CLINICAL PROGRESS

Cardiovascular Manifestations of the Hurler Syndrome

Hemodynamic and Angiocardioangiographic Observations in 15 Patients

By L. Jerome Krovetz, M.D., Ph.D., Andrew E. Lorincz, M.D., and Gerold L. Schiebler, M.D.

SINCE the original report of Hunter, cardiovascular disease has been recognized as an integral feature of the Hurler syndrome (gargoylism, lipochondrodystrophy). Hunter noted cardiomegaly and both systolic and diastolic murmurs in the older of two brothers with this syndrome who died at age 20 of "dropsy." Other publications have continued to record cardiac murmurs, cardiomegaly, and premature deaths secondary to cardiac disease. In several reports the murmurs were sufficiently striking to suggest congenital heart disease, particularly ventricular septal defect. Necropsies have not corroborated the presence of septal defects but have stressed the frequency of valvular deformities, endocardial fibroelastosis, and narrowing of the coronary arteries. Emanuel, reviewing the literature of the Hurler syndrome in 1954, found 32 necropsies, 22 of which had evidence of cardiovascular disease.

It is surprising that only four general re-

views of the cardiovascular involvement in the Hurler syndrome have appeared. Even in these reviews, detailed clinical descriptions of the cardiovascular system are lacking, and hemodynamic data are unavailable. The present study consisting of cardiac catheterization and angiocardioangiographic studies in 15 children with the Hurler syndrome was undertaken to obtain hemodynamic observations that could be correlated with the cardiovascular manifestations of this entity.

Methods

All the patients had classical clinical and radiologic manifestations of the Hurler syndrome. Elevated urinary acid mucopolysaccharide excretion was demonstrated indirectly by the acid albumin turbidity screening technic, and directly by isolation of crude mucopolysaccharide by the modified technique of Dorfman and Lorincz. All patients had positive screening tests. Crude mucopolysaccharide excretion ranged from 35 to 520 mg./L. (normal less than 10 mg./L.). Basic information concerning these patients is listed in Table 1. Eleven of the 15 patients were male. One was of the Negro race (case 11), the remainder Caucasian. The patients ranged in age from 5 months to 12 years.

Most of these patients were mentally retarded and uncooperative. A heavier than usual amount of sedation was necessary to achieve reliable studies. In two cases meperidine and a barbiturate were employed; in one, morphine and a barbiturate; in the remainder, a mixture of meperidine (2-3 mg./Kg.), promethazine (0.5-
0.8 mg./Kg.), and chlorpromazine (0.5-0.8 mg./Kg.) was given intramuscularly approximately one-half hour prior to catheterization. In spite of these relatively high dosages, most of the patients remained relatively alert during the procedure.

Pressures were measured by Statham gauges and recorded on ultraviolet-sensitive paper in a Minneapolis-Honeywell 1108 Visicorder. Gauges were located at mid-chest level and calibrated against a mercury manometer. Values for pressures listed in the tables were obtained during periods of rest or drowsiness and measured during expiration.

The left ventricle was entered in seven instances by the retrograde approach from the right brachial artery and in four instances by the transeptal technic.

Oxygen saturations were recorded with a Waters XC-50 cuvette oximeter and an Ensco amplifier. In all except one case, the cuvette oximeter was calibrated by simultaneous measurements of galvanometer deflections and Beckmann spectrophotometric or Van Slyke-Neill analysis of at least two samples of blood.

Lack of cooperation precluded the use of the direct Fick method for determining cardiac output in all except case 15. Arterial indicator-dilution curves, with indocyanine green, were recorded in 10 of the subjects. Calculations of cardiac outputs followed the usual Stewart-Hamilton procedure.

Angiocardiographic studies were performed by the injection of contrast media at a pressure of 700 pounds per square inch with a Cordis angiograph syringe. Filming was by either 16 mm. cine film at 60 fps or a biplane roll-film changer at 6 fps.

**Figure 1**

Systemic arterial blood pressures recorded during cardiac catheterization.

**Figure 2**

Example of notched ascending right ventricular pressure curves seen in six of the 15 subjects with the Hurler syndrome. This notch occurred after the end of diastole, and may represent an early sign of diminished myocardial contractility.

**Results**

The presence of abnormal shunts, especially a left-to-right shunt through a ventricular septal defect, was looked for by a variety of techniques. In no instance was such a shunt detected by either oximetry, indicator-dilution techniques, (including four double-catheter studies) or left ventricular angiocardiography. None of the seven patients with low arterial oxygen saturations (less than 94 per cent), had right-to-left shunts by indicator-dilution techniques, thus suggesting that the arterial desaturation was secondary to respiratory depression or pulmonary disease.

