Patterns of Disturbed Myocardial Perfusion in Patients with Coronary Artery Disease

Regional Myocardial Perfusion in Angina Pectoris

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SUMMARY Fifty patients who presented with angina pectoris were studied to examine the disturbances of regional myocardial perfusion during stress. Each patient underwent 16-point precordial mapping of the ECG during an exercise test, and coronary and left ventricular angiography. Regional myocardial perfusion was assessed using an atrial pacing test and a short-lived radionuclide, krypton-81m. Eleven patients had negative exercise tests and uniform increases in myocardial activity of krypton-81m of 98 ± 18.0% during pacing. Ten patients performed 30,000–43,000 J in positive exercise tests. These patients showed abnormal coronary anatomy and increases in myocardial activity of krypton-81m to remote and jeopardized myocardium at the onset of pacing. However, further pacing produced a decrease in activity in the affected segment of 68.0 ± 9.0% accompanied by ST-segment depression and angina. Twelve patients achieved 26,000–32,000 J in positive exercise tests and had significant coronary artery disease. Atrial pacing produced increased activity of krypton-81m to remote myocardium. The jeopardized segment at first showed no change and then a decrease in regional activity of krypton-81m (89.0 ± 17%) accompanied by ST-segment depression and chest pain. Seventeen patients achieved only 7000–22,000 J in positive exercise tests. These patients showed abnormal coronary anatomy and developed decreases in regional activity of krypton-81m to the affected segment of myocardium starting at the onset of atrial pacing and decreasing by 88 ± 7.0% below control. We conclude that different patterns of disturbed myocardial distribution of krypton-81m are present during stress-induced ischemia in patients with coronary artery disease. There was a close temporal relationship between these disturbances and ST-segment depression.

CLINICAL RESEARCH in patients with ischemic heart disease should take into account the coronary anatomy, hematologic and hemodynamic factors, as well as coronary vasomotor tone. A detailed understanding of the disturbances of regional perfusion is difficult because of methodologic problems.1-4 Krypton-81m, with a half-life of 13 seconds, has been introduced and used in patients to assess changes in myocardial perfusion.5-7

In this study we assessed disturbances of regional myocardial perfusion in patients with angina pectoris and coronary artery disease. Changes in the regional myocardial distribution of the short-lived krypton-81m has been measured during atrial pacing and then related to the patient's symptoms, ECG during exercise and the findings at coronary arteriography.

Methods

Fifty patients (42 male and eight females, ages 38–64 years, mean 52 years) were admitted to Hammersmith Hospital with a history of angina pectoris. The 50 patients in this study all underwent the same sequence of investigations. The patients were admitted into the study as outpatients, and were admitted to the wards within 1–3 weeks. Exercise electrocardiography was performed within 1–3 days of admission. Left ventricular and coronary arteriography and krypton-81m scintigraphy of myocardial perfusion...
were performed within 3–7 days of admission. Catheterization was performed either because a firm diagnosis of ischemic heart disease was in doubt or because the symptoms were not controlled by medical treatment.

Precordial Mapping of the ECG

Sixteen precardial electrocardiographic leads were positioned on the chest to cover the left hemithorax. Each patient performed an increasing work load on a bicycle ergometer using a standardized procedure. The exercise tests were limited by chest pain, dyspnea, fatigue or multiple ventricular ectopic complexes. From each exercise test, the total work load, the onset, set and duration of chest pain, and the onset and duration of ST-segment depression were noted. The method, reproducibility, sensitivity and specificity of this technique and interpretation of the records have been reported.

Left Ventricular and Coronary Angiography

Left ventricular angiography and selective coronary arteriography were performed using the Judkins technique. At the end of this procedure all the patients were free of chest pain and the ECG had returned to the control pattern.

A pacing catheter was inserted through the right femoral vein and advanced to the right atrium. The pacing threshold was tested until it was less than 1 V.

Each angiogram was reported by a radiologist and cardiologist who were unaware of the other investigations. A second cardiologist reported independently. Disagreement was settled by an independent cardiac radiologist. Each investigator was asked to report whether the left ventriculogram was normal, showed dyskinesia or diffuse failure of contraction.

Each investigator was asked to report whether the coronary arteries were normal or showed <50% stenosis, 50–70% stenosis, or >70% stenosis. These reports were made by inspection of the coronary arteriograms by doctors who routinely report more than 200 arteriograms per year.

