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Original Article

Postpericardiotomy syndrome: no evidence for a viral etiology

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Abstract *Background:* Postpericardiotomy syndrome has been considered a disorder induced by viral infection. This conclusion is based on serologic criterions, but these may be unreliable following either cardiopulmonary bypass or transfusion therapy. Previous studies have not verified the proposed etiology either by isolation of viruses, or by detection of their genome. We sought, therefore, to clarify the role, if any, of viruses in this syndrome. *Methods and Results:* We studied prospectively 149 children aged from 6 months to 16 years who were undergoing open heart surgery. Blood samples were collected from all prior to operation, and again 7 to 10 days post-operatively, and 47 were sampled at the time of development of symptoms of pericardial involvement. Serums were analyzed for the presence of IgM and IgG antibodies to cytomegalovirus, herpes simplex virus, and Epstein-Barr virus. The polymerase chain reaction was used for amplification when assessing the genome of the enteroviruses. Cultures for viruses were established on samples of stool, urine, and throat swabs collected 7 days post-operatively, and at the time of postpericardial symptoms. Pericardial fluid obtained from 5 patients with the syndrome was cultured for viruses, and tested for enterovirus genome. On the basis of clinical and echocardiographic findings, 34 children were determined to have definite evidence of the syndrome, 13 were considered to have possible evidence, and the results from these patients were compared to those from patients with no pericardial symptoms, the latter being matched for age and transfusion status. We isolated viruses from one or more sites in five patients with definite evidence (16%), from one (9%) of those with possible evidence, and from seven (19%) of the controls. All serums and pericardial samples were negative for enterovirus genome. IgM antibodies were found in only 5 patients, three with symptoms of pericardial involvement and two without. Rates of seroconversion to IgG for the viruses were lower in the patients with symptoms of pericardial involvement compared to controls, but were strongly influenced by transfusion status. *Conclusion:* Our study has provided no evidence to support a viral etiology for the postpericardiotomy syndrome.

Keywords: Enterovirus genome; open heart surgery; transfusion.

POSTPERICARDIOTOMY SYNDROME IS THE commonest complication of open heart surgery in childhood, occurring in up to one-third of patients undergoing intrapericardial procedures.[1,2] Although the syndrome has been recognized for over 40 years,[3,4] its pathophysiology remains poorly understood. Anti-cardiac antibodies have been closely associated with its development,[2,5–11] and Engle and co-workers have suggested that concurrent primary or reactivated viral infection plays a role in triggering this immunological response.[2,9–11] Evidence for this viral etiology has been based on serological findings of a rise in titers of antiviral antibodies in patients with symptoms of pericardial involvement compared to controls.[2,9–11] Proving an association between a viral infection and a clinical syndrome based solely on serology, however, is fraught with difficulties of interpretation,[12] particularly in

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patients who have been on cardiopulmonary bypass and received blood transfusions. Two subsequent studies failed to confirm the alleged rise in antiviral antibodies in patients with the syndrome.[6,7] Furthermore, to date, no prospective investigation has attempted to identify viruses in symptomatic patients, either by culture or detection of viral genome. With this in mind, we undertook a prospective study combining viral serology, cultures, and genomic detection of viruses in serum and pericardial fluid using polymerase chain reaction, seeking to confirm or refute the viral etiology for pericardial involvement.

Patients and methods

Patients

We enrolled children above the age of 6 months undergoing open heart surgery at our institution over a period of 20 months, having obtained informed parental consent. All aspects of the study were approved by the hospital and university committees for ethical review.

Definition of the syndrome

Children were examined daily following surgery by one of two investigators (SAW, NJW) looking for evidence of pericardial involvement. All patients had cross-sectional echocardiograms at around the 7th postoperative day, and whenever symptoms or signs of pericardial involvement developed. Diagnosis of the syndrome was made when at least 2 of the following 3 criterions were met:

- Fever of more than 37.8^{0}C for longer than 24 hours after the third postoperative day in the absence of clinical evidence of bacterial infection.
- Clinical evidence of pericarditis, such as characteristic chest pain or a pericardial rub.
- Echocardiographic evidence of pericardial effusion.

