Constrictive Pericarditis in Childhood Due to Mediastinal Irradiation

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SUMMARY

Between 1955 and 1972, eight children receiving mediastinal irradiation for intrathoracic malignancy developed constrictive pericarditis. Six of these followed irradiation for Hodgkin's disease and represent 7% of 86 children receiving irradiation for that disease. In patients with Hodgkin's disease, the development of constrictive pericarditis was related to the dose of radiation and the use of orthovoltage technique. Constrictive pericarditis has not yet developed among the 44 children radiated by supervoltage technique. Symptoms of constrictive pericarditis occurred an average of 15 months (2/3 to 3 2/3 years) after irradiation and were preceded in five of the eight patients by acute pericarditis. Prominent clinical findings included dyspnea, Kussmaul sign, pulsus paradoxicus, hepatomegaly, cardiomegaly and electrocardiographic evidence of low QRS voltages with ST-T wave changes. Pericardectomy was performed in six patients and resulted in immediate but only transient symptomatic relief. There was no operative mortality. Death occurred in six of the eight patients (1/3 to 6 1/4 years following irradiation) due to cardiac disease in three, progression of the malignancy in two and infection in one. In addition to constrictive pericarditis, extensive myocardial fibrosis and involvement of the anterolateral papillary muscle and chordae tendineae of the mitral valve were demonstrated at postmortem examination. These factors may explain the progression of cardiac disease despite an initial symptomatic improvement following pericardectomy.

Additional Indexing Words:
Hodgkin's disease
Chemotherapy
Myocardial disease
Physiopathology of heart disease

Injury to virtually all normal intrathoracic structures has been reported following radiation therapy for a variety of neoplastic conditions. Ionizing radiation has been reported to cause pathologic changes in the pleura, lungs, heart, coronary arteries and great vessels. Pericardial damage is the most commonly reported clinically significant effect on the heart. Radiation to the mediastinum may cause isolated electrocardiographic changes, acute pericarditis, pericardial effusion and, less commonly, constrictive pericarditis. Clinically significant pericardial disease following irradiation is related primarily to the pericardial radiation dose, elapsed time over which the radiation has been administered, daily fraction size and volume of heart irradiated. There are numerous reports on radiation-induced constrictive pericarditis in adults but only a few cases have been recorded in childhood. Because the incidence, course and prognosis of radiation-induced constrictive pericarditis in childhood is not known, we have reviewed the experience with this lesion at our institution.

Method and Patient Material

The diagnostic files in the record room, Departments of Cardiology and Radiotherapy and The Children's Cancer Research Foundation of the Children's Hospital Medical Center in Boston were searched. The records of all patients who had pericarditis, pericardial effusion or constrictive pericarditis associated with neoplastic disease were reviewed. Only patients with cardiac catheterization, surgery or postmortem evidence of constrictive pericarditis following mediastinal irradiation were then included in this report. Some patients whom we believe, clinically, represent mild constrictive pericarditis are not included. Thus, the incidence represented is felt to be the minimum incidence of constrictive pericarditis following mediastinal irradiation. The total number of patients, dose and mode of administration of radiation were tabulated. Irradiation of the mediastinum was begun shortly after diagnostic evaluation.
and the total mid-plane dose to the mediastinum varied from less than 2000 to 5000 rad. Co-planar anterior and posterior fields were used. Prior to 1970, either orthovoltage (250 kVp 15 mA, Thorgeus II filter) equipment or, less commonly, photons from either a 2 MV Van de Graaff generator or gamma rays from $^{60}$Co were used. Although the majority of patients prior to 1970 were irradiated using orthovoltage apparatus, selected patients received megavoltage radiation. More recently, X-ray photons from a 4 MV or 8 MV linear accelerator have been used exclusively. Patients treated by both methods have been followed for a sufficient length of time to justify comparisons. Using opposed anterior and posterior fields, the maximum pericardial dose has been calculated, for an average patient, to be approximately 20% greater for an equivalent mid-plane dose when orthovoltage equipment was used (fig. 1). Two of the patients included herein have been previously reported in a manuscript describing the surgical therapy of constrictive pericarditis.² Since mediastinal irradiation is a major component of the treatment of Hodgkin’s disease, the incidence of constrictive pericarditis in this condition was determined.

