Thallium-201 Uptake in Variant Angina: Probable Demonstration of Myocardial Reactive Hyperemia in Man

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SUMMARY Myocardial thallium scintigraphy was performed in four subjects with variant angina and in one subject with isolated, fixed coronary obstruction. Three subjects with variant angina had short episodes of ischemic ST-segment elevation that lasted 20–100 seconds. Thallium scintigrams demonstrated excess uptake in regions judged to be ischemic by angiographic and electrocardiographic criteria. Two subjects, one with variant angina and the other with a fixed coronary lesion, had prolonged episodes of ischemia that lasted 390–900 seconds. Both had reduced thallium uptake in the ischemic regions. We conclude that myocardial reactive hyperemia is the cause of excess thallium uptake in patients with variant angina who have short episodes of myocardial ischemia.

MYOCARDIAL reactive hyperemia occurs after transient coronary occlusion. The hyperemic response produces a considerable increase in flow in the normal coronary bed after release of an occlusion. However, with severe coronary stenosis, vasodilatory reserve is exhausted and reactive hyperemia is abolished. Myocardial thallium (201Tl) uptake is related to myocardial blood flow, and in canine studies, regional myocardial thallium uptake is high when the isotope is injected in the hyperemic state.

Patients with variant angina have episodes of transient myocardial ischemia due to transient coronary artery occlusion. The cause of these occlusions is uncertain, but it seemed likely that these patients might demonstrate reactive hyperemia on 201Tl scintigrams. However, previous studies have revealed perfusion defects rather than excess uptake. We suspected that the timing of the 201Tl injection and the duration of the ischemia might affect the pattern of uptake. Accordingly, we examined myocardial perfusion in patients with variant angina, studying the time of injection and the length of the ischemic period.

Case Reports

Patient 1

A 37-year-old white male had a 3-month history of progressive angina, occasionally after exertion but usually at rest. Figure 1 demonstrates representative, short episodes of electrocardiographic ST-segment elevation and subsequent coronary angiograms. There was a 50% lesion of the left anterior descending coronary artery proximal to the origin of the first diagonal branch, with spontaneous, transient coronary occlusion at this site. There were only minimal irregularities of the other coronary arteries, and none demonstrated spontaneous vasomotion. Ergonovine was not given.

Continuous two-channel electrocardiographic recording was begun using an ICR recorder for simultaneous evaluation of an anterior and an inferior lead. There were 25–40 episodes of transient anterior ST-segment elevation daily, although symptoms occurred in only 10–15%. No inferior ST elevation was seen. Two millicuries of 201Tl were injected intravenously 30 seconds after the onset of one episode of ST-segment elevation and subsequent chest pain. The pain and ST elevation resolved after 60 seconds, but recurred 8 minutes later. Four episodes that lasted 30–210 seconds occurred in the subsequent 30 minutes.

For this patient and the others, 201Tl images were collected using an Ohio Nuclear Series 120 mobile scintillation camera, a high-resolution collimator, the 80-keV 201Tl photopeak, a 25% window, and 300,000 counts per image, recorded on Polaroid film. Collection of the initial image of this patient was begun 9½ minutes after injection and was completed 20 minutes after the onset of pain. The image demonstrated high 201Tl uptake in the interventricular septum compared with the posterior wall, instead of the expected septal perfusion defect (fig. 2). Serial images showed a trend toward equalizing uptake in the septum and posterior wall.

With calcium-antagonist therapy, the patient became asymptomatic and was discharged. One month later, he discontinued his medications and suffered an acute anterior myocardial infarction. A repeat 201Tl scintigram demonstrated reduced uptake in the interventricular septum, where high uptake had previously occurred (fig. 2).

Patient 2

A 72-year-old white male had a several-month history of episodes of syncope and near-syncope without chest pain. ECGs demonstrated ST-segment elevation in leads II, III and aVF, 2–1 Minitz I atrioventricular block, and marked sinus bradycardia, occasionally as slow as 20 beats/min during episodes of light-headedness.

Thallium was injected 20 seconds after the onset of an episode of painless ST-segment elevation, and si-
multaneously, 0.4 mg of nitroglycerin was given sublingually. The ST-segment changes resolved in 90 seconds, and serial myocardial perfusion images were collected for the next 6 hours, beginning 30 minutes after injection. The next episode of ST elevation occurred 90 minutes later. Five similarly brief episodes occurred in the next 6 hours.

