Transient Reduction of Regional Myocardial Perfusion During Angina at Rest with ST-segment Depression or Normalization of Negative T Waves

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SUMMARY Previous studies have shown localized thallium-201 ($^{201}$Tl) defects during resting anginal episodes with ST-segment elevation. In this report, findings of $^{201}$Tl during spontaneous angina in 14 patients with ST-segment depression and seven with normalization of negative T waves are reported. One millicurie of $^{201}$Tl was injected i.v. during the ischemic episode and scintigrams were taken within 5–10 minutes and after 4 hours. One week later a new injection of $^{201}$Tl in a basal state provided control scintigrams.

Early scintigrams showed a regional reduction of $^{201}$Tl uptake in all patients with normalization of negative T waves and a close correspondence between the location of the defect and the site of the electrocardiographic changes. Conversely, scintigrams in patients with ST-segment depression showed a lesser relatively milder reduction of $^{201}$Tl activity in 12 and no defect in two. In these patients the defect, when present, was localized in eight and diffuse in four patients. The site of the $^{201}$Tl defect did not always correspond to the location of ST-segment depression. Overall, 4-hour scintigrams were similar to those taken in the absence of symptoms.

Heart rate and systolic blood pressure measured at the onset of the electrocardiographic changes were not significantly different from asymptomatic periods but were significantly lower than during effort-induced angina, so the defects should be related to a reduction of myocardial perfusion, as documented in variant angina, rather than to an inadequate increase of coronary blood flow.

From this study, angina at rest with normalization of negative T waves appears related to localized uniform reduction of myocardial perfusion, while angina with ST-segment depression is associated with a less uniform reduction of perfusion, probably located in the subendocardial layers, in the presence of severe coronary lesions.

WE DEMONSTRATED in previous studies a transient transmural reduction in regional myocardial blood flow during attacks of variant angina. Similar findings using the same or different techniques have appeared as case reports. In the present study we investigated whether a reduction in regional perfusion could also cause angina at rest, characterized by ST-segment depression or by normalization of negative T waves (NTW).

This hypothesis was suggested by three observations: (1) Attacks of angina at rest characterized by ST-segment depression or by NTW are not caused by an increase in the hemodynamic determinants of myocardial oxygen consumption. (2) Coronary vaso- spasms has been documented angiographically during anginal episodes with ST-segment depression and NTW. (3) Spontaneous attacks characterized by ST-segment elevation, depression or NTW may occur in the same patient with documented vasospastic angina.

The changes in the regional myocardial perfusion and the location of ischemic regions were evaluated by scintigraphy using thallium-201 ($^{201}$Tl).

Materials and Methods

Patients

We studied 21 patients, 34–65 years old (average age 53 years) admitted to our coronary care unit (CCU) because of frequent attacks of angina at rest. Thirteen of the patients also claimed exertional angina from 1–10 years before admission. Seven had a documented old myocardial infarction. Patients with signs of pulmonary congestion or recent myocardial infarction (within 2 months) were excluded.

At the time of admission, all patients were prophylactically treated with long-acting nitrates (isosorhde dinitrate, 5–10 mg every 2 hours). All medications but nitroglycerin were omitted the day of the study. Informed, written consent was obtained from all of the patients. Their physical and clinical characteristics are described in table 1.

Special Investigations

Eighteen patients performed an exercise test on a sitting bicycle; three did not perform the test because of severe and prolonged anginal attacks at rest. The exercise ECG was interpreted according to the criteria of the American Heart Association. All the exercise ECGs were analyzed by two cardiologists without knowledge of the angiographic or scintigraphic data.
The electrocardiographic changes during the effort test and the pressure-rate product at the time of effort-induced electrocardiographic alteration and during angina at rest are described in Table 1. During the attacks of spontaneous angina, five patients always showed negative T waves (NTW), eight ST-segment depression and the other eight different electrocardiographic patterns (ST-segment depression, elevation or NTW).

Twenty patients had coronary arteriography by Judkins technique, of these, eight showed three-vessel disease, seven two-vessel disease, four one-vessel disease and one normal coronary angiogram. In 11 patients coronary spasm was documented by angiography: spasm was spontaneous in six and after i.v. ergonovine maleate injection in the other five. Ergonovine test had been previously performed in the CCU using the multisteps injection (0.025, 0.05, 0.1, 0.2, 0.4 mg), which allowed us to determine the minimal effective dose.

In all cases the electrocardiographic changes during spasm were similar to those during the spontaneous ischemic episodes documented in the CCU. In all cases of ergonovine-induced spasm and in three cases of spontaneous spasm, the catheter was advanced in the coronary orifice after the onset of electrocardiographic changes. In the remaining three instances, the catheter tip was in the main coronary artery when spasm developed but in a vascular segment far from the catheter tip.

