Regional Myocardial Perfusion in Patients with Atherosclerotic Coronary Artery Disease, at Rest and during Angina Pectoris Induced by Tachycardia

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SUMMARY We studied regional myocardial perfusion by scintigraphic computer-assisted analysis of initial distribution, washout rates, and residual activity of $^{133}$Xe injected into the left coronary artery of four patients with normal arteriograms and 14 patients with coronary stenosis.

At rest, residual activity in poststenotic regions was always greater than in control regions, but initial washout rates were not slower.

During angina, following xenon injections, the amount of indicator distributed to the poststenotic regions was markedly reduced; the initial washout rates were slower than in control regions relative to rest, and residual activity was higher. Initial washout rates did not differ as much from those of normal myocardium because in severe ischemia too little indicator is deposited initially in these regions to produce a change of any magnitude. Indeed, when angina was induced immediately after the xenon injection, poststenotic washout rates became much slower during angina than at rest, a finding that implicates functional factors in impairing poststenotic myocardial perfusion during angina.

THE DETERMINATION OF REGIONAL MYOCARDIAL BLOOD FLOW by scintigraphic techniques represents a direct approach to the functional evaluation of the coronary circulation during ischemia. However, some studies have failed to find consistent differences of regional myocardial initial radioxenon washout rates that would reflect the site of coronary artery obstructions. These findings may be related to the heterogeneity of the groups of patients studied and/or to inadequacy of the initial part of $^{133}$Xe washout curves to reveal inhomogeneities of myocardial perfusion within the selected areas of interest.

We undertook a study of the alterations in regional myocardial perfusion as they related to the location of coronary stenosis in a group of patients with one isolated, severe stenotic lesion. In these patients, it was possible to identify a zone of myocardial distal to the obstructed vessel (generally the left anterior descending branch, less often the main diagonal branch or the circumflex) from that perfused by normal vessels, so that, during each measurement, each patient could serve as his own control. Because analysis of only the initial portion of the monoexponential washout curve might be inadequate for detection of localized ischemia, we recorded $^{133}$Xe washout curves until 90% of the injected indicator had been washed out from the myocardium. Constancy of counting geometry during this period was continuously checked by simultaneously recording the regional activity of a reference indicator fixed in the myocardium ($^{99}$Tc serum human albumin microspheres). We then considered initial $^{133}$Xe myocardial distribution, the initial and final washout rates, and residual activity in nine areas of interest singled out by computer analysis of the scintigram (unpublished observations).

Materials and Methods

Patients

We studied 18 patients referred to our ward for diagnostic evaluation. On the basis of electrocardiographic and hemodynamic data, and coronary arteriography they were assigned to one of three groups:

I) Normal coronary arteriogram, as a control group (4 patients)

II) Isolated stenosis (75% or greater) or occlusion of one of the three main left coronary artery branches with a) no other appreciable atherosclerotic lesions in the other two branches or in the right coronary artery; b) no previous myocardial infarction; c) typical ischemic changes on the ECG during stress testing which corresponded to the area perfused by the obstructed vessel (8 patients with left anterior descending [LAD], one with left circumflex [LC] involvement).

III) Normal LC, with a) severe obstruction or occlusion of the LAD or and main diagonal branch and lesions of varying severity in the right coronary artery; b) typical ischemic changes on the ECG during stress testing in the precordial leads (5 patients).
The physical characteristics of the patients, their ECGs and angiographic data are reported in Table 1.

The ECG effort test was performed on a bicycle ergometer with a progressively increased load every minute until symptoms appeared or 90% of the predicted maximum heart rate was attained. The results were evaluated according to the criteria recommended by WHO. Coronary arteriography was performed by the Judkins technique,9 and 25 × 25 cm spot films and/or 35 mm cine film at 50 frames/sec were obtained in at least three projections for both right and left coronary arteries.

Another prerequisite for entering the study was the presence of a long left coronary main stem (at least 2 cm); this assured the best possible mixing of the indicator with blood at the site of injection.

