Transient Transmural Reduction of Myocardial Blood Flow, Demonstrated by Thallium-201 Scintigraphy, as a Cause of Variant Angina

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SUMMARY In previous studies we demonstrated that variant angina could not be attributed to increased myocardial demands. In order to investigate whether a reduction of regional myocardial blood supply could be responsible for these ischemic episodes, we studied regional myocardial perfusion in six patients admitted to our coronary care unit. Myocardial scintigrams, obtained 5–7 min following i.v. injection of 1 mCi of thallium-201, performed during an episode of ST-segment elevation, showed transmural deficits of tracer uptake in the heart wall corresponding to the leads showing ST-segment elevation. These regional deficits had disappeared by 2 hours because of late uptake in previously ischemic myocardium. One week later, following injections performed in the absence of acute ischemia, no deficit was apparent. Tracer uptake in ischemic areas was 60% to 85% of that observed a week later. After adjusting for thallium-201 kinetics and counting geometry problems, these scintigrams actually represent large underestimations of actual flow reduction. Thus variant angina appears to be caused by massive transmural reduction of myocardial blood supply.

IN A SERIES OF STUDIES on the pathogenetic mechanisms of the so-called variant angina we have demonstrated that no increase of heart rate, left and right ventricular pressure and peak dp/dt precedes the onset of the ischemic attacks in these patients. 1-4 By contrast, often an obvious reduction of relaxation and/or contraction peak 1,4 dp/dt precedes the onset of the ST-segment elevation as observed in dogs upon sudden coronary ligation. 5 These findings, which support and extend those of Guazzi et al., 6 indicate that a transient acute reduction of regional blood supply rather than an increase of myocardial metabolic demands is responsible for the onset of the attacks, lending support to the hypothesis of coronary spasm postulated by Prinzmetal et al. 7,8

Indeed the possibility of spasm in a large coronary branch as the genesis of attacks of variant angina is supported by a number of isolated, occasional angiographic observations 9-15 and by studies from our group. 1,3,16 However, coronary artery spasm observed during selective angiology is not unanimously accepted as a demonstration of the cause of variant angina because of the possibility that the spasm is artificial (induced by the catheter).17

Because of the differing therapeutic implications derived from the pathogenetic mechanisms postulated in these patients, we decided to investigate the possible role of an acute reduction of blood supply by a noninvasive radioisotopic technique based on myocardial scintigraphy following the intravenous injection of thallium-201.

Theoretical Basis of Regional Myocardial Perfusion Studied with Thallium-201

Thallium-201 behaves under most circumstances like potassium tracers which are largely extracted (about 60%) by the myocardium during the first circulation, 16 and it is a suitable agent for myocardial imaging with a gamma camera. 17,18 Although we looked for only a semiquantitative evaluation of regional myocardial perfusion, the interpretation of our findings requires a brief outline of the principle on which the use of 201TI is based and of the practical limitations of the method.

The use of potassium tracers for the measurement of myocardial blood flow (MBF) is based on the fractionation principle: 19 the fraction of an indicator, evenly mixed with blood at the ventricular outlet and distributed to the various organs with the first circulation, is proportional to the fraction of cardiac output perfusing them. This initial distribution is obviously maintained (and can thus be measured) for particulate indicators which do not recirculate. 20

The flow dependent initial distribution to the heart is maintained for thallium-201 and potassium tracers in general only for the time during which a balance is maintained between the amount of indicator not extracted with the first circulation and the amount that re-enters the myocardium with recirculation. Preliminary studies 16 indicate that this condition is usually maintained only during the initial 2 min, in agreement with previous studies with potassium tracers, 21 while subsequently 201TI myocardial uptake continues progressively for at least 20 min. 18

The final equilibrium distribution of 201TI, as of the other potassium tracers, will tend to be proportional to the potassium pool of the different organs. Thus while myocardial scintigrams taken immediately after the injection will reflect predominantly the myocardial distribution of regional blood flow, scintigrams taken hours later will reflect the distribution of the potassium pool and hence of myocardial cellular mass. When ischemia is relieved 1 or 2 min after the 201TI injection, when tracer arterial concentration is still relatively high, the regional differences in 201TI uptake will rapidly disappear because of the wider blood-tissue tracer gradient in the ischemic areas. When ischemia lasts longer, until arterial concentration of 201TI is reduced to low levels (10–20 min), the initial regional differences will tend to be maintained for longer periods. Exact quantitation of total MBF by external counting requires the determination of: 1) the injected dose in the same geometrical counting conditions in which myocardial uptake is measured; 2) total activity included within the borders of the heart between 30 and 120 sec after the injection; 3) contribution to the total counting rate of activity in

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the blood and in the extracardiac tissues in the heart field.