Pressures obtained during the catheterizations are summarized in table 1. A striking incidence of systemic pressure elevation was noted (fig. 1). Only six (cases 1, 2, 4, 6, 14, and 15) fall within normal limits. Generally good agreement with auscultatory blood pressures, obtained without sedation, was found.

With the exception of case 15, every instance of elevation of right heart pressures was accompanied by systemic hypertension. Five of the available nine left ventricular end-
### Cardiac Catheterization Data in 15 Cases of the Hunter-Hurler Syndrome

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age (yr.)</th>
<th>Sex</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Surface area (M²)</th>
<th>Systemic arterial saturation</th>
<th>RA</th>
<th>RV†</th>
<th>PA</th>
<th>LA or PAc</th>
<th>LV†</th>
<th>SA</th>
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</thead>
<tbody>
<tr>
<td>1.</td>
<td>5/12</td>
<td>F</td>
<td>67</td>
<td>7</td>
<td>.40</td>
<td>91%</td>
<td>6/ 1</td>
<td>27</td>
<td>-1</td>
<td>4</td>
<td>18/ 9</td>
<td>10/ 7</td>
</tr>
<tr>
<td>2.</td>
<td>7/12</td>
<td>M</td>
<td>75</td>
<td>9</td>
<td>.46</td>
<td>88%</td>
<td>7/ 2</td>
<td>30</td>
<td>0</td>
<td>8</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3.</td>
<td>11/12</td>
<td>M</td>
<td>80</td>
<td>10</td>
<td>.49</td>
<td>97%</td>
<td>3/ 3</td>
<td>24</td>
<td>-1</td>
<td>3</td>
<td>22/ 9</td>
<td>11/ 5</td>
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<tr>
<td>4.</td>
<td>2</td>
<td>F</td>
<td>87</td>
<td>11</td>
<td>.55</td>
<td>97%</td>
<td>7/ 3</td>
<td>25</td>
<td>2</td>
<td>8§</td>
<td>22/ 9</td>
<td>16/ 8</td>
</tr>
<tr>
<td>5.</td>
<td>2</td>
<td>F</td>
<td>86</td>
<td>13</td>
<td>.59</td>
<td>91%</td>
<td>8/ 2</td>
<td>42</td>
<td>2</td>
<td>10</td>
<td>36/16</td>
<td>21/12</td>
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<tr>
<td>6.</td>
<td>2</td>
<td>M</td>
<td>95</td>
<td>19</td>
<td>.72</td>
<td>96%</td>
<td>7/ 3</td>
<td>33</td>
<td>1</td>
<td>6§</td>
<td>25/12</td>
<td>13/ 8</td>
</tr>
<tr>
<td>7.</td>
<td>4</td>
<td>M</td>
<td>98</td>
<td>18</td>
<td>.73</td>
<td>94%</td>
<td>7/ 0</td>
<td>32</td>
<td>-1</td>
<td>6§</td>
<td>26/10</td>
<td>12/ 8</td>
</tr>
<tr>
<td>8.</td>
<td>6</td>
<td>M</td>
<td>110</td>
<td>26</td>
<td>.89</td>
<td>96%</td>
<td>12/ 7</td>
<td>30</td>
<td>2</td>
<td>-</td>
<td>22/13</td>
<td>-</td>
</tr>
<tr>
<td>9.</td>
<td>7</td>
<td>M</td>
<td>115</td>
<td>23</td>
<td>.83</td>
<td>91%</td>
<td>7/ 3</td>
<td>33</td>
<td>1</td>
<td>7</td>
<td>28/12</td>
<td>18/ 4</td>
</tr>
<tr>
<td>10.</td>
<td>8</td>
<td>M</td>
<td>106</td>
<td>19</td>
<td>.76</td>
<td>100%</td>
<td>8/ 5</td>
<td>28</td>
<td>2</td>
<td>8§</td>
<td>24/16</td>
<td>-</td>
</tr>
<tr>
<td>11.</td>
<td>9</td>
<td>M</td>
<td>124</td>
<td>24</td>
<td>.92</td>
<td>90%</td>
<td>16/ 13</td>
<td>39</td>
<td>8</td>
<td>15§</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>12.</td>
<td>10</td>
<td>M</td>
<td>116</td>
<td>20</td>
<td>.82</td>
<td>95%</td>
<td>12/ 6</td>
<td>36</td>
<td>4</td>
<td>9§</td>
<td>25/11</td>
<td>12/ 9</td>
</tr>
<tr>
<td>13.</td>
<td>10</td>
<td>M</td>
<td>112</td>
<td>25</td>
<td>.87</td>
<td>93%</td>
<td>9/ 5</td>
<td>34</td>
<td>4</td>
<td>9</td>
<td>33/17</td>
<td>-</td>
</tr>
<tr>
<td>14.</td>
<td>10</td>
<td>M</td>
<td>118</td>
<td>25</td>
<td>.92</td>
<td>99%</td>
<td>6/ 0</td>
<td>22</td>
<td>-3</td>
<td>2</td>
<td>16/ 7</td>
<td>12/ 8</td>
</tr>
<tr>
<td>15.</td>
<td>12</td>
<td>M</td>
<td>158</td>
<td>49</td>
<td>1.48</td>
<td>89%</td>
<td>7/ 3</td>
<td>37</td>
<td>1</td>
<td>5</td>
<td>25/10</td>
<td>14/ 8</td>
</tr>
</tbody>
</table>

