Ischemia and Reperfusion during Intermittent Coronary Occlusion in Man*

Studies of Electrocardiographic Changes and CPK Release

Avio Mager, M.D.; Samuel Sclarovsky, M.D.; Mordechai Wurtzel, M.D.; Hanoch Menkes, M.D.; Boris Strasberg, M.D.; and Eldad Rechavia, M.D.

The course of 357 balloon inflations performed during 38 angioplasties for single-vessel coronary artery disease was prospectively studied using continuous ECG recording. Ischemic ECG changes appeared during 91 percent of the inflations at a mean of 20 ± 8 seconds after inflation and resolved in 97 percent of those at a mean of 11 ± 5 seconds after deflation. Elevation of the plasma CPK level was found in six patients who had ischemic ECG changes for at least 7.8 minutes. The duration of ischemia did not exceed 5.4 minutes in any of the patients without CPK elevation. Resolution of the ischemic changes was delayed in patients with CPK elevation and in last vs initial inflations. We conclude that in patients with noninfarcted myocardium, ECG changes follow coronary occlusion and reflow very rapidly, detecting these coronary events with a high sensitivity. Lack of rapid regression predicts lack of reperfusion, and persistence of ischemia for more than 7.8 minutes is sufficient to cause myocardial necrosis.

(Chest 1991; 99:386-92)

PTCA = percutaneous transluminal coronary angioplasty; LAD = left anterior descending coronary artery; CX = left circumflex artery; RAO = right anterior oblique; LAO = left anterior oblique; STE = ST-segment elevation; STD = ST-segment depression; RCA = right coronary artery; CK-MB = MB form of creatine kinase

It has been known for almost 70 years that STE is the main ECG sign of coronary artery occlusion. A rapid decrease in the STE has more recently been shown to be a reliable noninvasive marker of reperfusion during acute myocardial infarction; however, since in man acute coronary occlusion usually occurs spontaneously, pinpointing the exact time and location of the occlusion initiating the ischemic process and following the ensuing events from that point are until recently possible almost exclusively in animal experiments. In man the true time relationship between the duration of acute coronary occlusion and the evolution of ischemic ECG changes and the appearance of myocardial damage was difficult to investigate, leaving these issues not well established. The sensitivity of the ECG in detecting ischemia was found to vary from 30 to 84 percent. The specificity of the various ischemic changes to the site of coronary occlusion is also not satisfactory and requires further investigation. Regression of the ischemic ECG changes is now gaining renewed interest because of the need for a noninvasive method for identification of successful reperfusion. In man, most of the data have been obtained after at least some myocardial necrosis has occurred, and the true cascade of regression that follows reperfusion of undamaged myocardium is not well established.

Percutaneous transluminal coronary angioplasty, now widely used in the treatment of coronary artery disease, is unique also in that it enables investigation of clinical, ECG, and other features of acute myocardial ischemia caused by temporary coronary artery occlusion in humans, the evolution of these features from their initial point, and their regression after resumption of coronary flow, usually without myocardial necrosis, in a setting comparable to that of animal experiments. Our purposes were to study the time correlation between the duration of coronary occlusion in man and the appearance of ischemic ECG changes and of myocardial necrosis, to assess the sensitivity of the standard surface ECG in detecting acute myocardial ischemia caused by acute coronary occlusion, and to characterize the ECG manifestations of reperfusion of noninfarcted myocardium.

**MATERIALS AND METHODS**

**Patients**

Candidates for elective angioplasty for single-vessel coronary artery disease supplying noninfarcted myocardium were prospectively studied. Patients with ongoing myocardial ischemia or infarction, with ST-segment deviation on the baseline ECG, or with nonviable myocardium in the region supplied by the artery elected for PTCA (as judged from Q waves in the concordant ECG leads or the presence of akinesia or dyskinesia of this region on left ventriculography) and patients with total coronary occlusion before PTCA, with the presence of a significant (>50 percent) stenosis in other coronary arteries, or with evidence of a myocardial disease were not included.

