and 19 PVR was elevated in the normally draining lung but not in the lungs with PAPVD. In patients 14 and 18 it was elevated in each. In patients 15, 16 and 17 it was normal in the normally draining lung and elevated in the lobes with PAPVD. Thus, these studies give no clear-cut answer to the question of the location of the stimulus for the increase of PVR in mitral stenosis.

References

Relationship between Plasma Lipid Concentrations and Coronary Artery Disease in 496 Patients

ANTONIO M. GOTTO, M.D., D.PHIL., G. ANTHONY GORRY, PH.D., JAMES R. THOMPSON, PH.D., JAMES S. COLE, M.D., RUDOLPH TROST, PH.D., DANIEL YESHURUN, M.D., AND MICHAEL E. DEBAKEY, M.D.

SUMMARY The relationship between fasting plasma cholesterol and triglyceride concentrations and the frequency and extensiveness of coronary artery disease (CAD) was studied in 496 subjects evaluated for chest pain by coronary arteriography at The Methodist Hospital. One hundred six of the patients had no CAD while 390 had 25% or greater stenosis of one or more major vessels. Ninety-one percent had 75% or greater stenosis of at least one major vessel. Mean age for the group with CAD was 55.7 ± 8.7 and without disease 49.4 ± 11.6 (P < 0.01). Both cholesterol and triglyceride concentrations were higher (P < 0.001) in the group with CAD. Mean cholesterol concentration in males increased from 195 ± 36 mg/dl in the group without CAD to 219 ± 41 in the group with three vessel disease and in females from 207 ± 40 to 252 ± 42. A progressive increase in triglyceride values was also detected but was less consistent. At the level of 25% and greater obstruction, the partial correlation coefficients between the number of vessels involved and the cholesterol and triglyceride concentrations, respectively, were +0.201 and +0.181.

ELEVATED CONCENTRATIONS of serum cholesterol and triglycerides have both been implicated in the pathogenesis of coronary artery disease (CAD).1-7 Hypercholesterolemia is one of the three major risk factors for coronary atherosclerosis.8,9 The relationship between hypertriglyceridemia and CAD is less well defined.1-3, 5, 7 A study of familial hyperlipidemia in relatives of survivors of myocardial infarctions suggested that hypercholesterolemia in combination with hypertriglyceridemia was more common in these patients than was isolated hypercholesterolemia or hypertriglyceridemia.9

Although hyperlipidemia is generally recognized as a risk factor, the physician may be uncertain as to its significance in a given patient. From the results of the Framingham study, it appears that cholesterol is a risk factor for CAD over the entire range of concentrations studied. Hence the physician cannot define a single threshold above which the patient is at risk. In managing patients with hyperlipidemia,  

the physician needs a clearer delineation of the relationship between elevated serum lipids and the possible extent and severity of coronary artery disease.

Neither the severity nor the extent of CAD can be precisely determined from the clinical history or from electrocardiographic changes, so the relationship between hyperlipidemia and CAD can best be studied in patients for whom angiographic findings are available. Large groups of such patients provide an important opportunity to add to our understanding of the clinical significance of hyperlipidemia in CAD. For this reason, we undertook a study of almost 500 patients to assess the correlations between plasma cholesterol and plasma triglyceride concentrations and the frequency and the extensiveness of CAD as indicated by angiography. We realize that a single measure of the plasma lipids represents a static view of substances which are in dynamic equilibrium within the body. Furthermore, atherosclerosis is a disease which develops over a period of years. Nonetheless, single measurements of cholesterol at the time of entry in epidemiological studies have been shown to correlate with the risk of developing coronary heart disease.9-11 Also, single measurements of blood pressure have been correlated with coronary heart disease death in epidemiologic studies.9 We used selective cine-coronary angiography to obtain measurements of the "severity" or the percent of the obstruction of the vessel's lumen and "extent" as measured by the number of vessels involved. Our results have been reported in preliminary form.12 No critical cut-off point could be identified which defined those with disease and those without disease. A report by Cohn et al., published after this study was completed, supports our finding that CAD has continuous relationship with concentrations of serum cholesterol and to a lesser extent serum triglyceride.13

Methods

Patient Selection

The patients selected for this study were 496 subjects referred to the cardiology unit of The Methodist Hospital between January 1972 and March 1976 for evaluation of chest pain. Since these patients were preselected for chest pain, they did not constitute a random sample of the general population. However, they do represent a consecutive group of patients studied for chest pain in this laboratory. They were not referred because of hyperlipidemia. Each patient was examined by one of three cardiologists of the unit who determined the indication for cardiac catheterization. Patients were excluded if adequate visualization of both the right and left coronary artery systems was not obtained because of difficulties in the manipulation of the catheter. This occurred in less than 5% of the patient population. Patients with valvular disease, cardiomyopathy or with recent myocardial infarctions were also excluded. Because of these exclusions, the 496 subjects did not represent successive cases.

