Mulibrey Heart Disease

Clinical Manifestations, Long-Term Course, and Results of Pericardiectomy in a Series of 49 Patients Born Before 1985

Marita Lipsanen-Nyman, MD; Jaakko Perheentupa, MD; Juhani Rapola, MD; Anssi Sovijärvi, MD; Markku Kupari, MD

Background—Mulibrey nanism is a rare inherited disease characterized by growth failure and multiorgan manifestations, including constrictive pericarditis. Its long-term course, the results of pericardiectomy, and the details of myocardial involvement have not been reported previously.

Methods and Results—We studied 49 patients (26 men) born before 1985 and followed for up to 25 years. By 1999, 25 patients (51%) had developed congestive heart failure (CHF), 19 (39%) had undergone pericardiectomy for constrictive pericarditis, 10 (22%) had died of cardiac causes, and 5 (10%) had died of noncardiac causes. Of the 19 pericardiectomized patients, 12 derived lasting clinical benefit, whereas 1 patient suffered an early noncardiac death and 6 died later of unrelied or recurrent CHF. At echocardiography in 34 living patients, left ventricular mass adjusted for body height and weight averaged (±SEM) 149±5 g in 21 unoperated patients, 144±8 g in 13 pericardiectomized patients, and 104±7 g in 16 healthy persons matched for age and sex (P=0.000). Autopsies of 11 patients showed fibrotic thickening of the pericardial leaves with myocardial hypertrophy and variable but mostly mild myocardial fibrosis. Endocardial thickening was seen in 3 patients.

Conclusions—Constrictive pericarditis, myocardial hypertrophy, and variable myocardial fibrosis constitute the main elements of Mulibrey heart disease. At least one half of patients ultimately develop CHF. Pericardiectomy generally provides clinical benefit, but in approximately one third of patients, CHF may recur because of coexisting myocardial involvement. (Circulation. 2003;107:2810-2815.)

Key Words: pericardium • myocardium • heart failure • surgery
5 patients had heterozygous parents. Parental DNA was not available for 2 deceased patients who, however, fulfilled the clinical diagnostic criteria and were included in the present series. The institutional ethics committee approved the study protocol, and all participants gave informed consent.

**Principles of Clinical Follow-Up and Collection of Cardiovascular Data**

We followed each patient at 6- to 12-month intervals during the growth period and at 1- to 5-year intervals thereafter. Cardiac symptoms and findings in physical examination, 12-lead ECG, and chest x-rays were noted at each visit. The severity of exertional dyspnea or fatigue was graded according to the New York Heart Association (NYHA) classification. The symptoms of small children were evaluated by parental questioning and by observing the child at physical activity. Children with mild, marked, and severe limitation of physical performance were classified NYHA 2, 3, and 4, respectively. Congestive heart failure (CHF) was diagnosed if the patient had effort dyspnea (NYHA 2 or more) with elevated jugular venous pressure or pulmonary venous engorgement on chest x-rays. Patients with clinically diagnosed CHF generally underwent cardiac catheterization. The invasive studies were performed as part of clinical routine and included pressure measurements with fluid-filled catheters in the pulmonary artery, right ventricle, and right atrium. Children were studied under general anesthesia, whereas sedation and local anesthesia were used in adults. A fluid challenge test was not made. Surgical treatment (pericardectomy) was recommended when the patient had markedly limiting symptoms of CHF associated with elevated cardiac filling pressures at catheterization.

For the present report, we reviewed the patients' hospital records and the pressure tracings taken at cardiac catheterization. The time and cause of death were determined from death certificates, hospital charts, and autopsy records. When necessary, the deceased's relatives and physicians were interviewed for details of the fatal event. The pathology of the heart was reconstructed by reviewing the autopsy findings and the studies of pericardial and myocardial biopsies obtained at surgery.

**Cardiovascular Follow-Up Examination in 1999**

In 1999, the surviving 34 patients, 17 men and 17 women aged 15 to 70 years, were invited to a cardiovascular follow-up examination. All took part and underwent echocardiography, an exercise test, and measurement of plasma brain natriuretic peptide. MRI of the heart was also performed, but these results will be reported separately.