*From the Israel and Ione Massada Center for Heart Diseases, Beilinson Medical Center, Petah Tikva, and the Tel Aviv University Sackler School of Medicine, Tel Aviv, Israel.
Manuscript received March 12; revision accepted July 11.
Reprint requests: Dr. Mager, Massada Center for Heart Diseases, Beilinson Medical Center, Petah Tikva, Israel 49100
Electrocardiography

Continuous three-channel ECG recording was started before insertion of the guiding catheter and continued throughout the PTCA procedure until 15 minutes after its completion. The 12 standard ECG leads were rearrayed into groups of three (eg, L1, L2, and L3; aVR, aVL, and aVF; etc). Mapping of the ischemic and reperfusion changes was performed using rapid consecutive lead-group alterations (every 3 to 4 seconds). This method was utilized during the beginning of every first inflation until ischemic changes appeared, 15 seconds before and immediately after the end of the first three inflations at the same site, and occasionally as found appropriate. After the lead showing maximal ischemic changes was identified, it was subsequently used for continuous recording throughout the whole procedure, using the other two channels for simultaneous recording from two other leads which represented the margins of the ischemic area or showed reciprocal changes. Recordings were performed using paper speeds of 5 mm/s and 25 mm/s.

Standard 12-lead ECGs were obtained before and at 2, 24, and 48 hours after the first PTCA procedure.

Nomenclature. Electrocardiographic changes resulting from acute coronary occlusion (eg, STE) are referred to as progressive or ischemic changes, and changes which followed deflation (eg, return of an elevated ST segment to baseline) are referred to as regressive or reperfusion changes.

Coronary Angiography and Angioplasty

Written informed consent was obtained from all of the patients. Diazepam (10 mg) was administered orally 1 h before angioplasty.

The Judkins technique was used to obtain right and left coronary angiograms in multiple views. All of the angioplasty procedures were performed by the Seldinger technique through a femoral artery using dilating catheters (USCI or ACS). Cineangiograms were performed in multiple projections; PTCA to the LAD was usually performed using the craniocaudal view, and PTCA to the CX was usually performed using the caudocranial view. Left ventricular wall motion was assessed using left ventriculography in the RAO and LAO views. The presence of collaterals was determined from injections at the baseline angiography. Heparin (10,000 IU) was administered intravenously after the baseline angiograms and before insertion of the balloon catheter. Balloon inflations and deflations were performed at times and locations selected exclusively by the angiographers, who were blinded to the ECG findings. The exact time of each balloon inflation and deflation was marked on the ECG recording, together with the balloon's location and patients' complaints.

The durations of time from inflation to the appearance of ischemic changes, from the appearance of ischemic changes to balloon deflation, from balloon deflation to the return of the ECG to baseline pattern and to appearance of negative T waves (if they occurred), and between balloon deflation and the following inflation were measured later. Balloon occlusion time was defined as the time from inflation to deflation. The time from the appearance of ischemic changes after balloon inflation to their disappearance after deflation was defined as the ischemic period. Ischemic changes were defined as either ST-segment deviation of 1 mm or more from baseline or the change to positive of a negative T wave or a change in the amplitude of the T wave of at least 2 mm.

Measurements of the ischemic changes were taken at their peak (at the end of each inflation). The time of their appearance was determined when they reached 50 percent of the diagnostic values mentioned previously (eg, an STE of 0.5 mm or T-wave peaking of 1 mm above baseline values).

Reperfusion changes were measured at two points: (1) return of the ST segment and T waves to baseline levels; and (2) appearance of negative T waves. The time of their appearance was defined as for ischemic changes. All measurements were obtained from the lead showing maximal ischemic changes.

Table 1—Occurrence of Ischemic and Reperfusion ECG Changes During Intermittent Coronary Occlusion

<table>
<thead>
<tr>
<th>Manipulated Artery</th>
<th>PTCA Procedures</th>
<th>Balloon Inflations</th>
<th>Ischemic Changes</th>
<th>Reperfusion Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD</td>
<td>18</td>
<td>175</td>
<td>170 (96)</td>
<td>164 (96)</td>
</tr>
<tr>
<td>CK</td>
<td>16</td>
<td>148</td>
<td>129 (87)</td>
<td>124 (96)</td>
</tr>
<tr>
<td>RCA</td>
<td>2</td>
<td>19</td>
<td>11 (74)</td>
<td>11 (100)</td>
</tr>
<tr>
<td>DIAG*</td>
<td>2</td>
<td>19</td>
<td>14 (73)</td>
<td>14 (100)</td>
</tr>
<tr>
<td>Total</td>
<td>36</td>
<td>357</td>
<td>324 (91)</td>
<td>313 (97)</td>
</tr>
</tbody>
</table>

*DIAG, Diagonal branch of LAD.

lead showing maximal ischemic changes.