Lipid and Lipoprotein Measurements

A blood sample for plasma lipid determination was obtained after a 12 hour fast on the day after admission and prior to coronary arteriography. That determination was never more than 15 days before the arteriography. Plasma cholesterol and triglyceride concentrations were determined according to the procedures of The Lipid Research Clinics Program.14 The autoanalyzer II methodology was employed and the machines used were standardized by The Lipid Research Clinic protocol. Plasma lipoprotein quantification and lipoprotein typing were performed by the methodology of the Lipid Research Clinics Program.14 Lipoprotein quantification was performed if either the plasma cholesterol or triglyceride value was above the levels given in table 1. Since different cutpoints of plasma lipids and lipoproteins were used for operational purposes in various phases of the collaborative Lipid Research Clinics Program, the levels shown in table 1 apply to the noncollaborative project described in the communication. The values in this table cannot be equated with cut-offs to define hyperlipidemia for the entire Lipid Research Clinics Program. Such values have not yet been published. Type II was defined by an elevation of LDL-cholesterol (table 1) and by the absence of the floating beta lipoprotein which occurs in type III. Type IV was defined by an increase in the fasting plasma triglyceride concentration (table 1). The diagnosis required normal levels of LDL-cholesterol and the absence of both floating beta lipoprotein and fasting chylomicrons.

Coronary Arteriography

All patients were brought to the catheterization laboratory without sedation and in the fasting state. A cut down was performed on the brachial artery and an accompanying vein. After all right and left heart pressures were measured, a Fick cardiac output obtained, and a left ventricular cineangiogram recorded, selective coronary arteriograms were obtained using the Sones procedure.15 Both the right and left coronary arteries were selectively cannulated and injected with 3-5 cc of Renografin-76. In all cases multiple injections in the right and left anterior oblique projections were obtained for both right and left coronary arteries. Filming was obtained using a nine inch image intensifier and 35 mm cine film. In the majority of cases, single, large film (8 x 10 inch) radiographs were also obtained following selective injection of each coronary artery. Cine film was processed in the conventional manner and viewed on a Tagarno projector. The location and percentage stenosis of the individual coronary lesions were recorded on a computer readable mark sense form.16

The format for the mark sense form, illustrated in figure 1, was determined in the following manner. Five experienced coronary angiographers independently reviewed cineangiographic films from ten patients. On the initial evaluation, each observer was allowed to make his own interpretation of the film. After evaluating these initial data, it was apparent

<table>
<thead>
<tr>
<th>Age</th>
<th>Plasma cholesterol (mg/100 ml)</th>
<th>Plasma triglyceride (mg/100 ml)</th>
<th>LDL-cholesterol (mg/100 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-19</td>
<td>205</td>
<td>140</td>
<td>170</td>
</tr>
<tr>
<td>20-29</td>
<td>210</td>
<td>140</td>
<td>170</td>
</tr>
<tr>
<td>30-39</td>
<td>240</td>
<td>150</td>
<td>190</td>
</tr>
<tr>
<td>40-49</td>
<td>260</td>
<td>160</td>
<td>190</td>
</tr>
<tr>
<td>50-59</td>
<td>280</td>
<td>190</td>
<td>210</td>
</tr>
</tbody>
</table>
that the reviewers varied by as much as 25-30% in their estimation of diameter narrowing of coronary artery lesions. There was also some variation in the nomenclature used in describing the various branches of the coronary tree. It was therefore decided that the coronary arterial system would be identified, and the extent of the disease determined at each of the appropriate locations as indicated on the form. It was also agreed that at each location, the artery would be classified as either normal (i.e., there was no detectable disease) or as abnormal. In the latter case, one of five categories of cross sectional narrowing was specified. These categories were 25%, 50%, 75%, 95% narrowing or completely occluded (i.e., 100%). Using this set of criteria, another 10 cineangiograms were reviewed by the same observers. The 10 cineangiograms were randomly selected from 50 cases referred because of chest pain just prior to the beginning of the study. Two of the 10 were judged to be free of coronary artery disease. The other eight had narrowing of the coronary arteries ranging from 25% to 95%. Using these criteria, the agreement in classifying the severity of diameter stenosis was greater than 90%.

Each section of the arterial tree was viewed in multiple projections and the diameter of the stenosed region was compared with the nearest normal vessel diameter. Calipers were used on all 496 cases to compare normal and abnormal segments and stenoses were then classified as 25%, 50%, 75%, 95% or 100% reduction of the original diameter. If a significant difference existed between two views the average of the two views was used.

