Non-Q wave myocardial infarctions, also known as non-transmural myocardial infarctions or subendocardial myocardial infarctions, have been managed as "mild" coronary events in the past. Substantial evidence now requires modification of this approach. Because of their tendency to be associated with modest cardiac enzyme level elevations, non-Q wave infarcts often result in a favorable early or inhospital prognosis. However, their late complications include recurrent angina, transmural myocardial infarction, and sudden death. Previous myocardial infarction with residual myocardium "at risk" from recurrent ischemia probably bears responsibility for these late complications. Earlier identification of patients at risk and appropriate interventions may improve the long-term prognosis after nontransmural infarcts.

Viewpoints concerning the course and prognosis of non-Q wave myocardial infarction (NQMI) have evolved considerably in the last two decades. The NQMI or subendocardial myocardial infarction (SEMI) was once thought to be a relatively benign condition with an uncomplicated course and good prognosis.1 This idea has since been challenged. Two recent editorials2,3 emphasize the current controversy and necessity to review this clinical problem.

Subendocardial damage cannot be reliably identified by acute ECG changes.4,5 A direct correlation between serum level of myocardial enzyme rise and early mortality exists, and NQMI patients are usually associated with a lower peak enzyme elevation.6

Long-term prognosis after NQMI has been difficult to predict. Recurrent angina, subsequent transmural myocardial infarction (TMI), and sudden death occur with considerable frequency following NQMI.7-10 The long-term prognosis may be less favorable than following a TMI, particularly in the presence of previous infarction.11-19 These facts ought to influence the diagnostic and therapeutic management of patients after NQMI.

**PATHOPHYSIOLOGY**

As many as 60 percent of myocardial infarctions (MI) occur in the subendocardial region.20 Anatomically, the blood supply to the deep myocardial layers is adequate. A histopathologic study in 196620 using radiopaque media demonstrated that tree-like arterial branching in the subendocardial zone continues in the general line of the main artery and that the area supplied by each vessel was fairly small. However, the coronary circulation is unique because, in addition to its intrinsic vascular resistance, there is a significant superimposed extravascular resistance factor. The extravascular factor occurs during systolic compression by the contracting ventricular myocardium, producing a transmural gradient.21-23 This gradient most affects the subendocardium. In fact, coronary flow normally ceases in the left ventricular (LV) myocardium during systole. When coronary flow is maintained in a "normal" range, the LV endocardium is adequately perfused because of adaptations in coronary flow made during diastole. However, when the coronary perfusion pressure decreases or the systolic LV pressure increases, the systolic compressive effect outweighs the compensatory mechanism, and the perfusion of the subendocardium is compromised.24 As a result, the subendocardium may be rendered relatively ischemic.

Other factors which increase the susceptibility of the subendocardium to ischemic injury include a lower coronary vascular tone, higher metabolic demands, and a diminished reserve for vasodilatation.25 Inadequate "autoregulation" has been postulated as a reason for this propensity for ischemia.26 These factors partially explain the clinical occurrence of NQMI in the absence of occlusive phenomenon such as with carbon
monoxide toxicity, sickle cell trait, or hypotension. Although patients with NQMI demonstrate varying degrees of atherosclerosis, thrombotic occlusion occurs less frequently than in TMI. However, patients suffering NTMI may have significant coronary artery disease. Madigan et al performed coronary angiography in 50 patients within ten days of a NTMI and showed that all patients had at least one vessel significantly narrowed, multivessel disease occurring in 60 percent.

**Clinical Diagnosis**

In 1978, accepted diagnostic criteria for a NTMI included the following:
1. Chest pain typical of myocardial ischemia lasting greater than 15 minutes.
2. ST segment depression and/or T wave inversion persisting for 48 hours.
3. Elevation of cardiac enzyme levels.

However, by 1982 the definitions reflected growing controversy. "Nontransmural infarction" is said to be present when abnormal ST-T waves appear, but the QRS complex remains normal. There is no uniform agreement regarding the electrocardiographic criteria required to diagnose subendocardial infarction.

The ECG changes of subendocardial infarction are varied and inconsistent. Absence of Q waves is attributed to the fact that the inner half of the myocardium does not contribute to the formation of a QRS complex. The nonspecific findings of ST segment and T wave abnormalities have been ascribed to concurrent subepicardial ischemia overlying the infarct area, rather than necrosis occurring in the subendocardium.