Since the tracer injection was performed at bedside in the Coronary Care Unit at the onset of the attack, it was not possible to obtain measurements between 30 and 120 sec after the injection which would have provided the possibility of estimating total MBF.

**Evaluation of regional myocardial perfusion** can be derived from myocardial scintigrams obtained at later times (5–10 min after the injection), by comparison: 1) with scintigrams taken one or more hours later, when tracer distribution can be assumed to be proportional to the distribution of myocardial cellular mass; 2) with scintigrams taken at a few days interval, at corresponding times, following the injection of an equal dose of $^{201}$TI, performed in the absence of symptoms. The second approach offers the possibility of a semi-quantitative evaluation of the differences in regional tracer uptake in the two conditions. Ten minutes after the injection, arterial $^{201}$TI concentration is reduced to about 30% and myocardial uptake increased about 20% relative to the level reached between 30 and 120 sec. At this time differences in $^{201}$TI uptake between ischemic and nonischemic myocardium will underestimate the actual differences of flow because 1) the potassium tracer clearance is higher at low than at high flow;20 2) during restoration of flow the tissues that were ischemic (if ischemia does not persist up to the time of measurement) have a larger net tracer extraction than normal tissues. Furthermore, since the scintigram is two-dimensional, regional measurements of activity are likely to underestimate the maximum reduction of $^{201}$TI uptake in portions of the ischemic myocardium when the distribution is not uniform within the solid angle of view. This condition is likely, given the tridimensional arrangement of the heart muscle and its cyclic change in shape.

**Material and Methods**

**Patients**

We studied six patients admitted to our coronary care unit (CCU) with very frequent attacks of angina at rest characterized by ST-segment elevation. Their main physical, clinical, electrocardiographic, and arteriographic characteristics are described in table 1. Only patient B.A. had a small documented diaphragmatic myocardial infarction, 36 months prior to admission.

**Table 1. Physical, Clinical, ECG, and Coronary Arteriographic Characteristics of the Patients**

<table>
<thead>
<tr>
<th>Pt./Age</th>
<th>Effect angina</th>
<th>Asymptomatic episodes</th>
<th>Basal During spontaneous attacks</th>
<th>Exercise</th>
<th>Coronary arteriography</th>
</tr>
</thead>
<tbody>
<tr>
<td>C.R./54</td>
<td>No</td>
<td>Yes</td>
<td>Negative T:</td>
<td>V&lt;sub&gt;2&lt;/sub&gt;–V&lt;sub&gt;3&lt;/sub&gt;, Reciprocal changes II, III, aV&lt;sub&gt;F&lt;/sub&gt;, V&lt;sub&gt;1&lt;/sub&gt;–V&lt;sub&gt;6&lt;/sub&gt;</td>
<td>2 mm ST ↑ V&lt;sub&gt;1&lt;/sub&gt;–V&lt;sub&gt;4&lt;/sub&gt;</td>
</tr>
<tr>
<td>T.V./49</td>
<td>No</td>
<td>Yes</td>
<td>Negative T:</td>
<td>V&lt;sub&gt;1&lt;/sub&gt;–V&lt;sub&gt;6&lt;/sub&gt;, aV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>3 mm ST ↑ V&lt;sub&gt;1&lt;/sub&gt;–V&lt;sub&gt;4&lt;/sub&gt;</td>
</tr>
<tr>
<td>B.A./43</td>
<td>No</td>
<td>Yes</td>
<td>Negative T:</td>
<td>V&lt;sub&gt;1&lt;/sub&gt;–V&lt;sub&gt;6&lt;/sub&gt;, aV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Positive T waves in V&lt;sub&gt;1&lt;/sub&gt;</td>
</tr>
<tr>
<td>M.V./47</td>
<td>Yes</td>
<td>No</td>
<td>Flat T:</td>
<td>V&lt;sub&gt;1&lt;/sub&gt;–V&lt;sub&gt;6&lt;/sub&gt;, aV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Normal</td>
</tr>
<tr>
<td>F.F./70</td>
<td>No</td>
<td>Yes</td>
<td>rS in II–III, aV&lt;sub&gt;F&lt;/sub&gt;</td>
<td>Reciprocal changes II–III–aV&lt;sub&gt;F&lt;/sub&gt;</td>
<td></td>
</tr>
<tr>
<td>G.L./62</td>
<td>No</td>
<td>Yes</td>
<td>Normal</td>
<td>Reciprocal changes V&lt;sub&gt;1&lt;/sub&gt;–V&lt;sub&gt;6&lt;/sub&gt;</td>
<td>2 mm ST ↓ V&lt;sub&gt;1&lt;/sub&gt;–V&lt;sub&gt;6&lt;/sub&gt;</td>
</tr>
</tbody>
</table>

**Abbreviations:** LAD = left anterior descending; RCA = right coronary artery; CA = circumflex artery.

**Instrumentation**

Myocardial scintigrams were obtained using a Jumbo Toshiba gamma camera with a high sensitivity collimator on 35 cm × 35 cm film with a one-to-one spatial relation. Magnetic tape for data storage and computer analysis was not available.

