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Research Article

The relationship between early and late epicardial electrocardiographic changes as well as those in regional myocardial blood flow (MBF) and the severity of myocardial damage was determined in 12 anesthetized dogs with left anterior descending coronary artery ligation. Radioactive microspheres (15 mum) were used to measure regional MBF at 15 min (early) and 24 h (late) after coronary occlusion. Severity of myocardial damage was assessed by the extent of myocardial creatine phosphokinase depletion 24 h after coronary ligation. There was a close linear correlation between myocardial creatine phosphokinase activity and regional MBF both early (r=0.93, 2P less than 0.001) and late (r=0.88, 2P less than 0.001). An inverse but less precise relationship existed between acute epicardial ST-segment elevation and early (r=-0.41, 2P less than 0.001), or late (r=0.35, 2P less than 0.05) regional MBF. Similarly, a weak correlation was found between myocardial creatine phosphokinase (IU/mg protein) at 24 h and early epicardial ST (millivolt) elevation (r=-0.36, 2P less than 0.02). In the center zones of the infarct with MBF 1/10 of normal, about 35% of the areas with normal QRS width had no epicardial ST-segment elevation 15 min after coronary occlusion. About 44% of the areas which developed pathological Q-waves in the electrocardiogram at 24 h had no ST elevation 15 min after coronary ligation. Late evolution of abnormal Q-waves […]

Relationship between Epicardial ST-Segment Elevation and Myocardial Ischemic Damage after Experimental Coronary Artery Occlusion in Dogs

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ABSTRACT The relationship between early and late epicardial electrocardiographic changes as well as those in regional myocardial blood flow (MBF) and the severity of myocardial damage was determined in 12 anesthetized dogs with left anterior descending coronary artery ligation. Radioactive microspheres (15 μm) were used to measure regional MBF at 15 min (early) and 24 h (late) after coronary occlusion. Severity of myocardial damage was assessed by the extent of myocardial creatine phosphokinase depletion 24 h after coronary ligation. There was a close linear correlation between myocardial creatine phosphokinase activity and regional MBF both early ($r = 0.93$, $2P < 0.001$) and late ($r = 0.88$, $2P < 0.001$). An inverse but less precise relationship existed between acute epicardial ST-segment elevation and early ($r = -0.41$, $2P < 0.001$), or late ($r = -0.35$, $2P < 0.05$) regional MBF. Similarly, a weak correlation was found between myocardial creatine phosphokinase (IU/mg protein) at 24 h and early epicardial ST (millivolt) elevation ($r = -0.36$, $2P < 0.02$). In the center zones of the infarct with MBF 1/10 of normal, about 35% of the areas with normal QRS width had no epicardial ST-segment elevation 15 min after coronary occlusion. About 44% of the areas which developed pathological Q-waves in the electrocardiogram at 24 h had no ST elevation 15 min after coronary ligation. Late evolution of abnormal Q-waves occurred almost invariably in areas in which the early MBF was reduced to less than 50% of normal and in areas which subsequently had myocardial creatine phosphokinase levels reduced to less than 60% of normal. After coronary occlusion, the severity of the ultimate myocardial damage, which was directly proportional to the degree of reduction in MBF, was therefore not reliably predicted by the early epicardial ST-segment elevation. The data obtained in these studies suggest the need for caution in the use of acute ST-segment elevation as a predictive index of the extent or severity of myocardial ischemic damage.

INTRODUCTION

Elevation of the precordial ST segment of the electrocardiogram in myocardial ischemia, first noted by Pardee (1) in 1920, has been accepted for many years as the major diagnostic criterion of acute myocardial infarction (2) or its extension (3). Its electrophysiological correlates were established by Samson and Scher (4) who showed that acute epicardial ST-segment shifts in ischemia were due to accelerated repolarization when surface and intracellular cardiac potentials were recorded simultaneously. The possibility that a reduction in the magnitude of this electrophysiologic change may be associated with less ischemic injury was raised by the work of Sodi-Pallares et al. (5). They reported a reduction in the extent of ST-segment alterations by the use of "polariz-

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ing" solutions (5) and subsequently by the coronary vasodilator drug, verapamil (6).

