Asymptomatic Left Main Coronary Artery Disease in the Coronary Artery Surgery Study (CASS) Registry

Herman A. Taylor, MD, N. Joseph Deumite, MD, Bernard R. Chaitman, MD, Kathryn B. Davis, PhD, Thomas Killip, MD, and William J. Rogers, MD

Left main coronary artery disease (i.e., ≥50% stenosis) was found in 1,477 of 20,137 patients in the Coronary Artery Surgery Study (CASS) registry. Of these patients, 53 (3.6%) were asymptomatic. Asymptomatic and symptomatic patients were similar in regard to 1) severity of left main coronary artery stenosis (67% vs. 70%), 2) extent of proximal coronary artery disease (no differences in number of or severity of proximal stenoses), 3) left ventricular end-diastolic pressure (13 mm Hg vs. 14 mm Hg), 4) left ventricular wall motion score (9.1 vs. 8.7), and 5) number of coronary artery segments with greater than 70% stenosis (4.4 vs. 4.8). Among the asymptomatic patients, 47% received medical and 49% received surgical treatment. In the symptomatic group, 20% received medical and 78% received surgical therapy. The survival rate 5 years after surgery for treatment of left main coronary artery stenosis was 84% for the symptomatic patients and 88% for the asymptomatic patients (p = NS). Medical management of left main coronary artery disease produced a 5-year survival rate of 57% for asymptomatic patients and 58% for symptomatic patients. Within the asymptomatic subgroup, 88% of those surgically treated survived 5 years, whereas only 57% of those medically treated survived 5 years (p = 0.02). Thus, for CASS patients with left main coronary artery disease, the percentage of those that were asymptomatic is low (3.6%); asymptomatic and symptomatic patients with left main coronary artery disease had no significant difference in severity of left main coronary artery stenosis, extent of overall coronary artery disease, or left ventricular function. Finally, in this nonrandomized series, survival in patients with asymptomatic left main coronary artery disease was significantly improved with surgery compared with medical management. (Circulation 1989;79:1171–1179)

Several randomized and observational studies show that the surgical treatment of asymptomatic left main coronary artery disease improves survival significantly compared with medical management.1-17 Given the grim prognosis that left main disease has traditionally implied, these findings were not unexpected. However, close analysis of populations of patients with left main coronary artery disease suggests that the prognosis of such patients is not uniformly poor, but may vary, depending on certain clinical and angiographic characteristics.1,3,11,16 There is little information, however, on the prognosis of patients with left main coronary artery disease who are asymptomatic.18

Interest in the prognosis of patients with asymptomatic coronary artery disease has intensified because of a burgeoning body of information on the prevalence and importance of asymptomatic (or silent) myocardial ischemia.19-24 Also, large clinical trials have suggested that surgical intervention can improve survival in certain asymptomatic subsets of patients with coronary artery disease.25,26 The relevance of these findings to asymptomatic left main coronary artery disease has not been previously established.

This report addresses the prevalence of asymptomatic left main coronary artery disease in the Coronary Artery Surgery Study (CASS) registry population, the clinical and angiographic characteristics of symptomatic and asymptomatic patients
with left main disease, and the impact of surgical compared with medical treatment on the survival in the asymptomatic and symptomatic patients with left main coronary artery disease.

**Methods**

**Study Design**

The registry of CASS consists of 24,959 consecutive patients who underwent coronary angiography at 15 cooperating sites in the United States and Canada between 1974 and 1979. A comprehensive description of this study design has been published previously and includes description of the standardized protocol used for analysis of coronary arteriography and left ventriculography.

The patients described in this report are those with left main coronary stenosis of 50% or more and without history of coronary artery surgery and are among the 20,137 patients enrolled in the CASS registry between 1975 and 1979, the period when the registry data base was most extensive.

In this report, patients with left main coronary artery disease are subclassified as either being symptomatic or asymptomatic. Asymptomatic patients are those who on enrollment in CASS were prospectively classified as having absence of heart failure, angina, or significant arrhythmias at the time of the entry arteriogram.