**Experimental Protocol**

The patients were in their CCU beds under continuous ECG monitoring of the lead showing the most obvious changes during the anginal attacks. Arterial blood pressure was measured by a cuff manometer every 30 min when awake, at the appearance of the ECG changes and every 2 min during the attack and recovery. On appearance of the ECG changes the leads were connected to a three channel ECG recorder and a 12 lead ECG was obtained. Within 1–4 min after the onset of the attack a solution of 1 mCi of $^{201}$TI CI* was injected via an intravenous catheter, already in place, and the patient was moved to the nearby gamma camera room on his wheeled bed under ECG control. Within 6–10 min scintigrams were taken in the LAO and within 20 min also in LL and AP projections by collecting 300,000 counts with the window of the camera set between 72 and 88 keV to include the low energy peak of $^{201}$TI. When the episode did not subside spontaneously within about 5 min two tablets of nitroglycerin were administered sublingually. The sequence of events in each patient is illustrated in figure 1. Additional scintigrams in the same projection were taken 2–3 hours later.

*Supplied by Philips Duphar Co., Petten, Holland.
A week later, when the radioactive material had been eliminated and decayed and no anginal symptoms were present, 1 mCi of $^{201}$TI was injected and scintigrams were taken with the same procedure.

Coronary arteriography was obtained in 5/6 patients by the Judkins technique on 35 mm film at 30 frames/sec. One of them, G.L., had a spontaneous attack of variant angina during the angiographic procedure. Contrast medium injections were done during this typical episode.

**Analysis of the Data**

Densitometric measurements were performed by two independent observers on the scintigraphic films obtained in the two different conditions (during the attack and a week later) in the LAO projection in order to quantify the differences of tracer uptake in ischemic and normal myocardium. A densitometer with a round window 2 mm in diameter was used. Two square areas of interest of 1 cm $\times$ 1 cm were defined on the ischemic wall (ischemic area) and on the normally perfused wall (control area). These were placed in the center of the anterior and posterolateral walls on the control scintigram and in the corresponding areas of the scintigram obtained during ischemia. Two additional areas were selected on the lung field for the evaluation of extracardiac tissue activity. The areas were scanned every 2 mm and 16 readings taken and averaged for each.

**Results**

The values of heart rate and systolic blood pressure measured upon noticing the beginning of ST-segment elevation of the ECG were similar to those observed during the previous controls. Pain appeared 30 to 300 sec after the onset of the ST-segment elevation. Pressure and heart rate were elevated in some patients after the appearance of pain (fig. 1).

Myocardial scintigrams obtained immediately after the attack of angina showed a transmural deficit of tracer uptake in the ventricular wall corresponding to the location of the ST-segment elevation in all six patients. In contrast, the scintigrams obtained about two hours later and those obtained about a week later, at corresponding times following $^{201}$TI injection in the absence of symptoms, showed a normal pattern of myocardial $^{201}$TI distribution (figs. 2–4). Densitometric analysis of the scintigrams indicates a marked reduction of activity in the ischemic areas and an unchanged or slightly increased activity in the control areas. The values obtained in these two conditions in the “control” and “ischemic” areas in the LAO projection, after subtraction of the surrounding background, are illustrated in figure 5. Readings in ischemic and control areas on the scintigram obtained in the absence of symptoms are indicated as 100%. Density variations in the corresponding areas in the scintigram obtained during ischemia are expressed in percent changes. The values of the densitometric readings obtained by the two independent observers were in excellent agreement both in the scintigrams obtained in the absence of symptoms and in those obtained during ischemia.

