The Medical Management of Clinical Endocardial Fibroelastosis

By James A. Manning, M.D., Frank J. Sellers, M.D., Rufus S. Bynum, M.D., and John D. Keith, M.D.

The clinical diagnosis of primary endocardial fibroelastosis has carried with it a poor, almost hopeless, prognosis.1-4 Furthermore, it is a statistically significant cause of death from cardiac failure during the pediatric age range and has been defined as the leading cause of death from cardiac failure between the ages of 1 and 2 years of age.5 Although many clinicians have thought that the clinical diagnosis is a doubtful one,6,7 the experience of the present authors has been defined in a preceding article8 and has led us to the conclusion that, within certain well-defined bounds, the clinical diagnosis of primary endocardial fibroelastosis can be made with great accuracy.

This report deals with the evaluation of the clinical results following 9 years of medical management of the patients discussed in the previously mentioned report defining diagnosis.

Material

Patients utilized in this study have conformed to the criteria for accurate diagnosis previously defined.9 Therefore, inclusion has been restricted to those infants presenting in their initial bout of congestive heart failure, under the age of 2 years, with the clinical, fluoroscopic, and electrocardiographic diagnosis of primary endocardial fibroelastosis. All patients with fixed valvular disease have been excluded. Any patients who were thought by the authors to have a questionable diagnosis were excluded. Finally, no patients were included in the study who had not been under medical management for more than 2 years.

Treatment

Patients followed in this series have been treated with a rather standardized technic of vigorous decongestive therapy. Rapid-acting digitalis glycosides were used, most commonly digoxin. Digitalization was accomplished by intramuscular, oral, and, rarely, intravenous routes, depending upon the severity of clinical symptoms. The standardized digitalizing dose was between 60 and 80 μg. per Kg. in 24 hours. The highest digitalizing dose used in this series was 90 μg. per Kg. for 24 hours and the lowest 55 μg. per Kg. for 24 hours. Maintenance doses of digoxin have varied between 12 and 25 μg. per Kg. per day, with the average maintenance dose being 18 μg. per Kg. per day. When required, vigorous supportive measures of oxygen, low-salt diet, and diuretics have been used. These patients have been observed carefully on a long-term basis and have had extremely close supervision of medical therapy.

Results

Of 56 patients who have been included in this study, 25 or 44 per cent are dead and 31 or 56 per cent are alive and classified as long-term survivors. That is, they have survived for more than 2 years from the onset of their therapy and they are alive at the present time. Of the 25 deaths, 23 occurred within the first 2 years of observation and 20 occurred within the first month of observation. There were two late deaths. Reviewing all deaths it was fairly clear that many of them had occurred early in our experience. It further appeared that a significant group had not received adequate therapy by any reasonable standard. Some had had inadequate digitalization. Some had had digitalis therapy abruptly stopped for one reason or another, and some simply had not been under medical management long enough before demise to achieve adequate digitalization. Figure 1 reviews this experience. To define our clinical impression, that adequate digitalization was related to increas-
ing vigor of therapy rather than to a change in the number of fulminating cases with rapid demise, the adequacy of digitalization was reviewed in relation to the date the patient was treated. Arbitrarily, adequate digitalization was defined as four fifths of our lower level of standard dosage, that is a digitalizing dose of 48 μg of digoxin per Kg of body weight in 24 hours. Figure 2 shows these data and confirmed our clinical impression. Since approximately 1957, in all patients with the clinical diagnosis of primary endocardial fibroelastosis, our approach to therapy has been more vigorous. Figure 3 compares mortality in these two phases of our medical management as well as comparing mortality in the group with onset under 3 months versus those between 3 months and 2 years. Compared to the over-all mortality figure of 44 per cent, the mortality in the first half of our experience was 60 per cent and in the second half was 23 per cent. Furthermore, although there was a 71-per cent mortality in the group of patients under the age of 3 months in the first half of our experience, this mortality was 25 per cent in the second half.

Clinical Course

Morbidity

Of the 25 fatalities 20 had one hospital admission, two had two hospital admissions, and three had three or more. Of the 31 long-term survivors, 20 have required one hospital admission, five have required two hospital admissions, and six have required three or more hospital admissions.

Response to Therapy

Of the 20 patients who died during their first hospitalization, 14 had essentially no clinical response to therapy. Three had a temporary decrease of symptoms and evidence of congestive heart failure, but no decrease in heart size or change in electrocardiogram. Two were judged to have had symptomatic and clinical improvement for a short period of time and some decrease in heart size, again without change in electro-
cardiogram. Of this group, 12 had been judged to have received adequate digitalization. All of the patients with temporary improvement received adequate digitalization.

