Coronary Heart Disease in Women

Study of Risk Factors in 100 Patients Less Than
60 Years of Age

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SUMMARY
One hundred women with classical coronary heart disease were studied in an attempt to identify etiological factors. Three dominant factors were hypertension, cigarette smoking, and hypercholesterolemia. Cigarette smoking and hypertension were present together or separately in 80 to 90% of the patients. Four patients were diabetics; six had grossly abnormal serum cholesterol levels; and there was one case each of associated myxedema, aortic stenosis, and postoperative hypotension. Comments are made about the role of family history, obesity, hypercholesterolemia, abnormal glucose tolerance, exercise and dietary experience, and the influence of the menopause. It is believed that the proper control of hypertension in the population and the elimination of cigarette smoking would cause an appreciable or even dramatic reduction in the incidence of precocious and middle-aged coronary heart disease in women.

Additional Indexing Words:
Epidemiology of coronary disease
Cigarette smoking
Family history
Glucose tolerance
Menopause

The Importance of coronary heart disease (CHD) as a cause of illness and death in women has been somewhat overshadowed by the magnitude of this disease in males. Nevertheless CHD is the single most common certified cause of death in females of all ages in Ireland and is the cause of almost 25% of total female deaths. The mortality from CHD in women has remained static in this country, there being no significant change in the 12-year period 1952 through 1963. CHD occurs at a later age in women than in men so that in the groups under 60 years of age the reported ratio of affected males to females is of the order of 4 or 5 to 1. In our experience over a 6-year period, 100 female patients under 60 years of age with classical CHD were seen while in the same period about 450 male patients of the same age group were seen, giving a male-to-female ratio of about 4.5 to 1.

This paper is based on a clinical retrospective study of these 100 female patients. Sixty-three were from the hospital and 37 were from the private wards. Sixty-eight were from urban areas and 32 had a rural domicile. All patients seen, including those with angina pectoris, were admitted to the hospital for the purpose of this study. In each case a detailed history and full physical examination were recorded. Investigations included weight and dietary history, personality assessment, measurement of smoking, alcohol and exercise experience, occupation, blood pressure status, the condition of the arterial tree, the patient's...
family history, anthropometric data, and a variety of other measurements. Laboratory studies included serum cholesterol, triglycerides, glucose tolerance, hematocrit, serum magnesium, uric acid, blood group, and respiratory function.

This information was examined in an attempt to identify clinical or environmental factors which might be highly associated with CHD and which might be of significance in the causation of this disease. Only patients with typical cardiac pain and with characteristic ECG changes were included. Patients with atypical pain or with an atypical or negative ECG were not included. Among the 100 patients, 35 had angina pectoris (AP), 21 had acute coronary insufficiency (ACI), and 44 had cardiac infarction (CI).

This study is confined to patients under 60 years of age. Younger patients make the most satisfactory clinical material for a retrospective survey of CHD. CHD is most easily defined in younger people, and one is left with fewer borderline diagnostic cases. Also, recall of information is easier and more reliable in young people and atherogenic factors are likely to be easier to identify among them.

Results

Table 1 shows the distribution of patients according to diagnosis and shows the mean age, standard error of the mean, and the age range of each group. There was no significant difference in the mean ages of the three groups.

Blood Pressure

Each patient's blood pressure status was decided on the mean systolic and diastolic pressures recorded during the fourth day of hospitalization before any hypotensive treatment, when indicated, was prescribed. With a diastolic pressure of 90 mm Hg as a cut-off point, it was found that 50 patients (50%) had hypertension. In defining hypertension a figure of 90 mm Hg is of course an arbitrary one. No control Irish population is available for comparison either for casual outpatient figures or for basal hospital readings as used in this study. The best that can be done here is to refer to the American population study reported by the U. S. Public Health Service in which the average diastolic readings of the female population in the 45 to 54 age groups was reported to be 82.0 mm Hg. Twenty-eight per cent of this control female population had a figure of 90 mm Hg or more. These figures are based on casual readings. Basal hospital figures from the United States, if available, would probably be lower. Also, our own experience suggests a much lower proportion of patients with a diastolic blood pressure of 90 mm Hg or more in the general medical and surgical wards of the hospital.

