Angiographic and Hemodynamic Determinants of Myocardial Ischemia During Adenosine Thallium-201 Scintigraphy in Coronary Artery Disease

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Background. Myocardial ischemia attributed to coronary steal may occur in some patients receiving pharmacological coronary vasodilation. ECG ST-segment depression is a marker of myocardial ischemia in these patients, but the factors determining the presence or absence of ischemia are not well known.

Methods and Results. To examine the angiographic, hemodynamic, and scintigraphic determinants of adenosine-induced ischemic ST-segment depression in patients with coronary artery disease, we studied 65 consecutive patients (45 men and 20 women; mean age, 65±12 years) who showed reversible perfusion defects during adenosine (140 μg·kg⁻¹·min⁻¹ for 6 minutes) ²⁰¹TI single-photon emission computed tomography. Patients with prior myocardial infarction were excluded. Ischemic ST depression occurred in one third of the whole cohort (22 of 65 patients). The presence of coronary collateral vessels (p=0.001), systolic blood pressure at baseline (p=0.006), and adenosine-induced anginal chest pain (p=0.011) were the only significant independent predictors of ischemic ST-segment depression by stepwise logistic regression analysis. Rate-pressure product at baseline, systolic blood pressure, heart rate, rate-pressure product, increase in heart rate, and rate-pressure product during adenosine infusion and maximal percent stenosis were variables also significantly related to ischemic ST depression by univariate analysis but were not predictive after the three primary variables were included in the regression model. Perfusion defect size, number of diseased vessels, and age did not correlate with ST-segment depression.

Conclusions. The presence of collaterals, which may predispose to coronary collateral steal, is the most significant correlate of ischemic ST-segment depression during adenosine infusion. Systolic blood pressure at baseline, which may affect the myocardial oxygen supply/demand ratio and anginal chest pain induced by adenosine, are additional variables related to ischemic ST-segment depression during adenosine infusion. (Circulation 1993;87:1211-1219)

KEY WORDS • pharmacological perfusion imaging • coronary steal • coronary collateral circulation

Thallium-201 scintigraphy during pharmacological coronary vasodilatation with dipyridamole, which acts by increasing endogenous adenosine levels, has been used as an alternative approach to exercise stress for detecting coronary artery disease¹⁻⁶ and for risk stratification after an acute myocardial infarction⁷,⁸ in patients with stable angina⁹⁻¹¹ and in the preoperative risk evaluation of patients undergoing vascular noncardiac surgery.¹² In these studies, ECG ST-segment depression indicative of ischemia occurred in approximately 7⁻15% of patients with coronary artery disease, a frequency much lower than that reported during exercise testing.¹⁻⁶ Previous reports indicated that dipyridamole-induced ST-segment depression occurs predominantly in patients with three-artery coronary artery disease,³ in those with coronary collateral vessels,¹¹ or both.¹³ Ischemic ST-segment depression during dipyridamole administration has also been attributed to an increase in rate-pressure product, which parallels myocardial oxygen demand,¹¹ and to a decrease in arterial blood pressure,¹³⁻¹⁵ which may reduce coronary perfusion.

We have proposed the use of intravenous adenosine, a potent coronary vasodilator, in conjunction with ²⁰¹TI single-photon emission computed tomography for diagnosing coronary artery disease. In our initial studies, 12% of patients receiving adenosine developed ischemic ST-segment depression.¹⁶ Although ischemic ST changes typically occur several minutes after comple-
tion of intravenous dipyridamole injection, with adeno-
sine they occur during the infusion because of adeno-
sine's very rapid half-life, which may be as short as
0.6–1.5 seconds.17 The determinant factors of adeno-
sine-induced ST-segment depression have not been
investigated in patients with coronary artery disease.
Therefore, the goals of the present study were to
determine the hemodynamic, angiographic, and scinti-
graphic correlates of adenosine-induced ST-segment
depression in patients with significant coronary artery
disease.