Table 1. Physical, Clinical, and Electrocardiographic Characteristics of the Patients

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (years)</th>
<th>History</th>
<th>Previous myocardial infarction (Q$\text{v}$)</th>
<th>Exercise testing ECG changes</th>
<th>PRP effort ($\times$ 100)</th>
<th>PRP Rest angina ($\times$ 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>53</td>
<td>RA</td>
<td>$V_1-V_2$</td>
<td>NTW $V_1-V_4$</td>
<td>23.8</td>
<td>12.5</td>
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<td>$V_1-V_2$</td>
<td>NTW $V_1-V_4$</td>
<td>23.2</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>54</td>
<td>RA + EA</td>
<td>$V_1-V_2$</td>
<td></td>
<td></td>
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<tr>
<td>4</td>
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<td>NTW $V_1-V_2$</td>
<td>23.3</td>
<td>9.5</td>
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<td>11.5</td>
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<tr>
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<tr>
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<td>11.6</td>
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<td>12</td>
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<tr>
<td>11</td>
<td>60</td>
<td>RA + EA</td>
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<td>ST $V_3-V_5$</td>
<td>14.5</td>
<td>13.5</td>
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<td>12</td>
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<td>II–III–a$V_p$</td>
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<td>57</td>
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<tr>
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<td>RA</td>
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<tr>
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<td>RA + EA</td>
<td></td>
<td>ST $V_6-V_6$</td>
<td>19.5</td>
<td>14.2</td>
</tr>
</tbody>
</table>

Abbreviations: NTW = normalization of negative T waves; ST = ischemic ST-segment depression; PRP = pressure-rate product; RA = rest angina; EA = effort angina.

Experimental Protocol

The patients were continuously monitored in the CCU by the lead with the most obvious changes during the ischemic episodes. Arterial blood pressure was measured by a cuff manometer every 30 minutes when awake, at the appearance of ECG signs of ischemia and every 2 minutes during the attack and recovery. Heart rate was measured from the ECG strip chart of the monitored lead, taken at the beginning of ST-T changes. In the cases in whom angina was induced by ergonovine injection, arterial blood pressure and 12-lead ECG were taken every minute from the beginning of the procedure. One millicurie of thallium-201 (supplied by Byk-Mallinkrodt) was injected through a catheter already in place at the bedside in the CCU during the attacks that were spontaneous in 13 and induced by ergonovine maleate in eight. If pain or ST-segment changes did not disappear spontaneously within about 5 minutes, nitroglycerin (0.6 mg) was given sublingually. A 12-lead ECG was continuously...
recorded until the time of the first scintigram that was performed in the left anterior oblique (LAO) 45° projection within 5–10 minutes. Additional scintigrams in the anterior and lateral projections were taken in rapid sequence and also 4 hours later. A week later, a new injection of the same activity of ²⁰¹Tl, performed in basal conditions, provided another set of control scintigrams in addition to those already obtained 4 hours after the anginal attacks. Throughout each of the two studies performed in the same patients (in basal conditions and during pain), particular care was taken that the orientation between the heart and the gamma camera did not change.

Myocardial Perfusion Imaging

Myocardial scintigrams were obtained using a Jumbo Toshiba gamma camera with a high-sensitivity collimator on life-size 35 × 35 cm film. The light-spot intensity was set to use the whole dynamic range of the film and to avoid saturation on the maximum. The optimal setting has been verified by a densitometer. For every projection, 100 thousand counts were collected in a region of interest including the entire heart, with the window of the gamma camera set at 72–88 keV to include the low-energy peak of ²⁰¹Tl.

Subjective Analysis

The myocardial scintigrams were interpreted by three experienced observers without knowledge of the clinical data. A complete agreement of the scintigraphic interpretation was obtained in all seven cases with NTW and in the 86% (12 of 14) of the cases with ST-segment depression. When disagreement occurred, the agreement of two observers was accepted. A scintigram was classified as normal if it showed homogenous distribution of the tracer in the left ventricle, borderline if it showed small areas of diminished activity, and abnormal if it showed evident and large areas of diminished activity.

Quantitative Analysis

Direct computer analysis of the scintigrams was not available, so a densitometric computerized optical scanner (Cristal Structure) was used for the quantitative analysis of the scintigraphic films. The reliability and reproducibility of the technique has been reported. The scintigraphic images obtained in the LAO projection in 11 cases (three with NTW and eight with ST-segment depression) were analyzed by the den-
Figure 1. Myocardial thallium-201 scintigrams in left anterior oblique 45° projection with corresponding ECG obtained in absence of symptoms (left) and during spontaneous anginal episode (right) characterized by ST-segment depression in the left precordial (V₄-V₆) and inferior leads. A localized reduction of tracer uptake in the anteroseptal wall is evident in the scintigram obtained during the attack.