**Data Acquisition**

Data collected on each patient included a standardized medical history, baseline coronary and left ventricular angiography performed and analyzed according to a common protocol, and a standardized follow-up questionnaire administered at yearly intervals after entry. Additional data were obtained on asymptomatic patients by review of hospital discharge summaries. Definition of pertinent descriptors on these standardized forms have been previously reported. At the time of this analysis, 99.9% of patients had been followed for 3 years and 71% for 5 years. (Follow-up of CASS registry patients was terminated at the end of 1982.) In nonsurvivors, the circumstances of death were determined from the hospital records or by telephone interview with treating physicians or family members.

**Assignment to Treatment Groups for Analysis**

In this report, the surgical group consists of patients who had undergone surgery within 90 days of enrollment or within the time period for each hospital within which 95% of the surgeries were done in the 1st year, whichever was longer. The cut-off time in CASS hospitals ranges from 90 to 240 days. Survival time is dated from the day of surgery. All other patients are defined as being medically treated. Survival time for medically treated patients is dated from the average time to surgery at their hospital (range, 13–64 days). Medical-surgical assignment for patients who did not have surgery and died before the average time to surgery is not defined; these patients are not included in this report.

**Statistical Methods**

Univariate comparisons between patient characteristics were made by chi-square and t-tests. Survival estimates were computed by life-table methods and compared by log-rank statistics. A probability level greater than 0.05 was regarded as nonsignificant.

**Results**

**Patient Population**

Of the 20,137 patients enrolled in the CASS registry between 1975 and 1979, there were 1,477 patients (7.3%) with left main coronary artery stenosis of 50% or more and without history of coronary artery surgery. Of these 1,477 patients, 53 (3.6%) were categorized prospectively as asymptomatic, and 1,424 patients (96.4%) were categorized as symptomatic. The reasons for performing coronary arteriography in the asymptomatic patients are outlined in Table 1. Most patients underwent arteriography as part of a comprehensive evaluation after myocardial infarction or after an exercise test with positive results.

Of the 53 asymptomatic patients, two died before they could be classified into medical or surgical strategy groups by the defining algorithm. For purposes of analysis, 26 had coronary bypass surgery within the maximum time appropriate for their institution (average maximum, 126 days), and 25 received medical therapy because they did not have surgery within the maximum site-specific time. Of the 1,424 symptomatic patients, 32 (2%) died before assignment, 1,111 (78%) received surgery, and 281 (20%) received medical therapy.

**Asymptomatic Compared With Symptomatic Patients With Left Main Coronary Artery Disease**

Baseline clinical characteristics for the asymptomatic and symptomatic patients with left main coronary artery disease are shown in Table 2. Symptomatic patients were older than asymptom-
atic patients (57 vs. 53 years, \( p=0.001 \)), but otherwise, the groups were similar in prevalence of traditional risk factors for coronary artery disease (gender, smoking history, family history, hypertension, diabetes, and cholesterol level). Full-time employment and vigorous activity were more prevalent in the asymptomatic group, suggesting that the asymptomatic group status was not due to a sedentary lifestyle or lack of physical activity. Although more blacks than whites were asymptomatic (4% vs. 0.6%, \( p=0.02 \)), the actual number of patients in either group was small, and this difference was of questionable clinical significance. A higher percent-

age of asymptomatic patients had baseline electrocardiographic evidence of prior myocardial infarction (40% vs. 26%, \( p=0.032 \)). In the asymptomatic group, the interval from most recent infarction to CASS enrollment ranged from 21 to 3,118 days with a median time interval of 128 days.