Study Patients

The research protocol was approved by our institu-
tional review boards of human research, and all patients
signed informed consent. The study group consisted of
65 consecutive patients (45 men and 20 women; mean
age, 65±12 years; range, 31–86 years) with arterio-
graphically documented coronary artery disease and
redistribution on adenosine 201TI scintigraphy. Coronary
angiography was performed 6.4±7.7 days before tomog-
raphy in 39 patients and 7.8±8.2 days after tomography
in 26 patients. Most patients (82%) used oral antiangio-
 nal medication up to the time of scintigraphy: 45 (69%)
patients used a calcium channel blocker, 27 (42%) a
nitrate preparation, and 12 (18%) a β-adrenergic
blocker. None of these patients were taking digoxin or
had significant (≥0.5 mm) baseline ST-segment abnor-
malities, left bundle branch block, or any other conduction
abnormality on the baseline ECG. None of the
patients included in this study had history or ECG
evidence of prior myocardial infarction, previous coro-
nary artery bypass surgery, or transluminal coronary
angioplasty.

See p 1415

Adenosine Infusion Protocol

Adenosine was infused by the method previously
reported from our laboratory.16 All studies were per-
formed after approximately 12 hours of fasting. Patients
who were taking dipyridamole had this drug discontini-
ued at least 12 hours before the test. Adenosine (Ade-
noscan) was supplied by Medco Research, Inc. (Los
Angeles), as a sterile, isotonic aqueous solution at a
concentration of 6 mg/mL (2-mL vials). 201TI (3.0 mCi)
was injected into a contralateral vein and flushed 3
minutes before discontinuing the adenosine infusion.

Vital signs and a 12-lead ECG were recorded before,
at every minute during, and for the first 5 minutes after
completing the adenosine infusion. Three ECG leads
were continuously monitored during infusion.

Patients were frequently queried about the presence
of chest pain throughout the adenosine infusion. Chest
pain with a pressure, weight, or burning sensation that
seemed to mimic the patient's previously experienced
exertional anginal pains was considered typical of an-
gina. Other varieties of pains, with a sharp or sticking
quality, involving a very small precordial point, often
fleeting during the infusion, were considered nonangin-
al pain. Such a distinction between anginal and nonanginal pain entails, by necessity, a subjective judg-
ment and is not a precise but only an approximate marker of ischemic pain.

Tomographic imaging used a large-field-of-view, sin-
gle-crystal, rotating gamma camera (ADAC ARC 3000-
3300) equipped with a high-resolution, parallel-hole
collimator with septal length and thickness of 33 mm
and 0.15 mm, respectively. Image acquisition and pro-
cessing were performed using previously reported meth-
ods.16,18–21 Imaging commenced 5 minutes after comple-
tion of the infusion and was repeated 4 hours later.

Analysis of ECGs

The ECGs were blindly read by consensus between
three observers who had no knowledge of the clinical
history or tomographic results. The ECGs were inter-
preted as positive for ischemia in the presence of >1
mm flat or downsloping ST-segment depression or ≥1.5
mm upsloping ST-segment depression. All measure-
ments were made 80 msec after the J-point in the
12-lead ECGs.

Computer Quantification of Single-Photon Emission
Computed Tomography

201TI tomographic images were quantified using a
computerized two-dimensional polar map of the three-
dimensional myocardial radionuclide activity. This
method has been described in detail previously.16,18–21
The map of each patient was statistically compared with
a normal adenosine data bank previously generated in
our laboratory.16,21 The lowest thallium activity (percent
per pixel) present in the defect was chosen as an index
of perfusion defect severity.

We have reported recently the interobserver and
intraobserver reproducibility for 201TI single-photon
emission computed tomography in quantifying perfu-
sion defects and scintigraphic reversibility.20 The inter-
observer and intraobserver agreements for visually
identifying patients with reversible perfusion defects by
scintigraphy were 80% and 88%, respectively. The
interobserver and intraobserver agreements for assess-
ing the coronary artery corresponding to each perfusion
defect were 90% and 94%, respectively. Correlation
coefficients on the defect size were 0.95 (p<0.0001) and
0.95 (p<0.0001) for interobserver and intraobserver
comparison, respectively.