In all cases, the diagnosis was confirmed independently by two physicians, including the attending cardiologist. Children were grouped on clinical grounds as having definite, possible, or no pericardial involvement. Possible involvement was diagnosed when some features of the illness were present, but the above criterions were not fulfilled, such as late onset of a pericardial friction rub without fever or effusion, or unexplained fever without evidence of pericarditis. Where any uncertainty existed, or where there was disagreement between the assessments by the physicians, definite evidence of pericardial involvement was not diagnosed. In this way, stringent efforts were made to define a group of patients with unequivocal post-pericardiotomy syndrome.

All patients were reviewed in the outpatient clinic approximately 2 weeks, and then again 2 months, following discharge, at which time clinical review and echocardiography were repeated. When any symptoms arose suggestive of pericardial involvement following discharge, immediate clinical and echocardiographic review was arranged.

Samples

Blood samples were obtained before surgery, and 7–10 days post-operatively, and at the onset of development of symptoms or signs of postpericardiotomy syndrome. If hospital discharge was before the 7th postoperative day, samples were collected on the day of discharge. Serum was separated, aliquoted, and stored at –70^{0}C for subsequent analysis. For patients who developed pericardial involvement, follow-up samples were obtained 1 to 2 weeks after the onset of symptoms. Throat swabs, stool, and urinary samples were obtained for culture of viruses around the 7th post-operative day. These samples were also collected at the time of evidence of pericardial involvement. Samples of pericardial fluid were collected only when pericardial drainage was indicated on clinical grounds.

Serology

To assess any effects of cardiopulmonary bypass, blood transfusion, or pericardial involvement on viral serology, independent of viral infection, all the serum samples were also tested for IgG memory antibodies to diphtheria, tetanus toxoids, and rubella virus, against which all children had previously been vaccinated. Titers of diphtheria and tetanus antibodies were determined by enzyme-linked immunoassay (ELISA) using toxoids (Connaught Laboratories Ltd, Willowdale, ON). Rubella serostatus was determined by ELISA using antigen from a lysate of VERO cells infected with the M–33 rubella strain.

Commercially available (ELISA) kits were used to detect antibodies to herpes simplex, cytomegalovirus (Behring, Behringwerke AG, Marburgh, Germany) and Epstein-Barr viruses (Dupont, Billerica, MA). Findings were interpreted according to the instructions of the manufacturers. All serums from individual patients were tested concurrently on the same 96-well plate. In the tests for herpes simplex and cytomegaloviruses, a negative result was an absorbance value of less than 0.1, and a positive result was a value of greater than

0.2. Intermediate values for absorbance after 2 repeated tests were considered equivocal. When testing for Epstein-Barr virus, the presence or absence of IgG antibodies was determined by comparison of the absorbance of the test specimen to the cut-off value of each plate. Cut-off values were equal to the mean absorbance of a cut-off dilution of positive control serum as provided by the manufacturer. For IgM-specific ELISA, serums were preincubated with rheumatoid factor absorbent (RF Absorbent®) Behring, Behringwerke AG, Marburgh, Germany) to remove IgG antibodies. In nontransfused patients who were IgG seronegative preoperatively, the postoperative presence of IgM antibodies was considered to represent primary viral infection. The detection of IgM antibodies postoperatively in a patient determined to have preoperative IgG memory antibodies was considered suggestive of viral reinfection or reactivation.

Viral cultures

Specimens were processed by experienced staff of the Children's Hospital Virology Laboratory. Specimens were incubated with antibiotics for 30 minutes then centrifuged for 15 minutes at 2000rpm. The supernatant was frozen at −70°C pending later analysis. For cultures, primary Rhesus monkey kidney cells (Connaught Laboratories Ltd, Willowdale, ON or Viromed Laboratories Inc, MN), MRC–5 cells (Connaught Laboratories Ltd, Willowdale, ON) and Hep–2 cells (Bartel's Diagnostic Division, Baxter/Can Lab Corp., Edmonton, AL) were used. Each specimen (of 0.2ml) was inoculated onto one of each type of cells. Cell cultures were maintained and observed for 21 days for cytopathic effect. Haemadsorbtion was performed using guinea pig erythrocytes once between the seventh and tenth day of incubation on respiratory specimens. Cytomegalovirus was identified by direct immunofluorescence (Bartels Diagnostic Division, Baxter/CanLab Corp., Edmonton, AL), and adenovirus was identified by an indirect immunofluorescence test (Bartel's Diagnostic Division, Baxter/CanLab Corp., Edmonton, AL). Enteroviruses were identified by demonstration of typical cytopathic effect after passage, and by electron microscopy.