**Baseline angiographic variables.** Angiographic features (Table 3) in asymptomatic and symptomatic patients with left main coronary artery disease were generally quite similar except for ejection fraction, which was significantly lower in the asymptomatic group (51% vs. 57%, \( p=0.01 \)), who as noted above had a higher prevalence of baseline electro-

### Table 2. Asymptomatic Compared With Symptomatic Left Main Coronary Disease (>50% Stenosis): Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th>Clinical variables</th>
<th>Asymptomatic</th>
<th>Symptomatic</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yr)</td>
<td>53±7</td>
<td>57±9</td>
<td>0.001</td>
</tr>
<tr>
<td>Male (%)</td>
<td>92</td>
<td>85</td>
<td>NS</td>
</tr>
<tr>
<td>Black (%)</td>
<td>4</td>
<td>0.6</td>
<td>0.02</td>
</tr>
<tr>
<td>Smoking history (%)</td>
<td>75</td>
<td>76</td>
<td>NS</td>
</tr>
<tr>
<td>Family history of CAD (%)</td>
<td>40</td>
<td>41</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>34</td>
<td>37</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>13</td>
<td>13</td>
<td>NS</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>229±43</td>
<td>242±53</td>
<td>NS</td>
</tr>
<tr>
<td>Full-time employment (%)</td>
<td>75</td>
<td>53</td>
<td>0.01</td>
</tr>
<tr>
<td>Vigorous recreational activity* (%)</td>
<td>36</td>
<td>17</td>
<td>0.001</td>
</tr>
<tr>
<td>Myocardial infarction on baseline ECG (%)</td>
<td>40</td>
<td>26</td>
<td>0.03</td>
</tr>
</tbody>
</table>

CAD, coronary artery disease; ECG, electrocardiogram.

*Vigorous, moderate or strenuous (compared with mild or sedentary).

### Table 3. Asymptomatic Left Main Coronary Disease (>50% Stenosis): Baseline Angiographic and Hemodynamic Characteristics

<table>
<thead>
<tr>
<th>Angiographic variable</th>
<th>Asymptomatic</th>
<th>Symptomatic</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average LMCA stenosis (%)</td>
<td>67±16</td>
<td>70±16</td>
<td>NS</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One-vessel</td>
<td>11</td>
<td>13</td>
<td>NS</td>
</tr>
<tr>
<td>Two-vessel</td>
<td>38</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Three-vessel</td>
<td>47</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Average proximal stenosis (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>52±39</td>
<td>57±39</td>
<td>NS</td>
</tr>
<tr>
<td>LAD</td>
<td>47±37</td>
<td>55±38</td>
<td>NS</td>
</tr>
<tr>
<td>Cx</td>
<td>36±39</td>
<td>41±39</td>
<td>NS</td>
</tr>
<tr>
<td>Number segments ≥70% stenosis</td>
<td>4.4±2.3</td>
<td>4.8±2.6</td>
<td>NS</td>
</tr>
<tr>
<td>Degree of LMCA stenosis (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50–69</td>
<td>47</td>
<td>42</td>
<td>NS</td>
</tr>
<tr>
<td>70–79</td>
<td>23</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>80–89</td>
<td>11</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>90–99</td>
<td>19</td>
<td>20</td>
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</tr>
<tr>
<td>100%</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Presence of collaterals</td>
<td>52</td>
<td>62</td>
<td>NS (0.13)</td>
</tr>
<tr>
<td>Average LVEDP (mm Hg)</td>
<td>13.4±8.5</td>
<td>13.9±7.5</td>
<td>NS</td>
</tr>
<tr>
<td>Mean ejection fraction (%)</td>
<td>51±16</td>
<td>57±16</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean LV contraction score</td>
<td>9.1±4.1</td>
<td>8.7±4.0</td>
<td>NS</td>
</tr>
</tbody>
</table>

LMCA, left main coronary artery; CAD, coronary artery disease; RCA, right coronary artery; LAD, left anterior descending; Cx, circumflex; LVEDP, left ventricular end-diastolic pressure; LV, left ventricular.
cardiographic evidence of prior myocardial infarction.