Quantitative Analysis of 201TI Lung Activity

The unprocessed anterior frame acquired as part of
the early adenosine tomographic study was identified.
This anterior projection was selected because the ability
to spatially distinguish myocardial and lung regions of
interest was best with this view and for comparison with
previously published studies using similar techniques.22
The myocardial and lung 201TI activities on this anterior
image were determined using regions of interest mea-
suring 2.5×2.5 pixels in size. The regions of interest
were placed on three myocardial segments (anterolat-
eral, apical, and inferior) and in the medial aspect of the
left upper lung field, approximately 2.5 pixels superior
to the anterolateral myocardial segment and 2.5 pixels
lateral to the mediastinal photon-deficient area. The
lung/heart 201TI activity ratio was calculated as the mean
counts per pixel in the lung region divided by the
highest mean counts in the myocardial regions. The
upper limit of the normal lung/heart ratio during adeno-
sine scintigraphy is 0.42 in our institution.23
The interobserver and intraobserver reproducibilities in quantifying lung/heart ratio were determined in a random group of 30 patients with and without coronary artery disease. The absolute mean interobserver and intraobserver differences for quantitative lung/heart ratio were small (3.4±7.1% and 3.3±4.1%, respectively). Linear regression analysis yielded correlation coefficients of 0.98 (ratio 1 = 0.011 + 0.98 × ratio 2, p < 0.00001) and 0.95 (ratio 1 = 0.038 × 0.90 × ratio 2, p < 0.00001) for interobserver and intraobserver comparisons, respectively. Wilcoxon's signed rank tests for paired data yielded p = 0.63 and p = 0.83 for the interobserver and intraobserver comparisons, ruling out systematic changes as the measurement was repeated.

Coronary Angiography

Selective coronary cineangiography was performed in multiple views using standard techniques. Coronary stenoses in the three major coronary arteries were measured with calipers by an experienced angiographer and expressed as percent luminal diameter stenosis. Stenosis of the left main coronary artery was considered as two-vessel disease (involving the left anterior descending and left circumflex arteries). Stenosis severity was graded in the following manner: normal (<25% stenosis), insignificant (26–50%), moderate (51–69%), and severe (≥70%) stenosis.

We have reported previously our interobserver agreement for measuring the angiographic severity of stenoses in 51 patients with stenoses ranging from 0% to 100%. Linear regression analysis between the measured percent stenoses in all vessels by two observers yielded a correlation coefficient of 0.95 (p < 0.0001). In vessels with >50% stenosis, the correlation coefficient was 0.77 (p < 0.0001). The agreement between the two observers to classify vessels as normal or only insignificantly stenosed was 96%, whereas the interobserver agreement to classify vessels as having significant (≥50%) stenoses was 99%. Furthermore, interobserver agreement for classifying vessels having either moderate stenosis (51–69%) or severe stenosis (≥70%) was 84%.

Statistical Analysis

Repeated measures analysis of variance (BMPD2V, Health Services Computing Facility, University of California, Los Angeles) was used to evaluate changes during adenosine infusion in four hemodynamic variables for patients with and without ST-segment depression; using a Bonferroni correction adjusted for correlations, a probability value of ≤0.0125 was considered statistically significant for interpretation of these tests.

Stepwise multiple logistic regression analysis (BMDPLR) was used to determine which of several clinical, hemodynamic, and scintigraphic variables were predictors of ischemic ST-segment depression during adenosine infusion. In the stepwise multiple logistic regression analysis, the most significant predictor enters first, then the next most significant predictor is incorporated into the model, and the stepwise process is repeated until the recruitment of a new variable provides no additional improvement in the model at a level of p < 0.05.

For each significant predictor in the model, the regression coefficient, standard error, probability value, and the odds ratio and its lower and upper confidence limits are given. The interpretation of the odds ratio for a categorical predictor is that the likelihood of ST-segment depression in a patient with that characteristic (adjusted for other variables in the model) is multiplied (or divided) by that value. Confidence intervals indicate the range of the potential risk. For continuous variables, the likelihood is multiplied (or divided) for every unit of change in the predictor variable. Hence, continuous variables were expressed in clinically meaningful units of change, e.g., systolic blood pressure divided by 10 would yield a change in likelihood of ST depression for every 10 mm Hg in systolic blood pressure. Sensitivity was defined as the percentage of patients with ST depression correctly detected by the predictive model. Specificity was defined as the percentage of patients without ST depression correctly detected by the model. Data are expressed as mean±SD.