Plasma CPK levels were obtained before PTCA and at 12 to 18 hours later. Therapy with heparin was continued for 24 to 48 hours after completion of the procedure to achieve whole-blood clotting time of approximately 20 minutes.

Isosorbide dinitrate (Isoket) was administered intravenously at a rate of 2 mg/h for 24 hours starting immediately before PTCA. All patients were also given aspirin (500 mg/day), dipyridamole (225 mg/day), and a calcium channel antagonist (either nifedipine or diltiazem) starting one day before PTCA.

Statistical analysis was performed using Student's t-test. Data are presented as the mean ± SD.

RESULTS

Thirty-eight PTCA procedures were studied in 35 patients (29 men and six women) aged 41 to 74 years (mean ± SD, 57 ± 9 years). The course of 357 balloon inflations was studied, 175 in 18 LADs, 148 in 16 CXs, 19 in two diagonal arteries, and 15 in two RCAs (Table 1). There was no mortality, and emergency surgery was not performed in any of the patients. Angioplasty was successful in all of the cases.

Ischemic ECG changes appeared during 324 (91 percent) of the 357 balloon inflations studied, at a mean of 20 ± 8 seconds after inflation (range, 8 to 36 seconds). Rapid regression (<1 minute) of these changes appeared in 313 (97 percent) of the inflations accompanied by ischemia, at a mean of 11 ± 5 seconds after deflation (range, 5 to 45 seconds).

Myocardial Necrosis during Angioplasty

The CPK level obtained at 12 to 18 hours after angioplasty was elevated in six patients, four with LAD and two with CX manipulations. The mean CPK level in these six patients was 517 ± 152 IU (range, 241 to 650 IU), with the upper limit of normal range in our laboratory being 180 IU. Each one of these six patients had a prolonged period of ischemia during which the ischemic ECG changes continuously persisted for at least 468 seconds (7.8 minutes). In all six patients with CPK elevation, a total occlusion of the manipulated coronary artery was identified, and ECG signs of acute myocardial infarction evolved. In five of these patients, an emergency redilatation was successful, and the ischemic changes resolved at 0.2 to 3
minutes after reperfusion (mean, 1.5 minutes). In one patient a distal LAD occlusion could not be redilated. The duration of the ischemic ECG changes did not exceed 322 seconds (5.4 minutes) in any of the patients with CPK levels within the normal range. Cumulative ischemia, calculated as either the sum of ischemic periods or the sum of balloon occlusion periods, did not predict myocardial damage. The cumulative balloon occlusion period exceeded 400 seconds in all of the patients, reaching 1,000 seconds in three (none of whom had elevated CPK levels).

Ischemic Changes

Occlusion of the LAD resulted in STE in the chest leads. It was maximal and was always present in leads V4 and V5 and decreased both in frequency and magnitude in the neighboring chest leads (Fig 1 and 2). The STE was also frequently observed in leads 1 and aVL (in 56 percent and 76 percent of the patients, respectively). ST-segment depression was observed in leads 3 and aVF in 82 percent of the LAD patients; STD in the chest leads was found in this group only in lead V6 and, even there, only in 6 percent of the patients. None of the LAD patients had STD in leads V1 to V5.

In patients with occlusion of the proximal part of the LAD (Fig 3), only STE was observed in the chest leads and in leads 1 and aVL, occurring in the latter two leads in all of these patients. In leads 2, 3, and aVF, only STD was observed during proximal LAD occlusion, occurring in lead 2 in 50 percent and in leads 3 and aVF in all of the patients. During distal LAD occlusions, STE in leads 1 and aVL occurred less frequently and STD in those leads occurred more frequently than during proximal LAD occlusions, and only distal LAD occlusions resulted in STD in leads 1 and aVL and STE in leads 2, 3, and aVF, with STE in lead 2 being observed only in distal LAD patients, but those differences were not statistically significant.