**Echocardiography**

The echocardiographic studies were done with a Toshiba Powervision scanner equipped with a multifrequency transducer. A parasternal M-mode recording was used to measure the left atrial size and the left ventricular (LV) diameters and mass. 7,8 LV ejection fraction was measured from the apical 4-chamber view using Simpson's formula. Pulsed Doppler recordings of the transmitral flow were taken to determine the ratio of the early to late diastolic (atrial) peak velocities, the deceleration of the early diastolic flow (m/s²), and the duration of the late diastolic flow (ms). Pulmonary venous flow velocity was recorded with the sampling gate inside the right upper pulmonary vein. The systolic fraction (%) of the total antegrade flow velocity integral [ie, systolic/(systolic + diastolic)] was measured, as was the duration of the late diastolic flow reversal produced by the atrial contraction (ms). All echocardiographic measurements were averaged over at least 3 cycles.

For an echocardiographic control group, we studied 16 healthy persons (8 men) aged 19 to 45 years. Although we tried to recruit volunteers who were short in stature, the control subjects did not fully match the patients for their small body size (Table 1).

**Brain Natriuretic Peptide**

Plasma brain natriuretic peptide was determined from fasting venous blood samples taken from an antecubital vein after the patient had rested for 15 minutes in the sitting position. Plasma was stored at −20°C, and the determinations were made later using an immuno-radiometric assay (Shionoria BNP, CIS Bio International). The upper limit of the reference range was 5.4 pmol/L.

**Exercise Testing**

Exercise testing was made using a bicycle ergometer (ERG 551, Robert Bosch GmbH) with continuous 12-lead ECG recording and online respiratory gas analysis. The workload, initially 20 W, was increased with 20 W every 2 minutes until subjective limitation (grade 17 to 19/20 in the Borg scale). Oxygen consumption, carbon dioxide output, and minute ventilation were measured with an automatic gas exchange analyzer (EOS Sprint, Erich Jaeger GmbH). The oxygen uptake over the last 30 seconds (VO₂ max, mL/min per kg) was recorded and calculated also as percentage of a value predicted by the patient's age and sex. 10

**Statistics**

Comparisons across group means were made with ANOVA. To adjust for differences in body size, height and weight were used as covariates when comparing the echocardiographic data on cardiac anatomy between patients with Mulibrey nanism and the control subjects. When men and women were analyzed together, sex was used as an additional grouping factor in ANOVA. Grossly skewed data (plasma brain natriuretic peptide) were log transformed before analysis. Differences in frequency distributions were analyzed with χ² test. Survival curves were constructed using the Kaplan-Meier method with log-rank test to compare differences between groups. P<0.05 was considered statistically significant. All analyses were conducted using commercially available software (SYSTAT Version 10.1, Systat Inc.).

**Results**

**Clinical Manifestations and Findings at Cardiac Catheterization**

Mulibrey heart disease typically became manifest as effort intolerance associated with signs of predominantly rightsided venous congestion. Marked cardiac enlargement on chest x-rays was rare (8 patients). CHF was ultimately

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**TABLE 1. Age and Body Size in Male and Female Patients With Mulibrey Nanism and in the Control Subjects**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mulibrey (n=17)</th>
<th>Controls (n=8)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>26.4±7.6</td>
<td>27.2±8.8</td>
<td>0.807</td>
</tr>
<tr>
<td>Height, cm</td>
<td>153.1±7.1</td>
<td>159.0±3.7</td>
<td>0.012</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>43.8±9.5</td>
<td>60.0±13.7</td>
<td>0.013</td>
</tr>
<tr>
<td>Body mass index, kg/m</td>
<td>18.3±3.2</td>
<td>23.7±5.2</td>
<td>0.023</td>
</tr>
</tbody>
</table>

Data are mean±SD.
diagnosed in 25 of the 49 patients (51%) during follow-up; their median age at diagnosis was 8.0 years (range, 0.1 to 31 years). Six patients developed chronic atrial fibrillation in association with CHF, and 1 patient suffered a myocardial infarction at the age of 26 years. Importantly, 24 patients (49%) remained free of any symptomatic heart disease. ECG abnormalities were common and included nonspecific ST-segment and T-wave changes and QRS amplitudes indicative of LV hypertrophy. Only 5 of our 49 patients (10%) had a fully normal ECG throughout the follow-up.