All of the coronary cineangiograms used in this study were viewed independently by two observers. If there was a difference in classification of specific lesions between the two observers (i.e., one observer thought a stenosis was 75% and another thought it was 95%) then a third observer reviewed the film independently. After discussion among the three observers, a consensus of opinion was reached regarding the specific lesion. One set of data was entered into the computer on each subject studied.

Data from the mark sense form were entered into the computer to calculate two different CAD scores based on the percentage stenosis of lesions in the four major coronary arteries (left main, circumflex, left anterior descending, right coronary arteries). "Severity" of CAD was defined as a percentage equal to the maximum percentage stenosis found among each of the four major coronary arteries in a given patient. "Extent" of CAD was defined in terms of the total number of major coronary vessels (NOV) which contained at least one stenosis of 25% or greater. For example, a patient with a 25% stenosis in the left main, 50% stenosis in the right, and a 75% stenosis in the circumflex coronary arteries would be scored with the severity of disease as 75% while the extent of disease would be scored as NOV = 3. Coronary arteriograms were classified as normal (NOV = 0) if the left main, circumflex, left anterior descend-
The 390 patients with CAD were classified on the basis of the severity of disease in their coronary arteries (table 3). Approximately 91% of the patients in this group had 75% or greater stenosis of at least one of their coronary arteries. The distribution of the extent of CAD on the basis of the number of vessels with 25% or more stenosis is given in tables 4–6 for males, females and total patients, respectively. Eighty-eight percent of the males and 70% of the females had two or more affected coronary arteries. This difference was significant ($P < 0.01$). Thirty-nine percent of the group with CAD had two or fewer vessels involved.

### Relations of Plasma Cholesterol to Extent of Coronary Artery Disease

The number of vessels with 25% or more stenosis was compared with cholesterol levels for males, females and the total patient group (tables 4–6). Mean cholesterol concentrations for males increased from 195 ± 36 mg/dl to 219 ± 41 mg/dl in the group with three vessel disease, and to 223 ± 51 mg/dl in the group with four vessel disease (table 4). These differences between the mean cholesterol for the male control group and those with three and four vessel disease were significant ($P < 0.001$). An even sharper rise in mean plasma cholesterol for the females was observed with an increase in extent of vessel involvement. The difference between the mean plasma cholesterol for the female group (table 5) without CAD, 207 ± 40 mg/dl, and those with three vessel disease, 252 ± 42 mg/dl, was highly significant ($P < 0.001$).

### Table 3. Severity of Coronary Artery Disease in Patients with Abnormal Coronary Angiograms

<table>
<thead>
<tr>
<th>Severity of coronary artery disease</th>
<th>Males</th>
<th>Females</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maximum stenosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25%</td>
<td>11 (3.4%)</td>
<td>10 (14.3%)</td>
<td>21 (5.4%)</td>
</tr>
<tr>
<td>50%</td>
<td>10 (3.1%)</td>
<td>3 (4.3%)</td>
<td>13 (3.3%)</td>
</tr>
<tr>
<td>75%–100%</td>
<td>299 (93.5%)</td>
<td>57 (81.4%)</td>
<td>356 (91.3%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>320 (100%)</td>
<td>70 (100%)</td>
<td>390 (100%)</td>
</tr>
</tbody>
</table>
When data of males and females were combined (table 6) the same relationship was noted between the number of vessels involved and plasma cholesterol concentrations. The significance of this trend was further supported by computing the age-corrected correlation coefficient between levels of plasma cholesterol and the number of vessels involved. Using a criterion of 25% stenosis, the extent of disease (NOV) was found to be positively correlated with the plasma cholesterol concentration for all patients \( r = 0.226, N = 496 \). Age-corrected correlation coefficients were also computed separately for males \( r = 0.266, N = 371 \) and females \( r = 0.352, N = 125 \). There was no correlation between age and lipid levels, although there was a correlation between age and NOV which was smaller than that between NOV and cholesterol. We have found no age-corrected correlation between blood pressure (systolic or diastolic) measured at the time of catheterization and the number of vessels involved.

Finally, application of the Kruskal-Wallis test also confirmed that a significant difference \( (P = 0.037) \) exists among the four cholesterol distributions for each subgroup defined by one, two, three and four vessel involvement. In other words, differences between the mean cholesterol levels of patients with CAD, though small, are significant and increase with the extent of disease as measured by vessel involvement.

**Relation of Plasma Triglyceride to Extent of Coronary Artery Disease**

Table 4 shows data for comparison of triglyceride levels to the number of vessels involved. Mean triglyceride concentrations for males increased significantly from \( 140 \pm 74 \) mg/dl in the group with no CAD to \( 190 \pm 97 \) mg/dl in the group with three vessel involvement \( (P < 0.001) \). A very sharp rise in the mean plasma triglyceride for the females (table 5) was observed with increasing vessel involvement for NOV = 0, 1 and 2. The mean triglyceride concentration for females with no disease, \( 135 \pm 62 \) mg/dl, was significantly different from the mean of \( 181 \pm 86 \) mg/dl for females with three and four vessel involvement \( (P < 0.01) \).