Notably, the average degree of left main coronary artery stenosis and the average degree of proximal right coronary artery, proximal left anterior descending coronary artery, and proximal circumflex stenosis was similar between the two groups. Also, the average number of coronary segments with 70% or more stenosis and the prevalence of single-, double-, or triple-vessel coronary artery disease (evaluated independently of the presence of left main coronary artery stenosis) were similar. The percentages of patients from either group with left main coronary artery stenosis of 50–69%, 70–79%, and 80–89% were similar. Although the asymptomatic group tended to have less extensive collateralization than the symptomatic group (52% vs. 62%), this difference was not significant. Despite the slight difference in baseline ejection fraction between the two groups, the mean left ventricular end-diastolic pressure and mean left ventricular contraction scores were similar.

Survival. There was no significant difference in the 5-year cumulative survival rate by stratified direct adjustment between the asymptomatic and symptomatic groups of patients with left main coronary artery disease (82% vs. 79%, p=0.68; Figure 1). Beyond the 1st year of follow-up, the annual mortality rate was approximately 3% in both groups. There was almost identical 5-year cumulative survival rate for asymptomatic and symptomatic patients with left main coronary disease treated medically (Figure 2). Twenty-five asymptomatic patients receiving medical treatment had a 5-year survival rate of 57%, whereas 281 symptomatic patients receiving medical treatment had a 5-year survival rate of 58% (p=0.91). Similarly, there was no significant difference in survival rate between asymptomatic and symptomatic patients in the surgical treatment group (Figure 3). Twenty-six asympto-

matic patients were treated surgically and had a 5-year survival rate of 88%; 1,111 symptomatic patients were treated surgically and had a 5-year survival rate of 84% (p=0.56).

Five asymptomatic patients and 49 symptomatic patients who were initially medically managed eventually had surgery. By the end of year 1, 9% of medically treated patients had had surgery; over the course of follow-up, this number rose to 13% by year 2, 16% by year 3, 19% by year 4, and 23% by the end of year 5. The proportion of patients having surgery at years 2, 3, 4, and 5, respectively, was 10%, 10%, 22%, and 22% in the asymptomatic group and 13%, 17%, 19%, and 23% in the symptomatic group.

Angina at follow-up. During the 5-year follow-up period, there was no significant difference between the asymptomatic and symptomatic groups in the amount of nitroglycerin, nitrate or β-blocker usage, extent of recreational activity, limitation of activities, development of heart failure, or the prevalence of arrhythmias. Angina patterns in the asymptomatic and symptomatic groups tended to become more similar over the follow-up period (Figure 4). In fact, despite the highly significant difference in angina classification at baseline, at as early as 1 year after entry, there was no significant difference in angina classification between the two groups. The subsequent convergence of anginal patterns in the two groups was explained not only by the development of symptoms in the asymptomatic group but also by the return to the asymptomatic state among those patients in the symptomatic group who underwent coronary artery bypass surgery (78% of this group). By year 5 of follow-up, only 47% of the asymptomatic group remained free of angina.

Figure 4 also notes the presence of patients with angina Classes I and II (two patients) and Classes
III and IV (one patient) for the asymptomatic group at baseline. This apparent contradiction arises from CASS definitions: "angina status" refers to symptomatology during the 6 weeks before hospitalization; "asymptomatic" describes the patient's status at the time of admission.

Employment status. Similarly, although there was a significant difference in employment status at baseline between the asymptomatic and symptomatic groups (Figure 5), this difference gradually lessened. At year 5 of follow-up, there was no significant difference in employment status between the two groups.

Medical Compared With Surgical Management of Asymptomatic Patients With Left Main Coronary Artery Disease

Baseline clinical characteristics. In 53 asymptomatic patients with left main coronary artery disease, the prevalence of the traditional risk factors for coronary artery disease was similar between medically treated and surgically treated patients (Table 4). There was no significant difference between the two groups with respect to mean age, employment status, or evidence of prior myocardial infarction on the basis of electrocardiography. The only significant difference was in the higher number of surgical patients who reported participation in vigorous recreational activity.