Occlusion of the CX, in contrast to occlusion of the LAD, never resulted in STE in leads V1 to V5. Occlusion of the CX caused only STD in leads V1 to V4, which occurred most frequently and prominently in leads V3 and V4. In patients with ischemic ST-segment deviation in lead V3, it could be used to differentiate between LAD and CX occlusions with specificity and sensitivity of 100 percent. Monitoring lead V3 alone provided a sensitivity, specificity, and accuracy of 87.5 percent.

Occlusion of the RCA resulted in STE in leads 2, 3,
and aVF and STD in leads 1, aVL, V₂, and V₃. Occlusion of a diagonal branch of the LAD, which was the first diagonal in both patients studied, resulted in STE in leads 1, aVL, and V₂. This pattern differed from that observed in LAD occlusions by the absence of STE in the chest leads except lead V₂ and by higher STE in leads 1 and aVL, as compared to lead V₂.

Two patients with collaterals from RCA to LAD and one with collaterals from RCA to CX had ischemic ECG changes indistinguishable from those observed in patients without collaterals.

Electrocardiographic Manifestations of Reperfusion

Three types of ECG changes were noted following balloon deflation: return of the ST segment and T wave to baseline ("normalization"), inversion of the T wave from positive to negative, and transient STD evolving from STE before returning to baseline. These

![Figure 2. Twelve-lead distribution of ST-segment shift during coronary artery occlusion. D, Diagonal branch of LAD.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21624/)

![Figure 3. Distribution of ST-segment shift according to location of balloon inflation in LAD.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21624/)
reperfusional (regressive) changes always followed and never preceded balloon deflation.

In LAD patients, negative T waves appeared in the lead of maximal ischemic changes (usually lead V, or V.) after 78 deflations, return of the ST segment to baseline without T wave inversion appeared after 77 deflations, and transient STD appeared after nine deflations.

Negative T waves appeared in 10 (63 percent) of 16 CX patients after 58 (39 percent) out of 148 inflations. Negative T waves appeared in five cases after STE, in three after STD, and in two after occlusions which were not accompanied by visible ischemic changes.

In patients who had postischemic T-wave inversion, its appearance occurred more rapidly after the first than after the last inflations in the same patient (14 ± 13 seconds vs 70 ± 54 seconds after deflation; p<0.005). In the five patients who suffered myocardial damage but had a successful redilatation, regression occurred at 10 to 360 seconds after deflation and only 24 hours later in the patient who had myocardial damage and no reperfusion, a significant delay in comparison with the patients without myocardial damage (91 ± 135 seconds vs 13 ± 9 seconds, respectively; p<0.005).

**Chest Pain during Intermittent Coronary Occlusion**

Four patients were heavily sedated during PTCA and could not report any symptoms. Of the 34 patients who were awake during the procedure, 23 (68 percent) reported chest pain during balloon inflation. Chest pain was reported by 15 (94 percent) out of 16 awake patients with LAD manipulation vs only four (29 percent) out of 14 awake patients with a CX manipulation (p<0.001). No differences in the incidence of diabetes mellitus or of neurologic disturbances were found between the two groups of patients. Each of the patients had suffered anginal pain previously. The exact time of onset of chest pain was not documented, but it occurred within 60 seconds of inflation in all of the symptomatic patients.

**Discussion**

**Sensitivity of Surface ECG in Detecting Ischemia Caused by Acute Coronary Occlusion**

In various studies⁹⁻¹⁸ a variable sensitivity of the surface ECG was reported, ranging from 31 percent to 84 percent. Friedman et al¹⁸ found that the sensitivity of intracoronary ECG recording was superior to the surface ECG, being 70 percent and 31 percent, respectively. In our patients, ischemic changes occurred during 91 percent of all inflations and during 96 percent of the inflations in the LAD, incidences higher than that reported by Friedman et al.¹⁸ even for intracoronary recording, and in significant disagreement with the 31 percent sensitivity reported for the surface ECG. The difference may be due to the ease of identification of ischemic changes from recording at a paper speed of 5 mm/s, the use of a full 12-lead ECG, and possibly also due to the selection of patients, since we did not include patients with nonviable myocardium or a previous Q-wave infarction in the area supplied by the manipulated artery.