Results

Incidence. Between 1955 and 1972, 86 children with Hodgkin’s disease received mediastinal irradiation and were followed for a minimum period of one year. Six of these patients (7%) developed constrictive pericarditis following irradiation, (patients 1–4, 6, 8 in table 1). Two additional patients who received mediastinal irradiation for pulmonary metastases, one from a reticulum cell sarcoma of bone and one from Wilms’ tumor, (patients 7 and 5, respectively, in table 1) also developed constrictive pericarditis. The eight patients were first noted to have thoracic malignancy at age $1\frac{9}{12}$ to $17 \frac{1}{12}$ years (table 1). The patient with Wilms’ tumor was treated with actinomycin D concurrently with irradiation. The child with reticulum cell sarcoma received a cumulative dose of 400 $mg/m^2$ of the anthracyclines, daunorubicin and Adriamycin, three years after completion of mediastinal irradiation. Other chemotherapeutic agents employed in the eight patients included chlorambucil, vincristine, prednisone and methotrexate.

Risk Factors. Table 2 shows the radiation technique employed, dose delivered to the mid-plane and the number of patients with Hodgkin’s disease who subsequently developed constrictive pericarditis. There were no cases of constrictive pericarditis following the use of supravoltage technique whereas 15% of all patients treated by orthovoltage technique developed constrictive pericarditis ($P < 0.05$). Among patients in this latter group who received less than 4000 rad, two out of 35 (6%) developed constrictive pericarditis and in those who received more than 4000 rad, four out of seven (57%) ($P < 0.001$) developed constrictive pericarditis.

Diagnosis and Clinical Findings

Symptoms of constrictive pericarditis developed at an average of 15 months ($\frac{9}{12} - 3\frac{9}{12}$ years) after irradiation and were preceded in five patients by acute pericarditis and/or pericardial effusion, which developed from 1½ months to one year after irradiation (table 1). Dyspnea and decrease in exercise tolerance were invariably present. On physical examination, pulsum paradoxicus was present in six patients, neck vein distention in six, pericardial friction rub in three, gallop rhythms in four and muffled heart sounds in two. All eight patients had hepatomegaly. An apical regurgitant systolic murmur and mid-diastolic rumble were each noted in two patients. Protein losing enteropathy and atrial flutter were seen in one patient each (cases 5 and 7, respectively).

Laboratory Studies

The standard electrocardiogram revealed characteristic low QRS voltages and ST-T wave changes in all eight patients. Sinus tachycardia was present in six patients and atrial flutter in one. During the course of the disease process, right or left atrial hypertrophy or both developed in six of eight; intraventricular conduction delay developed in six of

Isodose comparison of orthovoltage technique (50 cm FSD, 250 kVp, HVL = 2.5 mm Cu, 10 x 10 cm field) and 4 MV (MEV) (supravoltage, linear accelerator, 80 cm FSD, 10 x 10 cm field) for 4000 rad mid-plane dose to the thorax. The increased dose to cardiac structures by orthovoltage technique is demonstrated.

Figure 1
eight; and two of the eight showed a characteristic development of ST-T change with initial ST elevation followed by flattening of the T and then T inversion seen in sequential electrocardiograms. Chest X-ray showed mild to moderate cardiomegaly in six. Jugular venous pulse tracing obtained in three cases was helpful in demonstrating the early peaked "V" wave, deep X and Y descent and Kussmaul sign. An apexcardiogram performed in one patient demonstrated systolic retractions with a sustained diastolic shoulder.

Cardiac Catheterization

Six cardiac catheterizations were performed in five of the eight patients. One additional patient (patient 1) was catheterized after pericardiectomy when tumor infiltration produced superior vena caval obstruction. Findings at catheterization (table 3) included an increased right atrial pressure in all patients with a rise in, or absence of normal fall of, a wave pressure on inspiration in four of five patients. Pulsus paradoxus (> 10 mm Hg) was demonstrated in four out of five catheterized patients. Right ventricular end-diastolic and pulmonary capillary wedge pressures were elevated in all patients and a definite "square wave" sign in the right ventricular pressure tracing was obtained in three. Mean resting cardiac index, measured by the Fick technique, was 2.8 L/min/m² (range 1.8 to 4.2). Intracardiac volumes were measured by angiocardiography in one patient. The patient had a very low end-diastolic volume (26 ml/m²) and low end-systolic volume (10 ml/m²). The ejection fraction was normal (0.61).