Results

Clinical, Angiographic, and Scintigraphic Variables Associated With ST-Segment Depression

Ischemic ECG changes during adenosine infusion occurred in 22 of 65 patients (34%) with reversible thallium perfusion defects. Table 1 shows a comparison of selected clinical and angiographic findings in patients with and without ST-segment depression during adenosine infusion. Significant differences between the two groups were present only for the frequency of coronary collaterals and maximal stenosis severity. Most of the collateral-dependent myocardial segments had corresponding perfusion defects (19 of 20 segments in patients with ST depression and nine of 10 segments in those without ST depression). No differences were found between the two groups in age, sex, medications used, and other coronary angiographic descriptors. Adenosine scintigraphy variables in patients with and without ischemic ST depression during adenosine infusion are shown in Table 2. The only significant difference between the two groups was the higher frequency of anginal chest pain in patients with ST-segment depression. No differences were seen in these two patient groups with respect to perfusion defect size, location of perfusion defect, presence of complete redistribution, lowest defect thallium activity, maximal 201T1 myocardial counts, thallium lung activity, and lung/heart ratio. The lowest percent thallium activity in the defects was similar between the two groups whether the regions were perfused by collaterals (52±14% versus 50±15%, respectively, p = NS) or not (56±15 versus 52±11%, respectively, p = NS).

The lung/heart ratios were above the upper limit of normal in seven patients (32%) with ST-segment depression and in six patients (14%) without ST-segment depression (p = 0.11). Five (23%) of the patients with ST-segment depression and eight (19%) of those without ST depression had either a history of hypertension or left ventricular hypertrophy (Table 1).

Hemodynamic Changes Associated With ST-Segment Depression

Significant hemodynamic changes occurred during adenosine infusion (Figure 1 and Table 3). Significant ST-segment depression first occurred at 3.9±1.1 min-
utes after beginning the adenosine infusion. Significant changes at minute 3 of the infusion occurred in all four hemodynamic variables (Table 3). The presence of interactions (borderline statistically significant) indicates that the rates of increase (slopes) in heart rate and rate-pressure product during adenosine infusion were greater in the ST depression group (see Figure 1). Systolic blood pressure and rate-pressure product were also significantly higher (before and during the infusion period) in the ST depression group.

### Predictors of Adenosine-Induced ST-Segment Depression

Table 4 shows the significant predictors of ST-segment depression by stepwise logistic regression analysis. Rate-pressure product at baseline, systolic blood pressure, rate-pressure product, heart rate at 3 minutes of adenosine infusion, maximal increases in heart rate and rate-pressure product during adenosine infusion, and maximal percent stenosis were significantly related to ST-segment depression by univariate analysis but were

### Table 1. Clinical and Angiographic Findings in Patients With and Without Adenosine-Induced ST-Segment Depression

<table>
<thead>
<tr>
<th></th>
<th>ST depression (n=22)</th>
<th>No ST depression (n=43)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68±9</td>
<td>63±13</td>
<td>0.13</td>
</tr>
<tr>
<td>Male sex</td>
<td>14 (64%)</td>
<td>31 (72%)</td>
<td>0.57</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blockers</td>
<td>3 (14%)</td>
<td>9 (21%)</td>
<td>0.74</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>16 (73%)</td>
<td>29 (67%)</td>
<td>0.78</td>
</tr>
<tr>
<td>Nitrates</td>
<td>10 (45%)</td>
<td>17 (40%)</td>
<td>0.79</td>
</tr>
<tr>
<td>Hypertension or LVH by ECG</td>
<td>5 (22%)</td>
<td>8 (19%)</td>
<td>0.75</td>
</tr>
<tr>
<td>Maximal stenosis severity (%)</td>
<td>94±9</td>
<td>86±13</td>
<td>0.01</td>
</tr>
<tr>
<td>Multi vessel disease</td>
<td>13 (59%)</td>
<td>26 (60%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Totally occluded lesions</td>
<td>10/34 (29%)</td>
<td>16/61 (26%)</td>
<td>0.81</td>
</tr>
<tr>
<td>Average diameter stenosis (%)</td>
<td>82±10</td>
<td>80±12</td>
<td>0.57</td>
</tr>
<tr>
<td>LAD stenosis</td>
<td>14 (64%)</td>
<td>27 (63%)</td>
<td>0.99</td>
</tr>
<tr>
<td>RCA stenosis</td>
<td>14 (64%)</td>
<td>26 (60%)</td>
<td>0.99</td>
</tr>
<tr>
<td>LCx stenosis</td>
<td>15 (68%)</td>
<td>25 (58%)</td>
<td>0.59</td>
</tr>
<tr>
<td>Collateral vessels</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>18 (82%)</td>
<td>10 (23%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Average diameter stenosis of recipient artery (%)</td>
<td>90±13</td>
<td>89±15</td>
<td>0.85</td>
</tr>
<tr>
<td>Jeopardized collateral vessels</td>
<td>7</td>
<td>4</td>
<td>0.99</td>
</tr>
</tbody>
</table>

Unless otherwise stated, data refer to numbers of patients in each group, with their percentage shown in parentheses. LVH, left ventricular hypertrophy; LAD, left anterior descending coronary artery; RCA, right coronary artery; LCx, left circumflex artery.