Figure 3 demonstrates the $^{201}$TI images and the coronary anatomy. The inferior wall was thought to be the site of ischemia based on commonly accepted ST-segment criteria. However, there was high $^{201}$TI uptake in this region compared with the other areas of the myocardium. On the final images, obtained 300 and 360 minutes after injection, there was reversal of these findings as inferior wall activity decreased below anterior wall activity. Coronary angiography the next morning demonstrated near-occlusion of the dominant right coronary artery on the first injection and marked dilatation of the narrowing after nitroglycerin, leaving only a 50% narrowing in the mid-right coronary artery. There were focal 70% stenoses in the proximal left anterior descending and circumflex arteries, but these did not demonstrate vasomotion.

On treatment with long-acting nitrates, he became asymptomatic and ST-segment changes ceased. Thallium scintigraphy was repeated after 2.0 mg of sublingual nitroglycerin. These scintigrams were identical to the final images in figure 3.

**Patient 3**

A 57-year-old white male had a 3-year history of chest pain, chiefly at rest, but occasionally on exertion. A treadmill exercise test demonstrated ST-segment elevation in leads II, III, aV_{6}, V_{5} and V_{6} after exercise. Similar changes occurred spontaneously at rest. Coronary angiography was performed 10 minutes after a spontaneous episode had resolved and showed 70% stenoses of an obtuse marginal branch of the left circumflex artery and the left anterior descending coronary artery (fig. 4A). During exercise testing using a bicycle ergometer, ST-segment elevation recurred; when angiography was repeated, the obtuse marginal branch was nearly occluded, and the anterior descending artery was unchanged (fig. 4B). After nitroglycerin, the obtuse marginal occlusion resolved almost completely, leaving only a 30% narrowing (fig. 4C). The left anterior descending narrowing opened slightly, leaving a 50% occlusion.

On two separate days, leg exercise was performed and $^{201}$TI scintigrams were obtained. On the first day, ST-segment elevation and chest pain occurred and resolved spontaneously after 100 seconds. Thallium was
FIGURE 2. Representative ECGs and serial thallium-201 ($^{201}$Tl) scintigrams (left anterior oblique projection) from patient 1. On 6/7/79, $^{201}$Tl was injected during transient ischemia, and excess radioactivity is seen in the interventricular septum on the first image after injection (20 minutes). The regional $^{201}$Tl radioactivity tended to equalize by 112 minutes after injection. On 7/31/79, there is a pronounced decrease in $^{201}$Tl radioactivity in the interventricular septum after acute anterior myocardial infarction.

injected 30 seconds after the onset of ST-segment elevation. There was minimal reduction in radioactivity in the posterior wall compared to the interventricular septum (fig. 5A).

On the second day, exercise-induced ST-segment elevation lasted 20 seconds. Thallium was injected as the ST-segment change resolved, and 0.4 mg of nitroglycerin was administered intravenously immediately. There was more uptake in the posterior wall than in the interventricular septum (fig. 5B). We postulate that this represents reactive hyperemia after coronary vasodilation induced by nitroglycerin. Such vasodilation was documented at angiography (fig. 4C).

The patient was treated with a calcium antagonist and discharged. Despite good compliance, 2 weeks later he had prolonged chest pain and suffered a posterior myocardial infarction. After recovery, $^{201}$Tl was injected during treadmill exercise, and a posterior perfusion defect was seen in the location of the original $^{201}$Tl defect (fig. 5C).

Patient 4

A 45-year-old white female had a 5-year history of exertional angina that progressed to prolonged episodes of angina at rest not preceded by a rise in intrarterial pressure or heart rate. These were associated
with inferior ischemic ST-segment elevation, and a 90% right coronary artery stenosis was demonstrated at catheterization. Thallium images obtained during a prolonged episode of pain (table 1) demonstrated a large inferoapical perfusion defect.

**Patient 5**

A 52-year-old white male had exertional angina and a single, fixed, high-grade left anterior descending coronary artery lesion. Thallium scintigrams were obtained at peak treadmill exercise and demonstrated an anteroseptal perfusion defect. On a second exercise study, the defect persisted in spite of large doses of nitroglycerin given immediately after $^{203}$TI injection (table 1).