Since the patients were selected on the basis of their coronary arteriographic findings, the regional myocardial perfusion study was not carried out at the time of coronary arteriography but a few days later. All patients, most of whom were candidates for coronary surgery, gave their written informed consent.

**Experimental Protocol**

The patients were studied in the supine position under diazepam premedication (10 mg), and heparinization (5000 I.U., i.v.). A bipolar pacing catheter was introduced percutaneously into the right atrium. The tip of the left coronary Judkins catheter was shortened by 3 mm in order that a longer segment of the left coronary trunk would be available for facilitating mixing of the injectate with blood. The catheter was advanced into the left coronary artery under fluoroscopy and its position checked by contrast medium injection. Then the supine patient was placed under a gamma-camera oriented at 45° over the heart in the left anterior oblique position. Expired air was collected in a Douglas bag, and the arterial pressure was constantly monitored via the left coronary catheter which was flushed every minute with 3 ml heparinized saline except during the recording of the 133Xe curves. No change in the pressure values or contour was ever noticed upon entering the left coronary artery in these patients. Following background recording, about 3–5 mCi of 133Xe diluted in 1 ml saline and preloaded into the catheter were flushed with 5 ml of the patient's own blood into the coronary artery over 2–3 sec. The initial distribution of activity was recorded, then the washout was recorded until the counting rate was less than 10% of the peak (3–5 min). An additional recording was taken about 15 min following the resting injection in order to visualize the final distribution of 133Xe.

In 13 patients (three in group I, eight in group II, two in group III) atrial pacing was performed by raising the heart rate abruptly to 160 beats/min in group I and to the level that induced angina pectoris (120–150 beats/min) in groups II and III. About 1 min after the onset of pacing a second 133Xe injection was performed, the activity was recorded until it decreased to less than 10% of the peak; then pacing was

<table>
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<tr>
<th>Pt/age/sex</th>
<th>Dx</th>
<th>ECG</th>
<th>Effort</th>
<th>Coronary Arteriography</th>
<th>Follow-up</th>
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<td>B.W. 53 M HCM, A-V block</td>
<td>Pacemaker induced rhythm</td>
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<td>Sudden death 24 months later</td>
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<td>Normal</td>
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<td>B.F. 23 M Idiopathic A-V block</td>
<td>A-V block, T wave inversion in V1-V5</td>
<td>Normal</td>
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<td>E.A. 46 M Atypical chest pain</td>
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<td>Normal</td>
<td>Continuing chest pain</td>
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<td>Group II</td>
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<td>D.G. 53 M AP</td>
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<td>2 mm ST elevation in V1-V5</td>
<td>90% sten LAD</td>
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<td>Successful by-pass op</td>
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<td>O.F. 45 M AP</td>
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<td>B.S. 46 M AP</td>
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<td>S.O. 48 M AP</td>
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<td>Group III</td>
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<td>V.E. 58 M AP, old MI</td>
<td>Q waves in D1-Da-AVF</td>
<td>2 mm ST depression in V5-V6 and T wave inversion</td>
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<td>M.F. 54 M AP</td>
<td>1 mm ST depression in V5-V6</td>
<td>4 mm ST depression in V5-V6</td>
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<tr>
<td>S.L. 58 M AP, old MI</td>
<td>Q waves in D1-Da-AVF</td>
<td>T wave inversion in V5-V6</td>
<td>90% sten LAD</td>
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<tr>
<td>S.P. 30 M AP</td>
<td>1 mm ST depression in V5-V6</td>
<td>2 mm ST depression and T wave inversion in V5-V6</td>
<td>Ocel LAD</td>
<td>By-pass op</td>
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<tr>
<td>B.S. 52 M AP</td>
<td>T wave inversion in V5-V6</td>
<td>3 mm ST depression in V5-V6</td>
<td>Obstruction LM diaq branch, 50% sten LAD, Multiple sten RCA</td>
<td>By-pass op, Continuing angina</td>
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Abbreviations: Dx = diagnosis; HCM = hypertrophic cardiomyopathy; AP = angina pectoris; MI = myocardial infarction; sten = stenosis; ocel = occlusion; post desc = posterior descending; LM = left main; op = operation; ant = anterior.
discontinued. In 10 patients a third 133Xe injection was performed 3 min following sublingual nitroglycerin. In four patients of group II and three patients of group III, we began pacing a second time about 30 sec after an injection of 133Xe performed in resting conditions. In this way the injection was performed in a resting state and allowed prelabeling of areas that would become ischemic after the onset of pacing. In two patients (V.E. and B.S. of group III) the protocol was modified according to experimental findings noted during the study: in patient V.E. of group III, during the first 133Xe injection (performed in the LAO projection) a marked reduction in the washout rates was observed in the poststenotic areas in the absence of ECG changes or subjective symptoms. A second injection was then performed with the gamma-camera in the anterior projection. Following sublingual nitroglycerin administration 133Xe washouts were obtained both in anterior and LAO projections. No pacing study was performed.