Twenty-six patients underwent right heart catheterization at a median age of 14.4 years (range, 0.3 to 38.5 years). Right atrial mean pressure was elevated (>8 mm Hg) in 22 of the 26 patients, and pulmonary wedge pressure was elevated (>12 mm Hg) in 10 of 12 patients with acceptable recordings. Equalization of right atrial and pulmonary wedge pressures (difference <5 mm Hg) was seen in 2 of 12 patients. A square root sign in the right ventricular pressure trace was observed in 15 of 21 patients (71%).

Effects of Pericardiectomy

Nineteen patients, 13 of 26 men and 6 of 23 women (P=0.086), underwent pericardiectomy for constrictive pericarditis at a median age of 12.8 years (range, 1.5 to 38 years). Figure 1 summarizes the effects of pericardiectomy on the effort tolerance by NYHA classification. Of the 6 patients in NYHA class 4 before surgery, 5 derived no benefit or improved only transiently and died of CHF within 1 to 12 years of pericardiectomy. The sixth patient in NYHA class 4 committed suicide soon after surgery. Of the 10 patients in NYHA class 3 preoperatively, 1 patient died of recurrent CHF 10 years after surgery. Among the 6 ultimate failures of pericardiectomy, 4 patients had a classical square root sign in the right ventricular pressure trace.

Survival

Fifteen patients died during follow-up. The cardiac deaths (n=10) occurred at a median age of 6.8 years (range, 1.4 to 48 years) and were all related to CHF. The noncardiac deaths (n=5), in turn, occurred at a median age of 33.7 years (range, 29.1 to 43.6 years) and were caused by accidents (2 patients), suicide (2 patients), and cancer (1 patient). Figure 2 shows the Kaplan-Meyer plots of the overall and cardiovascular survival (Figure 2A) and the sex-specific plots of cardiovascular survival free of pericardiectomy (Figure 2B).

Gross and Microscopic Pathology of the Heart

Cardiac weight exceeded the height-related reference range11 in 7 of 11 patients studied at autopsy. Pericardium and epicardium were thickened and fibrotic in 21 of 23 patients undergoing surgery or autopsy. Microscopically, normal pericardial tissue was replaced by scar-like fibrosis devoid of cellularity. Pericardial calcification was observed in 5 patients. Myocardial cells were hypertrophied with varying fiber diameter and occasional large multiform nuclei. Variable but mostly mild myocardial fibrosis was seen in 7 of 11 autopsied patients. Severe endocardial fibrosis and thickening was observed in 1 patient dying of CHF after pericardiectomy. Mild endocardial thickening was seen in 2 additional patients.

Cardiovascular Findings in Living Patients

Symptoms, Exercise Capacity, and Plasma Brain Natriuretic Peptide

Twenty-one of the 34 patients reexamined in 1999 were asymptomatic at ordinary activity, whereas 13 patients (4 of 21 unoperated and 9 of 13 pericardiectomized, P<0.003) had NYHA 2 effort dyspnea. VO2max ranged from 12 to 43 mL/kg per min, averaging 29.0±8.6 mL/kg per min. Relative VO2max ranged from 46% to 108% (mean, 74.3±15.9%) and was subnormal (<80%) in 20 patients irrespective of past pericardiectomy (Figure 3). Among unoperated patients, women had lower relative VO2max than men (P<0.001) (Figure 3).
Plasma brain natriuretic peptide was elevated in 10 of 12 pericardiectomized patients versus in 8 of 21 patients without past pericardiectomy ($P=0.012$). In unoperated patients, the peptide was elevated in 8 of 13 women versus in 0 of 8 men ($P=0.005$) (Figure 4).

Echocardiography
Tables 2 and 3 compare the echocardiographic measurements across the 2 patient groups (with and without past pericardectomy) and the control subjects. Patients with Mulibrey nanism had LV hypertrophy (Table 2) but normal LV systolic function (Table 3) relative to control subjects. LV filling, instead, was impaired as suggested by the prolongation of late diastolic pulmonary venous flow reversal (Table 3) and the increase in left atrial size (Table 2). Aside from systolic fraction of pulmonary venous flow (Table 3), the echocardiographic measurements did not differ between patients with and without past pericardectomy.