**Discussion**

Reactive hyperemia has been used as an index of coronary autoregulation and vasodilatory reserve. Numerous studies have demonstrated that the pronounced increase in coronary flow after the release of a transient coronary occlusion in the normal coronary bed more than repays the "flow debt" incurred during occlusion.¹ ³ ⁴ However, in the case of fixed, severe coronary stenosis, the distal coronary bed is dilated at rest.

**Table 1. Thallium Uptake and Duration of Ischemia in Study Patients**

<table>
<thead>
<tr>
<th>Pt</th>
<th>Thallium uptake in ischemic region</th>
<th>Duration of ST-segment abnormalities (sec)</th>
<th>Time of thallium injection after ST-segment abnormalities (sec)</th>
<th>Nitroglycerin (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Excess</td>
<td>60</td>
<td>30</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>Excess</td>
<td>90</td>
<td>20</td>
<td>0.4</td>
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<tr>
<td>3</td>
<td>Reduced</td>
<td>100</td>
<td>30</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>Reduced</td>
<td>900</td>
<td>30</td>
<td>1.2</td>
</tr>
<tr>
<td>5</td>
<td>Reduced</td>
<td>390</td>
<td>30</td>
<td>—</td>
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<tr>
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<td>Reduced</td>
<td>450</td>
<td>30</td>
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</table>
This exhausts vasodilatory reserve and abolishes reactive hyperemia.

Reactive hyperemia in the myocardium is quite pronounced compared with other circulatory beds. This phenomenon has been studied in multiple animal models, and abolition of reactive hyperemia has been used as an index of full coronary vasodilatation. Hillis and Friesinger demonstrated that both the degree and the length of coronary stenoses were factors affecting coronary flow reserve in the dog. Feldman et al. reported similar results.

The present study demonstrates excess $^{201}$TI uptake in regions of myocardium which had been transiently ischemic in three of four patients with variant angina (table 1). Episodes of ischemia lasted 20–90 seconds in these three patients who had excess regional uptake, while the fourth patient, who had a perfusion defect, had ischemia persisting for 15 minutes. Nitroglycerin did not produce excess uptake in the ischemic region of patient 5, who had a high-grade fixed coronary stenosis and no evidence of vasomotion. Transient episodes of ischemia due to coronary occlusion resolved spontaneously in one patient and after nitrates in two patients.

In each case, the regions of excess uptake were those supplied by arteries that exhibited vasomotion documented by angiography. Subsequent myocardial infarctions occurred in these same regions of myocardium in two patients, further confirming the area involved. These events support our contention that transient regional ischemia had been followed by excess regional $^{201}$TI uptake, and it is likely that this excess regional $^{201}$TI uptake was due to myocardial reactive hyperemia.

Radionuclide tracers have been used to demonstrate reactive hyperemia in animals. Strauss et al. demonstrated a close linear relationship between $^{201}$TI activity and myocardial blood flow during normal or reduced flow. Thallium uptake was increased during reactive hyperemia but appeared to be less than the flow increase. Weich et al. found that the $^{201}$TI extraction fraction was reduced considerably when coronary blood flow was increased in excess of apparent metabolic requirements.

Schwartz et al. found that $^{201}$TI activity increased to 69% of normal soon after release of transient coronary occlusions. This was likely to be a period of reactive hyperemia. Wharton et al. also demonstrated that $^{201}$TI uptake was 69% of normal when the isotope was injected before release of coronary occlusion so that the blood $^{201}$TI level was high during the hyperemic state. Nishiyama et al. demonstrated a threefold increment in coronary flow in dogs during reactive hyperemia with a twofold increase in regional $^{201}$TI activity over control.

Gould et al. induced vasodilatation by intracoronary injections of Hypaque-M in animals and man. Radiolabeled macroaggregated albumin demonstrated high activity in normal regions and low activity in regions supplied by stenosed arteries. Goldman et al. documented coronary vasodilatory reserve in man using intracoronary xenon-133 injections before and after papaverine, and Gould et al. demonstrated unequal perfusion on $^{201}$TI scintigraphy after i.v. dipyridamole.