In patient B.S. of group III, two additional 133Xe injections were performed after the control, one upon noticing a marked spontaneous increase of aortic and pulmonary wedge pressure, and one some minutes later when the patient developed ECG changes typical of ischemia and angina pectoris.

In the last eight studies (one patient of group I [E.A.], six of group II [except patients N.F. and O.F.] and one of group III [M.F.]), a dual counting apparatus was used. Following the positioning of the left coronary catheter, about 1 mCi of 99mTc labeled human albumin microspheres (25 micron average diameter, 0.2 mg total weight) was injected. The 99mTc scintigram was used for the selection of the areas of interest during the successive injections of 133Xe and, most important, for providing a check of the constancy of geometrical counting conditions during the 133Xe washout curves by continuous recording of 99mTc activity in each zone.

Data Acquisition

A Pho-Gamma III HP scintillation camera (Nuclear Chicago) with a dual isotope counting accessory and a high resolution collimator was used. The camera was interfaced to a 2116 B (16 bit) computer (Hewlett-Packard) equipped with magnetic disc and 30000 words/sec magnetic tape for data storage. The 133Xe gamma radiations were counted at the 81 keV photopeak with a 20% window. The 99mTc gamma emissions were separated by pulse height analysis and counted simultaneously with those of 133Xe on a second channel at the 140 keV photopeak.

The coordinates of each event, detected by the scinticamera, were acquired in list mode in blocks of 1000 counts with identification of the channel (low and high energy) for each event and with a time marker every hundredth of a second.

The blocks were dumped in real time on the magnetic tape. Subsequently the events were ordered in 64 × 64 matrix batches both for 133Xe and 99mTc. Centering and scale factors of the image from the high energy channel were previously matched with those of the low channel by an appropriate computer program, so that a 0.5 mm internal diameter tubing, forming a 10 × 10 cm square and containing a mixture of the two isotopes, gave exactly the same image on both channels.

Data Processing

The myocardial distribution of 133Xe was determined during the initial 10 sec following the peak counting rate, for 15 sec at the end of the washout curve (at 10% residual activity), and for 60 sec about 15 min following the injection. Correction was made for background activity. Hard copies were obtained in 64 × 64 matrix form from an incremental plotter.

The elements of the matrix with a counting level below 25% of maximum were excluded. A computer program subdivided the myocardial scintigram into eight areas, by four lines at 45° intersecting at the center of gravity of the scintigram. The inner part of these eight areas constituted a ninth area, which occupied the center of the scintigram up to the inner third of each axis.

The areas of interest were selected on the 99mTc scintigram, and from each of them, the time-activity curves for both 133Xe and 99mTc were obtained.