More recently, Maroko and his colleagues (7, 8) have demonstrated that after experimental coronary occlusion, interventions which augment myocardial oxygen consumption (MVO_2) tend to aggravate epicardial and precordial ST-segment elevation, whereas those which diminish MVO_2 lead to a reduction in ST-segment elevation.[1] In addition, they found a good linear correlation between the magnitude of ST-segment elevation 15 min after coronary artery branch occlusion, and the extent of myocardial creatine phosphokinase (CPK) enzyme depletion or the degree of histological disorganization 24 h later (7–9). These observations have formed the basis for the mapping of precordial ST-segment elevation as a method to measure extensions and reductions in the size of evolving clinical infarcts (10–13). In contrast, our own studies (14) and those of Cohen and Kirk in dogs (15) did not reveal a simple quantitative relationship between epicardial ST-segment elevation and the regional myocardial blood flow (MBF) at 15 min after experimental coronary occlusion. However, in these studies the ultimate fate of the ischemic myocardium relative to the degrees of the initial reduction in regional tissue blood flow after coronary occlusion was not defined. In particular, the acute changes in MBF were not correlated with the degree of myocardial CPK depletion which has been found to reflect accurately the severity of cellular damage demonstrated by histological techniques (9). The present investigation was therefore designed to extend the acute studies to examine more critically in the same animals on a regional basis the relationship of the early changes in epicardial ST-segment elevation as well as MBF with the alterations in the electrocardiogram (ECG) appearances, myocardial perfusion, and CPK depletion which occur 24 h after coronary artery ligation.

METHODS

Myocardial infarction was produced by ligation of the left anterior descending (LAD) coronary artery in 12 mongrel dogs weighing 22–30 kg which, after overnight fast, were anesthetized with thiopentone sodium (30 mg/kg i.v.). The animals were respired through a cuffed endotracheal tube connected to a Harvard positive pressure respirator (Harvard Apparatus Co., Inc., Millis, Mass.) delivering a mixture of air, nitrous oxide, and oxygen adjusted to maintain $PaCO_2$ at 30–40 mm Hg and PaO_2 at 80–110 mm Hg. Anesthesia was maintained with intermittent bolus injections of pentobarbital sodium.

Left lateral thoracotomy was performed in the fifth interspace under sterile conditions and the heart suspended in a pericardial cradle. A polyethylene cannula for injection of radioactive microspheres was introduced into the left atrium through an incision in the atrial appendage. The LAD coronary artery was dissected free about 2 cm from its origin. A polyethylene cannula was also placed in the right femoral artery through an arteriotomy and was left in situ for 24 h, being kept patent by regular flushing with heparinized saline.

The LAD coronary artery was ligated in two stages (16). The site of ligation was usually distal to the origin of the first diagonal branch. This level of LAD occlusion was previously found (14) to produce an infarct of approximately 20% (range 15–32) of the left ventricular mass. The variability of infarcts was not considered to be important since, in the present series of experiments, the correlations between measured parameters were made on a regional basis, and no attempt was made to measure overall "infarct size". Before coronary artery occlusion, epicardial ECGs were recorded over 14 positions on the anterior surface of the left ventricle. The electrode positions, schematically shown in Fig. 1, were determined by their relationship to the epicardial vessels so that electrode positions were at measured distances from the junction of the diagonal branches with the main LAD coronary artery. Four of these positions (normal zone: 1–4) were above the level of the LAD ligature, four (border zone: 5–8) were at the level of the ligature bordering the cyanotic area, and six (center zone: 9–14) were over the center of the evolving infarct. The center of each electrode position was measured at 1 cm from that of its neighbor. 15 min after complete occlusion, epicardial ECG map was taken again and regional MBF was measured by the injection of radioactive microspheres into the left atrium. The left atrial cannula was then removed and the pericardium approximated by interrupted sutures. The thoracotomy was closed in layers over the re-expanded lungs. Constant sedation and analgesia were maintained with 4–6 hourly intramuscular administration of papaveratrum (0.3–0.4 mg/kg) but no antiarrhythmic drugs were used. 24 h later, the animals were re-anesthetized and the heart exposed through the initial thoracotomy incision. The epicardial map over the previously defined electrode positions was repeated and MBF measured again using microspheres labeled with a different radionuclide.