Of the 31 long-term survivors, 20 had a rapid decrease in symptomatology and evidence of congestive heart failure and a significant decrease in heart size. Seven more had a significant decrease in symptomatology and evidence of congestive heart failure, but had no significant change in heart size until approximately 1 year after the onset of therapy. This entire group of 27 at the present time remains symptom-free and without significant cardiac restriction or cardiomegaly. Three others had a significant response to therapy but continued cardiomegaly without real change and remained in this situation for a period of 2 to 7 years of therapy. These patients have continued to have evidence of diminution in cardiac reserve with moderate exertional dyspnea and moderate activity restriction. One patient remains some 5 years following onset of therapy with minimal clinical improvement and no change in cardiomegaly. This youngster had a moderately rapid response to initial therapy and had some decrease in heart size approximately a year following onset of therapy (fig. 4).

**Rapidity of Onset and Mortality**

Patients were reviewed in regard to survival relative to type of onset. Type of onset was classified as acute when symptoms were of 1 week, subacute from 1 week to 1 month, and chronic when symptomatology had been present for greater than 1 month. The over-all mortality for the acute group was 60 per cent, subacute 25 per cent, and chronic 45 per cent. However, in the second half of the study group the acute mortality was 40 per cent, subacute onset 18 per cent, and chronic 20 per cent.

**Heart Size**

A comparison of the initial cardiothoracic ratio between patients who have survived and those who have failed to survive (fig. 5) has shown in general a somewhat higher cardiothoracic ratio for the fatalities than the long-term survivors. Eighty-three per cent of the fatalities have had a cardiothoracic ratio of 70 per cent or greater, whereas only 42 per cent of the survivors were in this group. Far more of the survivors were initially seen in their bout of congestive failure with a cardiothoracic ratio of between 60 and 70 per cent (52 per cent versus 14 per cent of the fatal patients). The heart size of the long-term survivors (fig. 6) has shown a significant decrease, 68 per cent having a cardiothoracic ratio of below 55 per cent. Fifty-five per cent may be taken as the upper limit of normal.

**Electrocardiographic Changes**

Although all patients when first seen of necessity had the electrocardiogram of left ventricular loading diagnostic of the clinical syndrome, significant alterations in this pattern have occurred following therapy. The two changes seen most frequently accompany-
ing clinical improvement and indicating the likelihood of a good result have been increasing positivity of the T wave over the left precordium and decreasing amplitude of the left ventricular R wave. Of the 31 long-term survivors, 10 were thought by the end of 2 years to have a normal electrocardiogram, 13 had reverted to a normal left ventricular electrocardiogram between 2 years and 5 years of therapy, and eight maintained an abnormal left ventricular electrocardiogram. Four of these are in the group with continued cardiomegaly and symptomatology and four are asymptomatic with normal or nearly normal heart size. The most favorable electrocardiographic sign has been the rapid appearance of a positive T wave over the left precordium.

**Duration and Termination of Digitalis**

Of the 31 long-term survivors 15 have been removed from digitalis therapy. Seven of these were removed after 2 to 3 years of therapy and another five were stopped between 3 and 4 years of therapy (fig. 7). Our criteria for stopping therapy have been of necessity somewhat arbitrary and cautious. We have been very loath to discontinue digoxin therapy when the cardiothoracic ratio was above 55 per cent. Furthermore, we have not discontinued therapy while the patient was in any way symptomatic. The reversion of the left ventricular T wave to an upright status even under digitalis therapy has appeared to be a good indication that digitalis might safely be discontinued. Our present policy is to stop digitalis therapy gradually, 2 years after the end of symptoms, the stabilization of the cardiothoracic ratio at or below 55 per cent, and the reversion of the left ventricular T wave to an upright status. Therapy has been discontinued gradually under close clinical, electrocardiographic, and roentgen supervision.

Despite previous reports, 6, 7 we have not encountered significant difficulties in digitalization due to "undue sensitivity or undue digitalis toxicity." On the contrary, these patients have seemed to tolerate digitalis therapy very well.

**Clinical Picture**

The presenting clinical syndrome (table 1)

**Table 1**

<table>
<thead>
<tr>
<th>Clinical signs and symptoms</th>
<th>No.</th>
<th>Dead</th>
<th>Per cent</th>
<th>Long-term survivors</th>
<th>No.</th>
<th>Per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tachypnea</td>
<td>25</td>
<td>100</td>
<td></td>
<td>31</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>25</td>
<td>100</td>
<td></td>
<td>27</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>25</td>
<td>100</td>
<td></td>
<td>31</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Lethargy</td>
<td>22</td>
<td>88</td>
<td></td>
<td>28</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>Cyanosis</td>
<td>12</td>
<td>48</td>
<td></td>
<td>15</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Poor appetite</td>
<td>18</td>
<td>72</td>
<td></td>
<td>22</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>Easy tiring</td>
<td>22</td>
<td>88</td>
<td></td>
<td>27</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>Moribund at time of admission</td>
<td>20</td>
<td>80</td>
<td></td>
<td>15</td>
<td>48</td>
<td></td>
</tr>
</tbody>
</table>
has been well defined by previous authors and in our preceding paper.\textsuperscript{4, 6, 8}

The rapidity of onset was quite variable, both in newborn and in older children.

