The Intermediate Coronary Syndrome*

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INTRODUCTION

The modern or accepted view of the "intermediate coronary syndrome" has been well stated by Friedberg:1 "an exact diagnosis in acute syndromes of coronary heart disease is difficult or impossible in many cases, particularly those cases in which the clinical syndrome is atypical and those in which cardiac pain of 'intermediate' or long duration is unaccompanied by the classic electrocardiogram of acute myocardial infarction. There is frequently difficulty in determining the specific anatomic substrates responsible for cardiac pain and the associated electrocardiographic changes."

Nevertheless, because of the greater and growing frequency of these small coronary attacks, every effort should be bent toward improving our knowledge of the etiology, pathogenesis, significance, prognosis and treatment of this condition.

The present report deals with a series of 57 cases of intermediate coronary syndrome which have been divided into various etiologic subgroups. In each of these six subgroups, mode of onset, duration of symptoms, prognosis, rationale of anticoagulant therapy and serum enzyme values are necessarily different. However, though the group is large and somewhat heterogenous, it has been possible to develop reasonably adequate clinical and electrocardiographic criteria which apply to the entire group.

MATERIAL AND METHODS

The clinical material on which this study is based consists of 47 patients (378 electrocardiograms) gathered over a ten-year period from the medical service of the Huntington Memorial Hospital. Patients were chosen who experienced a distinct episode of substernal oppression or pain subsiding over a period of several hours or days. To be acceptable for this series, at least three abnormal electrocardiograms had to be present, each being different from the others. Patients whose tracings showed no abnormality in addition to prior Q wave changes were excluded. In addition, minor changes in the ST segment or T wave in the presence of either tachycardia, fever or anemia were also rejected.

The 47 patients fell into six subgroups as follows:

(1) Primary—the attack of acute coronary pain was the first manifestation of heart disease.

(2) Premonitory—acute coronary pain was the first manifestation of heart disease, but shortly following the attack of apparent intermediate coronary syndrome, a frank myocardial infarction developed.

(3) Hypertensive—patients with evident heart disease, primarily hypertensive. However, a few patients with aortic valve disease and outflow tract obstruction were also included.

(4) Mixed—patients with tachycardia secondary to non-cardiac disease, such as hyperthyroidism or anemia.

(5) Coronary—patients with prior myocardial infarction.

(6) Cerebral—attack of coronary artery insufficiency was accompanied by acute cerebrovascular insufficiency.

The distribution of patients among these six groups is shown in Table 1.
TABLE 1—The Distribution of Patients with the Intermediate Coronary Syndrome Among Six Etiologic Classifications and Average Age of Patients in Three Groups

<table>
<thead>
<tr>
<th>Etiologic Classification</th>
<th>Cases</th>
<th>Average Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Primary (coronary pain first manifestation of heart disease)</td>
<td>17</td>
<td>50</td>
</tr>
<tr>
<td>2 Premonitory (coronary pain, followed by a frank myocardial infarction)</td>
<td>3</td>
<td>*</td>
</tr>
<tr>
<td>3 Hypertension (heart disease—usually hypertensive—present)</td>
<td>11</td>
<td>65</td>
</tr>
<tr>
<td>4 Mixed (coronary pain along with non-cardiac disease)</td>
<td>5</td>
<td>*</td>
</tr>
<tr>
<td>5 Coronary (patient with prior myocardial infarction)</td>
<td>8</td>
<td>59</td>
</tr>
<tr>
<td>6 Cerebral (coronary pain accompanied by cerebrovascular insufficiency)</td>
<td>3</td>
<td>*</td>
</tr>
</tbody>
</table>

* Insufficient numbers to calculate averages.

RESULTS

A. Location of greatest electrocardiographic abnormality:

In Table 2, the various etiologic groups are correlated with the location of the greatest electrocardiographic abnormality. In group 1 (patients in whom the insult was “primary”) there was an approximately equal distribution of anterior and posterior involvement, whereas in group 3 (patients in whom left ventricular hypertrophy was prominent) there was a pronounced preference for an anterior location.