Treatment

Supportive medical treatment included bed rest, use of cardiac glycosides and in the patient with atrial flutter, electrical cardioversion. Pericardiectomy (tables 1, 4) was performed in six patients, one of whom required a second pericardiectomy. Pericardial effusion was observed with the constriction in 5 of the 7 pericardiectomies. A large pericardial window was created in patients 3 and 4, one of whom required a second procedure. Extensive pericardial decortication was performed at the initial operation in the others.

Table 1

Pertinent Clinical Features in Patients With Constrictive Pericarditis Due to Irradiation

<table>
<thead>
<tr>
<th>No.</th>
<th>Age at diagnosis (year)</th>
<th>Sex</th>
<th>Radiation dose at mediastinum</th>
<th>Months between end of radiation and Death (D) or last visit (A) (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Amount (rad)</td>
<td>Duration (days)</td>
</tr>
<tr>
<td>1</td>
<td>15</td>
<td>M</td>
<td>3500</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>M</td>
<td>3165</td>
<td>32</td>
</tr>
<tr>
<td>3</td>
<td>16</td>
<td>M</td>
<td>4066</td>
<td>32</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>F</td>
<td>4000</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>10/12</td>
<td>M</td>
<td>1200</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>11</td>
<td>M</td>
<td>4500</td>
<td>39</td>
</tr>
<tr>
<td>7</td>
<td>14</td>
<td>M</td>
<td>2000</td>
<td>30</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>M</td>
<td>3540</td>
<td>30</td>
</tr>
</tbody>
</table>

Table 2

Incidence of Constrictive Pericarditis in Hodgkin's Disease Related to Radiation Dose and Technique Utilized

<table>
<thead>
<tr>
<th>Radiation</th>
<th>Midplane dose (rad)</th>
<th>No. patients</th>
<th>No. constrictive pericarditis</th>
<th>Months followed</th>
<th>&gt; 20 mo.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orthovoltage</td>
<td>≤3500</td>
<td>23</td>
<td>1 (4%)</td>
<td>64</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>3500–3999</td>
<td>12</td>
<td>1 (8%)</td>
<td>73</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>≥4000</td>
<td>7</td>
<td>4 (57%)</td>
<td>54</td>
<td>70</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>42</td>
<td>6 (15%)</td>
<td>34/42</td>
<td></td>
</tr>
<tr>
<td>Supravoltage</td>
<td>≤3500</td>
<td>7</td>
<td>0</td>
<td>37</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>3500–3999</td>
<td>15</td>
<td>0</td>
<td>46</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>≥4000</td>
<td>22</td>
<td>0</td>
<td>36</td>
<td>30</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>44</td>
<td>0</td>
<td>40/44</td>
<td></td>
</tr>
</tbody>
</table>

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Table 3

Cardiac Catheterization Data

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Right atrium (mm Hg)</th>
<th>Pulmonary arterial wedge (mm Hg)</th>
<th>Right ventricle (mm Hg)</th>
<th>Aorta (mm Hg)</th>
<th>Cardiac index (L/min/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&quot;a&quot;</td>
<td>&quot;a&quot;&quot;a&quot;</td>
<td>&quot;a&quot;&quot;a&quot;</td>
<td>&quot;a&quot;&quot;a&quot;</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>17</td>
<td>8</td>
<td>13</td>
<td>17</td>
</tr>
<tr>
<td>3a (rest)</td>
<td>14</td>
<td>16</td>
<td>10</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>3b (exercise)</td>
<td>22</td>
<td>23</td>
<td>18</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>27</td>
<td>21</td>
<td>25</td>
<td>26</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>12</td>
<td>12</td>
<td>6</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>10</td>
<td>6</td>
<td>7</td>
<td>11</td>
</tr>
</tbody>
</table>

Abbreviations: Exp. = Expiratory; Insp. = Inspiratory; | | = Oxygen consumption assumed.

Course and Prognosis

Following pericardiectomy, there was an immediate but transient relief of symptoms. Symptomatic improvement usually persisted for a few months with gradual deterioration thereafter. Postoperatively, four of six patients showed improvement in ST-T segment changes and voltage. One patient required a second pericardiectomy because of recurrence of symptoms. Of the two patients treated without surgery, one died with severe constrictive pericarditis and another remains symptomatic 1 ½ years after the onset of constriction. Six of the eight patients died an average of 3 ½ years (1 ½ to 6 ½ years) following irradiation. Death was due to cardiac constrictive or restrictive disease in three (3 ½ to 6 ½ years following irradiation), progression of the malignancy in two and systemic infection in one. Two patients are alive with mild cardiac symptoms and no known residual malignancy three and six years postirradiation (tables 1, 4).

