The Erysichthon Syndrome

Progression of Coronary Atherosclerosis and Dietary Hyperlipidemia

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SUMMARY One hundred nineteen patients with coronary artery disease confirmed by coronary arteriograms were studied. Cine coronary arteriography confirmed progression of atherosclerosis in 106 (89%) patients (mean age 50.9 yr) and nonprogression in 13 (11%) patients (mean age 50.3 yr). Progression was defined as follows: any increase to 50% stenosis, 50% to 75% narrowing, 75% to 90%, 90% to 99%, 99% to total occlusion.

Only one patient of the 106 who progressed (less than 1%) had ideal values for both cholesterol and triglyceride. Three of 13 patients (23%) who did not progress had ideal lipids ($P < 0.005$). Fifty four of 106 patients who progressed had cholesterol levels $\geq 250$ mg%; none of 13 patients who did not progress had such levels ($P < 0.005$).

Thirty-nine of 98 (40%) patients who progressed had hypertension; only one (8%) who did not progress had hypertension ($P < 0.025$). Seventy-four of 96 patients who progressed were smokers (77%); two of 13 nonprogression patients smoked (15%) ($P < 0.005$).

ERYSICHTHON WAS A CHARACTER in Greek mythology who offended Ceres, the Roman goddess of grain. Ceres punished Erysichthon bylicting insatiable hunger upon him. He became ravenous, yet the more he ate, the hungrier he grew. He spent his wealth, lost his power, and sold his daughter into slavery in order to appease his endless appetite. He finally destroyed himself by eating his own flesh. We can find a parallel today among individuals with accelerated vascular disease. They eat themselves to death because of diet-induced hyperlipidemia.

Studies have shown that angiographically demonstrated coronary atherosclerosis tends to progress.$^1$ Knowledge of the factors which accompany and influence progression is essential if we are to determine the best combination of medical and surgical therapies. Studies have identified risk factors in accelerated coronary atherosclerosis.$^5$ These initial studies all point to significant relationship between the level of serum lipids and risks of development and progression of coronary artery disease. There are data which demonstrate the reversibility of experimentally induced atherosclerosis in primates.$^8$ A recent study documents the reversibility of naturally occurring atherosclerotic lesions in the femoral artery of men.$^9$ Regression of coronary atherosclerosis has been reported after surgical treatment of hyperlipidemia.$^{10}$

Recently a report has documented the reversal of arteriographically proven renal artery atherosclerosis in a 49-year-old woman with hyperlipidemia, angina pectoris, and hypertension.$^{11}$ This patient had an increased peripheral vein plasma renin (32 ng/ml) and a renal arteriogram showed severe atherosclerotic obstruction of both renal arteries (90% right and 75% left). Coronary arteriogram revealed 95% narrowing of the left circumflex artery. She was treated with cholestyramine and clofibrate was added later. During three years of combined therapy her average cholesterol was 161 mg% and her triglyceride was 118 mg% (nine determinations). After three years of treatment the patient had repeat renal and coronary arteriograms. The right renal artery showed marked regression of narrowing. The authors found some regression in the left renal artery and coronary artery lesions. The significance of a single case report is limited but it is of interest that the patient’s cholesterol was maintained below 200 mg%. Her original cholesterol had been 340 mg%.

Materials and Methods

The patient material was gathered from the St. Joseph’s Hospital Health Center, Cardiovascular Laboratory, Syracuse, New York. Patients were selected on the basis of three criteria: 1) arteriographically proven coronary artery disease on the first arteriogram, 2) repeated arteriograms, and 3) availability of lipid values. Nonprogression patients had at least an 11 month interval between arteriograms. Patients in whom progression occurred were accepted without regard to intervals between arteriograms. Patients were excluded if they had significant valvular disease, cardiomyopathy, or normal coronary arteries.

Data were initially collected from 240 patients; only 119 met our criteria. Progression was defined as follows: any increase to 50% narrowing, progression from 50% to 75%, 75% to 90%, 90% to 99%, and 99% to total occlusion. This system of grading lesions has been used consistently for over ten years.

All arteriograms were reviewed by one of the authors and at least two other expert arteriographers. The final decision as to the degree of obstruction was based upon agreement between all observers. Questionable lesions were studied repeatedly in multiple views and with several contrast agent injections. The methodology for analysis has been previously documented.$^1$ The arteriographers were aware of the dates of each arteriogram. In all cases the repetitive arteriograms were compared and a decision reached on the presence or absence of progression without knowledge of the lipid values. In cases of discrepancy between observers the films in question were blindly scrambled by a technician and read again by all arteriographers as a team, without knowledge of names or dates. The team decision was then considered final.
The methodology used for determination of serum cholesterol was direct Lieberman Burchard (auto analyzer). Triglycerides were determined by Hantzch Condensation colorimetric manual technique. We defined as elevated a cholesterol level of 250 mg% or more, or a triglyceride level of 150 mg% or more. Average cholesterol and triglyceride levels were defined as 201–249 mg% and 101–149 mg%, respectively. The ideal lipid level was defined as cholesterol 200 mg% or less and triglyceride 100 mg% or less.