The precise location of the injury, as determined electrocardiographically, is seen in Table 3, along with a separation of those in whom depression of the ST segment was the outstanding abnormality and those in whom late T wave inversion occurred. There were 15 of the former and 28 of the latter. In the anterior leads, inversion of T occurred twice as frequently as J point depression. In the posterior leads, however, T wave inversion and J point depression were seen equally often.

B. Life expectancy:

There was an adequate follow-up period in 30 of the 47 patients, with an average follow-up period of six years. Of these 30 patients, six were dead (two of the premonitory group and four of the group with left ventricular hypertrophy). In the treatment of the acute attack, 37 of the 47 patients received anticoagulants. Of these, 20 were treated with warfarin sodium (Coumadin)* and 17 with bishydroxycoumarin (Dicumarol).

C. Persistence of anginal pain after attack as affected by anticoagulants:

In Table 4 are detailed the 13 patients with adequate follow-up who were maintained on anticoagulants. All 13 patients are now leading active lives and ten are considerably improved in regard to chest pain. There appears to be a positive correlations between the adequacy of anticoagulant control and freedom from chest pain.

D. Serum glutamic oxalo-acetic transaminase levels:

Of the 47 patients, 19 had transaminase (SGO-T) determinations. Two were above the normal of 40 units, 46 and 51, respectively (neither had an unusually severe attack). The average transaminase of the group was 27.1 units.

TABLE 2—Location of Lesion and Mortality by Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Anterior</th>
<th>Posterior</th>
<th>Total</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Primary</td>
<td>6</td>
<td>9</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>2 Premonitory</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>66%</td>
</tr>
<tr>
<td>3 Hypertension</td>
<td>8</td>
<td>2</td>
<td>11</td>
<td>50%</td>
</tr>
<tr>
<td>4 Mixed</td>
<td>4</td>
<td>1</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>5 Coronary</td>
<td>3</td>
<td>4</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>6 Cerebral</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

*Supplied by Endo Laboratories, Inc.
E. Two Illustrative Cases:

M. C., a 46-year-old housewife, was first seen 11 years ago, and was hospitalized with an attack of acute coronary insufficiency characterized by chest pain and the acute development and sudden disappearance of right bundle-branch block. She was then quite well for eight years and then was hospitalized with acute posterior infarction. For all episodes she received bishydroxycoumarin. In late 1960, because of angina, she was started on warfarin. Sodium bishydroxycoumarin (Dicumarol) is now on continuous anticoagulants. During the blood pressure was 160/100, the patient was completely incapacitated and the cholesterol was 161 mg per cent. During the period of two years, the blood cholesterol level is now 300 mg per cent. The blood pressure was 160/100. During the period of two years, the blood cholesterol level is now 300 mg per cent. In the latest electrocardiogram shows the pattern of left ventricular hypertrophy.

Discussion:
The term "intermediate coronary syndrome" is being used to encompass a variety of clinical entities which all fall within the general diagnosis of coronary insufficiency, and (c) acute coronary infarction. One of the problems in interpreting the results of Master's diagnosis of "acute coronary insufficiency" has always been that it appears to consist of two entirely different groups of cases. In approximately 60 per cent of patients, the attacks occur spontaneously, and the pattern of left ventricular hypertrophy.

The table below illustrates how these patients are selected.

<table>
<thead>
<tr>
<th>Patient Age</th>
<th>ECG Diag.</th>
<th>Severity of Anticoagulant Dosage</th>
<th>Rx. Anticoagulant Before Attack</th>
<th>Control of Attack</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>None</td>
<td>Poor</td>
<td>none</td>
<td>None</td>
</tr>
<tr>
<td>C</td>
<td>12</td>
<td>Good</td>
<td>none</td>
<td>None</td>
</tr>
<tr>
<td>C</td>
<td>12</td>
<td>None</td>
<td>none</td>
<td>None</td>
</tr>
<tr>
<td>C</td>
<td>12</td>
<td>None</td>
<td>none</td>
<td>None</td>
</tr>
</tbody>
</table>

THE COURSE OF PATIENTS 11 PATIENTS
eously; in the remainder, they are associated with the usual precipitating factors such as bleeding, fever, shock or pulmonary embolus.

