4%) had mild PPS.

The last 280 patients were in the triple-blind study. We found a fourfold or greater rise in titer of AHA in only 10 of 129 patients (7.8%) with negative AHA and no PPS, compared with 51 of 73 patients (69.9%) with positive AHA and PPS (p < 0.001) (fig. 2). Fifteen of the 78 patients in the intermediate group (19.2%) had a rise in AHA, but none of these had PPS. The rise in AHA was usually evident by the tenth day and was present in most who had a significant rise by the third week. The titer seldom rose higher than 1:64, and

\begin{figure}
\centering
\includegraphics[width=\textwidth]{chart.png}
\caption{Antiheart antibody (AHA) tested in 400 patients was negative in 173 (43\%, first column), none of whom had postpericardiotomy syndrome (PPS). Five of 124 patients in the intermediate group (second column) had mild PPS. All of the 103 patients with positive AHA (26\%, third column) had PPS (p < 0.001). The syndrome was severe in 27 patients, moderate in 36 and mild in 40.}
\end{figure}
remained elevated for 1–2 months. Rise in titer to *Mycoplasma pneumoniae* was rare and was not related to the presence or absence of PPS or AHA.

**Antiviral Antibody**

The rise in AVA was to no single agent. Figure 3 shows the percentage of patients with PPS among those who had a significant rise to the viruses indicated in the columns. Although the reaction was usually to one virus only, 16 patients (12 with positive and four with intermediate AHA) had a rise to two or more agents.

Among the first 137 patients so studied, the greatest numbers of rises in viral titer were to cytomegalovirus and to adenovirus.8,7 The incidence of PPS for each virus to which there was an increase in titer ranged from 50–100%. None of the first 137 subjects had a rise to coxsackievirus B 4, but by the next correlation of triple-blinded data that brought the total number studied to 190 patients, the rise in titer to coxsackievirus B 4 had become as frequent as that for cytomegalovirus.3,11 In the present analysis of 280 patients, coxsackievirus B 4 was by far the most prevalent virus to which there was a fourfold or greater rise in titer (fig. 3).

Such a rise is consistent with a viral infection, either reactivation of a latent virus or a fresh infection. To test whether the changes in frequency of viral agents might be due to changing prevalence of viral agents, we analyzed the pattern of viral response for each year of the study (fig. 4). The most striking change was in coxsackievirus B 4, which at first was absent and then began to appear and became the most prevalent virus for the next 2 years. In the fifth year of the study it declined to a low level. Similar trends of rise and fall in prevalence were seen in all agents tested.

Within each year, some monthly clustering of cases of PPS tended to occur. This was most evident in July and August 1975, when all nine children over the age of 2 years had PPS. The rises in AVA were to adenovirus and coxsackievirus B 3, 4 and 6. In 1976, five of the seven instances of PPS occurred in 12 patients over the age of 2 years who were operated on in March and April. Rises in viral titer in them were to coxsackievirus B 3, 4 and 5.

Although the cumulative incidence of PPS was 25–30%, the yearly incidence was 16.9–45.9% (table 1). The largest number of viral rises occurred in 1975, the year of the highest incidence of PPS and positive AHA (table 1, fig. 4). Thus, the yearly incidences of PPS and of immunologic and viral response paralleled one another closely.

To determine whether the rise in AVA in the children represented a response to a recent illness contemporaneously related to the operation or to reactivation of latent virus,12 we examined the titer on admission and the later response in each of the 280 subjects (fig. 5). We found that 53% of those with PPS and positive AHA had no detectable antibody on admission, followed by a significant rise. This suggested fresh illness. In 16%, a low preoperative titer followed by a rise suggested reactivation of a latent virus or an inapparent illness that was just beginning. On admission, 10% of patients with PPS had a high titer to a
virus and then a decline. These patients were probably convalescing from a viral infection when they came to surgery. It is common practice in children to delay cardiac surgery for a week or so to permit the child to recover from a respiratory tract infection. In 21% there was no change in titer. In that 21% could have been some with a reaction to a virus we did not test. In contrast, 78% of the intermediate group and 92% of the negative group showed no change, while 15% and 6%, respectively, showed a significant rise in titer. Only 1–4% had a lower titer on admission and a rise or a high titer and fourfold drop.