Detection of enterovirus genome

Preparation of serum samples: 10 μl of serum was added to a 1.5ml microcentrifuge tube containing 0.1 μmole dithiothreitol (Gibco BRL, Gaithersburg, MD) and 20 U RNade (Bio/Can Scientific, Mississauga, Ontario). To this was added water and 15 μl of 1% Nonident P–40 (Sigma, St Louis, MO) to a total volume of 300 μl. This was heated at 95°C for 10 minutes and cooled on ice. To precipitate the RNA, 900 μl of methanol was added and the mixture was kept at −20°C overnight and centrifuged at 17,000g at 2°C for 30 minutes. The supernatant was discarded and the pellet was air dried at room temperature.

Reverse transcription: To the dried precipitate was added 30 μl of a solution containing 40 nmoles deoxynucleoside triphosphates (Pharmacia), 3 μl 10x PCR buffer (25mM MgCl2, 500 mM KCl, 0.1% gelatin, 100mM tris-HC1 (pH 8.3)), 0.1 μmole dithiothreitol, 500 pmoles random hexamers (Pharmacia), 200 U reverse transcriptase M-MLV (Gibco BRL, Gaithersburg, MD), and RNade 20 U. The mixture was overlaid with 3 drops of paraffin oil and incubated at 37°C for 90 minutes.

PCR amplification: Reverse transcriptase product was amplified using the nested primer technique.[13] The outer primers were ENT1=GTGTGAA-GAGCCTATTGAGCTA and ENT2=TCACCG-GATGGCCAATCCAA. To the 30 μl reverse transcriptase product was added 40 pmoles of each primer, 1μl 10x PCR buffer, 1U Taq polymerase (Gibco BRL, Gaithersburg, MD) and water to a total volume of 40 μl. Each sample was subjected to 40 cycles on an Ericomp twin block thermocycler (San Diego, CA), each cycle consisting of 30 secs at 95°C, 30 sec at 55°C and 60 secs at 72°C. For nesting, 1 μl of the first reaction mixture was added to a fresh reaction mixture containing 4 μl 10x PCR buffer, 32 nmoles deoxynucleoside triphosphates, 40 pmoles of each of the nested primers ENT4=TCCGGCCCCT-GAATGCGGCTAATCC and ENT5=ATTGT-CACCATAAGCAGCCA[14] and 1U Taq polymerase in a total volume of 40 μl. This was subjected to 30 cycles as described above. The product, a 154 bp fragment, was detected by electrophoresis through a 4% Nusieve GTG agarose (FMC bioproducts, Rockland, ME) gel in the presence of ethidium bromide and photography under ultraviolet illumination.

The outer primers used correspond to the regions from bases 413 to 434 for ENT1, and 621 to 640 for ENT2 within poliovirus type 1 (Mahoney strain) (PV1) GenBank accession number J02281). These regions are well-conserved between poliovirus P3/Leon/37 and coxsackieviruses B1, B3 and B4 (GenBank accession numbers K01392, M16560, M16572 and D00149). The inner primers have been previously described.[14] On testing these primers, we were able to detect appro-

priate sized fragments from dilute poliovirus type 1, coxsackievirus A9, coxsackievirus B3, echovirus 4 and echovirus 27 suspensions. This 'nested primer' method allowed detection of 1 plaque-forming-unit in 10 μl of water, with approximately a ten-fold reduction of sensitivity when virus was seeded into treated serum. Standard techniques were carried out to avoid false positive results by carry-over.[15]

Transfusion status was documented for each child. Children were considered to have received a transfusion if blood or blood products were administered during the perioperative or postoperative period. This included use of any blood products for priming of the bypass circuit. All samples were analysed without knowledge of the clinical status of the patient, such as presence of absence of pericardial involvement or the transfusion status.