It would seem most difficult, if not impossible, to establish rigid electrocardiographic criteria for the diagnosis of the intermediate coronary syndrome. Certainly no such simple rule can be made as the classic definition of infarction, viz., the appearance of abnormal Q waves in conjunction with reciprocal ST deviation. However, the establishment of certain at least minimal criteria should not only be possible, but also helpful in clarification of the issue.

Several such attempts have been made. For example, Pruitt\(^4\) has attempted to define the group in which T wave inversion is the characteristic abnormality, stating that “subendocardial necrosis may also be reflected in an electrocardiogram by inverted T waves (more than 5 mm.) especially or only in the precordial leads.”

In reporting the findings on his group of 110 patients, Pruitt apparently did not consider electrocardiographic evidence of ST depression at all.

The second group most clearly represented and described clinically by the studies of Master shows ST and J depression as the principal feature and, according to Friedberg,\(^5\) the most common characteristics consist of persistent ST depression in leads I, II, AVL and leads V\(_2\) to V\(_6\), with definite ST elevation in lead AVR. Myers,\(^6\) on the other hand, has attempted to correlate the electrocardiogram and necropsy in this “group” and unlike Pruitt, makes no mention of inverted T tracings at all.

Edson\(^7\) has recently made an attempt to define electrocardiographic changes fairly rigidly according to the following two rules: (1) the RST segment depression present in the leads facing the injured area must be accompanied by RST segment elevation in lead AVR; (2) the deeply inverted T waves which are also present in leads approximating the lesion must develop progressively and disappear gradually in not less than several days and usually several weeks or months.

Edson’s definition has two significant points with which the author is in complete agreement. The first is that the intermediate coronary syndrome is characterized electrocardiographically by either predominant T wave inversion, or by ST and J point depression. No matter which pattern is present, there is a continuous, cyclic, slow progression and regression, most often a week or two in duration, resulting in a final tracing that tends to be borderline normal.

In the cases presented, we have therefore been most careful to distinguish those cases in which T wave inversion was the characteristic abnormality from those in whom depression of ST was usually present. In the 47 patients who comprise our series, the tracings are highly variable. In fact, one wonders what the basic difference is between a 5 to 8 mm. cove-shaped T wave inversion and a ½ to 1 mm. almost insignificant ST depression with slight lowering of T. These enormous variations of ST segment and T wave changes have undoubtedly been one of the chief causes of confusion and frustration in the careful definition of this frequently encountered lesion.

One of the most serious obstacles in the evaluation of prognosis, and of therapeutic programs for this group of patients is the lack of uniformity in either etiology or pathology. The small series of Levine and Ford\(^8\) is often quoted as representative of coronary insufficiency; they emphasized the generalized subendocardial ischemia and thought that shock was an important common denominator in this group. Others have referred to “patchy and segmental” myocardial necrosis in the subendocardial layer of the heart as the chief pathologic lesion. Miller et al.,\(^9\) have pointed out the greater incidence of atherosclerotic changes in the anterior descending coronary artery as being responsible for the frequent anterior location of the ischemic changes.
It is important to consider whether or not the cases here reported do indeed fall into the category of intermediate coronary artery syndrome, or whether, perhaps, they represent more specifically either patchy or uniform involvement of the subendocardial layer of the left ventricle. In this regard, it should be stated that every effort was made to select cases in whom there were sufficient consecutive electrocardiograms to show progressive and regressive changes over a ten-day to two-week period of time. These changes have been "vectorialized" in a previous communication.4

In considering the nature of the myocardial lesion, it is surprising to find out that only two of 19 transaminase studies were abnormal. It would seem strange that any significant amount of myocardium could undergo necrosis, particularly of the type described by Levine and Ford,4 without producing more of an elevation in the SGO-T level. However, in almost all cases, both the sedimentation rate and white count were elevated. These latter laboratory determinations appear, therefore, to reflect the ischemic process more adequately than does the level of SGO-T.