The 50 patients in this study with a diastolic pressure of less than 90 mm Hg included 21 who had suffered a recent attack of cardiac infarction. The tendency for blood pressure to fall immediately following cardiac infarction may have obscured hypertension in some of these 21 patients, and this possibility is confirmed by a history of treatment of hypertension in 10 of these "normotensive" patients. Some of these 10 patients had other objective changes of hypertensive disease and in a subsequent follow-up study four of the 10 patients now have persistently raised blood pressure. If these 10 patients with a history

| Table 1 |

<p>| Diagnosis and Mean Age of 100 Female Patients with Coronary Heart Disease (Age: 35 to 59 Years) |
|---------------------------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Mean age (yr) + standard error</th>
<th>Range (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina pectoris</td>
<td>35</td>
<td>52.2 ± 1.13</td>
</tr>
<tr>
<td>Acute coronary insufficiency</td>
<td>21</td>
<td>50.6 ± 1.24</td>
</tr>
<tr>
<td>Cardiac infarction</td>
<td>44</td>
<td>51.2 ± 1.01</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>51.4 ± 0.65</td>
</tr>
</tbody>
</table>

Circulation, Volume XXXVI, October 1967
Systolic blood pressure of 100 females with coronary heart disease (age, 35-39 years).

No significant difference in systolic blood pressure was noted in the three groups of patients.

In our experience hypertension appears to be positively associated with all forms of classical CHD although it has not yet been proved that hypertension is a specific causative factor. Prospective studies have shown however that increasing levels of systolic and diastolic blood pressure are associated with...
an increased incidence of CHD in the under-50 age group. In favor of a causative association too is our own finding that blood pressure figures do not correlate with any other risk factor and appear to be independently associated with CHD.

Cigarette Smoking

Sixty-three of the subjects (63%) were cigarette smokers at the onset of symptoms. Only four were ex-smokers and 33 (33%) were non-smokers. These data are shown in table 2, and comparison with similar data on the Irish female population of the same age group shows a significant excess (at the 1% level) of cigarette smokers in these patients. There is no significant difference in the smoking habits of the different social classes in Ireland and, while urban dwellers smoke more than rural dwellers, they do so by less than 20% more. It is reasonable, therefore, to compare our 100 patients with the general Irish female population of the same age group.

Apart from the excess of current smokers, our patients were on average about three times heavier smokers than the normal female population (table 3). The cigarette smoking experience is expressed as a cigarette index. This is a quantitative method of measuring smoking experience which has been described elsewhere and is an expression of the patient’s average daily consumption of cigarettes.

Figure 3

Diastolic blood pressure of women with angina pectoris, acute coronary insufficiency and cardiac infarction (age, 35-59 years).

Table 2

Distribution of Smokers, Ex-smokers and Non-smokers among 100 Female Patients with CHD and among the Female Population in Ireland

<table>
<thead>
<tr>
<th>Patients</th>
<th></th>
<th>Population *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Smokers</td>
<td>63</td>
<td>63</td>
</tr>
<tr>
<td>Nonsmokers</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>Ex-smokers</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

*Source: Statistics of smoking in the Irish Republic. (Females 35 to 59 years).
CORONARY HEART DISEASE IN WOMEN

Table 3
Mean Cigarette Index of 100 Females with Coronary Heart Disease (Age: 35 to 59)*