Within the group of respiratory, cardiac, and gastrointestinal symptoms, the most striking single symptom was tachypnea. All patients presented with it and a surprising number (40 per cent) presented with a long period of “appearing healthy but breathing rapidly.”

When the presenting clinical situation was reviewed in terms of success or failure of therapy, no clear picture could be defined. As might be expected, the patients sickest at admission did worse and fared more poorly than those in better health. However, a group presenting in a moribund state did survive. Indeed, if the term moribund was used to describe the initial clinical state, there was still a 42-per cent chance of long-term survival.

**Late Deaths**

Late deaths were classified as any occurring 1 month or later after onset of therapy. Five patients were in this category. Three were between 1 month and 2 years, one was at 2\(\frac{1}{2}\) years, and the last was at 3 years. Both patients who died after 2 years had never had a good clinical response, despite adequate therapy. Of the three who died between 1 month and 2 years, two had an excellent response symptomatically. Their heart sizes had decreased, but their electrocardiograms were still abnormal. In both cases digitalis therapy was stopped by the parents 4 weeks to 6 weeks before a recurring and fulminating fatal episode of congestive heart failure. One died at home, the other shortly after rehospitalization (2 hours) with clinical evidence of marked congestive heart failure. The third patient, who died between 1 month and 2 years, never had a good response to therapy. To our knowledge, there have been no late deaths associated with arrhythmia.

**Discussion**

Any evaluation of the results presented here must of necessity hinge upon the accuracy of diagnosis. One would like to have histologic evaluation of the cardiac pathology during life or be able to make use of specific diagnostic tests.

The diagnostic criteria that we have set forth appeared to be highly specific, however, and in our opinion are as accurate as those used routinely in the diagnosis of coronary thrombosis with infarction in adults. The authors have reviewed\textsuperscript{8} the clinical and autopsy material within their experience and believe that there should be little diagnostic crossover with this syndrome and such entities as acute myocarditis, anomalous origin of the left coronary artery, calcification of the coronary arteries, or glycogen-storage disease of the heart. Although it is possible that an occasional case will be erroneously diagnosed on clinical grounds alone, it would seem highly unlikely that these syndromes having so many diagnostic features in clinical and autopsy material would lose them simply due to the fact of survival.

The mechanism of response to therapy has not been defined. To date none of the surviving patients has been studied hemodynamically. It would seem reasonable to postulate that the inotropic effects of digitalis have effected a stabilization of cardiac reserve during a period of developmentally increasing myocardial strength.

It should be recognized that the diagnostic criteria utilized have essentially segregated one group of individuals with primary endocardial fibroelastosis; namely, those with a dilated left ventricle. Fibroelastosis with contracted left ventricle would appear to be a relatively rare entity as indicated in our autopsy material. If the clinical diagnosis could be made, it may well be that the same clinical course ensues.

Our experience emphasized that vigor of medical therapy is of utmost importance to management. Long-term, careful medical observation appears to be essential to the aim of maintaining adequate digitalization. We think that the major difference between these long-term clinical results and previous experience lies wholly in the area of early, persistent vigor.
ous digitalis therapy and long-term careful observation. Several of the late deaths, occurring when digoxin therapy was abruptly discontinued without evidence of long-term cardiac stability, emphasized this point.

Long-term prognosis would appear to be good in those patients with normal heart size and electrocardiogram. What happens to the thickened endocardium is unknown. Meager data at the present would indicate that endocardial thickening is maintained. It remains to be seen whether these hearts effectively handle the degenerative diseases of later life.

Summary

Fifty-six patients with the clinical diagnosis of primary endocardial fibroelastosis have been reviewed. There was an over-all mortality rate of 44 per cent and a long-term survival of 56 per cent. Of 31 long-term survivors, 27 are without cardiac symptomatology or cardiomegaly. The method and rationale of therapy are reviewed.

References


William Withering and Edward Jenner

Withering and Jenner lived and worked not far apart, the distance between Birmingham and Berkeley being no more than sixty miles. Withering was born in 1741 and Jenner in 1749. There is a close parallel between their lives and work. Both were essentially country bred and country doctors interested in natural history as well as medicine, Withering a botanist and Jenner an ornithologist. Both took a countryside tradition, in Withering's case a local herb remedy, in Jenner's case a disease of the dairy cattle of Gloucestershire. The herb remedy and the local tradition regarding cowpox were each converted into agents of estimable value in the treatment and the prevention of disease through the genius of these two country doctors.—Louis H. Roddis, M.D. William Withering: The Introduction of Digitalis Into Medical Practice. New York, Paul B. Hoeber, Inc., 1936, p. 121.
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