The fractional initial distribution of 133Xe (in each area outlined on the reference 99mTc scintigram) was calculated as the ratio of the average activity per matrix element of the area to the average activity per matrix element of the whole scintigram. In the analysis of the washout curves, the counting rate was integrated over 5 sec intervals down to 10% of the peak total activity. The washout curve was evaluated in two ways:

1) As an overall evaluation of the regional washout, we calculated the fraction of the initial activity remaining in each of the nine areas at the time when the activity in the whole scintigram decreased to 10% of the peak. The residual activity was integrated over a 15 sec interval. The coefficient of variation of the final levels was computed as the square root of the counting level divided by the counting level (based on using a Poisson distribution to characterize the counting statistics).

2) As quantitative characterization of the time course of the washout curves (but without implications of assuming a compartmental model), we chose to calculate (by the least squares method) the slope of the exponential, b, that fitted the curve down to 50% of its peak; successive points below the value were progressively included in the calculation of b until the chi² value, calculated between the curve described by the experimental points and the fitted monoeponential curve began to increase systematically for four successive points (time tₙ). When the values of chi² became greater than three times the average value calculated for the initial part (b₁) of the curve, the slope of a second exponential, b₂, was calculated between tₙ and the time the total washout curve reached 10% of its peak. The b₂ value was not considered where deviation occurred below 20% of the peak.

The limits of calculation of myocardial blood flow from the initial monoeponential slope have been reported and include the following: 1) according to Kety's formula perfusion in the tissue labeled by the indicator must be uniform; 2) the partition coefficient of the indicator (tissue + blood/blood) must be known; 3) the indicator must be removed from the tissue only by blood and recirculation must be negligible or a correction factor for recirculation must have been used. When perfusion is not completely homogeneous but the flow values are symmetrically distributed about the mean with minimal dispersion, this analysis would still fit. This approach has been validated in dogs.
with normal coronary circulation. In man perfusion is inhomogeneous and collection of tracer in fat has been reported.

Thus since our data do not fit the theoretical framework for single monoexponential analysis, we selected the above-described method based on two monoexponential washout curves. Our method has the practical advantages of fitting our washout data more closely while still allowing our results to be compared with those of earlier studies based on single monoexponential analysis. We recognize that our choice of cut-off points between the two curves is arbitrary and not yet confirmed by theory. However, practically, the method worked well. Further studies of the method of analysis of radioxenon washout curves are needed to confirm the most appropriate method.

We also compared washout rates and residual activity in poststenotic and control areas which had similar 133Xe activity 15 min after the injection, on the assumption that they were each affected to a similar extent by hold-up in epicardial fat.

In order to adopt a more commonly used expression, the values of the slopes $b_1$ and $b_2$, were expressed as their $t_1$, that is, as the time taken by the monoexponentials to decrease by 50% ($t_1 = 0.693/b$). We elected not to express these measurements as flow per unit mass of myocardium in view of the still unsolved practical problems in the analysis of 133Xe myocardial washout curves in man in the presence of inhomogeneous perfusion and possible collection of tracer in fat.

Results

The results are summarized in table 2 and illustrated in Figures 1-9.

Static Imaging

At Rest

No consistent patterns were observed in the initial distribution of 133Xe in relation to the site of coronary obstructions. Appreciable 133Xe activity was consistently detected in the 15 min scintigram. Predominantly concentrated at the base and apex of the heart, the activity always extended outside the zone of the initial distribution.

At the time 90% of the injected 133Xe had been washed out, the variability of residual activity in the nine areas was significantly larger than expected on the basis of the counting statistics. In fact, while the mean and standard deviation of the coefficient of variation of the final levels in the three groups was 10.2 ± 3.8; 9.5 ± 2.3 and 9.4 ± 3.6, the mean and standard deviation of the coefficient of variation of the final levels within the nine areas was 24.5 ± 8.4; 23.0 ± 7.5 and 34.7 ± 9.6. Some of this variability could be accounted for by 133Xe accumulation in fat, as detected in the 15 min scintigram, or possibly, by a combination of the effects of variable quantities remaining in the lung and of the presence of coronary stenosis. In fact, comparing areas distal to stenosed vessels and control areas which had similar amounts of 133Xe accumulation in the 15 min scintigram, residual activity was consistently higher in the poststenotic areas than in control areas, independent of the location of the stenosis (on the average 38% in group II) (fig. 4, top).