*Case 1 and 5 and 2 and 9 are siblings.
†Ventricular pressures are reported as peak systolic/minimum diastolic to end-diastolic levels.
‡Sex-linked inheritance.
§Right ventricular notch.

Abbreviations: RA, right atrium; RV, right ventricle; PA, pulmonary artery; LA, left atrium; LV, left ventricle; SA, systemic artery; PAc, pulmonary artery capillary wedge.
diastolic pressures were elevated, and four of the right ventricular end-diastolic pressures were abnormally high. One patient (no. 11) had a right ventricular end-diastolic pressure of 15, reflecting his clinically evident congestive heart failure.

One unexpected finding was an unusual notch on the rising limb of the right ventricular pressure curves. Six of the subjects exhibited this wave form. In no instance was this seen in the left ventricular tracings (fig. 2).

Cardiac indices (liters/minute/square meter) were within normal limits except for four instances. Cases 6, 13, and 14 had cardiac indices slightly above the upper limits of normal, while case 4 had a slightly low cardiac index (fig. 3) (table 2). Arteriovenous oxygen differences varied from 17 to 58 ml. of oxygen per liter. Normal standards, for this value are available only for adult men. Based on these values, three subjects had higher and two others lower than normal values. Estimates of systemic, total pulmonary, and pulmonary arteriolar resistances were above the usually accepted normal

![Figure 3](https://example.com/figure3.png)

**Figure 3**

Cardiac indices as measured in nine of the subjects.

**Table 2**

![Figure 4](https://example.com/figure4.png)

**Figure 4**

Calculated resistances of subjects with the Hurler syndrome. They were elevated except in the two oldest children.
ranges in all except cases 14 and 15 (fig. 4).

The first derivatives of ventricular pressure tracings (dp/dt) were calculated in 12 cases from oscillographic tracings run at a paper speed of 200 mm. per second (table 2). Six of the nine satisfactory left ventricular first derivatives were lower than those obtained from a group of pediatric patients with functional murmurs. Seven of the 10 right ventricular first derivatives were elevated; in six of the seven, this correlated with an elevated right ventricular systolic pressure. Unfortunately, this “contractility rate” is available on too few normal subjects to justify rigid criteria of normality based on both rate and the ultimate level of systolic pressure attained. Since elevations of either of these elevate the rate of contractility, a determination of the normality of this criterion in our cases with the Hurler syndrome must await a more extensive collection of normal data. Our tentative conclusion is that the contractility rate of the left ventricle is lowered in the Hurler syndrome.

A total of 25 angiocardiograms were performed in 11 patients (table 3). In 10 of these patients significant left-to-right shunts were excluded by these studies. Six cases had selective left ventricular angiocardiography and only one (case 4) demonstrated any mitral insufficiency (fig. 5).

Moderate aortic insufficiency was noted in cases 10 and 12 and minimal pulmonary insufficiency in case 6. Case 11, in which the right ventricular pressure was 39/8, demonstrated a moderately enlarged pulmonary artery, and a decrease in the number and size of peripheral arterial vessels.

Six studies included visualization of the coronary arterial system. No instances of plaque formation, narrowing or blockage were seen.