Krypton-81m Scintigraphy

After coronary angiography, a specialized catheter was advanced into the left and right aortic sinuses. Krypton-81m was continuously eluted in sterile 5% dextrose from a portable pyrogen-free store of rubidium-81 (20–35 mCi) and then delivered to the cardiac catheter at 10 ml/min by a roller pump (Watson-Marlow MHRE 88). The patient was then positioned with the chest in the field of a General Electric max psi gamma camera (type 400 T) that was linked to a Deltron-Nova 1220 digital computer. The energy detection was set at 190 keV ± 15% and images of the myocardial distribution of krypton-81m were recorded by collecting 200,000 counts on 35-mm film.

During each study an equilibrium of activity was achieved and held in areas of interest over the aortic sinuses. An equilibrium of activity was also achieved over the myocardium before and after pacing. Research has shown that decreases in the regional myocardial counts of krypton-81m will linearly represent decreases in perfusion. Within the physiologic range of myocardial perfusion, increases in regional myocardial krypton-81m counts will indicate an increase in perfusion with a small (10–15%) systematic underestimation.

Krypton-81m scintigrams of the heart were recorded with each patient in the anterior, right anterior oblique and left anterior oblique positions. With each patient in the left anterior oblique position, the heart rate was increased by 10 beats/min at 2-minute intervals until the patient complained of chest pain, shortness of breath, discomfort or had a heart rate of 140 beats/min.

Digital images measuring the regional myocardial activity of krypton-81m were recorded every 30 seconds for 10 minutes before, during and for 10 minutes after each pacing test. At the end of each study a cardiologist, radiologist and technician were asked to analyze the data independently. An electronic light pen and visual display unit were used to enclose up to seven areas of interest. The areas included background, the catheter containing krypton-81m, the aortic sinuses, the total myocardial image, any area of myocardium showing abnormal changes or defects during pacing, and finally, the rest of the myocardium remote from the defects. Care was taken that any region of the myocardium chosen as an area of interest did not move out of the constructed area on the visual display unit during the pacing test. Areas with less than 3000 counts/sec were not used. Previous studies using line-spread functions in models, dogs and cadavers lead us to construct areas of interest that attempted to identify areas of the myocardium of at least 3 cm². Time-activity graphs with tables of the counts per minute in each area of interest were recorded with the serial images of regional myocardial perfusion from each study.

The nature, intention and potential dangers of the procedure were explained to each patient before each study. Subjects gave signed consent as required by the Hospital Ethics Committee, and Isotope Panel clearance was obtained before the studies. Analysis of variance was used to assess changes in regional myocardial activity of krypton-81m. The radiologist, cardiologist and technician were asked to analyze the regional changes in myocardial activity of krypton-81m without knowledge of the ECG or clinical data. They were asked to assess separately whether there were any patterns or trends in these changes in myocardial activity during the stress test. All disagreements were settled by an independent cardiologist. Results are expressed as a mean ± SD unless otherwise stated.

Results

Seven patients had a history of myocardial infarction. The 12-lead ECG recorded at rest showed
anterior Q waves in four and inferior Q waves in three. Anterior pathologic Q waves were found in two patients and inferior Q waves in two more patients with no history of myocardial infarction.

Electrocardiographic Mapping

The 12-lead ECG showed all the patients were in sinus rhythm with no significant ST-segment depression at rest.

The heart rate during exercise changed from 77 ± 14.0 to 144 ± 19.0 beats/min. Nine patients did not experience pain during the exercise test and 41 complained of chest pain.

Tables 1 and 2 summarize the relationships between the precordial distribution of ischemic ECG signs during exercise, the coronary angiographic findings and the changes in regional myocardial distribution of krypton-81m during pacing.