When the triglyceride data for males and females were combined (table 6), the relationship between increased vessel involvement and increased mean triglyceride concentrations was maintained from NOV = 0 through NOV = 3. The number of female patients with four vessel involvement was too small to allow statistical comparison.

An age-corrected correlation coefficient between triglyceride level and the number of vessels with 25% or greater stenosis was calculated for all patients \( r = 0.181, N = 496 \). Age-corrected correlation coefficients were also computed separately for males \( r = 0.139, N = 371 \) and females \( r = 0.266, N = 125 \). The Kruskal-Wallis test was used again to confirm that a significant difference \( (P = 0.033) \) exists among the four triglyceride distributions for each subgroup defined by one, two, three and four vessel involvement.

**Frequency of Coronary Artery Disease in Different Lipid Quartiles**

The total patient population was divided into quartiles based on either their plasma cholesterol or triglyceride concentration. Cholesterol values ranged from less than \( 184 \) mg/dl for the first quartile to greater than \( 236 \) mg/dl for the fourth quartile (table 7). Triglyceride quartile levels ranged from less than \( 101 \) mg/dl for the first to greater than \( 179 \) mg/dl for the last (table 8). For both cholesterol and triglyceride concentrations, the percentage of patients with CAD increased progressively from quartile I to quartile IV. These increases were significant \( (P < 0.02) \) for males, females and the total patient population. There was no significant difference between males and females in the frequency of CAD within each quartile.

---

**TABLE 4. Mean Age, Cholesterol, and Triglyceride Levels for 371 Males**

<table>
<thead>
<tr>
<th>Extent of disease</th>
<th>No. of male patients</th>
<th>Mean age ± SD (yr)</th>
<th>Mean cholesterol ± SD (mg/dl)</th>
<th>Mean triglyceride ± SD (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Without CAD</td>
<td>With CAD*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NOV = 4</td>
<td>39 (12.2%)</td>
<td>57.0 ± 7.5</td>
<td>223 ± 51</td>
<td>168 ± 96</td>
</tr>
<tr>
<td>NOV = 3</td>
<td>173 (54.0%)</td>
<td>55.2 ± 9.1</td>
<td>219 ± 41</td>
<td>190 ± 97</td>
</tr>
<tr>
<td>NOV = 2</td>
<td>69 (21.6%)</td>
<td>55.0 ± 8.2</td>
<td>213 ± 40</td>
<td>166 ± 90</td>
</tr>
<tr>
<td>NOV = 1</td>
<td>39 (12.2%)</td>
<td>55.3 ± 10.3</td>
<td>201 ± 47</td>
<td>167 ± 40</td>
</tr>
<tr>
<td>NOV = 0</td>
<td>51</td>
<td>48.0 ± 12.8</td>
<td>195 ± 36</td>
<td>140 ± 74</td>
</tr>
<tr>
<td>Total</td>
<td>51</td>
<td>320 (100%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*25% stenosis or greater.

---

**TABLE 5. Mean Age, Cholesterol, and Triglyceride Levels for 185 Females**

<table>
<thead>
<tr>
<th>Extent of disease</th>
<th>No. of female patients</th>
<th>Mean age ± SD (yr)</th>
<th>Mean cholesterol ± SD (mg/dl)</th>
<th>Mean triglyceride ± SD (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Without CAD</td>
<td>With CAD*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NOV = 4</td>
<td>2 (35.7%)</td>
<td>57.7 ± 7.4</td>
<td>252 ± 42</td>
<td>181 ± 86</td>
</tr>
<tr>
<td>NOV = 3</td>
<td>23</td>
<td>57.2 ± 9.3</td>
<td>243 ± 49</td>
<td>200 ± 97</td>
</tr>
<tr>
<td>NOV = 2</td>
<td>24 (34.3%)</td>
<td>56.7 ± 6.6</td>
<td>214 ± 56</td>
<td>147 ± 72</td>
</tr>
<tr>
<td>NOV = 1</td>
<td>21 (30%)</td>
<td>50.7 ± 10.3</td>
<td>207 ± 40</td>
<td>135 ± 62</td>
</tr>
<tr>
<td>NOV = 0</td>
<td>55</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>55</td>
<td>70 (100%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*25% stenosis or greater.


It should be pointed out that for each of the three columns in table 7 we normalized the data so as to produce an average frequency of 50% coronary artery disease in males, females and total patient population. This is equivalent to adjusting the data for equal numbers of patients with and without disease. Therefore, our results for the total population can be compared directly to Cohn's results.\textsuperscript{18}

Results for Coronary Artery Disease Defined by ≥50% and ≥75% Stenosis

The above results in tables 4 through 7 were obtained for the 390 patients with CAD defined as ≥25% stenosis in any one or more of the four major coronary arteries. In order to evaluate the effect of using different criteria for defining CAD, we reclassified the 390 patients according to a 50% criterion, and again for a 75% criterion.