Pathology

Autopsy (table 4) was performed in five of the six patients who died. Examination of the heart revealed

Table 4

Summary of Treatment, Course and Pertinent Postmortem Findings

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Surgery</th>
<th>Surgical findings</th>
<th>Course</th>
<th>Postmortem</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>P</td>
<td>E: CP</td>
<td>SVC syndrome due to radiation and tumor: Cardio-respiratory failure and death</td>
<td>Extensive tumor with SVC obstruction; CM, PF, MF</td>
</tr>
<tr>
<td>2</td>
<td>P</td>
<td>E: CP</td>
<td>Mild symptoms of CP and tricuspid regurgitation</td>
<td>——</td>
</tr>
<tr>
<td>3a</td>
<td>P</td>
<td>E: CP</td>
<td>Progressive CP, chronic CHF and death</td>
<td>——</td>
</tr>
<tr>
<td>3b</td>
<td>P</td>
<td>CP</td>
<td>Mild symptoms of CP, respiratory failure and death</td>
<td>No tumor: resp. infection; CM, PF, MF, MVT</td>
</tr>
<tr>
<td>4</td>
<td>P</td>
<td>E: CP</td>
<td>Severe restrictive lung disease, symptoms of CP, chronic CHF, death</td>
<td>No tumor: CM, PF, MF, MVT</td>
</tr>
<tr>
<td>5</td>
<td>P</td>
<td>CP</td>
<td>Improved, mild symptoms of CP; distended veins, hepatomegaly</td>
<td>——</td>
</tr>
<tr>
<td>6</td>
<td>None</td>
<td>—</td>
<td>Atrial flutter, marked rapid progression of CP and CHF, and death</td>
<td>No tumor, CM, PF, MF, MVT</td>
</tr>
<tr>
<td>7</td>
<td>None</td>
<td>—</td>
<td>Rapid tumor progression and death</td>
<td>Extensive tumor; CM, PF, MF</td>
</tr>
</tbody>
</table>

Abbreviations: P = pericardiectomy; E = effusion; CP = constriction; SVC = superior vena cava; CHF = congestive heart failure; CM = cardiomegaly; PF = pericardial fibrosis; MF = myocardial fibrosis; MVT = thick mitral valve.
cardiomegaly and fibrosis of the pericardium in each patient with additional myocardial cellular degeneration and fibrosis in all (figs. 2, 3). There was marked right ventricular enlargement and hypertrophy in three of the cases (patients 1, 4, and 5) and left ventricular hypertrophy in one (patient 7). Focal endocardial thickening of the left ventricular papillary muscles and chordae tendineae of the mitral valve were observed in patients 4, 5, and 7. In two of these, the mitral valve edges were rolled, thickened and nodular; the presence of jet lesions in the left atrium was strongly suggestive of mitral regurgitation (fig. 4).

Discussion

The development of constrictive pericarditis following mediastinal irradiation has been previously reported in adults aged 22 to 68 years and in four children aged 13 to 15 years. In our patients, the development of constrictive pericarditis was related both to pericardial radiation dose and to the technique utilized. The effect of total cardiac volume irradiated and the presence or absence of tumor invading the pericardium prior to irradiation has not been evaluated. All pertinent data indicate that pericarditis and constrictive pericarditis are dose related and that the radiation dose per fraction and the total elapsed time of irradiation are important factors. Calculations of dosage reaching the anterior pericardium in orthovoltage vs supravoltage techniques revealed that the pericardial dose delivered is much greater with orthovoltage than with supravoltage when the mid-plane dose is equivalent (fig. 1). Although constrictive pericarditis did not develop in our patients who received 4000-4400 rad total mid-plane utilizing supravoltage equipment, a striking incidence of 57% (P < .001) was encountered. Thus, careful attention to technique should reduce the incidence of constrictive pericarditis.