### TABLE 1. Site of Exercise-induced ST-segment Changes in Relation to the Findings at Coronary Arteriography

<table>
<thead>
<tr>
<th>Site of ECG changes</th>
<th>Anterior + lateral</th>
<th>Anterior inferior + lateral</th>
<th>Anterior inferior lateral</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessels involved</td>
<td>No change</td>
<td>Anterior</td>
<td>Inferior</td>
<td></td>
</tr>
<tr>
<td>Normal arteriogram</td>
<td>9</td>
<td>2</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>≤ 50% stenosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD alone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD + RCA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 70% stenosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD alone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD + ≤ 50% of RCA</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>LAD + ≤ 50% of RCA + Cx</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>LAD + RCA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD + RCA + ≤ 50% of Cx</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>RCA + ≤ 50% of LAD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD + RCA + Cx</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>1</td>
<td>1</td>
<td>7</td>
</tr>
</tbody>
</table>

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

### TABLE 2. Site of Abnormal Regional Myocardial Perfusion in Relation to the Findings at Coronary Arteriography

<table>
<thead>
<tr>
<th>Site of abnormal perfusion during pacing</th>
<th>Inferior and lateral</th>
<th>Septal and apical</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessels involved</td>
<td>No change</td>
<td>Inferior</td>
<td></td>
</tr>
<tr>
<td>Normal arteriogram</td>
<td>9</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>50% stenosis</td>
<td></td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>LAD alone</td>
<td></td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>LAD + RCA</td>
<td></td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>LAD + 50% of RCA</td>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>LAD + 50% of RCA + Cx</td>
<td></td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>LAD + RCA</td>
<td>2</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>LAD + RCA + 50% of Cx</td>
<td>1</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>RCA + 50% of LAD</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>LAD + RCA + Cx</td>
<td>3</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td></td>
<td>50</td>
</tr>
</tbody>
</table>

Abbreviations: LAD = left anterior descending coronary artery; RCA = right coronary artery; Cx = left circumflex artery.
TABLE 3. Site of Exercise-induced ST segment Changes in Relation to the Site of Abnormal Regional Myocardial Perfusion

<table>
<thead>
<tr>
<th>Site of abnormal perfusion</th>
<th>Site of ECG changes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No changes</td>
</tr>
<tr>
<td>No changes</td>
<td>11</td>
</tr>
<tr>
<td>Inferior</td>
<td>2</td>
</tr>
<tr>
<td>Septal and apical</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>31</td>
</tr>
</tbody>
</table>

The background activity, recorded from an area over the lung fields throughout each study was never more than 5% of the total activity in the myocardial images. The activity in the aortic root area varied by ± 5% throughout each study.

Table 1 describes the relationship between the precordial areas showing ischemic ECG signs during stress and the findings at coronary arteriography. One patient with < 50% stenosis and one with > 70% stenosis had negative exercise tests, whereas the majority of patients with > 70% stenosis had positive precordial areas of ST depression. Table 3 describes the relationship between the disturbances of regional myocardial activity of krypton-81m and the findings at coronary arteriography. Again, the same two patients with < 50% and > 70% stenosis showed no abnormal perfusion during pacing. The majority of patients with ≥ 70% stenosis showed disturbed perfusion during pacing.

Figure 1 shows examples of the krypton-81m scintigrams. Figure 2 shows an example of serial scintigrams recorded before, during and after atrial pacing in a patient who presented with angina pectoris.

Table 2 shows the relationship between precordial ST changes on exercise and abnormal regional perfusion during pacing. There was agreement between these two tests as to the presence of ischemia (in the ECG signs) and disturbed perfusion (krypton-81m scintigraphy).

The three independent assessors all reported four patterns of changes in the regional myocardial activity of krypton-81m with pacing in this study. They reported that 11 patients showed progressive and homogeneous increases in myocardial activity of krypton-81m (group 1). The other 39 patients showed increases in activity during pacing in most segments of ventricular myocardium. In each of these 39 patients, a jeopardized segment was also identified in which activity eventually fell during pacing after either an initial rise (10 patients, group 2), no change (12 patients, group 3) or a fall at the onset of pacing (17 patients, group 4).

Group 1

Figure 3 shows regional changes in the myocardial activity of krypton-81m in the 11 patients with negative exercise tests. These patients achieved 43,000–56,000 J during exercise. There are uniform increases in activity with pacing and a prompt return to the control state after pacing in two regions of left ventricular myocardium. An analysis of variance shows that there are no significant differences between changes in activity in the two areas.