When a 50% criterion was applied, 21 patients with a maximum stenosis of 25% (table 3) were excluded from analysis. Thus, 369 patients had the extent of their CAD redefined for NOV = 1 through NOV = 4 (69, 113, 166, and 21 patients in each category, respectively). For a 75% criterion, 34 patients with a maximum stenosis not exceeding 50% were excluded from analysis. The distribution of the extent of disease for the remaining 356 patients was redefined for NOV = 1 through NOV = 4 (93, 126, 124 and 13 patients, respectively). Regardless of the criterion used to define CAD, the same 106 patients were used in each analysis as the control group with NOV = 0 (i.e., all vessels had 0% stenosis).

Analysis of the data using 50% and 75% stenosis criteria did not significantly alter our findings when compared to those using 25% criterion. With a 75% criterion, for example, the age-corrected correlation coefficient between cholesterol and the number of vessels involved was $r = 0.156$, while between triglyceride and NOV it was $r = 0.196$ (N = 462). When the quartiles and the frequency of CAD were computed for the 75% criterion, the percentages of patients with disease in quartiles I through IV, respectively, were 42%, 42%, 48% and 69% for cholesterol ($P < 0.02$), and 35%, 46%, 51% and 69% for triglyceride ($P < 0.01$).

Frequency of Coronary Artery Disease in Various Lipid Combinations

To examine the relationship between the combination of cholesterol and triglyceride levels and CAD, the patients were divided into four groups. Group A contained the lower two quartiles for both cholesterol and triglycerides, group B had the higher two quartiles of cholesterol and the lower two quartiles for triglycerides, group C had the higher two quartiles for triglycerides and the lower two quartiles for cholesterol and group D had the higher two quartiles for both cholesterol and triglycerides. The frequency of CAD in group A was 33%, in group B 45%, in group C 51% and in group D 65% (table 9). These frequencies are statistically significant at $P = 0.013$ using the Chi-squared goodness of fit test.

Frequency of Coronary Artery Disease for Different Lipoprotein Phenotypes

Patients were categorized into lipoprotein phenotypes in accordance with the World Health Organization classification and the criteria suggested by the Lipid Research Clinic protocol.\textsuperscript{19, 19} Cut-off values for cholesterol and tri-

\begin{table}[h]
\centering
\caption{Mean Age, Cholesterol, and Triglyceride Levels for 496 Patients}
\begin{tabular}{|l|c|c|c|c|}
\hline
Extent of disease & No. of patients & Without CAD & With CAD* & Mean age ± SD (yr) & Mean cholesterol ± SD (mg/dl) & Mean triglyceride ± SD (mg/dl) \\
\hline
NOV = 4 & 41 (10.5%) & 57.2 ± 7.4 & 224 ± 52 & 170 ± 96 \\
NOV = 3 & 196 (50.3%) & 55.4 ± 9.0 & 223 ± 42 & 189 ± 96 \\
NOV = 2 & 93 (23.8%) & 55.6 ± 8.5 & 221 ± 44 & 175 ± 92 \\
NOV = 1 & 60 (15.4%) & 55.8 ± 9.1 & 205 ± 50 & 160 ± 121 \\
NOV = 0 & 106 & 49.4 ± 11.6 & 201 ± 38 & 138 ± 88 \\
Total & 106 & 390 (100%) & & & \\
\hline
\end{tabular}

\textsuperscript{*25% stenosis or greater.}
\end{table}

\begin{table}[h]
\centering
\caption{Results of Cholesterol Quartile Analysis}
\begin{tabular}{|l|c|c|c|}
\hline
Cholesterol quartiles & 371 Males & 125 Females & 496 Total patients \\
\hline
Quartile IV limits (mg/dl) & >234 & >249 & >236 \\
% CAD* & 70% & 69% & 67% \\
Mean age & 54.5 ± 9.5 & 54.1 ± 9.3 & 54.8 ± 9.3 \\
Mean triglyceride (mg/dl) & 196 ± 117 & 196 ± 94 & 194 ± 110 \\
Quartile III limits (mg/dl) & 205–234 & 221–249 & 209–236 \\
% CAD & 52% & 61% & 47% \\
Mean age & 53.7 ± 8.8 & 56.2 ± 8.1 & 54.4 ± 8.7 \\
Mean triglyceride (mg/dl) & 188 ± 103 & 174 ± 79 & 181 ± 99 \\
Quartile II limits (mg/dl) & 178–204 & 194–220 & 184–208 \\
% CAD & 48% & 42% & 45% \\
Mean age & 54.3 ± 9.6 & 54.3 ± 9.4 & 53.7 ± 9.8 \\
Mean triglyceride (mg/dl) & 163 ± 78 & 147 ± 67 & 167 ± 76 \\
Quartile I limits (mg/dl) & <178 & <194 & <184 \\
% CAD & 34% & 30% & 41% \\
Mean age & 55.4 ± 12 & 52.8 ± 11.1 & 54.5 ± 11.4 \\
Mean triglyceride (mg/dl) & 144 ± 102 & 128 ± 67 & 130 ± 70 \\
\hline
\end{tabular}