The recent therapeutic trend has been toward the uniform use of anticoagulants such as warfarin sodium (Coumadin) or bishydroxycoumarin (Dicumarol) routinely not only in the treatment of acute myocardial infarction, but also in all varieties of the intermediate coronary artery syndrome, and also in chronic angina pectoris. The striking improvement in life expectancy and the amelioration of anginal symptoms described by Borchgrevink4a in his well-controlled study of patients on intensive treatment with anticoagulants as compared with patients on moderate therapy is quite suggestive. Certainly, the high mortality figures for groups 2 and 3 suggest strongly that anticoagulation be considered mandatory in the management of the intermediate coronary syndrome. In point of fact, it seems only logical to advise long-term anticoagulant therapy routinely whenever a patient suffering from heart disease enters upon and passes through any period of acute cardiac pain.

In this connection, it seems almost superfluous to mention again the fact that it is almost impossible to make the differential diagnosis clinically between the intermediate coronary syndrome and the early stages of acute myocardial infarction. As Nichol17 has stated, "the distinction except in retrospect between the syndrome of acute coronary insufficiency and impending myocardial infarction is wholly artificial. Only time certifies the diagnosis." The failure of the SGO-T levels to rise, as noted above in the cases reported here, adds point to this comment.

The 17 patients in group 1 might be considered in a separate category. All were patients with an initial "coronary" episode. Most of them have been maintained on anticoagulants: all are fairly young and, thus far, the group has done well and appears to have a good prognosis. The possibility of improving life expectancy in this syndrome by anticoagulation has also been underscored by Proger.18

Statistically significant data cannot be derived from the group of patients presented in this paper because of the small number of patients. Nevertheless, the impression is gathered that these initial episodes in young people are at least as common as initial episodes of acute myocardial infarction. Our personal experience indicates that continuous anticoagulant therapy may well be the treatment of choice here in such cases.

**SUMMARY**

1. Forty-seven patients with the intermediate coronary artery syndrome have been etiologically divided into six subgroups, depending upon the presence or absence of heart disease, and the precipitating factors. Each subclassification varies in course, prognosis, therapy and significance.

2. Although etiologically diverse, certain basic electrocardiographic criteria define the entire group. There are two
patterns, both more frequent over the anterior and lateral surface of the heart; (a) the more frequent T wave inversion, and (b) the less frequent ST and J point depression with lowered T wave. Anterior ST and J point depression is usually accompanied by elevation of ST in AVR. Continuous cyclic progression and regression is the rule over a time period of ten days to two weeks.

3. The prognosis is impossible to ascertain at the start of the attack. It depends largely upon the underlying heart disease, and the SGO-T is almost always within the normal range.

4. Because of the difficulties in prognosis and the frequency of underlying serious heart disease, early and long-term anticoagulant therapy should be considered the therapy of choice at this time.

**Resumen**

1. Un grupo de 47 enfermos del síndrome coronario intermedio se dividió en seis subgrupos, dependiendo de la presencia o no de enfermedad cardiaca y de los factores precipitantes. Cada subclasificación varía, el pronóstico, tratamiento y significación.

2. Aunque son etiológicamente diversos, existe cierto criterio electrocardiográfico que define todo el grupo. Hay dos cuadros, ambos más frecuentes en las superficies anterior y lateral del corazón: (a) el que tiene más frecuentemente inversión de la onda T, y (b) el que tiene menos frecuente ST y el punto de la depresión J con onda T decrecida La ST anterior y el punto de depresión J generalmente se acompañan de elevación de ST y AVR. La regla es la progresión y regresión continuas en un período de tiempo de diez días a dos semanas.


4. Por la dificultad del pronóstico y la frecuencia con que hay en el fondo una enfermedad cardiaca debe considerarse el uso de terapéutica con anticoagulantes tempranamente.

**Resumé**

1. 47 malades ayant le syndrome coronarien intermédiaire ont été divisés suivant l'étiologie en 6 sous-groupes, basés sur la présence ou l'absence de cardiopathie et de facteurs déclenchant. Chaque sous-groupe varie dans son évolution, son pronostic sa thérapeutique, et sa signification.