<table>
<thead>
<tr>
<th>Condition</th>
<th>No. of patients</th>
<th>% of smokers in group†</th>
<th>Cig index of smokers</th>
<th>SE of mean</th>
<th>Cig index of all smokers</th>
<th>SE of mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina pectoris</td>
<td>35</td>
<td>57</td>
<td>414.8</td>
<td>44</td>
<td>237.0</td>
<td>43.0</td>
</tr>
<tr>
<td>Acute coronary insufficiency</td>
<td>21</td>
<td>81</td>
<td>469.0</td>
<td>59</td>
<td>379.7</td>
<td>63.1</td>
</tr>
<tr>
<td>Cardiac infarction</td>
<td>44</td>
<td>72</td>
<td>463.8</td>
<td>41</td>
<td>316.2</td>
<td>43.2</td>
</tr>
<tr>
<td>All patients</td>
<td>100</td>
<td>67</td>
<td>450.5</td>
<td>27</td>
<td>301.8</td>
<td>27.9</td>
</tr>
</tbody>
</table>

*Estimated cigarette index of the Irish female population at 52 years is 90.
†Current and ex-smokers.

multiplied by the number of years of smoking.

Table 3 shows that the 35 patients with angina pectoris were lighter smokers than the patients with acute CHD although they were still above the level of the control population. This lighter smoking experience among patients with AP conforms with the experience of Oliver (personal communication from M.F. Oliver, 1966) in studying young female patients with CHD, and with the experience of the Framingham group who found no excess of smokers in male patients with AP, in sharp contradistinction to those with CI or to those dying suddenly.

Cholesterol

The Framingham and other prospective studies have shown a significant risk gradient of CHD with increasing cholesterol levels in women. Figure 4 shows the distribution of serum cholesterol in 88 of our 100 subjects. They had a mean value for serum cholesterol of 280 mg% and 28 patients (32%) had a cholesterol value in excess of 300 mg%.

A previous study in this hospital showed that a suitable group of control male patients had a mean serum cholesterol of 230 mg%, and in a continuing study of 159 women between the ages of 35 and 59 years attending the National Blood Transfusion Centre, a mean cholesterol figure of 229 mg% was noted. Other workers have shown that the cholesterol of males and females in a healthy population does not differ significantly at the age group under study.11

Female control subjects and patients were grouped into ages 35 to 44 and 45 to 59. The
mean serum cholesterol in the group 35 to 44 years of age was 209 mg% (± 37.8) in the controls as against 256 mg% (± 72.7) in the patients (P < 0.0001). In the age group 45 to 59, the mean control serum cholesterol was 245 mg% (± 27.3) and the patients’ figure was 278 mg% (± 67) (P < 0.001). It is clear that our female patients have a significantly higher cholesterol level than the control Irish population.

In no patient with a cholesterol level of less than 400 mg% was this an isolated finding. In other words, all these patients had one or more other apparent risk factors such as hypertension or cigarette smoking.

**Glucose Tolerance**

There were four patients with diabetes mellitus among our subjects. Eighty-five of the other 96 patients had glucose tolerance tests performed by the Folin and Wu method. Thirteen of the 85 curves were classified arbitrarily as abnormal on the basis of an aggregate of the fasting, ½ hour, 1 hour, and 2 hour readings being in excess of 600 mg%.

Figure 5, which records the results of glucose tolerance tests in 85 patients, shows that another 13 patients had borderline figures between 550 and 600 mg%.

A control series of 34 males and 10 females with a mean age of 2 years less than our patients showed a mean glucose tolerance aggregate of 480 mg% compared to the 519 mg% noted in our patients. It is probably legitimate to include males in this control group in the light of the Tecumseh study, which showed that the nonfasting 1-hour blood sugar findings in males and females are identical at the same ages. Statistical analysis reveals a difference, significant at the 1% level, between our patients and controls.