Regional deficits of perfusion were observed also in the AP and LL projections corresponding to the location observed in the LAO projection, in which they were usually more evident. In the scintigrams obtained about two hours after the $^{201}$TI injection, both in the presence or in the absence of symptoms, the contrast between the heart and surrounding structures appeared greater than in the scintigrams obtained at about 10 min for all the projections (figs. 2–4). The deficits of $^{201}$TI uptake in the scintigrams performed
FIGURE 2. LAO myocardial scintigrams obtained in patient T.V. Upper left) Immediately after the injection performed during the episode of ST-segment elevation demonstrated by ECG. Opposite) About 2 hours after the injection. Upper right) One week later, the same technique and timing of the used on the left but in the absence of signs of acute ischemia. The ECG is unchanged. A large transmural deficit of $^{201}$TI uptake can be observed in the anterior and septal wall during the episode of ST-segment elevation.
FIGURE 3. Scintigrams obtained in patient C.R. Upper left) Immediately after the episode. Opposite) 2 hours after the injection. Upper right) A week later; the ECG is similar to those obtained prior to the episode on the left. A massive transmural reduction of tracer uptake in the anterior wall and septum is apparent during the episode of ST-segment elevation.
Figure 4. Scintigrams obtained in patient G.L. Panels follow the same sequence as 2 and 3. A deficit of tracer uptake is apparent in the inferior wall during the episode of ST-segment elevation in II, III, aVF.
The appearance of the scintigrams obtained during the attack is in all instances consistent with transmural ischemia. Based on the considerations discussed in the theory section which imply a systematic underestimate of the degree of ischemia, the regional flow reduction is undoubtedly much more severe than indicated by the changes of regional myocardial activity reported in figure 5. In fact, besides the greater extraction fraction in the ischemic zones during the period of reduced flow, and the greater net accumulation relative to the normal myocardium during the subsequent period of reactive hyperemia, it is reasonable to assume that not all the myocardium included within the solid angle of the "cold areas" was equally ischemic.

The slight increase in $^{201}$TI uptake in control zones seen in the scintigrams obtained immediately after the attack might be related to compensatory hyperfunction of the non-ischemic myocardium and to the increased heart rate and blood pressure levels observed after the appearance of pain. The reversibility of this transmural ischemia is indicated by the disappearance of the cold areas in the scintigrams taken about two hours after the attack; these scintigrams indeed were similar to those taken a week later in the absence of symptoms of acute ischemia. The areas of ischemia on the scintigram closely correspond to the location of the ST-segment elevation and confirm the hypothesis that in these patients the ischemia is related to an acute, reversible, transmural reduction of myocardial blood supply. This reduction of myocardial blood supply, responsible for the anginal attacks in these patients, appears determined by spasm of a large coronary branch with complete occlusion of its lumen above a long segment of the vessel. It is sometimes but not always associated with obstruction of the peripheral resistance vessels, an action which seems responsible for the very delayed run-off observed in patient G.L. in the present series. Thus the role of coronary vasoconstriction postulated by Osler and Wilson and Johnston and subsequently considered by several authors has found experimental confirmation.

The mechanism by which coronary vasoconstriction is brought about probably has multiple determinants. Attacks of variant angina have been reported following cigarette smoking, meals, alcohol intake, cold water ingestion, exercise, as in two patients of this series and as reported by others, and following withdrawal from nitroderivative exposure in a rocket propellant. We were unable to reproduce the attacks by i.v. injections of epinephrine, norepinephrine, and prostigmine in doses that gave obvious systemic effects, nor were we ever able to prevent them by atropine administration, as recently reported by some authors. Recent reports indicate that ergot derivatives can induce similar episodes in patients with angina at rest. These drugs had been proposed as a diagnostic ECG test but had also been reported to cause myocardial infarction. Although the established vasoconstrictor effects of these compounds suggests the possibility of a vasospastic action on coronary vessels, the presence of a time lag of 2-8 min following its i.v. administration indicates that they may have an indirect mechanism of action which can be also triggered by several other stimuli. It is possible that the different response of these patients to treatment relates to the differing primary stimuli in individual patients and at different times in the
same patient. In fact, in contrast to other reports, while we had no consistent results\textsuperscript{48} with beta-stimulating drugs,\textsuperscript{7} beta-blocking drugs,\textsuperscript{49} nor with reserpine therapy,\textsuperscript{41} we were able to prevent the attacks in all patients we studied by i.v. infusion of nitrates at adequate doses,\textsuperscript{44} probably by a direct action on coronary vessels. Whatever the general trigger mechanism, the consistency of the localization of the ST-segment changes in the same leads, with rare exceptions,\textsuperscript{48} indicates the presence of a local hypersensitivity in the coronary vessel supplying this myocardial territory.

Since coronary bypass surgery does not appear beneficial in these patients,\textsuperscript{44} the therapeutic requirements of a functional reduction of blood supply, taking place in a hypersensitive coronary vessel, are of particular importance and the study of the pathogenetic mechanism of the syndrome as well as the establishment of its clinical incidence appear to deserve the utmost attention.

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