Results

Values of heart rate and blood pressure, measured upon the beginning of ST-T changes, were significantly lower than those at the onset of effort-induced ischemia (table 1).

Pain always appeared late, 20–250 seconds after the onset of the ECG changes. Blood pressure and heart rate increased in 15 patients after the appearance of pain. In patient 17, 201TI was injected during an asymptomatic ischemic attack with electrocardiographic changes similar to those during the symptomatic episodes.

In the eight patients in whom ergonovine maleate was injected to induce the attack, the ECG changes were consistently similar to those during spontaneous attacks.

The attacks during which 201TI was injected showed ST-segment depression in 14 instances (seven spontaneous and seven ergonovine-induced) and normalization of previously negative T wave in seven (six spontaneous and one ergonovine-induced).

A complete agreement in the detection and loca-
ST-segment Depression During the Attacks

ST-segment depression was recorded in the precordial leads in all 14 patients and also in the diaphragmatic leads in two patients.

The basal scintigram was normal in 12, while in the other two (patients 11 and 12), it showed an area of decreased activity corresponding to the location of an old infarction.

During ischemia in eight patients myocardial scintigrams showed a reduction of tracer activity localized in only one wall of the heart (fig. 1). In four patients the reduction of tracer activity was diffuse to more than one segment (figs. 2 and 3). In patients 10 and 16, scintigrams failed to show areas of decreased 201TI activity, despite clear signs of ischemia at the ECG. In patient 12, a transient defect of perfusion appeared in the anterolateral wall, while a persistent deficit was observed in the inferior wall. Patient 11 had both transient and persistent defects of perfusion in the anterior wall.

The densitometric analysis showed, in seven of eight cases, a regional reduction of 201TI activity of 23–56% (average reduction 35%) relative to control. In patient 16 also, the computerized image did not allow detection of cold areas (fig. 4).

The location and extent of the defects did not always correspond to the electrocardiographic site of ischemia, as shown in patients 14 and 21, in whom the defect was observed in a different wall, and in patients 8, 9 and 15, in whom only a partial correspondence was present (table 2).

In patients in whom the spasm was documented angiographically, a similar poor correspondence between ECG and location of the spasm appeared. Conversely, the location of the spasm was in agreement with the location of the major scintigraphic defects (table 2).
Normalization of Negative T Waves

Seven patients showed NTW during the anginal attacks in which the scintigraphy was performed. In four, the normalization involved the precordial leads. Their tracings obtained in absence of symptoms showed an anteroseptal infarction with V1-V2 Q waves and deep negative T waves from V1-V4. All patients had basal scintigrams that showed a small deficit of tracer uptake in the high septal wall. Myocardial scintigrams performed during the attacks showed a massive reduction of 201Tl activity in the side corresponding to the location of T-wave changes (fig. 5).

Three patients showed NTW in the inferior leads. The alteration was associated with a marked ST-segment depression in the precordial leads (from V5-V6). In patient 7, the basal ECG showed an old septal infarction, tall positive T waves in the precordial leads and negative T waves in the inferior leads. The control scintigrams showed a slight reduction of 201Tl activity in the septal wall. In patients 5 and 6, the basal ECG showed negative T waves in the inferior leads, and the basal scintigrams appeared normal.

During anginal attacks at rest, scintigrams showed an apparently transmural defect that was localized at the inferior wall in patient 6 and involved both the inferior and the posterolateral walls in patients 5 and 7 (fig. 6).

The densitometric analysis, performed in scintigrams of three patients with NTW (nos. 1-3), demonstrated that the reduction of 201Tl activity was more severe than that observed in scintigrams of patients with ST-segment depression, the percent reduction being 46%, 69%, and 50%.

The defects were always located at the wall of the heart corresponding to the site of the T-wave changes. Thus, the most obvious changes of ECG in these
Figure 4. Analog (left) and digital (right) images obtained after the densitometric analysis. The scintigram was obtained in patient 16 during an anginal attack at rest characterized by ST-segment depression in the precordial leads (V2-V6). Despite obvious ECG signs of ischemia, subjective and objective analysis do not show areas of decreased thallium-201 activity.

Figure 5. Myocardial thallium-201 scintigrams in the left anterior oblique 45° projection with corresponding ECG in absence of symptoms (left) and during a spontaneous attack (right). Coronary arteriography performed during a similar episode revealed a severe diffuse narrowing with delayed filling and runoff of the left anterior descending artery. There is a localized anteroseptal myocardial infarction of recent onset and negative T waves in the precordial leads (left). Pseudonormalization of the T waves is associated with a severe anteroseptal reduction of tracer uptake in the scintigram (right).
patients, the ST-segment depression, could be interpreted, in light of the behavior of the regional perfusion, like reciprocal signs of ischemia.

In six patients in whom spasm was documented angiographically during an anginal attack with ECG changes similar to those observed during the scintigraphic study, the site of the spasm always corresponded to the location of the T-wave changes and the perfusion defect.