### Table 2. Adenosine Thallium-201 Scintigraphy Variables in Patients With and Without Adenosine-Induced ST-Segment Depression

<table>
<thead>
<tr>
<th></th>
<th>ST depression (n=22)</th>
<th>No ST depression (n=43)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perfusion defect size (%)</td>
<td>14±18</td>
<td>16±16</td>
<td>0.70</td>
</tr>
<tr>
<td>Location of perfusion defect</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD territory</td>
<td>12 (55%)</td>
<td>24 (56%)</td>
<td>0.99</td>
</tr>
<tr>
<td>RCA territory</td>
<td>10 (45%)</td>
<td>21 (49%)</td>
<td>0.99</td>
</tr>
<tr>
<td>LCx territory</td>
<td>7 (32%)</td>
<td>17 (40%)</td>
<td>0.60</td>
</tr>
<tr>
<td>Complete redistribution</td>
<td>20 (91%)</td>
<td>37 (86%)</td>
<td>0.71</td>
</tr>
<tr>
<td>Lowest % 201TI activity</td>
<td>54±14</td>
<td>52±11</td>
<td>0.53</td>
</tr>
<tr>
<td>Maximal 201TI myocardial counts/pixel</td>
<td>93±27</td>
<td>88±34</td>
<td>0.55</td>
</tr>
<tr>
<td>201TI lung counts/pixel</td>
<td>30±7</td>
<td>26±8</td>
<td>0.20</td>
</tr>
<tr>
<td>Lung/heart ratio</td>
<td>0.35±0.07</td>
<td>0.31±0.08</td>
<td>0.10</td>
</tr>
<tr>
<td>Adenosine-induced chest pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>16 (73%)</td>
<td>20 (47%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Anginal</td>
<td>14 (64%)</td>
<td>8 (19%)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Nonanginal</td>
<td>2 (9%)</td>
<td>12 (28%)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

LAD, left anterior descending coronary artery; RCA, right coronary artery; LCx, left circumflex artery.
not predictive after the following primary variables entered the regression model (Tables 4 and 5): 1) the presence of angiographic collaterals, 2) systolic blood pressure at baseline, and 3) typical anginal chest pain during adenosine infusion.

The presence of angiographic collaterals was the strongest predictor with an odds ratio of 23 and confidence limits of 4–144, which indicates that patients with collaterals were from four to 144 times more likely to have ST-segment depression than patients without collaterals. With respect to the relation of the baseline systolic blood pressure to the presence of ST-segment depression during adenosine infusion, the odds ratio portends that for every positive increment of 10 mm Hg in systolic blood pressure at baseline, the likelihood of patients developing ST-segment depression increases by 1.1 to two times (odds ratio, 1.6). Likewise, the presence of anginal chest pain increases the likelihood of ST depression from two to 57 times (odds ratio, 10). Using a predicted value of 0.5 or above, the combined sensitivity of angiographic collaterals, systolic blood pressure at baseline, and anginal chest pain during adenosine infusion for correctly detecting ST depression in this study group was 77% (17 of 22). The specificity of these predictive variables in detecting no ST depression in patients without ST depression was 95% (41 of 43).

Predictive probabilities of the model were summarized by calculating the predictive probability of ST depression when collateral vessels and anginal chest pain were present (or absent) and systolic blood pressure was greater (or less) than 150 mm Hg at baseline. The summary model (Table 6) predicted ST depression in 1–6% of patients with or without anginal chest pain who had baseline systolic blood pressure <150 mm Hg and had no angiographic collaterals. Conversely, ST depression was predicted to occur in 80–97% of patients with or without anginal chest pain who had baseline systolic blood pressure ≥150 mm Hg and angiographic collaterals. Other combinations of risk factors gave intermediate probabilities. The sensitivity of the summary model was 86%, and the specificity was 91%.