Because a rise in AVA bore such a close temporal relation to AHA and to PPS, we wondered whether patients coming from afar for surgery behaved differently in this regard from children living in or near New York, as their previous exposures to viruses might have been different. Table 2 compares 197 local children with 68 from the Mediterranean area and 15 from the Caribbean area. The responses in PPS, AHA and AVA were similar. The slightly higher incidence of PPS in the foreign children can be accounted for by the greater percentage of patients older than 2 years of age with tetralogy of Fallot and complex anomalies together with ventricular septal defect (VSD), the two malformations associated with the highest incidence of PPS. Two-thirds of the Mediterranean and one-half of the Caribbean children were referred for those two kinds of surgery.

Age

Infants younger than 2 years of age rarely had PPS, in contrast to older children. The 3.5% incidence of PPS in babies was only one tenth that in children older than age 2 years, in whom the incidence of PPS was around 36% in all age groups.

Type of Surgery

The type of operation was related to the frequency of PPS; this was evident midway into the study and

<table>
<thead>
<tr>
<th>Year</th>
<th>Operations (n)</th>
<th>PPS (n) (%)</th>
<th>Positive AHA (n) (%)</th>
<th>Rise in AVA and PPS (n) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1973</td>
<td>47</td>
<td>14 (29.8)</td>
<td>14 (29.8)</td>
<td>7 (14.9)</td>
</tr>
<tr>
<td>1974</td>
<td>92</td>
<td>19 (20.6)</td>
<td>18 (19.6)</td>
<td>13 (14.1)</td>
</tr>
<tr>
<td>1975</td>
<td>51</td>
<td>23 (45.9)</td>
<td>22 (43.1)</td>
<td>18 (35.3)</td>
</tr>
<tr>
<td>1976</td>
<td>59</td>
<td>10 (16.9)</td>
<td>10 (16.9)</td>
<td>7 (11.9)</td>
</tr>
<tr>
<td>1977</td>
<td>31</td>
<td>9 (28.6)</td>
<td>9 (28.6)</td>
<td>6 (19.3)</td>
</tr>
<tr>
<td>Total</td>
<td>280</td>
<td>75 (26.8)</td>
<td>73 (26.1)</td>
<td>51 (18.2)</td>
</tr>
</tbody>
</table>

Abbreviations: AHA = antihem antibody; AVA = antiviral antibody; PPS = postpericardiotomy syndrome.

Figure 4. Annual analysis of viral agents according to significant rise in viral titer shows the changing frequency of individual viruses as the study progressed. The bars indicate the numbers of patients with significant rise in titer to that agent. The most striking change was in coxsackievirus B 4, which began to appear during the second year, was the virus most frequently found during the third and fourth years, when it began to decline and became infrequent in the fifth year. PPS = postpericardiotomy syndrome.
was confirmed in the latest cumulative analysis (fig. 7). The different surgical procedures were ranked in order of frequency of performance for the malformations shown and the numbers of patients with PPS in each category were analyzed for 400 patients according to heart-reactive antibody response and for the 280 studied for both AHA and AVA responses. For each malformation, the results from both means of serologic analysis were consistent. The operation with the lowest incidence of PPS was the Mustard procedure for repair of transposition of the great arteries (TGA) (atriotomy, removal of atrial septum and placement of an intracardiac pericardial baffle). The two operations with the highest incidence of PPS were tetralogy of Fallot (44% for AHA) and VSD plus some other anomaly, often infundibular pulmonic stenosis (46% for AHA). Both of these operations provided the greatest opportunity for myocardial trauma of all of the surgical procedures, as they entailed both a right ventriculotomy and resection of obstructing musculature in the outflow tract of the right ventricle. The time to complete the operation was longer for tetralogy of Fallot, complex VSD and TGA than for the other procedures.

The experience for the infants younger than 2 years of age undergoing these same operations markedly contrasted to the overall experience presented above (fig. 8). The types of malformations operated upon were similar, but repair of atrial septal defect (ASD) was less common and Mustard operation for TGA was more common than for the group as a whole. The low incidence of PPS in the babies undergoing the various procedures was noteworthy (figs. 6 and 8).