Many studies show a high incidence of abnormal glucose tolerance and abnormal blood sugar levels in the absence of diabetes in patients with arterial disease. Apart from the well-documented and probably causative association between diabetes mellitus and CHD, it is difficult to assess the significance of the high frequency of abnormal or pre-diabetic glucose tolerance curves in these patients. There is no positive proof that abnormal glucose tolerance has a causative significance, but much work needs to be done to clarify the association. In our own experience many patients, both male and female, show a return to more normal figures when the test is repeated 3 or 6 months later. Also during a 5-year experience, no patients with such an abnormal curve have developed frank diabetes.

**Family History**

Twenty-three of our patients (23%) presented with a family history of CHD; that is, 23 patients had at least one parent under 70 years or at least one sibling under 60 years who had suffered or died from CHD. Ten others gave a family history of the appearance of CHD for the first time in one parent over 70 years or one sibling over 60 years of age. They were considered to have a weakly positive family history. In the families of the
other 66 patients (66%), no history of the disease was reported.

Only isolated reports in the literature support the view that there is a significant genetic background to CHD. One would expect a certain degree of familial aggregation of CHD because of the common aggregation of risk factors in certain families. The significance of environmental risk factors in families is referred to elsewhere. Pickering, for instance, has shown that relatives of hypertensives tend to have higher blood pressure at all ages. Also, essential hypercholesterolemia is relatively rare but may present as a familial condition. Parents who smoke tend to have children who smoke, and diabetes is well known to occur more in some families than in others. On the evidence so far available, it is reasonable to assume that family aggregation of CHD is at least partly due to the higher frequency of risk factors in some families than others. Indeed, there is little confirming support for more profound hereditary factors. None of our 100 patients presented with a positive family history as the only apparent or likely risk factor.

**Weight**

Patient’s weight is expressed as a percentage above or below ideal weight, the latter being derived from tables based on age, sex, height, and body build data. These tables provide at the present time the most reliable index to an individual’s proper weight although recent work suggests that the population of the United States has a mean weight considerably in excess of the ideal as expressed in these tables. Figure 6 shows in histogramic form the highest weight reported during the 10 years preceding the date of the onset of CHD in 86 of our patients. Thirty-four (40%) of the 86 patients had a weight experience 15% or more above their ideal weight and the mean for the whole group was 13.2% above the ideal weight. This corresponds with the experience of the average person in contemporary United States society. No figures are available about the average weight of the normal middle-aged female population in Ireland, but a study of 200 healthy male controls of the same average age (50 years) carried out by us shows them to be 8.5% above the top value of their ideal weight. In other words the present Irish experience of widespread “overweight” is following the pattern reported by Seltzer from the North American continent. Excluding the six female patients who were grossly overweight at 40% or more, the weight distribution of our patients in relation to their ideal weights corresponds closely to the weight distribution of the average Irish male population.

The complex interaction of weight, diet, and exercise makes it difficult to assess each parameter separately, but these three factors, either alone or in combination, do not appear to play an obvious isolated part in the causation of CHD in our younger patients. Whether they are important as contributory factors and in the older age groups remains to be seen.

In general, our patients share the same exercise experience as the general female population. Most were housewives with the usual housewife’s experience of light but continuous and fairly prolonged activity.

A careful dietary history has been taken from 50 of our 100 patients. Data collected include total calories, and carbohydrate, protein, and fat intake. Details of sugar, cholesterol, and saturated and unsaturated fats are also noted. This information will be compared
with information from a control group. However, there is nothing remarkable about the pattern of the patients’ food intake, and in general, their dietetic experience does not differ remarkably from that of the normal British female population. In a similar retrospective study of CHD, no significant difference was noted in the dietary experience of patients compared to a control group. We would postulate that while the pattern of over-nutrition and high intake of saturated fat in our population may be a contributory factor to the incidence of CHD in the country, the diet pattern does not appear in our younger patients as an isolated factor.