Statistical analysis

The proportions of children in each group developing positive viral serology or viral cultures were compared using the chi-square test.

Results

We studied prospectively 149 children, aged from 6 months to 16 years, with a mean age of 4.5 years. Definite symptoms of pericardial involvement developed in 34 children, possible symptoms in 13 children, and there was no evidence of pericardial involvement in 102. Adequate samples of serum for serology and polymerase chain reaction were obtained in the majority of patients with obvious or suspected pericardial involvement (Table 1). Similarly, a total of 179 viral cultures were available from at least 2 out of the 3 sampled sites in 42 of 47 children (89%) with definite or possible pericardial involvement. Results of serology, polymerase chain reaction and viral culture, were compared to those obtained from 39 patients without evidence of pericardial involvement. The latter patients were matched for age, type of operation, and transfusion status to those with evidence of the syndrome. Of 5 samples of pericardial fluid subjected to polymerase chain reaction, 3 were collected during the period of study, and 2 were from patients who developed cardiac tamponade due to the syndrome shortly after completion of the study.

Serology

Regardless of transfusion status or evidence of pericardial involvement, there was evidence of decreasing titers of antibody to diphtheria and tetanus in post-operative compared to pre-operative samples of serum, and there was no correlation between changes in these antibody titers and titers of antiviral antibodies. Rubella titres increased significantly in approximately two-fifths of patients, all but two of whom had received blood transfusions. There was no association with the development of postpericardiotomy syndrome.

The results of viral IgG serology are shown in Table 2. Conversion rates from seronegative to seropositive status for cytomegalovirus, herpes simplex and Epstein-Barr viruses were high overall (37%, 42%, and 37% respectively) and did not differ on the basis of pericardial involvement.

Table 1. Characteristics and numbers of patients with adequate samples for viral studies

	Definite pericardial involvement	Possible pericardial involvement	No pericardial involvement
Number of patients	34	13	39/102*
Age in years (mean)	0.5–13 (4.8)	0.5–16 (4.9)	0.7–16 (4.0)
Gender: Female to Male	21:13	4:9	17:22
Onset of syndrome (days)	8.4	10.9	–
Number of patients undergoing serologic studies	27	11	38
Number of patients with serologic studies who received transfusion of blood products	21 (78%)	10 (91%)	29 (76%)
Number of patients with samples for viral culture	31	11	36
Number of patients undergoing analysis of serum with polymerase chain reaction	32	11	39
Number of patients with pericardial fluid samples for viral culture & polymerase chain reaction	5	–	–

*Note: Of 102 patients without postpericardiotomy syndrome, 39 were selected for viral studies after matching as closely as possible with patients with the syndrome for age, type of operation, and transfusion status.

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Seroconversion was strongly influenced by transfusion status. Overall, 60 of the 76 children with serological data (79%) had received transfusions of blood or blood products during the perioperative period. Seroconversion to cytomegalovirus, herpes simplex or Epstein-Barr viruses occurred in 43%, 52%, and 43% of transfused children, respectively. In those who had not been transfused, two children seroconverted to cytomegalovirus (13%), one to herpes simplex (6%), and two to Epstein-Barr virus (13%). The differences in rates of seroconversion between children receiving and not receiving transfusions was statistically significant for all three viruses (cytomegalovirus and Epstein-Barr virus $p=0.023$, herpes simplex virus $p=0.001$)

The IgM antibody to herpes simplex was not detected in any child. One child without evidence of pericardial involvement had IgM antibody to cytomegalovirus detected on her pre-operative serum, and developed IgG antibodies to this virus in the postoperative period. In two further children, one with and one without the syndrome, IgM antibody against Epstein-Barr virus was detected preoperatively and IgG antibody developed in the postoperative period. The IgM antibody to this virus was also detected in the first postoperative serum obtained from two other children with the syndrome who had not been transfused. In these, IgG antibody could not be detected on the last sample of serum from one taken 2 weeks postoperatively. Analysis of IgG antibodies showed that the other had seroconverted.

Cultures

Results of viral isolates from stool, urine, and throat swabs are shown in Table 3. There were no differences in number ($p=0.72$) or type of isolate between the three groups. No viruses were isolated from the 5 samples of pericardial fluid obtained from patients with the syndrome.