Many circumstances occur in which the ECG findings are misleading. In these situations, the criteria for NQMI are fulfilled, but at autopsy the patient is found to have sustained an acute TMI. Absence of a new Q wave in such cases may be the result of QRS alterations from previous infarctions or an infarction in an electrically silent area. This latter observation particularly holds in cases of inferior or true posterior infarcts and occasionally in cases of TMI of a small size. On the other hand, transient Q waves may occur with NQMI. The presence of intraventricular conduction defects or ventricular hypertrophy further obscures the criteria. Additionally, isolated ST and T wave changes have appeared in patients who were later found at post mortem to have both recent and old TMI. A balancing of myocardial forces opposite each other may also render the ECG suggestive of a NQMI in the face of multiple previous TMI. In patients with coronary artery disease, the longest QT intervals occur during the acute MI period, especially in cases of subendocardial infarction.

Cardiac enzymes play an important role in the diagnosis of NQMI. Most investigators agree that the rise in serum enzyme activity is grossly proportional to the mass of the infarcted tissue. Consistent with this view, TMI tend to be associated with a greater rise in enzyme activity when compared to NQMI. This fact may have fostered the earlier belief that a NQMI represented a "mild coronary." The importance of the rate of enzyme release has been shown by Shell et al, who observed that CK-MB isoenzyme appears earlier in the serum of patients with a NTMI than with a TMI. If reproducible, such a finding might permit earlier identification of those patients presenting with a nondiagnostic ECG and new myocardial necrosis. Flow dynamics variably influence interpretation of serum cardiac enzyme levels. The flow rate both to and from the necrotic area is a major determinant of the rate of enzyme appearance in the peripheral circulation. Whereas TMI is characterized by complete coronary artery occlusion and cessation of flow to the ischemic zones, NQMI are generally associated with persistence of blood flow and early reperfusion of the infarct, a possible explanation for the observation of Shell and his colleagues.

Other potential diagnostic studies for identifying NQMI include myocardial scintigraphy, and precordial ST mapping. Technetium 99m stannous pyrophosphate scintigrams indicate NQMI either by increased uptake in a faintly but diffusely positive pattern or in a well-localized strongly positive one. Willerson and his co-workers confirmed these diagnostic patterns of NQMI by isoenzyme values in the setting of prolonged chest pain and nonspecific electrocardiographic changes. ST-segment mapping, reflecting the sum of ST-segment elevation in MI, correlates with the degree of cardiac isoenzyme rise.

**Early Prognosis**

In 1967, Lown et al emphasized the distinction between benign and complicated infarcts. He suggested that those patients without complications be managed with an abbreviated hospitalization and noted that, although the ECG was not generally considered helpful in predicting the outcome following infarction, it tended to return toward normal in uncomplicated infarcts. He then postulated that patients with infarctions associated with isolated T wave abnormalities were those with a "mild coronary."

Some current evidence suggests that the short-term prognosis of a NTMI is similar or less favorable than that of TMI (Table 1). The early or inhospital prognosis following an acute myocardial infarction cannot be predicted solely on the basis of the ECG diagnosis of TMI versus a NQMI. Abbott and Scheinman and Madias et al demonstrated indistinguishable inhospital courses for both types of infarctions. In these
Table 1—Comparison of Mortality After Nontransmural and Transmural Myocardial Infarction