Prospective studies on the prevalence of acute pericarditis have set the incidence of this complication at 7% to 21% of all patients with Hodgkin’s disease who were treated with irradiation. The effect of radiation is, of course, not limited to the pericardium. It has been demonstrated in patients and experimental animal studies that the myocardium is also damaged. Myocardial changes have been documented by both light and electron microscopy. These studies suggest that there is an initial acute

Figure 2
Photomicrograph of the left ventricle of case 5. There is thickening of the endocardium (upper left) with fibrosis, necrosis and round cell infiltration of the myocardium. (× 40)

Figure 3
Photomicrograph of the left ventricle of case 5. There is fibrosis, necrosis and round cell infiltration of the myocardium. (× 100)

Figure 4
Photograph of the heart (case 5) viewing the opened left ventricle and left atrium. There is thickening of leaflets and rolling of the margins of the mitral valve, (lower black arrow), thickening of the chordae and papillary muscles (lower white arrow) and jet lesions (upper arrow) in the left atrium. The ventricular and atrial surfaces exhibit endothelial thickening and sclerosis.
radiation pancarditis which is followed by a latent stage with progression to severe pericardial and myocardial lesions which may lead to death.\textsuperscript{25, 26} The pericardium shows thickening due to progressive deposition of collagen and fibrinous exudate, and the myocardium shows diffuse fibrosis; the latter is due to rupture and occlusion of capillaries which results in muscle ischemia and leads in the late stage to diffuse, progressive and irreversible fibrosis of the myocardium.\textsuperscript{25, 26}

Constrictive pericarditis may develop as early as five weeks or as late as 45 years after mediastinal irradiation.\textsuperscript{2-20} In our patients, the average interval was 15 months. The symptoms and signs of constrictive pericarditis induced by mediastinal irradiation are similar to those produced by other etiologies. Cardiomegaly, diffuse myocardial fibrosis and thickening of the anterolateral papillary muscle and chordae of the mitral valve are frequently present. The pathologic changes in the mitral valve and its attachments may interfere with valve closure and opening and explain the apical systolic and diastolic murmurs heard in our patients.

Although pericardiectomy is usually followed by an immediate and adequate symptomatic relief in constrictive pericarditis,\textsuperscript{27-29} failure to respond may occur because of severe myocardial involvement,\textsuperscript{28, 30} endomyocardial restrictive disease\textsuperscript{5} or incomplete pericardiectomy.\textsuperscript{31} In adults, the operative mortality is 13\%\textsuperscript{27} with surgery considered to be beneficial in 84–86\% of the survivors.\textsuperscript{28, 29} Since radiation frequently affects both pericardium and myocardium, one would expect a poorer response following pericardiectomy for constrictive pericarditis induced by radiation than that due to other causes. The transient symptomatic response and eventual progression of the cardiac disease in our patients is probably related to the severe myocardial involvement. This is supported by the gross cardiomegaly and histologic myocardial findings at autopsy in four patients.

The expected finding of a small quiet heart in constrictive pericarditis has previously been pointed out to be a common misconception.\textsuperscript{32} Cardiomegaly was a prominent finding in our patients and is probably due to cardiac chamber enlargement and the frequent coexistence of effusion.

The influence of chemotherapy in the pathogenesis of constrictive pericarditis and the symptomatology in these patients deserves comment. Actinomycin D potentiates the action of radiation therapy\textsuperscript{23} and probably contributed additionally to the deleterious effects of irradiation in the mediastinal structures of the patient who received this antibiotic concurrently with irradiation. Further, the anthracyclines are cardiotoxic.\textsuperscript{24-26} The maximum cumulative dose recommended should not exceed 600 mg/m\textsuperscript{2}, particularly for adriamycin.\textsuperscript{24} Since irradiation may promote cardiac damage, these chemotherapeutic agents probably contributed to the abnormal cardiac findings in patient 7. Experience in the latter and in several other patients who developed cardiac abnormalities with the anthracyclines at this institution have led us to limit the maximum cumulative dose of these drugs to 300 mg/m\textsuperscript{2} in patients who receive mediastinal irradiation. We are unaware of a cardiotoxic relationship with the antitumor agents employed in the other patients.

With current supravoltage technique, pericardial complications are infrequent. Our study strongly suggests that with the use of supravoltage technique and carefully controlled radiation dosage, the frequency of constrictive pericarditis after mediastinal irradiation may be significantly reduced. Patients who have received mediastinal irradiation should be carefully monitored, probably for an indefinite period of time, for the possible iatrogenic cardiac complications of the therapy. In those who develop constrictive pericarditis, complete decortication of the constrictive pericardium is indicated. Significant improvement in cardiac symptomatology may be anticipated but the prognosis remains guarded.

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