Detection of enteroviral genome

The polymerase chain reaction was negative on all 82 samples of serum, and also on the five samples of pericardial fluid obtained from patients with definite postpericardiotomy syndrome.

Discussion

Although the postpericardiotomy syndrome has been recognized for over 40 years,[3,4] the mechanisms involved in its development remain ill-defined. Engle and colleagues [2,9–11] proposed that the syndrome is an immune-mediated disorder promoted by a fresh or reactivated viral infection. They based their theory on observations showing that up to four-fifths of patients with the syndrome developed a four-fold, or greater, rise in antiviral antibodies to one or more of the 8 viruses studied. These were the cytomegalovirus, adenovirus, and groups B1 through 6 of the coxsackie virus. By contrast, less than one-tenth of their controls developed such a rise.[2,9–11] Several of their observations are worthy of comment. Firstly, viral titers were low, seldom rising to higher than 1 in 64. Secondly, all patients had received perioperative blood transfusions. Thirdly, in up to one-third of the patients, a four-fold rise in antibody titre occurred against more than 1 virus.[11] In certain instances, a four-fold rise was noted to as many as four viruses.[9] These considerations are important, since it is well recognised that the interpretation of viral IgG serology for the diagnosis of acute viral infections can be difficult, and is often associated with low diagnostic yield. This is particularly true for enteroviral infections.[12] It is surprising,

Table 2. Results of IgG serology with reference to postpericardiotomy syndrome and transfusion status

	Definite involvement	Possible involvement	No involvement
Seroconversion for cytomegalovirus			
Transfused	8/21	4/10	14/29
Not transfused	0/6	1/1	1/9
Seroconversion for herpes simplex			
Transfused	7/21	3/10	21/29
Not transfused	1/6	0/1	0/9
Seroconversion for Epstein-Barr virus			
Transfused	6/21	3/10	17/29
Not transfused	1/6	0/1	1/9

Notes: 1. No significant difference in proportion of patients with positive, equivocal, or no evidence of the syndrome who seroconverted to cytomegalovirus, herpes simplex or Epstein-Barr virus ($p=0.586$, 0.067 and 0.163 respectively). 2. Seroconversion significantly related to transfusion status for all three viruses ($p=0.023$, 0.001, 0.023 respectively).

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Table 3. Results of viral cultures

	Definite involvement	Possible involvement	No involvement
Stool / urine/ throat swab cultures			
Patients studied	31	11	36
Total samples cultured	71	27	81
Patients with positive cultures			
Cytomegalovirus	3 (urine)	0	3 (urine 2, throat swab 1)
Adenovirus	1 (stool & throat swab)	0	4 (stool)
Enterovirus	1 (stool)	1 (stool)	0
Total*	5	1	7
Pericardial fluid culture			
Positive cultures	0/5	–	–

Note: * No significant difference between groups for proportion of patients with positive viral cultures.

therefore, that the incidence of positive serology noted by Engle and colleagues[2,9–11] far exceeded that usually found for clinical syndromes, such as myocarditis or pericarditis, conditions which are known to be associated with enteroviral disease.

Few studies since have attempted to confirm or refute this viral hypothesis. Two subsequent groups, nonetheless, failed to confirm the findings of a rise in antiviral antibodies in patients diagnosed with the syndrome.[6,7] Only de Scheerder and colleagues[6] have sought IgM antiviral antibodies, albeit only to the Epstein-Barr virus. They found no association with the syndrome. Caul and coworkers[16] performed a prospective study of infection with cytomegalovirus after open heart surgery. Although not primarily designed to study the etiology of the syndrome, none of the patients acquiring infection developed symptoms of the disease. Importantly, there have been no reports of isolation of virus in patients with the classical syndrome. Kahn and colleagues[17] reported the isolation of parainfluenzae type 3 virus, a common nosocomial pathogen, from several patients after cardiac surgery with a biphasic illness, atypical for postpericardiotomy syndrome. The illness was characterized by oral mucosal lesions, hepatosplenomegaly, and atypical lymphocytes, as well as pleuro-pericardial friction rubs. Symptoms and signs frequently took several months to subside.