\textsuperscript{*CAD defined as 25% and greater stenosis.}
glycerides were those used by the Lipid Research Clinic. The results are summarized in tables 10 and 11. There were no significant differences in the frequency of CAD (25% stenosis criterion) between 53 patients with type II hyperlipidemia, 128 patients with type IV hyperlipidemia, and 315 patients without hyperlipidemia, as defined by the Lipid Research Clinic criteria (table 10). The percentages were computed twice again for a 50% and 75% criteria in defining those patients with CAD and still there were no significant differences between the type II, type IV and normolipemic groups.

We were unable to find any difference in either the extent or the severity of disease between patients with type II and type IV patterns (table 11). Type II patients did not differ from normolipemic subjects when analyzed for extent of coronary artery disease. A significant difference (P < 0.01) was observed when the type IV and normolipemic groups were compared. However, when the comparison was confined to only those patients with CAD, there was no significant difference between the frequencies of single and multivessel disease in the type IV and normolipemic groups.

Analysis of the severity of CAD showed no significant differences between the type II, type IV and normolipemic groups.

Discussion

Numerous studies have reported that hypercholesterolemia, hypertriglyceridemia or both carry an increased risk of developing premature CAD. Many of the studies have defined hyperlipidemia or hyperlipoproteinemia based on arbitrary cut-off points for the concentrations of serum plasma lipids or lipoproteins, although the Framingham study suggested that serum cholesterol is related to risk of CAD as a continuous function. The clinical history itself cannot precisely define the extent and/or severity of CAD, nor can the electrocardiographic changes or exercise tolerance test. Introduction of selective coronary cineangiography by Sones et al. in 1962 and subsequent refinements of these techniques have made it possible to determine with a considerable degree of accuracy the extent and severity of stenosis of the coronary arteries. Earlier attempts have been made to relate cineangiographic findings to hyperlipidemia. Proudfit et al. concluded that the level of serum cholesterol was of limited diagnostic value in the individual patient, although the frequency of normal coronary arteriograms was high when the serum cholesterol was less than 225 mg/dl and that of abnormal coronary arteriograms was high when the serum cholesterol was greater than 300 mg%. Cramer et al., in a study of 224 patients subjected to coronary cineangiography reported that the total serum cholesterol had only a minor influence in the frequency of CAD in males, but that hypertriglyceridemia was found with a greater frequency in diseased patients. Falsetti et al., reporting on 27 patients with arteriographically established CAD, found that 63% had an elevation of serum cholesterol.

Table 8. Results of Triglyceride Quartile Analysis

<table>
<thead>
<tr>
<th>Triglyceride quartiles</th>
<th>371 Males</th>
<th>125 Females</th>
<th>496 Total patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quartile IV limits (mg/dl)</td>
<td>&gt;179</td>
<td>&gt;188</td>
<td>&gt;179</td>
</tr>
<tr>
<td>% CAD*</td>
<td>71%</td>
<td>66%</td>
<td>69%</td>
</tr>
<tr>
<td>Mean age</td>
<td>53.9 ± 9.0</td>
<td>54.5 ± 7.2</td>
<td>54.2 ± 8.6</td>
</tr>
<tr>
<td>Mean cholesterol (mg/dl)</td>
<td>228 ± 43</td>
<td>246 ± 51</td>
<td>233 ± 48</td>
</tr>
<tr>
<td>Quartile III limits (mg/dl)</td>
<td>140-179</td>
<td>142-188</td>
<td>141-179</td>
</tr>
<tr>
<td>% CAD</td>
<td>50%</td>
<td>54%</td>
<td>51%</td>
</tr>
<tr>
<td>Mean age</td>
<td>54.2 ± 9.7</td>
<td>57.7 ± 9.2</td>
<td>54.9 ± 9.7</td>
</tr>
<tr>
<td>Mean cholesterol (mg/dl)</td>
<td>221 ± 41</td>
<td>229 ± 44</td>
<td>221 ± 41</td>
</tr>
<tr>
<td>Quartile II limits (mg/dl)</td>
<td>101-139</td>
<td>103-141</td>
<td>101-140</td>
</tr>
<tr>
<td>% CAD</td>
<td>48%</td>
<td>48%</td>
<td>46%</td>
</tr>
<tr>
<td>Mean age</td>
<td>56.7 ± 8.9</td>
<td>53.1 ± 10.1</td>
<td>55.9 ± 9.3</td>
</tr>
<tr>
<td>Mean cholesterol (mg/dl)</td>
<td>202 ± 96</td>
<td>221 ± 44</td>
<td>207 ± 38</td>
</tr>
<tr>
<td>Quartile I limits (mg/dl)</td>
<td>&lt;101</td>
<td>&lt;103</td>
<td>&lt;101</td>
</tr>
<tr>
<td>% CAD</td>
<td>33%</td>
<td>34%</td>
<td>35%</td>
</tr>
<tr>
<td>Mean age</td>
<td>523 ± 11.9</td>
<td>517 ± 10.6</td>
<td>52.1 ± 11.5</td>
</tr>
<tr>
<td>Mean cholesterol (mg/dl)</td>
<td>193 ± 42</td>
<td>201 ± 45</td>
<td>195 ± 43</td>
</tr>
</tbody>
</table>