**Discussion**

**Frequency of Ischemic ST-Segment Depression During Adenosine Scintigraphy**

In our previously reported series of 607 patients, not all of whom had coronary angiography, ST-segment depression occurred in 12.5% of all patients and was usually associated with the presence of reversible perfusion defects.24 In the series of 101 patients reported by Nishimura et al31 from our laboratory, all patients had coronary angiography, and ischemic ST-segment depression occurred in 24 patients, all of whom had significant coronary artery disease and 20 of whom had reversible defects by thallium tomography. In the present series, where all patients had angiographically documented coronary artery disease and transient perfusion defects, 34% of the patients had ischemic ST-segment depression. Thus, ST-segment depression during adenosine scintigraphy is a specific although not a sensitive marker of reversible perfusion defects and significant coronary disease.

**Coronary Collateral Circulation: An Important Predictor of Ischemic ST Depression During Adenosine Infusion**

The presence of collateral circulation was singled out among several angiographic and scintigraphic variables as the most important independent predictor of ischemic ST-segment depression during adenosine infusion. The angiographic distribution and extent of coronary artery disease were similar in patients with or without ischemic ST-segment depression, a finding that is in keeping with previous studies during dipyridamole thallium scintigraphy.10,25

The frequency of angiographic collateral circulation was significantly higher in patients with than in those without ST depression (83% versus 23%). However, the presence of collaterals in some patients without ST depression as well as the lack of collaterals in a few patients with ST depression may be related to different

**Table 3. Hemodynamic Changes During Adenosine Infusion**

<table>
<thead>
<tr>
<th></th>
<th>ST depression</th>
<th>No ST depression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart rate (bpm)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>76±15</td>
<td>76±13</td>
</tr>
<tr>
<td>At 3 minutes</td>
<td>90±17</td>
<td>82±15</td>
</tr>
<tr>
<td>Pr* (group)</td>
<td>0.23</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pr* (time)</td>
<td>0.01</td>
<td>0.16</td>
</tr>
<tr>
<td>Pr* (interaction)</td>
<td></td>
<td>0.71</td>
</tr>
<tr>
<td><strong>Systolic blood pressure (mm Hg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>163±34</td>
<td>135±22</td>
</tr>
<tr>
<td>At 3 minutes</td>
<td>149±29</td>
<td>129±23</td>
</tr>
<tr>
<td>Pr* (group)</td>
<td>0.0002</td>
<td>0.0001</td>
</tr>
<tr>
<td>Pr* (time)</td>
<td>0.03</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Diastolic blood pressure (mm Hg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>83±13</td>
<td>78±12</td>
</tr>
<tr>
<td>At 3 minutes</td>
<td>76±12</td>
<td>72±12</td>
</tr>
<tr>
<td>Pr* (group)</td>
<td>0.09</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pr* (time)</td>
<td>0.71</td>
<td></td>
</tr>
<tr>
<td><strong>Rate–pressure product (bpm × mm Hg × 10^-7)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>124±35</td>
<td>103±29</td>
</tr>
<tr>
<td>At 3 minutes</td>
<td>134±33</td>
<td>102±28</td>
</tr>
<tr>
<td>Pr* (group)</td>
<td>0.001</td>
<td>0.003</td>
</tr>
<tr>
<td>Pr* (time)</td>
<td>0.05</td>
<td></td>
</tr>
</tbody>
</table>

*Probability of differences between groups (ST depression/no ST depression)/3-minute changes/interaction. bpm, Beats per minute.
TABLE 4. Potential Predictors of ST-Segment Depression During Adenosine Infusion

<table>
<thead>
<tr>
<th>Presence of collaterals</th>
<th>After three predictors in model*</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>p</td>
</tr>
<tr>
<td>28.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>16.7</td>
<td>0.0001</td>
</tr>
<tr>
<td>16.0</td>
<td>0.0002</td>
</tr>
<tr>
<td>14.3</td>
<td>0.0004</td>
</tr>
<tr>
<td>12.2</td>
<td>0.001</td>
</tr>
<tr>
<td>7.2</td>
<td>0.01</td>
</tr>
<tr>
<td>6.9</td>
<td>0.01</td>
</tr>
<tr>
<td>6.8</td>
<td>0.01</td>
</tr>
<tr>
<td>4.3</td>
<td>0.04</td>
</tr>
<tr>
<td>4.1</td>
<td>0.05</td>
</tr>
<tr>
<td>2.8</td>
<td>0.10</td>
</tr>
<tr>
<td>2.7</td>
<td>0.10</td>
</tr>
<tr>
<td>2.3</td>
<td>0.13</td>
</tr>
<tr>
<td>2.0</td>
<td>0.17</td>
</tr>
<tr>
<td>0.3</td>
<td>0.57</td>
</tr>
</tbody>
</table>

*Presence of collaterals, systolic blood pressure at baseline, and typical chest pain are in model.

degrees of collateralization, which we did not attempt to quantify because of the lack of a well-validated, meaningful angiographic method to quantify coronary collateral vessels and the inability of coronary angiography to visualize small collateral vessels.