**Discussion**

**Thallium-201 Uptake and Myocardial Blood Flow**

Thallium-201 myocardial scintigraphy, performed in patients with anginal attacks at rest characterized by ST-segment depression or NTW, has demonstrated the presence of an obvious deficit of uptake.

Theoretically, these deficits may result from either inadequate increase of regional myocardial perfusion during increase of metabolic demand or an actual reduction of flow, as in variant angina.

In these patients, the increases in heart rate and blood pressure did not precede the attacks, and the pressure-rate product recorded at the onset of the ECG changes was much smaller than that achieved during the stress test. Thus, one could assume that the large defects during angina at rest were caused by an actual transient reduction of regional perfusion rather than by increase in flow limited to the healthy areas.

This conclusion is supported by two considerations. First, over an intermediate range of myocardial blood flow (100–250 ml/min/100 g myocardium), a 40% difference in $^{201}$Tl uptake between two areas, which would result in a detectable difference in tracer activity, should be associated with a 100% difference in flow between ischemic and nonischemic regions. These relevant differences in flow, if related to an increased flow to the healthy area, cannot occur without obvious, large increases of blood pressure and heart

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**Figure 6.** Myocardial thallium-201 scintigrams in the left anterior oblique 45° projection with corresponding ECG obtained in absence of symptoms (left) and during a spontaneous anginal attack (right) characterized by normalization of negative T wave in the inferior leads and marked ST-segment depression in the precordial leads. Coronary arteriography performed during a similar episode revealed a spasm completely occluding the circumflex artery, proximally to an organic stenosis. A marked deficit of tracer uptake in the inferior and posterolateral walls is evident in the scintigrams obtained during the attack.
rate. Second, the evidence that defects are better detected in scintigrams performed during anginal attacks at rest than in those in the same patient during effort angina, in the presence of similar electrocardiographic changes, supports the theoretical considerations previously discussed: Regional differences of $^{201}$TI uptake are better appreciated when regional blood flow shows an absolute reduction rather than when it shows an inadequate increase relative to surrounding areas.

**Regional Myocardial Perfusion and Electrocardiogram**

As in previous studies, we demonstrated that resting angina with ST-segment elevation, the variant form of angina, is not preceded by an increased myocardial metabolic demand and is characterized by a marked reduction of regional perfusion, it is reasonable to infer that angina at rest, independent from the electrocardiographic pattern (ST-segment elevation, depression or NTW) is usually caused by an absolute reduction of blood supply.

A more convincing explanation of this acute primary reduction of myocardial perfusion is coronary spasm, which is a frequent observation in coronary arteriograms performed during angina. In the present study coronary vasospasm was documented in all 11 instances when the contrast medium was injected during episodes of transient electrocardiographic changes identical to those observed during $^{201}$TI injection.

During episodes of angina characterized by NTW, the reduction in perfusion appears to be similar to that observed in a study in patients with variant angina.

The NTW must actually be regarded as a sign of severe ischemia, superimposed on previous injury or infarction, involving the whole thickness of the myocardial wall underlying the leads in which the NTW is observed.

In six patients with episodes characterized by NTW, the angiographic observation of a coronary spasm of a large branch without distal filling accounts for the marked reduction of $^{201}$TI uptake in these circumstances.

Conversely, the angiographic evidence of a good collaterals circulation or of an incomplete spasm in the patients with attacks characterized by ST-segment depression supports the hypothesis that in these cases, nontransmural ischemia is present, probably located in the subendocardial layers. This hypothesis is compatible with the less obvious, less well localized reduction in $^{201}$TI activity during ST-segment depression compared with that observed during episodes with ST-segment elevation or NTW.

The diffuse distribution of ischemia and the poor resolution of the scintigraphic technique, resulting from superposition of normally perfused regions, do not always allow a precise localization of the site of ischemia, so the reduction of regional perfusion can be underestimated. This might explain the apparently normal scintigrams observed in two patients despite clear signs of ischemia on the ECG.

A final consideration on the meaning of ST-segment depression can be made. NTWs were accompanied by ST-segment depression in opposite leads. The latter alteration was apparently the most striking change; however, regional myocardial perfusion studies showed that the perfusion defect was spatially correlated to the site of NTW rather than to the site of ST-segment depression.

Thus, the major site of ischemia may be overlooked on the ECG as the alteration in the corresponding leads may be limited to the NTW, while apparently more severe changes may be present in other leads. Many physiologic, pathologic, clinical and pharmacologic variables, as reported by Holland and Brooks, modify the TQ and the ST segment during ischemia and infarction. The present study clearly shows that sensitivity of ST-segment depression in angina at rest to predict the site and extent of major reduction of coronary blood flow is limited.

**Acknowledgment**

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