Discussion
Myocardial Involvement in Mulibrey Nanism
The present work establishes myocardial involvement as an essential component of Mulibrey heart disease. An increased cardiac weight was common at autopsy, and echocardiography revealed marked LV hypertrophy in both pericardiectomized and unoperated patients. Microscopy of myocardial samples also exposed signs of myocyte hypertrophy and variable myocardial fibrosis in most autopsied patients. Finally, plasma brain natriuretic peptide, a sensitive marker of LV hypertrophy and high filling pressure, was commonly elevated even in patients with successful past pericardiectomy (Figure 4).

According to our echocardiographic data, the myocardial abnormality of Mulibrey heart disease spares cardiac systolic function. Although the Doppler indexes of transmural flow were relatively little altered, the changes in the pulmonary venous flow profile (see Table 3) suggest impaired LV filling. Viewed together with increased LV wall thickness and enlarged left atrial size, these alterations are compatible with restrictive LV filling physiology. Because the LV filling abnormality was clear even in patients whose pericardium had been removed (Table 3), its mechanism must be at least partly related to myocardial hypertrophy and fibrosis.

### TABLE 2. Left Atrial Diameter and Left Ventricular Diameters, Wall Thickness, and Mass in Patients With Mulibrey Nanism and in the Control Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unoperated (n=21)</th>
<th>Past Pericardiectomy (n=13)</th>
<th>Control Subjects (n=16)</th>
<th>$P^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left atrial diameter, mm</td>
<td>38.1±0.9†</td>
<td>39.8±1.4†</td>
<td>30.5±1.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left ventricular diastolic diameter, mm</td>
<td>44.8±0.7</td>
<td>45.8±1.0</td>
<td>43.7±0.9</td>
<td>0.373</td>
</tr>
<tr>
<td>Left ventricular systolic diameter, mm</td>
<td>29.7±0.7</td>
<td>30.2±1.1</td>
<td>29.3±1.0</td>
<td>0.881</td>
</tr>
<tr>
<td>Interventricular septal thickness, mm</td>
<td>9.3±0.3†</td>
<td>9.0±0.4</td>
<td>7.7±0.4</td>
<td>0.015</td>
</tr>
<tr>
<td>Posterior wall thickness, mm</td>
<td>10.0±0.3†</td>
<td>9.4±0.5‡</td>
<td>7.8±0.5</td>
<td>0.003</td>
</tr>
<tr>
<td>Left ventricular mass, g</td>
<td>149±5‡</td>
<td>144±8†</td>
<td>104±7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are mean±SEM, adjusted for body height and weight.

$*P$ values across the 3 groups from ANOVA with sex as a second grouping factor and height and weight as covariates. Sex had no statistically significant main effects or interactions with the disease status.

$†P<0.01$, $‡P<0.05$ compared with the control group.
Pericardiectomy

Pericardiectomy was associated with zero early surgical mortality and helped most patients. The lack of long-term benefit in one third of operated patients was apparently attributable to the (restrictive) cardiomyopathy of Mulibrey heart disease. Because the possibility of myocardial disease was insufficiency recognized earlier, preoperative studies did not include any systematic approach to distinguish the respective roles of pericardial and myocardial involvement. Our analyses showed that the pressure recordings taken during preoperative right heart catheterization did not predict the results of pericardiectomy. Equalization of the right atrial and pulmonary wedge pressures was absent in many patients with lasting benefit, whereas, on the other hand, 4 of the 6 patients with ultimate surgical failures had a classical square root sign in their right ventricular pressure trace. Simultaneous left and right ventricular pressure recordings during fluid challenge can improve the differentiation between pericardial and myocardial disease. As can the study of respiratory variation in intracardiac flow velocities. The combination of these techniques and others like MRI and tissue or color M-mode Doppler may provide the best available way to predict the outcome of pericardiectomy in Mulibrey heart disease. Although these methods need to be included and analyzed in future studies, they are not required for the diagnosis of diastolic heart failure.

Why a larger proportion of male patients (52%) than female (23%) underwent pericardiectomy for CHF is difficult to explain. Although this could represent a sex difference in the severity of cardiac involvement, it could also be attributable either to a chance occurrence in a small population or to a bias in the preoperative evaluation. One possibility of bias is that, because of their generally greater physical activity, young boys were more symptomatic than young girls and were therefore sent to surgery more easily. Of note, at our reexamination in 1999, unoperated women had higher plasma brain natriuretic peptide and lower relative Vo2max than unoperated men. These differences speak against a universally more severe cardiac disease in male patients.