We used chi-square to test for statistical significance.

Results

Of the 119 patients with coronary artery disease, 106 progressed (mean age 50.9 yr, (sd 8), range 32–67) and 13 did not progress (mean age 50.3 yr, (sd 7.4), range 36–63). There were 88 males who progressed, and 10 who did not progress. An average of 20.9 months elapsed between arteriograms in patients who progressed (range 2–67 months). In patients who did not progress an average of 21.3 months (range 11–54 months) elapsed between arteriograms.

Fifty-eight of ninety-eight (60%) patients who had family history recorded and who progressed had a positive family history of stroke, myocardial infarction, angina, or hypertension. In patients who did not progress, three of 13 (23%) had a positive family history. A definite diagnosis of diabetes mellitus was documented in 16 of the 87 (18%) patients who developed adequate information who progressed, and in two of the 12 (17%) patients who did not progress. A history of hypertension was documented in 39 of 98 (40%) patients who progressed in whom a history of blood pressure was available. Only one of 13 (8%) who did not progress had hypertension (P < 0.025). Seventy-four of 96 (77%) patients who progressed smoked. Eleven of 13 (85%) who did not progress did not smoke or had stopped smoking previously (P < 0.005). Table 1 provides the percent prevalence for these risks.

In the 106 progressive patients, 54 had cholesterol values of 250 mg% or more (mean 281.8, sd 35.96), 36 had values between 201–249 mg% (mean 231.9, sd 16.78), and only 16 had a cholesterol level of 200 mg% or less (mean 184.8, sd 13.42). None of the 13 patients with nonprogression had elevated cholesterol levels, four had average cholesterol levels (mean 229.3, sd 21.03), and nine had ideal cholesterol levels (mean 171.4, sd 28.02) of 200 mg% or less (P < 0.005). Only nine of 106 patients who progressed had ideal triglyceride levels 100 mg% or below.

A more direct correspondence is apparent when we examine patients with ideal levels of both cholesterol and triglycerides. Only one patient with progressive coronary artery disease had ideal lipid values. Three of 13 nonprogressive patients had ideal lipid levels (P < 0.005).

The effect of saphenous vein bypass surgery is documented in Table 2. Surgery was performed in 45 of 106 patients who progressed and 4 of 13 patients who did not progress. In those who had surgery, progression occurred in the aorta vein graft in 23/45 and 22/45 in a nongrafted vessel.

Both groups were examined for evidence of previous myocardial infarction either by history or by electrocardiography. In the progression group, there were 48 of 106 with evidence of previous myocardial infarction. Such evidence was present in 7 of the 13 nonprogression patients.

Discussion

There were no significant differences between the average age of the 106 patients who progressed (50.9, range 32–67 yr) and the 13 patients who did not show progression (average 50.3, range 36–63 yr). There was significant coronary artery disease in every patient studied. Patients who had less than 50% narrowing were specifically excluded. Almost all the patients had lesions greater than 50% narrowing. Only three of the 106 in the progression group and one of the 13 patients in the nonprogression group had no lesion greater than 50%. Conversely, 103 of 106 progressive patients and 12 of 13 nonprogressive patients had 75% or greater lesions. In most the lesion was 90% or greater; 84 of the 106 progressive patients and 12 of the nonprogressive patients had at least one 90% obstruction.

In order to address the question of minimal progression, we examined the data to identify those patients who progressed only from 90% to 99% or from 99% to total occlusion. Only three patients fell into this category. Such minor progression may, however, have had major clinical consequences.

The duration of the atherosclerotic disease could not be measured accurately in this retrospective study. Some charts lacked fundamental information on smoking, hypertension, and family history of vascular disease. Most of the original 121 patients with repetitive arteriograms who could not be included in this study were rejected because of inadequate lipid determinations. Most did not have a single triglyceride determination documented.

The interval between arteriograms averaged 20.9 months (range 2–67) in the patients who progressed and 21.3 months