**Table 3**

<table>
<thead>
<tr>
<th>Angiocardiographic Studies</th>
</tr>
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<tbody>
<tr>
<td>Case no.</td>
</tr>
<tr>
<td>2.</td>
</tr>
<tr>
<td>4.</td>
</tr>
<tr>
<td>6.</td>
</tr>
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<td>7.</td>
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<td>9.</td>
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<td>10.</td>
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<td>11.</td>
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<td>12.</td>
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<tr>
<td>13.</td>
</tr>
<tr>
<td>14.</td>
</tr>
<tr>
<td>15.</td>
</tr>
</tbody>
</table>

Abbreviations: LA, left atrium; MI, mitral insufficiency; AI, aortic insufficiency; AR, aortic root; NE, not entered; N, normal.
Discussion

Keith, Rowe, and Vlad noted that sudden death and congestive heart failure accounted for approximately one half of the stated causes of death in 39 reported cases. Table 4 lists 75 cases that we have found in the literature.\(^1,3,5,6,8,13-46\)

Table 5 tabulates the pathologic findings of 58 necropsies in the literature\(^5,8,13-17,19,20,22-29,31-46\) plus four previously unreported cases from this institution. Mitral valvular involvement was noted in 39 of these combined reports, the tricuspid and the aortic valves were involved in 19 and 16 cases respectively, while the pulmonic valve was involved in eight cases. Thus the mitral valve seems to be the most frequently damaged while the tricuspid and the aortic valve are involved in about the same incidence, and the pulmonic valve only infrequently.

The valvular abnormalities in most cases have consisted of small nodules along the free margins of the valve edge. These were accompanied in some cases by shortening and thickening of the chordae tendineae. Although in most instances it would appear that valvular insufficiency was the predominant hemodynamic lesion, mitral stenosis has also been reported.\(^46\) In this series of 15 cases, only one child (case 10) had definite clinical and laboratory evidence of valvular insufficiency and in whom angiocardiography demonstrated moderate aortic insufficiency. One other child (case 4) had mitral insufficiency demonstrated by left ventricular angiocardiography, but it was not evident clinically. The paucity of significant valvular alterations in our series may be explained by the fact that the literature has concentrated on necropsy studies that represent the end stages of the disease process.

Narrowing of the coronary arteries was found in 20 of 58 necropsied cases of the Hurler syndrome (table 5). Dramatic photographs of coronary artery narrowing\(^2\) and the one reported case\(^8\) in which there was a clinical history suggestive of angina and coronary occlusion in a 4-year-old child suggest that individuals with Hurler's syndrome may have significant coronary artery disease early in life.

None of the patients in the group reported here had any clinical or electrocardiographic evidence of coronary insufficiency. Their retarded mental development, however, generally prohibited adequate communication. Coronary angiocardiography was satisfactory in six of these 15 cases; in none was there evidence of coronary artery involvement.

A brachiocephalic artery was found in two of the cases (no. 11 and 14). In this anomaly, the innominate and the left common carotid arteries arise from a single trunk. This has been reported in about 15 to 20 per cent of normal individuals,\(^47\) and thus may have no particular significance in this clinical entity.

Endocardial fibroelastosis has been reported in 11 of the necropsied cases reviewed; myocarditis was reported in an additional eight; and epicardial thickening, in two cases.

Table 4

<table>
<thead>
<tr>
<th>Congestive Causes of Death in 75 Reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Pneumonia</td>
</tr>
<tr>
<td>Pulmonary tuberculosis</td>
</tr>
<tr>
<td>Other respiratory conditions</td>
</tr>
<tr>
<td>“Sudden death”</td>
</tr>
<tr>
<td>“Heart attack”</td>
</tr>
<tr>
<td>Anesthesia</td>
</tr>
<tr>
<td>Not definitely stated</td>
</tr>
</tbody>
</table>

Circulation, Volume XXXI, January 1965
The presence of endocardial fibroelastosis or an infiltrative myopathy might well cause an impairment on the contractility of the ventricular myocardium. In spite of normal cardiac indices, the rate of pressure rise (dp/dt) developed by the left ventricle appears to be lower than normal in six instances.

Only case 11 was in obvious congestive heart failure at the time of catheterization. A normal cardiac output was present as well as a normal arterial-venous oxygen difference in the majority of our cases, even in the presence of relatively high doses of premedication.

Clinical evidence of endocardial fibroelastosis or of epicardial involvement, although reported, was not evident in this series. The diffuse infiltrative myopathy associated with the Hurler syndrome may have manifested itself in our catheterization data by influencing the ventricular pressure curves. As shown in figure 2, the right ventricular pressure curve was frequently notched on the upstroke and may be another manifestation of altered contractility. The authors do not intend to suggest that these abnormal right ventricular pressure contours are specific for this disease. Even more distortion of right ventricular pressure curves has been reported in endomyocardial fibrosis found in Africa.