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No. of Subjects</th>
<th>TMI</th>
<th>NTMI</th>
<th>Duration of Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scheinman and Abbott</td>
<td>1973</td>
<td>230</td>
<td>19</td>
<td>37</td>
<td>In hospital</td>
</tr>
<tr>
<td>Madias et al'</td>
<td>1974</td>
<td>104</td>
<td>9.8</td>
<td>9.3</td>
<td>In hospital</td>
</tr>
<tr>
<td>Rigo et al'</td>
<td>1975</td>
<td>160</td>
<td>22</td>
<td>13</td>
<td>In hospital</td>
</tr>
<tr>
<td>Cannom et al'</td>
<td>1976</td>
<td>188</td>
<td>16.8</td>
<td>7.5</td>
<td>In hospital</td>
</tr>
<tr>
<td>Madigan et al'</td>
<td>1976</td>
<td>50</td>
<td>2</td>
<td>4</td>
<td>In hospital</td>
</tr>
<tr>
<td>Szklar et al'</td>
<td>1978</td>
<td>1236</td>
<td>30.2</td>
<td>13.3</td>
<td>In hospital</td>
</tr>
<tr>
<td>Mahony et al'</td>
<td>1980</td>
<td>635</td>
<td>8*</td>
<td>0*</td>
<td>In hospital</td>
</tr>
<tr>
<td>Thanavaro et al'</td>
<td>1980</td>
<td>745</td>
<td>11</td>
<td>3</td>
<td>In hospital</td>
</tr>
<tr>
<td>Hutter et al'</td>
<td>1981</td>
<td>196</td>
<td>20</td>
<td>9</td>
<td>In hospital</td>
</tr>
<tr>
<td>Marmor et al'</td>
<td>1981</td>
<td>200</td>
<td>15</td>
<td>12</td>
<td>In hospital</td>
</tr>
<tr>
<td>Coll et al'</td>
<td>1983</td>
<td>458</td>
<td>6</td>
<td>0*</td>
<td>In hospital</td>
</tr>
</tbody>
</table>

*Normal initial QRS.  
†Abnormal initial QRS.

studies, mortality in patients with a premortem diagnosis of NTMI correlated with previous myocardial infarction by autopsy, history, or histologic evidence of a recent transmural infarction.

The peak serum level of myocardial enzyme concentration also correlates with early prognosis following an infarction. Abbott and Scheinman's data suggested this relationship in their 1973 study. Geltman et al in 1974 measured the level of enzyme rise as the infarct size index (CPK/m2) and found higher values to be predictive of the occurrence of ventricular ectopy and mortality. However, no significant difference in the incidence of arrhythmias or early mortality appeared when comparing TMI and NTMI.

Eliminating the variable of previous myocardial damage, Thanavaro et al studied patients suffering their first cardiac event. In this group, patients with NTMI tended to have a better early prognosis. The observed correlation was attributed to a lower peak enzyme rise.

Patients with an ECG diagnosis of a NTMI and a normal initial QRS complex may represent those without previous myocardial damage and therefore a more favorable early prognosis. Rigo et al studied 111 patients with TMI and 49 patients with NTMI. They identified a group of patients with a NTMI and a normal presenting QRS complex as a particularly favorable finding with respect to inhospital mortality. None of those patients presenting with a normal QRS died during hospitalization, compared to 27 percent of patients with a NTMI and an abnormal initial QRS, and 22 percent of patients having sustained a TMI. This study added hemodynamic evaluation to the comparison of prognoses after NTMI and TMI. No significant difference in left ventricular end-diastolic pressure, ejection fraction, or stroke work index was found between NTMI and TMI. Mahony and her colleagues confirmed the significance of a previous infarction in terms of mortality by examining the initial QRS complex. Ninety-six percent of patients with an initially normal QRS were free of complications during the post-MI period compared with only 46 percent in the group with an abnormal initial QRS, regardless of whether the MI was nontransmural or transmural.

**POSTHOSPITAL PROGNOSIS**

Patients with NQMI and prior infarction have a greater likelihood of subsequent cardiac events compared with TMI patients. Marmor et al examined the incidence of early recurrent infarction in a study of 200 consecutive patients with acute myocardial infarction and documented the similar inhospital mortalities of TMI and NTMI (15 percent and 12 percent, respectively). In addition, 43 percent of patients with NTMI exhibited early recurrent infarction compared with only 8 percent of those with an initial TMI. Rigo et al demonstrated a converging late mortality of all infarct patients as early as 20.3 months following new cardiac necrosis.

Significant morbidity occurs after NQMI. Madigan and co-workers' prospective study in 1976 followed patients with NTMI for a mean period of 10.6 months during which time 30 percent of these patients developed stable angina and 46 percent noted unstable angina. Of the medically treated patients, 21 percent suffered an acute TMI during the follow-up period. Similar data demonstrating a greater morbidity and mortality following NTMI vs TMI was published by Cannon et al in 1978. After a mean follow-up period of 36 months, patients with NTMI had an incidence of sudden death after discharge of 33 percent, compared to 15 percent after TMI. Furthermore, recurrent or persistent class 2 angina was more frequent after NTMI (61 percent vs 36 percent).