During Pacing

In four patients of group II and two of group III, in whom ischemic changes became evident in the electrocardiogram before the injection of 133Xe, the initial distribution of the tracer showed obvious cold areas of the myocardium distal to the stenosed coronary branch (fig. 1). In four patients of group II, and in one patient of group III, the reference 99mTc scintigram allowed quantification of the extent to which 133Xe was redistributed after pacing-induced tachycardia (fig. 2). In patient S.O. the change in xenon redistribution resulted in a decrease of as much as 50% in some poststenotic areas and an increase of 50% in some control areas when compared with the initial distribution at rest (fig. 2).

In all patients when 90% of the injectate had been washed out, the residual activity was consistently higher in the poststenotic area than in the control area although the regions had had the same degree of 133Xe activity at 15 min (fig. 4, bottom). In group II, the average differences were 85%.

Following Nitroglycerin

No consistent differences in the initial distribution or in the residual activity (except in patient V.E., see below) were observed relative to resting conditions.

Regional Washout Curves

In 31 washout curves of 36, the geometrical counting conditions remained constant during the recording of each 133Xe washout curve obtained at rest, during pacing, and following nitroglycerin, as confirmed by the simultaneously recorded 99mTc activity. In two instances, when pacing was begun during the course of the washout, sudden variations of 99mTc counting rate in some areas indicated changes in counting geometry.

At Rest

Only occasionally could the 133Xe washout curves be fitted by a single monoexponential down to 10% of their peak values. The difference between the location of the data points and the location theoretically determined by the monoexponential curve that fitted the data down to 50% of the initial washout became progressively larger, exceeding three times its average value in 39 instances between 50% and 40% of the peak, in 34 instances between 39% and 30%, and in 27 instances between 29% and 20%. In these cases the $t_1$ of the second exponential curve was 70%, 83%, and 90% in groups I, II, and III, respectively, larger than that of the first exponential.

The average standard error of $b_1$ (the initial slope of the washout curves) was 3.6 ± 1.7, 5.8 ± 2.3, and 6.1 ± 1.0, in the three groups of patients. By contrast the coefficient of variation was significantly larger than these standard errors would suggest: 14.3 ± 6.2, 10.8 ± 3.5, and 18.2 ± 13.0 (P < 0.05). In the patients of group II in whom the simultaneous 99mTc scintigram allowed us to rule out changes in geometry during the washout, the coefficient of variation of the nine initial slopes was the same as that for the whole group: 10.6 ± 2.5 (fig. 3).
In general, the initial washout appeared slower in the areas with the greater $^{133}$Xe activity 15 min following injection (fig. 3), but no consistent difference was observed between the initial slopes of the areas with the same final $^{133}$Xe activity distal to the stenosed vessel and those in the control region, except in patient V.E.

During Pacing

Following the injections performed during atrial pacing, the overall myocardial washout was significantly faster than following the control injections in all groups: the $t_4$ of the initial washout from the whole scintigram decreased on the average from 47 to 28 sec, from 44 to 23 sec, and from 52 to