*CAD defined as 25% and greater stenosis.

Table 9. Percentage of Patients Having Coronary Artery Disease (25% and Greater Stenosis) within Each Subgroup Defined by Combining the Cholesterol and Triglyceride Upper and Lower Two Quartiles

<table>
<thead>
<tr>
<th>Group</th>
<th>Definition</th>
<th>No. pts.</th>
<th>% CAD</th>
<th>Age</th>
<th>Cholesterol</th>
<th>Triglyceride</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>CHOL &lt; 209 and TRIG &lt; 141</td>
<td>129</td>
<td>33%</td>
<td>53.7 ± 10.8</td>
<td>175 ± 23</td>
<td>101 ± 24</td>
</tr>
<tr>
<td>B</td>
<td>CHOL &gt; 208 and TRIG &lt; 141</td>
<td>91</td>
<td>45%</td>
<td>54.9 ± 10.1</td>
<td>240 ± 27</td>
<td>105 ± 24</td>
</tr>
<tr>
<td>C</td>
<td>TRIG &gt; 140 and CHOL &lt; 200</td>
<td>97</td>
<td>51%</td>
<td>54.6 ± 10.3</td>
<td>185 ± 18</td>
<td>213 ± 73</td>
</tr>
<tr>
<td>D</td>
<td>CHOL &gt; 208 and TRIG &gt; 140</td>
<td>179</td>
<td>65%</td>
<td>54.4 ± 8.5</td>
<td>251 ± 36</td>
<td>230 ± 106</td>
</tr>
</tbody>
</table>
or triglyceride or both. Heinle et al. in 1969 described 134 patients with coronary artery disease. Fifty-four percent had hyperlipoproteinemia and 67% had an abnormal glucose tolerance test. Ninety-six percent of patients under age 50 had at least one of these metabolic abnormalities. They concluded that recognition and treatment of hyperlipoproteinemia and diabetes mellitus are very important in the management and prevention of atherosclerosis.

Crowley compared findings in 70 patients with CAD and in 50 patients having no disease. Hypercholesterolemia, as defined by an age-dependent cut-off point of between 240–330 mg/dl, occurred almost equally in the two groups. Hypertriglyceridemia, defined as an age-dependent threshold of 140–190 mg/dl occurred with greater frequency in the group with CAD. In 1974, Kübler et al. studied 71 of 541 patients who underwent coronary arteriography. They subdivided the patients with coronary artery disease into four quartiles based on the extent and severity of coronary occlusion and separately with the degree of peripheral atherosclerosis. They observed correlations between the severity of CAD without peripheral arteriosclerosis and with serum cholesterol concentrations and with the frequency of occurrence of type II hyperlipidemia. They were unable to establish correlations between the severity of CAD and the concentration of plasma triglycerides or elevation of blood pressure.

Cohn et al. have recently published results from 100 patients with angiographically documented CAD matched with 100 patients who had no CAD on cineangiography. These authors studied the correlations between concentrations of serum cholesterol, triglyceride and both with the occurrence of CAD. They found that the group with CAD, defined as ≥75% stenosis, had significantly higher concentrations of both serum cholesterol and triglyceride than did those without disease. By performing analyses of quartile distribution of these serum lipids, they concluded that serum cholesterol has a stronger degree of correlation with CAD than does triglyceride, particularly in multi-vessel disease. They also concluded that the association between concentrations of serum lipids and CAD was continuous and they were unable to establish any critical serum level which would separate risk from non-risk for either the cholesterol or triglyceride concentrations or both. For purposes of comparison, we have adjusted some of our data to the method used by these workers. They did not analyze their results on the basis of extent of disease involved and did not assess correlations with degrees of stenosis less than 75%. A comparison of the extent of disease was limited to one of "healthy" versus single vessel or multi-vessel disease. Also, their study did not classify subjects with respect to lipoprotein phenotype and did not make correlations based on lipoprotein patterns.