The difference between the response of babies and children was further emphasized by comparison of the two age groups according to surgery for the two conditions associated with the highest incidence overall of PPS, tetralogy of Fallot and VSD complicated by another anomaly. For tetralogy repair, no infant had PPS, whereas 39 of 69 patients older than 2 years of age (57%) studied for AHA and 21 of 40 (53%) studied for both AHA and AVA did have PPS (p < 0.001). In surgery for complicated VSD, two of 15 babies studied for AHA (13%) had PPS, compared with 19 of

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**FIGURE 5.** Antiviral antibody on admission and antihemt antibody (AHA) response in 280 patients. Most patients with positive AHA had no titer on admission and a fourfold or greater rise, 16% had a low titer that rose and 10% had a high titer that fell. Only 21% had no change, whereas 78% of the intermediate and 92% of the negative groups did not change.

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**TABLE 2.** Origin of 280 Patients Studied for Postpericardiotomy Syndrome, Antihemt Antibody and Antiviral Antibody

<table>
<thead>
<tr>
<th>Operations</th>
<th>PPS (n)</th>
<th>PPS (%)</th>
<th>Positive AHA (n)</th>
<th>Positive AHA (%)</th>
<th>Rise in AHA and PPS (n)</th>
<th>Rise in AHA and PPS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>New York</td>
<td>197</td>
<td>48</td>
<td>24.4</td>
<td>46</td>
<td>33</td>
<td>17.1</td>
</tr>
<tr>
<td>Mediterranean</td>
<td>68</td>
<td>22</td>
<td>32.3</td>
<td>22</td>
<td>16</td>
<td>23.5</td>
</tr>
<tr>
<td>Caribbean</td>
<td>15</td>
<td>5</td>
<td>33.3</td>
<td>5</td>
<td>5</td>
<td>13.3</td>
</tr>
<tr>
<td>Total</td>
<td>280</td>
<td>75</td>
<td>26.8</td>
<td>73</td>
<td>51</td>
<td>18.2</td>
</tr>
</tbody>
</table>

Abbreviations: PPS = postpericardiomy syndrome; AHA = antihemt antibody; AVA = antiviral antibody.
31 children (61%) \( (p < 0.01) \). When both AHA and AVA were measured after that same operation, one of 12 babies (8%) and 11 of 17 children (65%) had PPS \( (p < 0.01) \). Thus, the patients with the highest risk of PPS were children older than 2 years of age who were undergoing open heart surgery for repair of tetralogy of Fallot (> 50% incidence) or closure of VSD plus repair of some other condition, usually infundibular pulmonic stenosis (> 60%). This contrast between infants and children showed that myocardial trauma per se and the duration of the procedure were not the sole determinants of PPS. Some additional feature was required, perhaps the ability to respond to challenge by formation of AHA or the capacity to mount an autoimmune response manifest as clinical syndrome.

### Second Intraparicardial Operation

If an immune response against the patient's myocardium were the only determinant of PPS, one might expect a higher incidence of PPS in patients undergoing a second intrapericardial operation than in those undergoing a first procedure.\(^5\) Fifty of the 400 patients had undergone a second pericardiotomy. Instead of clustering chiefly in the group with positive AHA and PPS, these 50 patients constituted 13.5\% of the negative, 8.1\% of the intermediate and 16.5\% of the positive AHA responses. As in the overall group, only patients with positive AHA and a significant rise in AVA had PPS.

### Discussion

This prospective study has shown that AHA appears in the serum of some children who undergo pericardiotomy and that the presence of AHA in high titer correlates with clinical PPS. Further, 70\% of the patients with PPS and high AHA had a fourfold or greater rise in titer to one or more of eight viral agents.

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**Figure 6.** Incidence of postpericardiotomy syndrome (PPS) according to age in 400 operated patients. The incidence in babies was only 3.5\%, compared with approximately 36\% in all of the other age groups. AHA = antihemate antibody.

**Figure 7.** The relationship between postpericardiotomy syndrome (PPS) and types of surgery according to antihemate antibody (AHA) response and rise in antiviral antibody (AVA). The operations with the highest incidence of the complication were tetralogy of Fallot (TOF) (first bar) and ventricular septal defect (VSD) plus some additional abnormality (fourth bar), while the incidence was lowest for physiologic repair of simple transposition (the fifth bar). ASD = atrial septal defect; PS = pulmonic stenosis.
tested, suggesting that recent or reactivated viral illness is associated with PPS. Had we used a larger battery of agents for screening, the association of rise in AVA and PPS might have been even higher.