How, then, is the presence of transient perfusion defects, which were present in all patients in this series, reconciled with the lack of other evidence of ischemia? 201TI perfusion defects during coronary vasodilation are not necessarily ischemic in origin but are produced by heterogeneity in coronary blood flow, which is in turn dependent on coronary stenosis severity and consequent abnormalities in flow reserve. However, it has been postulated that in some cases, true myocardial ischemia may indeed occur during adenosine or dipyridamole infusion secondary to a fall in regional coronary flow below resting levels caused by a steal phenomenon. In experimental studies, two types of coronary steal, collateral-dependent steal and subendocardial steal, have been demonstrated. These two different varieties of steal have different anatomic milieus. In the collateral-dependent steal, there is a fall in transmural collateral flow, whereas the flow increases normally in the territory of the donor artery. In the non–collateral-dependent steal, there is a fall in subendocardial flow concomitant with a rise or no change in subepicardial flow. In our study, perfusion defect size and percent myocardial thallium activity during adenosine 201TI scintigraphy failed to predict ST-segment depression. The mean perfusion defect sizes in this cohort were similar to the defect sizes measured in a multicenter trial of patients who underwent adenosine scintigraphy (mean defect, 15.3±13%). In that trial, the single-photon emission computed tomography defect size obtained during exercise stress in the same patients (12.6±13%) was smaller than the adenosine defect size (p=0.0073).30

Coronary flow reserve ratio (maximal flow/rest flow) is fourfold to fivefold in normal coronary arteries, gradually decreases relative to stenosis severity, and is below one in collateralized regions because of the steal phenomenon. Therefore, in view of the high degree of correlation between collateral vessels and ST depression by logistic regression analysis, the ratio of maximal coronary flow ratio between the normal and the stenotic arterial territory may theoretically be higher in patients with than in those without ischemic ST-segment changes. However, patients with and without ST-segment changes did not differ with respect to the lowest percent thallium activity on the defect, probably because 201TI myocardial extraction does not precisely correlate with true myocardial blood flow during adenosine-induced hyperemia. This is so because of the well-known fall in myocardial tracer extraction at very high unphysiological flows. Moreover, other factors such

TABLE 5. Coefficients, Standard Errors, and Odds Ratios for Logistic Regression Model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>SEM</th>
<th>p</th>
<th>Odds ratio</th>
<th>95% Confidence limits for odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of collaterals</td>
<td>3.15</td>
<td>0.91</td>
<td>0.001</td>
<td>23</td>
<td>4–144</td>
</tr>
<tr>
<td>Anginal chest pain</td>
<td>2.29</td>
<td>0.88</td>
<td>0.011</td>
<td>10</td>
<td>1.7–57</td>
</tr>
<tr>
<td>SBP at baseline</td>
<td>0.44</td>
<td>0.16</td>
<td>0.006</td>
<td>1.6*</td>
<td>1.1–2.1</td>
</tr>
</tbody>
</table>

*Likelihood of increase for positive increments of 10 mm Hg in systolic blood pressure (SBP) at baseline. The odds ratio for baseline SBP in hypertensive (≥150 mm Hg) vs. normotensive patients was 19 (confidence limits, 2.9–117). Sensitivity, 77%; specificity, 95%.
as thallium scatter, background activity, and partial volume effect may contribute to the similarities in defect size and severity in patients with or without ST-segment depression.

Although wall motion abnormalities are a more sensitive marker of ischemia than ST-segment depression, a previous study suggested that transient wall motion abnormalities by two-dimensional echocardiography are quite infrequent during adenosine infusion. Others have observed more frequent transient wall motion abnormalities during adenosine echocardiography. Abnormal wall motion during adenosine scintigraphy may also be a manifestation of collateral-dependent steal in patients with coronary artery disease, but this remains to be shown.