Baseline angiography variables. The average degree of left main coronary artery stenosis was significantly greater in the surgical group than in the medical group (71% vs. 62%) (Table 5). However, no significant difference was found between the two groups in the average degree of proximal right coronary artery, proximal left anterior descending coronary artery, or proximal circumflex coronary artery stenosis. The average number of coronary artery segments with at least 70% stenosis was identical in the two subgroups. Further, no signifi-

**FIGURE 3.** Plot of cumulative survival rate of patients with left main coronary disease (LMCD) in the surgical group.

**FIGURE 4.** Stacked bar graph of angina status at various follow-up intervals. A, asymptomatic; S, symptomatic.

**FIGURE 5.** Stacked bar graph of employment status at different time intervals. A, asymptomatic; S, symptomatic.
cant difference was found in the number of vessels (i.e., one, two, or three vessels) involved or in the extent of collateralization. Although the left ventricular end-diastolic pressure was significantly higher in the surgical group (15 vs. 11 mm Hg), there was no significant difference in the mean ejection fraction or the mean left ventricular contraction score. The two groups showed similar prevalence of left dominant coronary arterial systems.

Follow-up. The 5-year survival rate in those asymptomatic patients with left main coronary artery disease receiving surgical therapy was significantly greater than for those receiving medical therapy (88% vs. 57%, p=0.02; Figure 6). This improvement in long-term survival for the surgically treated patients occurred despite a significantly greater degree of left main coronary artery stenosis in the surgical group. By the end of year 1 of follow-up, 38% (eight of 21 patients) of the medically treated group had developed chest pain, whereas only 4% (one of 23 patients) of the surgical group had experienced chest pain (p=0.006, Figure 7). This difference in prevalence of chest pain persisted through the end of year 3 of follow-up. Between years 3 and 5 of follow-up, the tendency toward greater prevalence of angina in the medically treated group continued, but the difference was not significant. No difference in the incidence of heart failure or arrhythmias was observed between the two groups during the follow-up period.

Cause of death among patients with asymptomatic left main coronary artery disease. Both of the patients who died before assignment into medical or surgical groups succumbed to cardiac events. Three patients in the surgical group died, one of gastrointestinal bleeding and two of cardiac causes (one of whom died with congestive heart failure within 24 hours of coronary bypass surgery). Ten patients in the medically treated group died, eight of cardiac causes and two of causes unrelated to cardiac events (one malignancy and one traumatic). Of the 10 cardiac deaths occurring in the asymptomatic left main population assigned to treatment groups, eight occurred within 24 hours of admission to the hospital. Each death occurred during return hospitalizations subsequent to the initial CASS enrollment hospitalization.

Discussion

This observational study analyzes patients with asymptomatic left main coronary artery disease drawn from over 20,000 patients who had coronary arteriograms at 15 CASS centers from 1975 to 1979. As such, this series provides the best available data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Medical</th>
<th>Surgical</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average LMCA stenosis (%)</td>
<td>62±17</td>
<td>71±17</td>
<td>0.04</td>
</tr>
<tr>
<td>Average proximal stenosis (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>52±41</td>
<td>48±37</td>
<td>NS</td>
</tr>
<tr>
<td>LAD</td>
<td>47±31</td>
<td>45±42</td>
<td>NS</td>
</tr>
<tr>
<td>Cx</td>
<td>37±39</td>
<td>33±38</td>
<td>NS</td>
</tr>
<tr>
<td>Average number of segments ≥70% stenosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One-vessel</td>
<td>4.4±2.7</td>
<td>4.4±2.1</td>
<td>NS</td>
</tr>
<tr>
<td>Two-vessel</td>
<td>8</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Three-vessel</td>
<td>48</td>
<td>31</td>
<td>NS</td>
</tr>
<tr>
<td>Presence of collaterals (%)</td>
<td>54</td>
<td>50</td>
<td>NS</td>
</tr>
<tr>
<td>Average LVEDP (mm Hg)</td>
<td>11±5</td>
<td>15±11</td>
<td>0.10</td>
</tr>
<tr>
<td>Mean ejection fraction (%)</td>
<td>51±17</td>
<td>51±17</td>
<td>NS</td>
</tr>
<tr>
<td>Mean LV contraction score</td>
<td>8.9±3.8</td>
<td>9.1±4.4</td>
<td>NS</td>
</tr>
<tr>
<td>Left dominant coronary system (%)</td>
<td>8</td>
<td>4</td>
<td>NS</td>
</tr>
</tbody>
</table>