Studies continue to support the concept of significant long-term morbidity following a NTMI. Szklar and his colleagues followed the post infarction course for up to ten years in 853 patients with a TMI and 283 patients with a NTMI. The inhospital outlook appeared better for NTMI patients. Fatality rates were adjusted for 17 variables that may have altered inhospital mortality, including past medical history and age. The ratio between the inhospital case-fatality rate in patients with TMI and those with NTMI was 1.7 (p<0.01). However, an adjusted risk ratio at three
years, also derived from adjusted case-fatality rates, was 0.96 (not statistically significant), underscoring similarity of long-term NTMI and TMI courses.

Confounding simultaneous variables detracted from many of the earlier studies. To minimize this problem, Hutter et al. examined 67 patients after NTMI and compared the acute and long-term mortality with groups of patients with anterior TMI and inferior TMI computer-matched for age, sex, and the presence or absence of prior myocardial infarction and congestive heart failure. While in the hospital, the patients with NTMI had significantly less congestive heart failure (25 percent vs. 55 percent) and fewer intraventricular conduction defects (6 percent vs. 10 percent) than did those with anterior myocardial infarction. The in-hospital mortality rate for NTMI was 9 percent; for anterior TMI, 20 percent; and for inferior TMI, 19 percent. At three months, these rates were 14 percent, 29 percent, and 27 percent, respectively. During the mean follow-up period of 28.6 months, angina occurred frequently in all three groups. However, the incidence of subsequent infarction was higher at nine months in patients with NTMI (21 percent) than those with anterior TMI (3 percent) or inferior TMI (2 percent). By 54 months, these figures were 57 percent vs. 12 percent and 22 percent, respectively. The location of these second infarcts tended to be the same as the initial nontransmural infarct. This study confirms earlier data supporting the fact that patients with a NQMI have more favorable early mortality but an overall late mortality no different from those with a transmural infarction. The frequent occurrence of subsequent myocardial infarction supports the hypothesis that patients with non-Q wave MI have additional myocardium at risk. Based on this conclusion, Hutter et al. suggested that early angiography may be indicated in these patients.

In contrast to the work of Hutter et al., Coll and his colleagues recently published their prospective experience with first infarction in 458 consecutive patients. "Nontransmural" MI was present in 6 percent of their patients (defined only by absent Q waves and peak enzymes twice normal). Their clinical findings tended to parallel those of most earlier studies (Table I). However, the survival rates for NTMI and TMI, while parallel, indicated rather a very benign Coronary Care Unit course and favorable Kaplan-Maier four-year survival probably for both groups. These observations contrast sharply with the findings of Hutter et al., who noted much higher mortality rates for both groups, particularly at the 54 month follow-up. The difference between these two studies may derive in part from the fact that Hutter and his colleagues studied many patients in whom the index infarct was not their first (approximately 45 percent of all cases studied, apparently normalized in the analysis) and included both men and women. These facts may also account for a major difference in re-infarction rates between the two studies, again strongly supporting a benign course in the 24 patients with initial NTMI followed by Coll (no nonfatal MIs, 94 percent survival at four years) compared with Hutter's subjects (57 percent subsequent transmural MI and with a 48 percent survival at 54 months).

**Conclusion**

The following points warrant emphasis concerning NQMI: (1) the subendocardium is the region that is most susceptible to ischemic insult; (2) the ECG changes in the setting of an acute infarction may not be reliable indicators of transmural vs. nontransmural involvement; (3) early prognosis generally correlates with acute level of cardiac enzyme rise; and, (4) previous documented myocardial infarction is a major determinant of poor prognosis following NQMI.

Non-Q wave infarctions, once considered relatively benign, now appear to be more ominous in terms of their prognostic implications. Because the diagnosis of NQMI is imprecise, recognition of the potential untoward consequences in individual patients remains obscure. Emphasis must be brought to bear on assessing residual ischemic myocardium. Recognition of ongoing ischemia would allow for earlier therapeutic intervention. Post infarction angina and ST-T changes on the resting electrocardiogram are easily obtained valuable sources of information about post-infarction ischemia. The NQMI's with lower peak enzyme elevations suggest that much more myocardium may remain at risk. Electrocardiographic stress testing, exercise radionuclide ventriculography, and radionuclide perfusion scintigraphy are newer, more accurate means of quantifying reversible regional and global ischemia after NQMI. However, the true value of early aggressive surgical or other invasive intervention following NQMI, while hypothetically appealing in order to preserve myocardium "at risk," requires testing by prospective trials.

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