Because more than half of the patients with PPS and positive AHA had no detectable AVA preoperatively and then had a rise, the viral illness may have been acquired in connection with the operation, perhaps in the operating room while the pericardium was open. Many opportunities exist for a nosocomial viral illness to occur, because children undergoing heart surgery come into close and sometimes frequent contact with a large number of physicians, nurses and other hospital personnel as well as with other hospitalized children and their parents. Cytomegalovirus can be transmitted not only via the respiratory tract but also on the red cells of transfused blood. Hemodilution was used for extracorporeal circulation, but all patients received some blood from the pump and/or by transfusion. Children from the New York area and from afar reacted alike in incidence of PPS, positive AHA, and rise in AVA. This is consistent with a nosocomial and otherwise inapparent viral illness.

Patients who had a low titer on admission and then a rise may have suffered reactivation of a recent or remote viral illness. The few with high titer on admission followed by a drop were likely convalescing from a fresh viral infection when the trauma of surgery occurred.

We reviewed the original data on patients included in an epidemiologic survey of the PPS in this medical center between 1958–1963. At that time clinical criteria for diagnosis were the same as now, but tests for heart-reactive antibody or complement-fixation testing for viral illness were not possible. That study of 262 survivors of intrapericardial surgery included 85 adults over the age of 30 years as well as children. Only two were younger than two years of age. Those results resembled closely the present findings, with clustering of cases within each year and with yearly incidence of PPS ranging from 23.5% in 1958 to 40.4% in 1962 (average 30.5%). The significance of the differences in frequency of syndrome in relation to numbers of operations performed each year was obscured by combining the data from all 6 years into consecutive 6-month periods. More cases of PPS occurred between February and July than between August and January. Rereview by months for each year of the study was consistent with the changing seasonal and yearly patterns of viral illness that this prospective study revealed.

The degree of myocardial injury at operation was related to the incidence of PPS, perhaps because of the number of binding sites for antigen-antibody reaction as well as because of the amount of traumatized tissue available for viral invasion. The two conditions with the greatest degree of injury to heart muscle at operation were those with the highest incidence of PPS. Overall, the chance of manifesting PPS was 27%; with repair of tetralogy of Fallot or complicated VSD, it was 44–46%, and in children older than 2 years of age, the risk was 57–61%. The pericardium was open longer for these two kinds of surgery than for the other operations, except for the Mustard procedure for TGA.

The incidence of PPS was 36% in children older than 2 years of age, compared with 3.5% in infants younger than 2 years of age. The reason for this difference is unclear. The infants appeared to be as immunologically competent as the older children; indeed, in no patient was immunologic compromise suggested. That no infant younger than 6 months of age had PPS might be due to protection from viral illness during the first few months by transplacentally transmitted antibody from the mother. By the second year of life, after increased exposure to viruses and reaction to them, the infant may have matured to the point of being able to mount the immune response that we recognize as PPS when intrapericardial trauma and viral exposure occur.

We cannot exclude the possibility that an
anamnestic reaction triggered by myocardial injury at surgery caused the rise in antiviral antibody. We propose to evaluate this explanation and to test our working hypothesis that PPS represents an immune response to traumatized myocardium in the presence of a recent or reactivated viral illness. Virus invasion of the myocardial cells on the surface of the heart or within the walls transforms self into nonself, and the AHA is produced against the neoantigen. It appears that the greater the myocardial injury at operation, the greater the opportunity for viral invasion and the larger the number of antigen-binding sites. Evidence from viral titers suggests that the viral illness may be acquired as a nosocomial infection. If so, measures to modify care in the hospital and operating room might minimize the risk of this postoperative complication.

Acknowledgment

We express our gratitude to the Pediatric Cardiology fellows who contributed greatly to the acquisition of clinical information and timed samples for serologic study, to Ethel Longo for coordination of serologic studies, to Sheila Reams for statistical analyses, and Jeanne Macaluso for secretarial skills.

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Viral illness and the postpericardiotomy syndrome. A prospective study in children.

_Circulation._ 1980;62:1151-1158
doi: 10.1161/01.CIR.62.6.1151

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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