Group 2

Figure 4 shows regional changes in myocardial activity of krypton-81m in the 10 patients who had a
positive exercise ECG test and achieved 30,000–43,000 J. One of the areas of interest encloses a region of myocardium that the three reviewers agreed showed abnormalities during pacing. The second area encloses the remote myocardium and both areas show stable activity before pacing (variation during control ± 5%). During atrial pacing the remote myocardium showed significant and progressive increases in counts of krypton-81m ($p < 0.01$, 98.0 ± 14%). The abnormal area in each of the 10 patients showed increases in activity during the first 3.5–7 minutes (range 17.0 ± 8%). These increases were significant ($p < 0.05$). The counts in this area then decreased rapidly and significantly ($p < 0.1$) throughout the rest of the atrial pacing test. This regional decrease was 68.0 ± 9% for the 10 patients in this group. After atrial pacing the regional activity in both areas returned to control levels.

**Group 3**

Figure 5 shows the regional changes in myocardial activity of krypton-81m in the 12 patients who had...
positive exercise ECG tests and achieved 26,000–33,000 J. One of the areas of interest encloses a region of the myocardium that the three reviewers agreed showed abnormalities during pacing. The second area encloses the remote myocardium and both areas showed stable activity (±5%) before pacing. During atrial pacing the remote myocardium showed significant (p < 0.01) and progressive (102 ± 20%) increases in myocardial counts of krypton-81m. The abnormal areas in each of the 12 patients showed no significant changes in activity for 4–7 minutes after the onset of atrial pacing (p < 0.01) and progressive decreases of 89.0 ± 17% in regional activity during the rest of the pacing test. When atrial pacing was stopped, the regional activity in both areas returned to the control state.

**Group 4**

Figure 6 shows the regional changes in myocardial activity of krypton-81m in the 17 patients who had a positive exercise ECG test and achieved 7000–22,000 J. One of the areas of interest encloses a region of the myocardium that the three reviewers agreed showed abnormalities during pacing. The second area encloses the remote myocardium and both areas showed stable activity (±5%) before pacing. During atrial pacing the remote myocardium showed significant (p < 0.01) and progressive (91.0 ± 7%) increases in myocardial counts of krypton-81m. The abnormal areas in all the 17 patients showed a decrease in regional myocardial activity within 60 seconds of the onset of atrial pacing. This was significant (p < 0.01) and progressive, decreasing below control values by 88.0 ± 7.0%. When atrial pacing was stopped, the regional activity in both areas returned to the control state.

The relationship between the disturbances of regional myocardial activity and the appearances of significant ST-segment depression in the ECG is shown in figures 4, 5 and 6. Significant ST-segment depression appeared at 140 ± 18 seconds (mean ± SD) after the decrease in regional myocardial perfusion to the affected segment.

**Discussion**

A proportion of people with significant coronary atherosclerosis die after the age of 65 years without symptoms or signs of heart disease. The traditional view, that myocardial ischemia results from fixed regional myocardial perfusion and variable myocardial oxygen requirements, is clearly incomplete.

**Krypton-81m and Myocardial Perfusion**

Krypton-81m is used as a gas in solution and has a half-life of 13 seconds (turnover rate 3.2/min). If krypton-81m is delivered to the myocardium by coronary blood flow, the majority of the tracer will decay within the myocardial water space.

In this study one must know if this method measures regional increases and decreases in myocardial perfusion or simply regional flow differences. Regional myocardial activity of krypton-81m will only represent changes in regional perfusion if the delivered arterial concentration of the tracer is determined in the aortic sinuses and is not significantly altered by changes in blood flow in each sinus. The problems of afferent mixing, delivered concentration and distribution according to coronary flow were investigated in experiments, and, using a reference technique, the method was shown to measure regional increases and decreases in myocardial perfusion during a wide range of changes in heart rate and cardiac output. In this study the arterial concentration was con-
stantly checked by measuring the stability of counts per minute in an area of interest enclosing the aortic root.°

However, some limitations must be considered. The technique using krypton-81m is invasive, depends on planar imaging to assess an object with three dimensions and cannot separate endocardial from epicardial events.

The background of experimental research and the stable aortic sinus activity both mean that in this clinical study the increases and decreases in regional myocardial activity represented increases and decreases in regional myocardial perfusion.4,7

Myocardial Activity of Krypton-81m in Patients with Chest Pain

The patients in this study presented with chest pain. Although we tried not to select and distort the results too few patients were studied to make conclusions about all disturbances of myocardial perfusion in patients with chest pain. We found four patterns of changes in myocardial activity of krypton-81m. However, we do not suggest that four separate conditions exist in the population of patients presenting with chest pain.