As reported by others, a high consistency of the ECG changes and the time of their appearance was also found in our patients. As long as myocardial necrosis had not occurred, these times were not changed, and ischemia caused by balloon inflation was neither delayed nor shortened by previous inflations.

Mapping of ischemic changes is of considerable importance, and much effort has been made in order to find ECG patterns that will predict the location of coronary obstruction or the existence of collateral. According to our findings, ischemic ECG changes can be used to differentiate between LAD or CX occlusions with a high sensitivity and specificity. The use of lead V₃ alone may serve the same purpose and may be especially useful for Holter ECG monitoring and to monitor ischemia during PTCA. The different patterns found in our patients with proximal vs distal LAD occlusions did not reach statistical significance but, if confirmed in a larger series of patients, will have significant clinical importance.

**Time Relationship between Coronary Occlusion and Appearance of Ischemic Changes**

In dogs, STE occurs only 30 to 60 seconds after coronary occlusion and reaches a maximum level at 5 to 7 minutes after occlusion. Sugisita et al.¹⁴ found ischemic ECG changes at 90 ± 60 seconds of exercise, but in their study, ischemia was caused by an increase of oxygen demand, rather than by acute coronary occlusion. Macdonald et al.¹⁵ detected ischemic changes at approximately 10 seconds after coronary occlusion; Hauser et al.¹⁶ reported that in their patients, ischemic changes occurred at a mean of 30 ± 5 seconds after coronary occlusion; and Brymer et al.¹⁷ noted these changes at 10 to 15 seconds after occlusion, but their data were not detailed. Quyyumi et al.¹⁸ reported a time of onset of ST-segment change of 15 ± 8 seconds (range, 6 to 36 seconds). Friedman et al.¹² noted STE to appear on the intracoronary lead "several seconds" after balloon inflation, but again, data were not specified.

In our study, the recording of multiple balloon inflations shows that in humans, acute myocardial ischemia, as reflected in the surface ECG, occurs at a mean of 20 ± 8 seconds after acute total occlusion of a coronary artery under standard conditions of rest and probably normal oxygen consumption, regardless of the coronary artery involved. The difference between our findings and experiments in animals may
be due to differences in basal oxygen consumption by the myocardium, myocardial energy reserve, and differences in collateral function.

Finally, according to our findings, as well as those reviewed, it can be concluded that myocardial ischemia in man evolves very shortly after an acute occlusion of a major coronary artery, and this phenomenon is consistent in every patient.

**Reperfusional Changes**

Rapid and distinct resolution of STE was reported to be a clear indicator of successful reperfusion with thrombolytic agents. It has been demonstrated that the best ECG outcome may be seen in those patients with early reperfusion. In our patients, rapid resolution of the ischemic changes was found in those with uncomplicated procedures, while in those with long ischemic episodes and periprocedural infarction, such resolution was delayed. In addition, the appearance of negative T waves was delayed in final vs initial inflations. These data suggest that reversibility of ischemic changes and rapidity of their occurrence are inversely related to the duration of ischemia and possibly also to the extent of myocardial damage. The longer it persists, the smaller the probability for resolution faster than the natural ECG course. It can be speculated that in patients with an acute myocardial infarction and late reperfusion, rapid resolution of the ischemic changes should not be expected, since a large proportion of the jeopardized myocardium is already necrotic. Whether successful early reperfusion will always result in rapid resolution of the ischemic ECG changes is also unclear. Five of our patients had evidence of myocardial necrosis after long periods of ischemia (ranging from 7.8 to 60 minutes) and can be regarded as having a myocardial infarction with early reperfusion. Although reperfusion was achieved early (within 1 h from occlusion), regression of the ischemic changes was significantly delayed, but occurred in all of the five patients. Hackworthy et al reported that in patients with spontaneously occurring reperfusion, regression of the ischemic changes occurred earlier than in those without reperfusion. In our patients with early reperfusion, both the duration of ischemia and the delay in appearance of reperfusional ECG changes were shorter than those reported previously, and in those of our patients without myocardial damage, the appearance of these changes was the earliest. These data further support our thesis, namely: that there is a direct relationship between the duration of ischemia and the delay in appearance of reperfusional changes.