LMCA, left main coronary artery; RCA, right coronary artery; LAD, left anterior descending; Cx, circumflex; CAD, coronary artery disease; LVEDP, left ventricular end-diastolic pressure; LV, left ventricular.
on prevalence, clinical and angiographic features, and prognosis of patients with left main disease who are asymptomatic. We have presented evidence that 1) asymptomatic left main disease is a relatively rare entity comprising about 3.6% of all left main coronary artery disease and is found in 0.26% of all patients undergoing cardiac catheterization for suspected or proven coronary artery disease, 2) asymptomatic and symptomatic patients do not differ in severity of left main stenosis or overall extent of coronary artery disease; and 3) survival in these nonrandomized patients with asymptomatic left main disease may be significantly enhanced when surgery is elected over medical therapy.

**Surgery in Left Main Coronary Artery Disease**

Since Herrick's original clinical description in 1912, left main coronary disease has come to be regarded as a lesion with a uniformly malignant course. Earlier clinical studies have examined heterogenous populations of left coronary artery disease and have shown that, in clinically and angiographically mixed groups, coronary revascularization surgery improves survival to a greater degree than does medical management.

However, Chaitman et al and Conley et al have presented evidence that there are low-risk subgroups of patients with left main disease for whom surgery offers no improvement in prognosis. The lower-risk groups of these studies were distinguished chiefly by angiographic criteria. These studies indicate that prognosis of left main disease is usually but not universally dire. However, the importance of anginal symptoms in defining risk has not been previously addressed.

Through analysis of the largest series yet assembled, of asymptomatic patients with left main disease, the present study shows that the presence or absence of symptoms does not influence prognosis in left main disease and that surgery may substantially improve prognosis in symptomatic and asymptomatic patients with left main coronary artery disease.

**Asymptomatic Left Main Coronary Artery Disease: Its Relevance to the Concept of Silent Myocardial Ischemia**

That 3.6% of patients with left main stenosis have no symptoms is remarkable, especially in light of the fact that a substantial amount of myocardium is jeopardized by the lesion and the advanced lesions
in other vessels that usually accompany left main stenosis. The finding that such advanced disease can exist without symptoms underscores the validity and importance of the concept of silent myocardial ischemia and may offer some insights into its mechanism.

**Asymptomatic Coronary Artery Disease Compared With Silent Ischemia**

Before discussing possible mechanisms of silent ischemia in left main coronary disease patients, it must be acknowledged that asymptomatic coronary artery disease is not equivalent to silent myocardial ischemia. Morphologic stenosis as seen by coronary angiography is only indirect evidence of ischemia. In the present study, systematic testing for evidence of silent myocardial ischemia (e.g., ambulatory electrocardiographic monitoring and radionuclide studies) was not undertaken; however, we have reason to believe ischemia did indeed occur in the asymptomatic patients. Cohn and Larson\(^3\) showed recently that normal activities of daily living precipitate silent ischemic episodes in patients with angiographically proven coronary artery disease. Their study further suggested that the more severe the disease, the more frequent the episodes. The fact that our patients with advanced coronary artery disease were enjoying active lifestyles, therefore, suggests that there were ample opportunities for silent ischemia to occur.

How, then, can ischemic episodes secondary to left main disease in an active population occur without symptoms? Several hypotheses have been advanced to explain the phenomenon of silent ischemia in general; our observations in left main disease may serve to support or challenge some of them.