Patients with vasotonic angina should provide a clinical model for reactive hyperemia and vasodilatory...
reserve. Several studies of myocardial perfusion in patients with this disorder have demonstrated reduced radioactivity in regions of ischemia. Berman et al.\textsuperscript{15} used intracoronary radiolabeled macroaggregated albumin to demonstrate perfusion defects during pacing-induced coronary spasm in a patient with variant angina. The duration of ischemic episodes was not reported. Maseri et al.\textsuperscript{16} reported initial $^{201}$TI findings in six patients with variant angina. Episodes of ST-segment elevation lasted 3–7 minutes. The time of $^{201}$TI injection averaged 2 minutes after the onset of ST-segment elevation, and each image demonstrated a pronounced perfusion defect in the ECG region of ST-segment elevation. Subsequently, Maseri et al.\textsuperscript{17} reported scintigrams in 32 patients who were part of a group of 138 patients who had transient ST-segment elevation. The degree of coronary atherosclerosis ranged from none to severe three-vessel disease. Thirty-one of 32 patients who were studied with $^{201}$TI demonstrated perfusion defects. In one patient with a "negative scan," the attack subsided about 1 minute after injection, and scintigraphy was performed 10 minutes later. The latter may correspond to the findings in our patients with transient ischemia.

McLaughlin et al.\textsuperscript{18} demonstrated reproducible $^{201}$TI defects in a patient with exercise-induced coronary spasm. Their patient had ischemic episodes that lasted more than 5–8 minutes. Our patient 3, who had exercise-induced spasm, had 20–100-second episodes of ischemia. His excess regional $^{201}$TI uptake was most apparent after the 20-second episode and nitroglycerin treatment, and we believe this was due to coronary vasodilatation and reactive hyperemia.

Coronary spasm has been demonstrated in two vascular regions in one patient by means of $^{201}$TI perfusion defects and ischemic ST-segment changes in different areas.\textsuperscript{19} The interpretation of our data depends on the location of the ischemic regions. We believe we have accurately localized these regions in each of our patients, based on a combination of ECG changes and angiographic evidence. Subsequent myocardial infarctions in these same regions in two patients with excess regional uptake provide further confirmation.

In conclusion, $^{201}$TI can demonstrate myocardial reactive hyperemia in man. The phenomenon is complex, based on the work cited above and the present data. It apparently depends on the duration of ischemia, the blood level of $^{201}$TI during periods of reactive hyperemia, the $^{201}$TI extraction fraction and myocardial metabolic requirements, the severity of coronary stenosis, the availability of collateral vessels and the degree of vasodilatory reserve, all of which may influence myocardial $^{201}$TI uptake.

Our findings of excess regional $^{201}$TI uptake imply reactive hyperemia in three of our patients with variant angina. All three patients had very short episodes of ischemic ST-segment elevation and little residual atherosclerosis in the vessel with excess vasomotion. High levels of $^{201}$TI were probably circulating during the hyperemic state. These patients probably had con-

\textbf{FIGURE 5.} Thallium-201 scintigrams (left anterior oblique projection) in patient 3. (A) Arrows denote minimal reduction in the posterior wall radioactivity compared with the interventricular septum after transient exercise-induced ischemia. (B) Excess posterior wall activity occurred after exercise-induced ischemia, which was followed by simultaneous thallium and nitroglycerin injection (see text). (C) Reduced posterior wall uptake on exercise in the same region after a myocardial infarction.
siderable vasodialatory reserve, which permitted high levels of myocardial $^{201}$Tl uptake. Excess regional $^{201}$Tl uptake was not seen in patient 4, who had severe atherosclerosis and prolonged ischemia, or in patient 5, who had a single, fixed, subtotal coronary occlusion.

Thallium scintigraphy indicates relative regional perfusion. The findings are influenced by the perfusion in the region in question and in adjacent regions. Excess regional $^{201}$Tl uptake may be useful as a marker of reactive hyperemia and coronary vasodialatory reserve both in animals and in man. At present, correlative data (ECG or coronary angiography) are necessary before a scintigraphic diagnosis of myocardial reactive hyperemia can be validated.

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References
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M W Kronenberg, R M Robertson, M L Born, R A Steckley, D Robertson and G C Friesinger

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