<table>
<thead>
<tr>
<th>Group I</th>
<th>Projection</th>
<th>Control $v_{1/4}$</th>
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<th>Control Areas</th>
<th>TNG $v_{1/4}$</th>
<th>TNG $v_{1/3}$</th>
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<th>Pacing $v_{1/4}$</th>
<th>Pacing $v_{1/3}$</th>
<th>Pacing Areas</th>
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<tr>
<td>B.W.</td>
<td>LAO</td>
<td>65 96 2</td>
<td>—</td>
<td>—</td>
<td>34 40 1</td>
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<tr>
<td>C.B.</td>
<td>LAO</td>
<td>34 59 7</td>
<td>—</td>
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<td>24 —</td>
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<td>—</td>
<td>35 44 4</td>
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<td>D.G.</td>
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<td>48 85 9</td>
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<td>N.F.</td>
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<td>46 73 7</td>
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<td>30 —</td>
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<td>—</td>
<td>—</td>
<td>14 33 8</td>
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<td>—</td>
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<td>S.O.</td>
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<td>—</td>
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<td>15 26 4</td>
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Abbreviations: LAO = left anterior oblique; AP = Anteroposterior; $v_{1/4}$ = half time of initial slope; $v_{1/3}$ = half time of final slope; TNG = nitroglycerin.

**TABLE 2. $^{133}$Xe Washout Slopes**

![Figure 1. Initial $^{133}$Xe distribution obtained with six successive injections performed under different hemodynamic conditions in patient B.S. of group III (occlusion of main diagonal branch plus 50% stenosis of LAD). Top left) At rest. Bottom left) During a "spontaneous" increase of systemic and pulmonary wedge pressure. Top center) During a "spontaneous" anginal attack. Bottom center) Following nitroglycerin. Top right) Xenon injected before pacing. Bottom right) Xenon injected during pacing induced angina. A cold area is present during angina in the poststenotic area but is already noticeable in the bottom left scintigram. The levels of background cut-off and contrast are the same and approximately equal doses of $^{133}$Xe were used.**
36 sec in the three groups, respectively. In group II the decreased overall washout time was accompanied by a significant increase in the variability of the initial slopes: the coefficient of variation of the nine $b_1$ values increased from 10.8% (resting) to 23.1% (pacing) ($P < 0.05$). In groups I and III the numbers were too small to allow meaningful statistical evaluation.

In nine of the ten patients of groups II and III the initial washout was slower in the poststenotic area than in the control area (figs. 5 and 6), which had comparable levels of activity in the 15 min scintigram.

In five of the seven patients in whom pacing was begun a second time, immediately after the injection of $^{133}$Xe performed under resting conditions, signs of severe acute myocardial ischemia occurred a few seconds after the onset of pacing (fig. 7). In these five patients the final slope of the washout curve in the poststenotic area became much flatter than it had been in the resting conditions and it was only slightly steeper than at rest in the control area (fig. 8). By contrast, in two patients in whom ECG signs of ischemia did not appear during the $^{133}$Xe washout, the final slope of the curves became steeper than in the resting conditions both in the poststenotic and the control areas (fig. 9).

**Following Nitroglycerin**

No consistent changes were observed with respect to the initial slopes or the residual activity in the resting state, except in patient V.E. of group III. In this patient the resting xenon washout curves were markedly slower distal to a greater than 90% stenosis of the LAD; this was observed both in LAO and anterior projections. No signs or symptoms of acute myocardial ischemia were present. Following sublingual nitroglycerin repeated injections in LAO and anterior projection showed normalization of the initial washout slopes in the poststenotic areas.

**Discussion**

**Perfusion Alterations at Rest**

Our findings, observed by others, confirm the presence of regional differences in initial $^{133}$Xe washout slopes not related to the presence of coronary obstructions.

![Graphs showing perfusion alterations at rest](https://example.com/graphs.png)
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**Figure 3.** Half-times of regional washout slopes obtained at rest with standard deviations for the six patients of group II in whom a reference $^{99m}$Tc scintigram in the LAO projection allowed a continuous check on geometry. Asterisks indicate the extent of $^{133}$Xe accumulation in the 15 min scintigram. The narrow bars above indicate the half-time of the second exponential when present: black when appearing between 30 and 40% of peak, hatched when appearing between 40 and 30% of peak, and white between 30 and 20% of peak. No consistent differences in relation to the site of the stenosis are noticeable.