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Table 1. Prevalence

<table>
<thead>
<tr>
<th></th>
<th>Progression (106 pts)</th>
<th>No progression (13 pts)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family Hx vas. dis.</td>
<td>60% (98)*</td>
<td>23%</td>
<td>&lt;0.025</td>
</tr>
<tr>
<td>Diabetes</td>
<td>18% (87)</td>
<td>17% (12)</td>
<td></td>
</tr>
<tr>
<td>High blood pressure</td>
<td>40% (98)</td>
<td>8%</td>
<td>&lt;0.025</td>
</tr>
<tr>
<td>Smokers</td>
<td>77% (96)</td>
<td>15%</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Nonsmokers</td>
<td>25% (23)</td>
<td>85%</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Cholesterol ≥250</td>
<td>51% (23)</td>
<td>0</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Cholesterol 201–249</td>
<td>34% (34)</td>
<td>31%</td>
<td></td>
</tr>
<tr>
<td>Cholesterol ≤200</td>
<td>15% (15)</td>
<td>69%</td>
<td></td>
</tr>
<tr>
<td>Triglyceride ≥150</td>
<td>55% (55)</td>
<td>54%</td>
<td></td>
</tr>
<tr>
<td>Triglyceride 101–149</td>
<td>37% (37)</td>
<td>23%</td>
<td></td>
</tr>
<tr>
<td>Triglyceride &lt;100</td>
<td>8% (8)</td>
<td>23%</td>
<td></td>
</tr>
<tr>
<td>Cholesterol ≤200,</td>
<td>1% (1)</td>
<td>23%</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>triglyceride ≤100</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Numbers in parentheses indicate number of patients from whom less than complete data were available.

Table 2. Surgery

<table>
<thead>
<tr>
<th></th>
<th>Total with saphenous vein bypass surgery</th>
<th>Progression and surgery</th>
<th>Progression same vessel as surgery</th>
<th>Progression nongrafted vessel</th>
<th>Progression without surgery</th>
<th>Nonprogression and surgery</th>
<th>Nonprogression without surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>49/119 (46%)</td>
<td>45/49 (49%)</td>
<td>23/45 (51%)</td>
<td>22/45 (50%)</td>
<td>61/71 (87%)</td>
<td>4/13 (31%)</td>
<td>9/13 (69%)</td>
</tr>
</tbody>
</table>

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were significant differences in the prevalence of family history of cardiovascular disease, hypertension, cigarette smoking, and lipid levels.

Despite the many publications which have documented the relationship between hyperlipidemia and coronary artery disease, patients and some physicians remain unconvinced. Some authors would prefer to believe that cholesterol is not a risk factor for coronary artery disease. In a recent editorial Oliver stated that dietary cholesterol is not an important cause of coronary heart disease. Connor and Connor have supplied evidence which refutes this stand. Nitter-Hauge and Enge found no relationship between lipids and the severity of coronary artery disease. Careful review of their data demonstrates that only one of their 71 patients with angiographically proven coronary artery disease had a cholesterol below 200 and the average cholesterol was in excess of 300 mg%. They considered cholesterol up to 300 mg% as normal.

Most patients do not have severe genetically determined hyperlipidemia. They do have modestly elevated cholesterol and triglyceride levels induced by diet. The degree of the elevation depends on what is considered normal and we must redefine normal. Serum cholesterol less than 200 mg% and serum triglycerides less than 100 mg% should be considered ideal; cholesterol values between 201–249 mg% and triglyceride values between 101–150 mg% should be considered normal; cholesterol greater than 250 mg% and/or triglyceride greater than 150 mg% should be considered abnormal.

Although these levels are arbitrary, they provide a useful frame of reference. Levels of cholesterol previously considered normal are often associated with accelerated vascular disease. Those patients who had ideal lipid values in the nonprogressive group had various degrees of hypertension or diabetes and/or were cigarette smokers. Some had several risk factors. No individual in either group was completely devoid of risk factors. Heredity clearly plays a role in the development of atherosclerosis. While a rare individual may develop coronary artery disease despite ideal lipid levels, progression is usually associated with average or abnormal values. The results of this study clearly demonstrate the strong relationship between progression of coronary artery disease and normal or abnormal lipid values.

While average values do not inhibit progression of coronary artery disease, ideal values may. In the small group who demonstrated no progression of their disease, three of 13 had ideal lipids. Hypertension was absent in 92% of those who did not progress, and 85% were nonsmokers. The patient least likely to progress once coronary artery disease is present does not smoke, has a normal blood pressure and ideal lipid values.

Ross and Harker have recently demonstrated in monkeys that elevated cholesterol levels can cause intimal injury. They described progression of atherosclerotic-like lesions if an initial lesion was exposed to a continuous hypercholesteremic state. We have now developed evidence that hyperlipidemia in man is also associated with progression of coronary atherosclerosis. Lipid treatment programs have not influenced the mortality from coronary artery disease because they have failed to reduce lipids to ideal levels. Other studies found a reduction in death rate without relation to lipids. Cohn reported clofibrate ineffective in halting progression measured by repetitive coronary angiography. In reviewing his data, it is apparent that clofibrate failed to lower the cholesterol levels of treated patients. The effect of lower cholesterol on progression can not be documented in studies in which the cholesterol is not adequately reduced.

Coronary artery disease is an enigma, a mosaic of risks and causes, but once we can identify the interaction, treatment can be more specific. Physicians responsible for patients with documented coronary artery disease should insist upon a return to ideal values. Our study and others suggest that we have reached a watershed in medicine. The evidence, although limited, suggests that we can halt the progress of coronary artery disease.

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