The only cardiac catheterization data published to date in this entity consist of a footnote in Emanuel's excellent report of two brothers with cardiovascular disease. The surviving brother was noted to have a pulmonary artery pressure of 88/50 with a mean of 61 mm. Hg.

As a group the mean pulmonary artery pressures in this series were elevated. The total pulmonary vascular resistance and the total pulmonary arteriolar resistance are both elevated, documenting an increase in resistance at the arteriolar level. The pulmonary artery pressure may also eventually be raised by a higher than normal left atrial pressure, secondary to mitral valve disease or to a decreased compliance of the left ventricle.

The presence of aortic plaques in 15 of the 58 necropsied cases reviewed by the authors—and generalized arterial involvement in five other cases—may be correlated with the reported values of systemic blood pressure. In most cases, neither a systemic blood pressure nor the auscultatory findings of the heart are recorded. Figure 6 illustrates the few available blood pressure determinations in the literature; 3, 5, 13, 21, 29, 34, 40, 42, 43, 45, 49-54 32 per cent of blood pressures were abnormally elevated. In our series the incidence of systemic hypertension was impressive. Peripheral vasoconstriction causing cyanosis of the hands and feet was a not infrequent finding. None

![Figure 6](image-url)

**Figure 6**

*Systemic arterial blood pressures reported in the literature*.

*Of these 22 pressures, seven are elevated above the usually accepted normal limits.*
CARDIOVASCULAR MANIFESTATIONS OF HURLER SYNDROME

A greater incidence of male subjects in this disease was found in our series (12 of 15) and has been previously noted in other reviews. Only three of our patients were definitely of the sex-linked variety; their exclusion still leaves an unexplained 3 to 1 male to female ratio. Whether the excess male frequency is due to unrecognized sex-linked cases or to as yet unknown factors has not been definitely established.

Congenital heart disease suspected because of the presence of loud systolic murmurs in four of the 16 of Lindsey’s cases, and three of the 20 cases reported by McKusick, has not been documented by laboratory or necropsy data. Our catheterization data are characterized by the complete lack of evidence pointing to any congenital malformation of the heart.

It might be added that these diagnostic studies were performed without the occurrence of significant arrhythmias, major complications, or deaths. Cardiac catheterization and angiocardiography in these individuals probably carry no more than the usual risks.

Summary

Hemodynamic observations in 15 cases of the Hunter-Hurler syndrome are reported. Required premedication was two to three times that usually needed. No major complications or deaths occurred. As a group, these individuals tend to have slight elevations of pulmonary artery pressures and more definite elevations of systemic arterial pressures. They generally have normal cardiac outputs and, thus, elevations of total systemic, total pulmonary, and pulmonary arteriolar resistances.

In only one case was there clinical and angiocardiographic evidence of valvular involvement, that case having aortic insufficiency. In another case there was only angiocardiographic evidence of mitral insufficiency. Only one child was in congestive heart failure at the time of the study. There was no evidence of coronary artery disease. The ascending limb right ventricular pressure curve was frequently notched and the pressure rise time of the left ventricle (dp/dt) was low. No

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*One woman, reported as having the Hurler syndrome, died at age 37. We think that a more likely diagnosis was gonadal dysgenesis, particularly since the gonads could not be identified at necropsy and there was no ballooning of nerve cells. We have not included this case in figure 7.

Circulation, Volume XXXI, January 1965
case had a congenital malformation of the heart.

Those individuals who have normal vascular bed resistances appear to live longer than those who have elevated resistances early in life. The prognosis is also better for the male Hurler of the sex-linked variety than for those cases due to autosomal recessive inheritance.

Acknowledgment

The authors would like to thank Dr. Frank La-Camera of St. Petersburg, Florida, for the use of the catheterization and angiographic data of case 10.

References


Treatment of Angina Pectoris

Excision of the cervico-thoracic sympathetic containing the sensory nerves of the heart and aorta as a means of relieving the pain of angina was suggested in 1899 by Francois-Franck, the physiologist, but not put into practice until 1916 by Jonsnesco of Bucarest. The treatment by amyl nitrite was initiated in 1867 by Lauder Brunton (1844-1916), when a house physician, on the grounds that he found the blood pressure high in an attack and, having heard from Arthur Gamgee that amyl nitrite lowered the blood pressure, logically and successfully employed this drug.—Sm HUMPHRY DAVY ROLLESTON. The Harveian Oration. Great Britain, Cambridge University Press, 1928, p. 91.
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L. JEROME KROVETZ, ANDREW E. LORINCZ and GEROLD L. SCHIEBLER

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