**Inaccurate History**

Conceivably, some patients may minimize or even deny the symptoms of coronary heart disease. Also, patients may make subtle, perhaps subconscious, adjustments in their level of exertion (e.g., avoiding stairs, frequent resting while walking, etc.) to avoid precipitating uncomfortable symptoms and therefore would not report the symptoms to medical personnel. This possibility was minimized in CASS participants by adherence to a standardized questionnaire administered by cardiologists.

**Little Myocardium in Jeopardy**

A second hypothesis suggests that ischemic episodes remain “silent” when less myocardium is jeopardized, that is, when the episode is very brief or when there is substantial protection of jeopardized myocardium by collateral circulation. We do not know the duration of painless ischemic episodes in these asymptomatic patients, but other investigators have shown the common occurrence of prolonged periods (greater than 20 minutes) of symptomless ST segment depression on ambulatory electrocardiographic monitoring among patients with coronary artery disease.\(^3\) Deanfield et al\(^3\) have shown a strong correlation between ambulatory ST segment changes and the recurrence of reversible regional myocardial perfusion deficits with positron emission tomography using Rubidium 82. Collaterals in the asymptomatic left main disease patients of this study tended to be no different than that seen in the symptomatic group. This fact challenges the notion that the presence of collaterals somehow prevents the development of anginal pain during ischemia. Also, as noted above, the angiographic results suggest a large amount of jeopardized myocardium in these asymptomatic patients because of extensive coronary artery disease in addition to the left main stenosis.

**“Defective Anginal-Warning System”**

Cohn originally formulated the concept that silent ischemia may reflect a patient’s inability to perceive anginal pain.\(^20\) Underlying reasons for the “defect” have been the subject of much speculation and investigation. Important possibilities include 1) neuropathy (e.g., alcoholic, diabetic), 2) excess plasma \(\beta\)-endorphin secretion, 3) altered pain thresholds, and 4) destruction of afferent neural pathways by myocardial infarction or diffuse ischemia. The first of these mechanisms, neuropathy, is a known cause of impaired anginal perception in diabetics, but the two groups in this study have the same frequency of diabetes mellitus at baseline (approximately 13%; see Table 2). Relative frequencies of alcoholism or renal failure, which are other possible causes of neuropathy, are not available. Conflicting data have been published on the possible role of \(\beta\)-endorphin secretion.\(^32,33\) A third theory suggests that patients with asymptomatic coronary artery disease and infarctions have higher pain thresholds, as assessed by ischemic arm pain, cold pressor tests, and electrical pain.\(^34,35\) Though the data appear convincing, the authors recognize that “personalities, ethnic and social backgrounds, emotional state and psychological expectations”\(^35\) are confounding variables that detract from a purely physiologic explanation of their findings.

Observations made in this study seem most congruent with a fourth putative mechanism underlying the defective anginal warning system: neuronal destruction by myocardial infarction or diffuse ischemia. As noted previously, a significantly higher percentage of asymptomatic patients had a history of prior myocardial infarction than did symptomatic patients. Infarctions may lead to greater disruption of afferent neural pathways that originate within the myocardium; the loss of a critical number of afferent fibers may produce a pathophysiologic substrate in which silent ischemia can occur.

The retrospective nonrandomized design of this study is not ideal, but it is well suited to the analysis of the relatively rare phenomenon of asymptomatic left main coronary artery disease. (Note that 2,137 patients with left main coronary disease were
required to identify 53 asymptomatic patients.) Also, even if left main coronary artery disease were more prevalent, it is unlikely that a randomized trial of surgical management could be mounted because of the widespread enthusiasm for revascularizing patients with left main coronary artery disease. We feel, therefore, that the data presented here carry important clinical and theoretical implications.

References

Key Words • left main coronary artery disease • silent myocardial ischemia • coronary artery disease, surgical therapy • coronary artery disease, medical therapy
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Circulation. 1989;79:1171-1179
doi: 10.1161/01.CIR.79.6.1171

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