2. Quoique leur étiologie soit diverse, certains critères électrocardiographiques de base définissent le groupe entier. Il y a deux types, l'un et l'autre plus fréquents sur la paroi antérieure et sur la paroi latérale du cœur: (a) le plus fréquemment inversion de l'onde T, et (b) le moins fréquent, la dépression de l'espace ST et du point J avec un abaissement de T. La dépression antérieure de ST et du point J est habituellement accompagnée par une élévation de ST en a VR. L'évolution puis la régression cyclique continue est la règle pendant une période de temps allant de 10 jours à 2 semaines.

3. Le pronostic est impossible à préciser au début des attaques coronariennes. Il dépend largement de la maladie cardiaque sous-jacente, et les transaminases SGO-T sont presque toujours dans les limites normales.

4. En raison de la difficulté du pronostic et de la fréquence de cardiopathies sérieuses sous-jacentes, le traitement anticoagulant précoce et à long terme doit être considéré comme le traitement de choix à l'époque présente.

**Zusammenfassung**


2. Obwohl ätiologisch voneinander verschieden, definieren bestimmte grundlegende elektrokardiographische Kriterien die gesamte Gruppe. Es sind zwei Typen, beide häufiger an der Vorder-und Seitenfläche des Herzens vorkommen (a) häufiger eine Umkehr der T-Zacke und (b) weniger häufig eine Senkung des ST-Stückes und des J-Punktes mit abgeflachter T-Zacke. Eine anteriore ST-Senkung ist gewöhnlich verbunden mit einem Anstieg des ST-Stückes im AVR. Eine fortlaufende zyklische Progression und Regression ist die Regel über einen Zeitabschnitt von 10 Tagen bis 2 Wochen.


4. Wegen der Schwierigkeiten in der Prognose und dem Umstand, daß häufig schwere Herzbe funde zugrunde liegen, muss man eine frühzeitige und langdauernde Anticoagulans-Behandlung in Erwägung ziehen, die zum gegenwärtigen Zeit punkt als Therapie der Wahl zu betrachten ist.
REFERENCES

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SURGICAL TREATMENT OF BRONCHOGENIC CARCINOMA

Of the 1097 patients with bronchogenic carcinoma in this study, 624 were subjected to operation, pneumonectomy having been performed in 263 patients and lobectomy or lesser resections in 66. Of the nonresectable neoplasms, 41 per cent were anaplastic, while of the resected neoplasms 21 per cent were anaplastic. The 30-day mortality rate in the nonresected group was 15 per cent. The mortality rate was 11 per cent in the pneumonectomy group and 21 per cent in the group treated by lobectomy or lesser resections. In 12 per cent of the patients treated by pneumonectomy, arrhythmia developed postoperatively, all converting to normal sinus rhythm. The incidence for lobectomy was 4.5 per cent and in those undergoing exploration only, it was 1.5 per cent. Cor pulmonale occurred infrequently, even though preoperative pulmonary function tests were not performed routinely. There were seven instances of postoperative empyemas in the pneumonectomy group and one in the lobectomy group. The five-year survival rate following pneumonectomy was 22 per cent, and 36 per cent of the survivors had lymph node metastases in the resected specimen. The five-year survival rate after a lobectomy was 23 per cent. Only three patients in whom exploration only was carried out lived for more than two years.


SEVERE HISTOPLASMOSIS

A total of 194 patients with severe histoplasmosis who were treated with amphotericin B are presented. These consist of 172 cases of the chronic pulmonary type and 22 cases of the disseminated type. All cases were proved by culture or pathologic demonstration of the organism. Although not strictly comparable, the results in the treated patients are compared with 115 cases of untreated histoplasmosis, most of which were the subject of a previous report. With disseminated cases, the drug is life-saving, as illustrated by an 83 per cent mortality rate among the untreated patients, compared with a 28 per cent mortality rate among those who received amphotericin B.

In chronic pulmonary histoplasmosis, the results are closely related to the total dosage of amphotericin B administered. Smaller amounts (up to 25 mg./kg. body weight) appear to decrease the mortality rate and slow progression of the disease. The disease, however, tends to progress again after cessation of therapy, so that progression is about as great after three years as it is in the untreated group. Adequate treatment (more than 25 mg./kg. body weight) decreases progression of the disease, increases improvement, and lowers the mortality rate. At the end of four years of followup, the crude mortality rate among the adequately treated group is only one-half of that of the untreated group.