Menopause

It is often suggested that the lower morbidity and mortality from CHD in women than in men and the decreasing sex differential with increasing age are due to estrogen protection. This view is expressed although overt CHD is far from being rare in pre-menopausal women. Data on the menopause are only available about the last 52 patients studied by us. Thirteen (25%) were pre-menopausal; six (11.5%) were menopausal; and 33 (63.5%) were postmenopausal. Our experience agrees with the work of others25–27 who show that the menopause does not appear to have a specific effect on the prevalence of overt coronary disease in women. It is possible that pre-menopausal women have a lower incidence of CHD than males of the same age group because women at this stage are exposed to fewer or less powerful risk factors. This will include cigarette smoking in this country but other contributory factors, such as a high fat intake, might also be considered.

Discussion

This study supports the widely accepted view that CHD is of multifactorial origin. High blood pressure, cigarette smoking, and high serum cholesterol concentrations are the outstanding conditions associated with CHD in women under 60 years, and it is important to know whether these factors play a major role in its causation. Abnormal glucose toler-

ance has a less striking association with CHD.

Together or separately, hypertension and cigarette smoking were present in 80% of our subjects, and if a history of hypertension in 10 of our apparently normotensive subjects with CI is accepted as significant, this figure exceeds 80%. The role of hypertension and cigarette smoking conforms to our wider experience of 400 male patients under 60 with classical CHD. In men however cigarette smoking is of greater importance than hypertension, and at least part of the excess of CHD in men compared to that of women may be attributed to the fact that men in this country smoke three times as heavily as women.

This strong background of smoking and hypertension noted in other studies as well as our own does not necessarily prove a cause and effect relationship. However, there is now every reason to incriminate cigarette smoking as a primary causative factor in the light of the massive clinical, epidemiological, and basic research evidence, and because of its certain role in the causation of atherosclerosis of the peripheral vessels.

With hypertension the evidence of a causative relationship is less clear-cut. There is no evidence to support the contention that atherosclerosis and hypertension have a common etiology, and the experimental production of one does not lead to the other. Neither is there convincing evidence to suggest that widespread atherosclerosis may cause hypertension, except perhaps in the case of stenosis of a renal artery. The view that hypertension is causally related to CHD is supported only by the strong clinical and epidemiological association between the two and also between hypertension and cerebrovascular disease. Also, pulmonary hypertension is often associated with an unusual degree of atherosclerosis of the larger pulmonary vessels.

In elderly people with CHD, hypertension and cigarette smoking are less commonly found. This strengthens the belief that both factors accelerate the development of atherosclerosis in the young. Thus, in both sexes, CHD may remain submerged until the
seventh or eighth decade in the absence of hypertension and cigarette smoking, and in the absence of other rarer risk factors such as diabetes, idiopathic hypercholesterolemia, or myxedema. It is believed that widespread control of smoking and a better understanding and more effective treatment of hypertension would appreciably reduce CHD as an important cause of morbidity and mortality in young and middle-aged women. We have already expressed this view about men.20

The results of a number of prospective epidemiological studies lend support to the importance of hypertension and cigarette smoking as risk factors in precocious CHD. Prospective studies also advert to the importance of high serum cholesterol, obesity, family history, high fat intake, and a number of other factors, but our own experience fails to identify these factors as influences sufficient in isolation to cause overt CHD, at least in people under 60 years. These different views may eventually be reconciled by concluding that these latter risk factors have in fact a causative association, but they may only be weakly atherogenic and they perhaps lack a thrombogenic influence. On the other hand, it may be that some of these factors are associated with CHD because of a common etiology, or because of association with other more important atherogenic influences.

The highly significant increase in cholesterol in our patients compared to the control population conforms closely to population studies. These high cholesterol figures require further study and evaluation, particularly to determine their significance as a primary risk factor.

Other conditions found in isolation in single patients in this group were myxedema, post-operative hypotension, and aortic stenosis. Fifteen patients gave a previous history of hysterectomy. Insufficient information is available about the number of these who had associated oophorectomy and no information is available about the incidence of hysterectomy in the Irish female population.

References


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