Long-Term Survival

Mortality in Mulibrey nanism was mainly cardiac in origin. A considerable death rate in early childhood was followed by no mortality between 10 and 20 years of age. Thereafter, cardiac deaths again started to occur. The difference between men and women in survival free of cardiac death and pericardiectomy was mainly attributable to the difference in the frequency of surgery (Figure 2B). Although the average survival in Mulibrey nanism is clearly shortened, a normal life span is not excluded; we saw an elderly lady doing fine unoperated at the age of 70 years.

Molecular Genetics

Recent studies at our institution have classified Mulibrey nanism as a new peroxisomal disorder. Peroxisomes are membrane-bound subcellular organelles involved in a variety of cellular functions including oxidation of fatty acids. Peroxisomal disorders typically manifest themselves in the nervous system, but cardiac involvement is also possible. Moreover, recent studies have indicated that genetic variation in the transcriptional regulation of peroxisomal and mitochondrial fatty acid oxidation can contribute to the development of LV hypertrophy. In Mulibrey nanism, the exact alteration of peroxisomal function caused by the mutated RING-B-box-Coiled-coil zinc protein is still unknown. Research to expose the basic metabolic defect is underway, and we expect it will provide insight not only into the pathogenesis of Mulibrey heart disease but also into the general pathways of cardiac hypertrophy and fibrosis.

Conclusions

The clinical spectrum of Mulibrey heart disease extends from severe CHF unresponsive to pericardiectomy in early childhood to asymptomatic LV hypertrophy and filling impairment in middle-aged and, exceptionally, elderly individuals.

### Table 3. Left Ventricular Ejection Fraction and the Doppler Measurements of Transmural and Pulmonary Venous Flow Velocities in Patients With Mulibrey Nanism and in the Control Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients With Mulibrey Nanism</th>
<th>Control Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unoperated (n=21)</td>
<td>Past Pericardiectomy (n=13)</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>64±2</td>
<td>62±3</td>
</tr>
<tr>
<td>Early-to-atrial transmural peak velocity ratio</td>
<td>1.85±0.13</td>
<td>2.16±0.19</td>
</tr>
<tr>
<td>Deceleration of early transmural flow, cm/s</td>
<td>5.9±0.4</td>
<td>6.8±0.6</td>
</tr>
<tr>
<td>Duration of late diastolic (atrial) transmural flow, ms</td>
<td>116±5</td>
<td>113±7</td>
</tr>
<tr>
<td>Systolic fraction of antegrad PV flow, %</td>
<td>55±2</td>
<td>44±3†</td>
</tr>
<tr>
<td>Duration of late diastolic retrograde PV flow, ms</td>
<td>128±5†</td>
<td>130±6§</td>
</tr>
<tr>
<td>Difference between late diastolic flow durations, ms</td>
<td>−14±5†</td>
<td>−17±7†</td>
</tr>
</tbody>
</table>

*P values across the 3 groups from ANOVA with sex as a second grouping factor. Sex had no statistically significant main effects or interactions on any variable.

†P<0.01 compared with the control group; †P<0.05 compared with the unoperated patient group; §P<0.05 compared with the control group.

<table>
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<tr>
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<tr>
<td>Duration of late diastolic transmural flow minus duration of late diastolic retrograde pulmonary venous (PV) flow.</td>
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The data are mean±SEM.

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</tbody>
</table>
At least one half of patients ultimately develop CHF. Although pericardial constriction is the key underlying mechanism, myocardial hypertrophy and fibrosis and, rarely, endocardial fibrosis may also contribute. Pericardiectomy relieves symptoms and signs of CHF in most patients. However, a few patients do not benefit from surgery or are only transiently improved because of coexisting myocardial involvement.

Acknowledgments
This work was supported by grants from the Finnish Foundation for Pediatric Research and the Finnish Foundation for Cardiovascular Research. The authors are indebted to the pediatric and adult cardiologists and cardiac surgeons at Helsinki and Oulu University Hospitals. The authors express special gratitude to Professor Leena Tuuteri, MD, for her pivotal early role in the diagnosis and treatment of patients with Mulibrey nanism.

References
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