**Hemodynamic Variables and Ischemic ST Depression**

In our study, systolic blood pressure at baseline was also a predictor of ST-segment depression during adenosine infusion. Coronary flow to collateralized myocardial regions is dependent on aortic perfusion pressure and collateral resistance because the autoregulatory mechanisms of coronary flow are exhausted in collateralized regions. Thus, the baseline coronary collateral flow may be directly proportional to the systolic blood pressure. Moreover, previous experimental studies demonstrated that myocardial oxygen demand is related to myocardial tension, which is directly related to systolic blood pressure. Hence, a higher baseline systolic blood pressure may be associated with lower flow reserve and higher oxygen demand and may set the milieu for ischemic ST depression to occur during adenosine infusion.

An increase in heart rate, systolic blood pressure, and double product during adenosine infusion were also predictors of ST-segment depression by univariate analysis. An increase in heart rate is followed by an increase in myocardial oxygen demand because of an increase in the frequency of tension development per unit of time as well as by an increase in contractility. A previous study suggested that an increase in rate-pressure product is a significant predictor of ischemic ST changes during dipyridamole-induced vasodilation; the heart rate increase is clearly responsible for the increased double product during dipyridamole administration. Although the increase in myocardial oxygen demand resulting from the 20% increase in heart rate that occurred in our patients is modest, it might be a contributing factor in the production of myocardial ischemia.

Another mechanism has been suggested to explain ischemic ST-segment depression that may be independent of coronary steal. A decrease in driving pressure may lead to a proportional decrease in blood flow in vascular beds distal to coronary stenoses during adenosine-induced vasodilation.

The changes in hemodynamic variables that we observed during adenosine infusion are similar to those reported after intravenous dipyridamole injection. However, because adenosine has a rapid onset of action and produces uniform, near-maximal coronary vasodilation, it is possible to record instantaneous changes in ST-segment level and hemodynamic variables during the infusion. Ogilvy et al have recently reported the hemodynamic changes during adenosine infusion. Significant increases occurred in cardiac output and pulmonary artery wedge pressure. These changes occurred in normal subjects as well as in those with coronary artery disease and were usually not accompanied by regional wall motion abnormalities or fall in ejection fraction. The authors suggested that adenosine causes changes in left ventricular distensibility, probably because of increased myocardial turgor and stiffness associated with large increases in myocardial blood flow.

**Limitations of the Study**

We studied only patients with both angiographically documented coronary artery disease and abnormal perfusion defects on 201Tl tomography in order to 1) minimize the likelihood of false-positive ST changes, and 2) examine whether scintigraphic findings were quantitatively different between patients with and without ischemic ST-segment depression.

The presence of collateral circulation emerged as the most important predictor of ischemic ST-segment depression and highlights the prime importance of collateral-related coronary steal in our patients. Subendocardial steal may be a more important mechanism of ischemia (and ST depression) in patients who have angina of recent onset and in those with unstable angina at rest, in whom collaterals may not have yet developed. Typically, these patients are excluded from stress scintigraphy. Obviously, our findings cannot be extrapolated to patients with different clinical characteristics than the ones we have studied and certainly not to the occasional patient who may have ST-segment depression during

**Table 6. Summary of Predicted Probabilities of ST-Segment Depression**

<table>
<thead>
<tr>
<th>Collaterals present</th>
<th>Anginal chest pain</th>
<th>Baseline systolic blood pressure</th>
<th>Predicted probability* (ST depression)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>No</td>
<td>&lt;150</td>
<td>0.01</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>&lt;150</td>
<td>0.06</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>≥150</td>
<td>0.16</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>&lt;150</td>
<td>0.19</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>≥150</td>
<td>0.55</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>&lt;150</td>
<td>0.60</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>≥150</td>
<td>0.81</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>≥150</td>
<td>0.97</td>
</tr>
</tbody>
</table>

*Predictive probabilities from logistic regression model including collateral vessels, chest pain, and systolic blood pressure greater (less) than 150 mm Hg. Sensitivity, 86%; specificity, 91%.
Clinical Implications

The occurrence of ST-segment depression during adenosine scintigraphy is a marker of significant coronary artery disease. Our data demonstrate that transient perfusion defects in combination with ischemic ST-segment changes during adenosine \(^{203}\)TI perfusion imaging are useful clues of coronary steal under maximal vasodilation. Adenosine-induced ST-segment depression may thus be a marker of severe coronary stenosis associated with angiographic collateral circulation and viable myocardium.

References


Angiographic and hemodynamic determinants of myocardial ischemia during adenosine thallium-201 scintigraphy in coronary artery disease.

S Nishimura, K T Kimball, J J Mahmarian and M S Verani

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