The transient STD found in some of our patients has not been described after infarction or reperfusion. We believe that this phenomenon represents transient subendocardial ischemia as a transitional state between transmural ischemia and complete reperfusion, which may affect initially the subepicardial myocardium.

**CPK Release after Angioplasty**

In animal experiments, coronary occlusion for 30 minutes caused myocardial necrosis, while ligation for 20 minutes did not. In our patients, myocardial necrosis evolved after ischemic episodes as short as 7.8 minutes. To the best of our knowledge, no previous attempt has been made to determine the shortest duration of ischemia that causes myocardial damage in man.

The significance and the context of myocardial necrosis in our patients are of some interest. Oh et al found elevation of CK-MB after successful angioplasty in 20 percent of their patients. The variables significantly related to the enzyme elevation were chest pain, small branch vessel occlusion, and recent myocardial infarction. Release of CK-MB did not increase the risk of in-hospital or late morbidity or mortality. Using their definition, all of our patients also had successful angioplasty, and none was referred to emergency surgery. Myocardial damage occurred in 16 percent of our patients (6 of 38). In our patients the occurrence of myocardial necrosis could be related only to the duration of myocardial ischemia. Side-branch vessels were occluded in two of our patients, but none had enzyme elevation. None of our patients had had a recent myocardial infarction. Chest pain, although occurring in all six patients with CPK enzyme elevation, also occurred in 60 percent of the patients who did not suffer myocardial damage. Thus, chest pain was not a good predictor of myocardial damage in our patients. Even balloon occlusion time, calculated as the time between balloon inflation and deflation, did not predict myocardial necrosis in our patients, and the only predictor of myocardial necrosis was the duration of ischemic ECG changes, which was more sensitive than the duration of balloon inflation or the cumulative time of ischemia or coronary occlusion. These findings differ from those reported by Geft et al, since cumulative ischemia was not a predictor of myocardial damage in our patients, possibly because it was not quantitatively sufficient.

In our study, patients with ischemic periods as long as 322 seconds did not have evidence of myocardial necrosis. This may suggest that the dilating balloon may be inflated for longer than the upper limit of 90 seconds used in our patients without causing myocardial damage. Additionally, it can be assumed that in those patients with spontaneously occurring acute total coronary occlusion, myocardial necrosis will occur in less than the 20 to 30 minutes commonly considered to be the borderline between acute myocardial ischemia and infarction, and this may influence...
the decision as to when to administer thrombolytic agents.

CONCLUSIONS

We conclude that in patients with noninfarcted myocardium, the ECG detects coronary occlusion and reperfusion with a very high sensitivity. The ECG changes follow those coronary events within seconds. Some patterns of ischemic changes are specific to the site of coronary occlusion, but reperfusion changes are not. Lack of rapid regression predicts lack of reperfusion, and persistence of the ischemic changes for more than 7.8 minutes predicts myocardial necrosis, while coronary occlusion for less than 5.4 minutes carries no such risk.

REFERENCES

1 Pardee HEB. An electrocardiographic sign of coronary artery occlusion. Arch Intern Med 1920; 26:244-50
2 Richardson SC, Norton P, Murtagh JC, Scott ME, O'Keeffe B. Relation of coronary arterial patency and left ventricular function to electrocardiographic changes after streptokinase treatment during acute myocardial infarction. Am J Cardiol 1968; 61:961-65
7 Hackworth RA, Vogel MB, Harris PJ. Relationship between changes in ST segment elevation and patency of the infarct-related coronary artery in acute myocardial infarction. Am Heart J 1986; 112:279-84
18 Ross AM, for the TIMI investigators. Electrocardiographic and angiographic correlations in myocardial infarction patients treated with thrombolytic agents: a report from the NHLBI Thrombolysis in Myocardial Infarction (TIMI) trial. J Am Coll Cardiol 1985; 2:495-501
20 Geft IL, Fishbein M, Ninomiya K, Hashida J, Choux E, Yan J, et al. Intermittent brief periods of ischemia have a cumulative effect and may cause myocardial necrosis. Circulation 1982; 66:1150-53