We had patients with negative exercise tests, coronary arteriograms reported as normal and uniform increases in regional myocardial activity during pacing. These patients either had no cardiovascular disease or a transient condition causing myocardial ischemia that could not be precipitated by pacing. The increase in activity of krypton-81m with pacing is in accord with research that showed a relationship between the level of coronary perfusion and myocardial oxygen requirements.

One patient who had > 70% stenosis of a coronary artery had negative ECG and krypton-81m tests, suggesting that the angiographic appearance may have overestimated the physiologic severity of the lesion or that an adequate collateral circulation was active.

The 39 patients with positive exercise tests all showed stable regional myocardial activity before atrial pacing. During pacing, the region of the myocardium thought to be supplied by a normal coronary artery, or the least severely affected vessel, showed progressive increases in regional activity with pacing. Even the patients with three-vessel disease always had at least one area of the myocardium showing significant increases in activity during pacing. Patients in this study could endure some atrial pacing without chest pain or manifest heart failure. Presumably, they could still increase perfusion on demand to a significant amount of ventricular myocardium. Those regions of the myocardium showing abnormal changes or defects of activity during pacing showed a completely different sequence of changes in regional myocardial activity of the tracer with stress. Ten patients could increase regional activity in the jeopardized area but during the atrial pacing this increase stopped and then decreased progressively.

Twelve patients showed no changes in the jeopardized area after the onset of atrial pacing. However, during pacing these patients showed a significant decrease of activity. The last group of 17 patients had decreasing regional activity during the first minute of atrial pacing.

All patients showed a close temporal relationship between regional decreases in the myocardial activity of krypton-81m and ST-segment depression.

Regional decreases in myocardial perfusion with chest pain in patients with coronary artery disease have been identified with difficulty using other techniques.6 In this study we could examine this pathophysiology in detail. The group showing increases in activity early in the pacing test may have been able to regulate regional blood flow, to a limited extent. The groups showing no regional increases in activity to jeopardized segments probably had fixed limitations of blood flow, possibly imposed by the atherosclerotic coronary arteries. In addition, the collaterals, if any, could not effectively diminish the total resistance to blood flow at the arterial level.

At different times during atrial pacing, 39 of the patients showed progressive decreases of regional myocardial activity. These decreases were accompanied by electrocardiographic and symptomatic evidence of acute myocardial ischemia. These decreases of activity may have been caused by a decrease of regional perfusion during the ischemic event. The pacing may have produced an inhomogeneous distribution of regional vascular resistances to blood flow, with competition between the jeopardized segment, which cannot diminish resistance, and remote areas, which can adapt. In addition, with the onset of ischemia, the affected tissue fails to contract and relax normally, changes shape and thickness and develops increased diastolic tension with increases in left ventricular cavity pressure and volume. Edema of ischemic myocardium, particularly swelling of capillary endothelial cells, may also contribute to decreases in tissue perfusion within the ischemic segment.10-32

It has been suggested that coronary spasm occurs during ischemic events caused by exercise or pacing. This may be related to the regional decreases in myocardial perfusion and activity of krypton-81m during the acute event.4,7,32 In these circumstances, the affected segment thins. The equilibrium of krypton-81m is dominated by flow and decay and the tracer has not equilibrated in the volume. The decrease in volume alone will not cause a change in activity. However, a decrease in wall thickness will result in some loss of regional counts because of the drop in counting efficiency as the object decreases in size.

Clinical Implications

This study has shown a temporal relationship between ST-segment depression in the ECG and different patterns of disturbed regional myocardial activity of krypton-81m during stress in patients with coronary artery disease. These findings strengthen our understanding of the noninvasive test. The patho-
physiologic correlations in this study suggest that the work load achieved and the onset of ST-segment changes are an indication of disturbed regional myocardial perfusion in patients with coronary artery disease. It may be useful to use the technique outlined in this study to assess the effects of mental stress, exercise and coronary vasodilation on the coronary circulation in patients and then to use this method to assess the effects of therapies on these disturbances.

References

Patterns of disturbed myocardial perfusion in patients with coronary artery disease.
Regional myocardial perfusion in angina pectoris.
A P Selwyn, G Forse, K Fox, A Jonathan and R Steiner

Circulation. 1981;64:83-90
doi: 10.1161/01.CIR.64.1.83
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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