**Figure 4.** Residual activity at 90% total washout in areas with similar $^{133}$Xe accumulation in the 15 min scintigram. The activity is consistently larger in the poststenotic area at rest. The difference approximately doubles during exercise. $^{133}$Xe was administered after pacing was initiated.
Furthermore, they indicate that these differences must be attributed to actual differences in regional tracer removal and not changes in geometry on the basis of the constancy of the simultaneously recorded $^{99m}$Tc activity. These regional differences of $^{133}$Xe removal, also present in patients with no detectable coronary obstructions, can be attributed to variation in the degree of collection of $^{133}$Xe in epicardial fat or of recirculation to surrounding extracardiac tissues, but they may also be explained by regional temporal variability of myocardial perfusion, observed in dogs.

The lack of consistent differences in the initial washout slopes between poststenotic and control area (fig. 6) is in basic agreement with the data obtained in other studies, based on initial slope analysis, of patients with varying degrees of arterial obstructions. Furthermore, neither the deviation from the initial monoexponential course nor the value of the second exponential curve was consistently different between poststenotic and control areas (fig. 3).

However, $^{133}$Xe residual activity was greater in poststenotic than in control areas at the time 90% of the injectate was washed out, independently of the location of the coronary obstruction (13 out of 14 patients). This systematic difference strongly suggests the presence of localized myocardial ischemia. The levels of activity of the two areas at 15 min were comparable, ruling out any significant contribution from variations in retention in epicardial fat or in myocardium with altered lipid composition. This localized ischemia appears limited to a fraction of the myocardium included in the area of interest because it does not appear consistently in the initial washout slopes (fig. 6). The one exception was patient V.E. who had a greater than 90% obstruction of the LAD. Other recent reports indicate the frequent

![Figure 5](http://circ.ahajournals.org/). Computer print-out of washout curves in semilogarithmic scale in patient B.S. when radioxenon was injected after pacing was induced (the initial distribution is shown at bottom right in figure 1). The values of the initial $t_s$ and percent of the peak at which the slopes deviate significantly from a monoexponential course are indicated for each area. Differences in slopes between control and poststenotic areas are much smaller than expected on the basis of the large differences in tracer distribution observed in the initial scintigram and suggests that some regions were too ischemic to receive enough indicator to influence the initial slope of the washout curve appreciably.
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Figure 6. Half-times of initial slopes in control and poststenotic regions during rest and pacing-induced angina pectoris. At rest, the points cluster about the line of identity; with pacing all points but one lie above the line. This results from a less profound decrease of t₁₀₀ in poststenotic areas than in control areas. (Circles = patients with microsphere check of constancy of counting geometry.)

detection of areas with reduced slopes of initial activity distal to an obstructed vessel. It is conceivable that severe degrees of arterial obstruction may produce a more uniform reduction of regional perfusion, reflected in initial washout rates. The arterial obstruction present in our patients may not have been severe enough to produce such changes. In our patients without reduced initial slopes the presence of localized myocardial ischemia at rest was not associated with acute clinical symptoms, or consistently with ECG abnormalities, and was not apparently influenced by nitroglycerin administration.

Alterations of Perfusion during Acute Transient Ischemia

The changes in the initial washout slope for the whole scintigram with pacing are large. The calculated flow figures/100 g of myocardium from the initial t₁₀₀ using a blood/tissue xenon partition coefficient of 0.72 would be 64, 68, and 58 for the three groups, respectively, at rest; and 107, 130, and 83, during pacing. Although there was an increase in flow calculated for the whole heart during angina, similar to that reported in the literature and that observed in the control group, a severe reduction of myocardial perfusion relative to control areas occurred in poststenotic areas. This was indicated 1) by the changes in the initial distribution (figs. 1 and 2); 2) by the smaller increase of initial washout rates in the poststenotic areas (figs. 5 and 6); and 3) by the larger residual activity in poststenotic regions when 90% of the injectate had been washed out overall (fig. 4, bottom).