Our study, therefore, to the best of our knowledge, is the first which has evaluated prospectively the role of viruses by use of IgM and IgG serology, viral cultures, and detection of viral genome. We chose to examine antiviral antibodies to the herpes group of viruses because these are known to persist in the body, and to be capable of causing clinical illness during reactivation. Engle and coworkers,[2,9–11] using complement fixation techniques, have previously suggested that such a reactivation might trigger some cases of the syndrome, and cytomegalovirus was one of the viruses implicated. We used the extremely sensitive ELISA technique to distinguish detection of acute phase IgM-type antibodies from late-phase memory IgG-type antibodies. We have not been able to demonstrate any association between our chosen viruses and the development of the syndrome. There was, however, a strong association between seroconversion of IgG antibodies and transfusion of blood or blood products. The small number of patients developing IgM antibodies suggests that, for the most part, seroconversion to IgG represents passive transfer of antibody. The fall in antibodies to diphtheria and tetanus in the majority of patients in our study probably reflects the lower levels of these antibodies in adults, as routine revaccination is not performed after leaving grade school. By contrast, we noted a rise in antibodies to rubella in many children. This may reflect maintenance of levels of these antibodies in adults due to reexposure to the wild type virus during the epidemics which continue to occur periodically in British Columbia, as well as to routine reimmunization of adolescents and seronegative pregnant women following delivery. Our observations lead us to believe that it is impossible to interpret the results of testing for IgG antibodies in children who have received transfusions of large volumes of blood or blood products. Although several of our patients had positive viral cultures, no difference was found in the number or type of viral isolates between those having positive pericardial involvement as compared to controls. Furthermore, we were unable to isolate viruses from the pericardial fluid taken from five patients known to have the syndrome.

Because of the recognised difficulties of serological evaluation of enteroviral illness[12], we chose to rely on viral cultures, and detection of enteroviral genome utilizing the highly sensitive

amplification technique. The results of our analysis do not support a prominent role for these agents in the etiology of the syndrome. Studies conducted during standardisation of our assay indicate it to be highly sensitive in detecting virus even at low concentrations. Moreover, this assay has shown an excellent correlation with results from culture of cerebrospinal fluid obtained from patients with enteroviral neurologic disease who were studied at our centre (unpublished observations, 1994). Our methodology was designed to study the patients at the time of development of symptoms of the syndrome, a time when viraemia, if present, should have been maximal.[18] Since enteroviruses may be isolated from blood in symptomatic children with enteroviral disease,[18] the highly sensitive technique of amplification would have been anticipated to yield positive results if enteroviruses were important in the pathogenesis of the syndrome. High levels of RNase activity, or of enzymatic inhibitors in some clinical specimens, may lead to false negative results. In our study, samples were frozen shortly after collection, and an RNase inhibitor was added immediately after rethawing. Although viral degradation may occur, it is encouraging to note that Thoren and colleagues[19] were able to detect evidence of enterovirus by using the polymerase chain reaction in more than half their samples of serum stored for up to seven years from patients with enteroviral meningitis. Muir and colleagues[20] have, likewise, successfully used this technique to detect enterovirus in a variety of clinical specimens, including serum and pericardial fluid. Olive and co-workers[21] also reported the successful use of the technique for detecting enterovirus in pericardial fluid. The lack of detection of enterovirus genome in pericardial fluid from 5 of our patients with the syndrome is additional strong evidence against the involvement of enteroviruses at this site.

The reason why positive viral serological findings were found previously in patients with the syndrome[2,9–11] is unclear. The results, however, should now be interpreted with caution, since the findings could not be confirmed two other groups,[6,7] and our own findings have provided no endorsement. Our analysis of changes in antibody titers to diphtheria and tetanus toxoids and rubella virus also militate against generalized activation of polyclonal B lymphocytes as an explanation for the increase in antiviral antibodies noted previously in patients with the syndrome. In our study, increases in antiviral IgG antibody were primarily related to blood transfusion, and were independent of development of the postpericardiotomy syndrome. Our investigation, therefore, provides strong evidence against the theory that postpericardiotomy syndrome is caused by, or is associated with, a viral illness.

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