In the present study we evaluated 496 patients for both the severity and extent of coronary artery disease by cineangiography. We analyzed the relationship of frequency and extent of CAD to the levels of plasma cholesterol and triglycerides. Fewer than 5% of the patients were on lipid lowering medication, the most common of which was clofibrate. Some of the patients had received dietary instructions at one time or another, but it was impossible to generalize about the dietary characteristics of the overall groups.

Approximately 21% of the patients undergoing the study were found to have less than 25% stenosis of any coronary artery. This incidence of normal coronary arteries is consistent with other reported series. The mean ages of the two groups were 49.6 years for those without coronary artery disease and 55.7 years for those with CAD. The differences in age were taken into account in calculating the age-corrected correlation coefficients to establish the relationship between serum and number of vessels involved.

We found significant correlations between the frequency of CAD and the levels of plasma cholesterol and triglyceride concentrations. The correlations between plasma cholesterol concentration and the number of vessels involved was greater than that between plasma triglyceride and number of vessels involved. The group of subjects in the highest quartiles of cholesterol and triglyceride concentrations had the highest frequency of CAD. We were unable to identify a critical cut-off point for either cholesterol or triglyceride levels which separated those with CAD and those without disease. This observation is consistent with that of Cohn et al.

We were unable to confirm the observation by Bloch et al. concerning the differences in extent and severity of CAD in type II versus type IV hyperlipoproteinemia. We wish to emphasize again the point that many patients with severe coronary disease had lipid levels below the criteria usually applied for defining hyperlipidemia. The fourth and highest quartile in our patients starts from 236 mg/dl. Based on criteria commonly used for defining hyperlipoproteinemia, we could distinguish no significant

---

**Table 10. Comparison of the Frequency of Coronary Artery Disease (≥5% and Greater Stenosis) in Type II, Type IV and Normolipemic Patients**

<table>
<thead>
<tr>
<th>Type</th>
<th>Type II</th>
<th>Type IV</th>
<th>Normolipemic</th>
</tr>
</thead>
<tbody>
<tr>
<td>No disease</td>
<td>8 (15%)</td>
<td>22 (17%)</td>
<td>76 (24%)</td>
</tr>
<tr>
<td>With disease</td>
<td>45 (85%)</td>
<td>106 (83%)</td>
<td>239 (76%)</td>
</tr>
</tbody>
</table>

---

**Table 11. Comparison of the Extent and Severity of Coronary Artery Disease (≥5% and Stenosis and Greater) in 496 Patients with Type II, Type IV or Normolipemic Patterns**

<table>
<thead>
<tr>
<th>Extent*</th>
<th>Type II</th>
<th>Type IV</th>
<th>Normolipemic</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOV = 4</td>
<td>5 (9%)</td>
<td>9 (7%)</td>
<td>27 (9%)</td>
</tr>
<tr>
<td>NOV = 3</td>
<td>24 (43%)</td>
<td>67 (32%)</td>
<td>105 (35%)</td>
</tr>
<tr>
<td>NOV = 2</td>
<td>9 (17%)</td>
<td>10 (15%)</td>
<td>65 (21%)</td>
</tr>
<tr>
<td>NOV = 1</td>
<td>7 (14%)</td>
<td>11 (16%)</td>
<td>42 (13%)</td>
</tr>
<tr>
<td>NOV = 0</td>
<td>8 (15%)</td>
<td>22 (17%)</td>
<td>76 (24%)</td>
</tr>
<tr>
<td>Maximum % Stenosis*</td>
<td>53 (100%)</td>
<td>128 (100%)</td>
<td>315 (100%)</td>
</tr>
</tbody>
</table>

---

*Only significant difference between the percentages is for type IV and normolipemic group (P < 0.01).
*No significant difference between the percentage for type II, type IV and normolipemic groups.
differences in the extent of severity of CAD between patients with types II and IV hyperlipoproteinemia.

In our population we found a continuous relation between cholesterol and triglyceride levels and the frequency and extent of the CAD. We conclude from this study that the use of arbitrary cut-off values to define hyperlipidemia or hyperlipoproteinemia may be misleading. In regard to CAD, the physician may find it of greater value to consider the actual plasma lipid levels in the patient's management.

References
Relationship between plasma lipid concentrations and coronary artery disease in 496 patients.
A M Gotto, G A Gorry, J R Thompson, J S Cole, R Trost, D Yeshurun and M E DeBakey

Circulation. 1977;56:875-883
doi: 10.1161/01.CIR.56.5.875

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1977 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/56/5/875

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/