The profound changes in the initial distribution of indicator observed when Xe was injected during angina (figs. 1 and 2), and the slower initial washout suggests that a much larger mass of tissue is ischemic during angina than during resting conditions. However, the differences of initial washout rates between poststenotic and control areas do not agree with the extent of ischemia postulated on the basis of the initial distribution. The washout rates in poststenotic regions are not as slow as expected. Since in these patients no visible intercoronary collaterals were observed, this observation suggests 1) that initial washout slopes reflect predominantly the washout from the myocardium that is the least underperfused; 2) that ischemia is so severe in some regions that the indicator deposited in them initially is too small to make any detectable contribution to the initial washout. Thus, if all the myocardium in the poststenotic region could be uniformly labeled by the indicator prior to the onset of ischemia, the initial washout from the poststenotic region would be much slower. This fact was confirmed experimentally in the patients in whom angina was induced immediately after the injection of Xe (figs. 8, 9). Under these circumstances, a steady state was not maintained during the course of the washout because of the induced change of heart rate; thus one of the prerequisites of using diffusible indicators for blood flow measurement was violated. However, as we were essentially interested in the relative behavior of the tracer in poststenotic areas compared to control areas, this approach seems acceptable in the absence of changes in counting geometry.

This observation indicates that during severe ischemia in-

Figure 7. Experimental record of the aortic and pulmonary wedge pressures in patient S.L. Mean aortic pressure (Ao) 30 and 60 sec after pacing is similar to control and slightly elevated at 120 sec. Pulmonary wedge pressure (PW) increases progressively. The ECG (top tracing) shows negative T waves about 10 beats after the beginning of pacing and reversible ST-segment elevation at 120 sec suggestive of transmural ischemia.
duced by raising myocardial demands above the potential supply, flow to the ischemic area may become dramatically impaired because of the addition of functional factors which in some areas of the myocardium reduce blood supply far below the resting level. The substantial increase in pulmonary wedge pressure observed in some patients (fig. 7) suggests this reduction of perfusion might be caused by diffuse subendocardial ischemia but other factors such as the vasoconstriction observed during angina at rest cannot be ruled out. The potential vicious cycle producing interdependent increases in demand and decreases in supply may play a role in the duration and extension of ischemia.

Conclusions

The design of this study had two main features: 1) the possibility of a continuous check of the constancy of counting geometry has allowed us to analyze myocardial washout of $^{133}$Xe until 10% total residual activity was reached; 2) the choice of patients with isolated obstructions and large poststenotic and control myocardial areas facilitated selection of the areas of interest and minimized topographical differences in the various hemodynamic conditions.

At rest, localized myocardial ischemia in poststenotic regions appears as greater residual activity when 90% of the injectate has been washed out. This relatively simple analysis proved to be more sensitive for the detection of localized ischemia in our patients than the analysis of the washout curves in terms of compartmental systems.

During angina induced by pacing, myocardial ischemia was much more easily detectable. It was indicated by the changes in the initial distribution of the tracer (as compared to the fairly constant distribution at rest and following nitroglycerin) and by differences in the initial washout slopes and in residual activity between poststenotic and control areas.
The relatively small differences in initial washout rates, in comparison with the larger differences observed in initial distribution between poststenotic and control areas during angina, indicates a severe impairment of perfusion during angina, with reductions well below control levels in some poststenotic regions. This is confirmed by poststenotic washout rates below resting levels when angina was induced during the course of the washout.

The diagnostic application of this method has certain limitations (unpublished observations): 1) flow dependent $^{133}$Xe distribution in patients with a short left coronary main stem or intracoronary collaterals; 2) spatial resolution and counting statistics when ischemic areas are small; 3) spatial separation of right ventricular myocardium from ischemic left ventricular myocardium when the indicator is injected into the right coronary artery.

We believe that these findings contribute to our understanding of the pathophysiology of coronary artery disease and may have practical application in the development and use of methods for the objective evaluation of patients, and for the interpretation of the results.

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