At the end of the experiment, the heart was removed after ventricular fibrillation was induced with an injection into the left atrium of 10–15 ml saturated potassium chloride. Seven transmural myocardial biopsies, each corresponding to two contiguous electrode positions (see Fig. 1) and measuring approximately 2 × 1 × 1 cm, were excised from the anterior left ventricular wall. An additional biopsy specimen was taken from the posterior left ventricular wall perfused by the circumflex branch of the left coronary artery. Each of the resulting eight pieces of the myocardium was divided into two equal halves for the measurement of MBF and tissue CPK, respectively. The biopsy specimen used for the measurement of MBF was further subdivided into epicardial and endocardial halves for computation of fractional regional blood flow from the radioactivity counts (see below). The experimental design was such that the electrocardiographic appearances, both early and late, could be correlated with the values for regional perfusion and CPK activity of the myocardium directly beneath the recording electrode.

Analysis of electrocardiographic data. Epicardial ECGs were recorded using a smooth rounded tip steel electrode which was mounted on a flexible platinum-coated wire so

[1] *Abbreviations used in this paper*: CPK, creatine phosphokinase; ECG, electrocardiogram; LAD, left anterior descending (coronary artery); LV, left ventricle; MBF, myocardial blood flow; MVO_2, myocardial oxygen consumption.

that relatively uniform and gentle pressure could be maintained on the epicardial surface during cardiac contraction. The epicardium was moistened with isotonic saline before the epicardial ECG map was recorded. The ECGs were displayed on a Sanborn 350 (Hewlett-Packard Co., Waltham Div., Waltham, Mass.) or Gould B 480 recorder (Gould Inc., Instrument Systems Div., Cleveland, Ohio) and recorded at paper speed of 50 mm/s, and sensitivity 1 mV = 1 mm. In the present series of studies, two animals developed late ventricular fibrillation (between 15 and 24 h after coronary occlusion). The data from these studies were excluded from the final analysis. In the remaining 12 dogs surviving 24 h, ECG maps were taken during sinus rhythm. ST-segment elevation was measured 0.06 s after the end of the S-wave, and the value for each epicardial ECG position was obtained by averaging the mean of at least five complexes to minimize beat-to-beat variability of ST-segment measurement. This was about 10% in our hands. Whenever the end of the S-wave was indistinct, ST-segment elevation was measured 0.06 s from the J-point. In practice, this was often necessary. The TP interval was considered the isoelectric line, any degree of ST-segment deviation above this being measured and included in the analysis. Abnormal Q-waves were defined as those with a duration of 0.03 s or greater. To exclude the possibility of different observers exerting varying electrode pressures on the epicardial surface and thus introducing unacceptably large errors in the measurement of ST-segment changes, observer-to-observer variation was tested in six experiments. The ECG maps were recorded alternately in rapid succession by two different observers and mean results compared. The interobserver variation was less than 5%. The variability in the ST segment in duplicate ECG maps by the same observer was also the same order.

Measurement of myocardial flow. The details of the technique used to measure regional MBF has been described previously (14). MBF was measured at 15 min and 24 h after complete LAD occlusion by injecting into the left atrium about 1,000,000 carbonized plastic microspheres (15 ±5 μm diameter) labeled with ^{141}Ce or ^{85}Sr (3M Company, St. Paul, Minn.). Immediately before the injection, arterial blood (reference sample) was withdrawn from the femoral artery at 7 ml/min with a Harvard pump, withdrawal being maintained for 3 min. The tip of the arterial catheter was left in the external iliac artery to ensure cross-sectional sampling of the blood flow (17). The order of injection of microspheres was reversed in consecutive experiments. The radioactivity of the myocardial biopsies (about 1 g specimens) and reference blood samples was measured in a Packard Autogamma well-type scintillation counter (Packard Instrument Co., Inc., Downers Grove, Ill.) using an integral counting technique (14).

Biochemical estimations. Myocardial CPK was estimated by the method of Shell et al. (18). Whole thickness biopsies taken from the left ventricle were homogenized in an Ultra-Turrax TP 18-10 (Janke and Kunkel Co., Germany) by two 60-s bursts at 20,000 rpm. CPK activity was assayed by the method of Rosalki (19), with a spectrophotometer at 340 nm fitted with an accessory SP 850 scale expansion set to give tenfold expansion of absorbance. A commercial test kit (Calbiochem, San Diego, Calif.) was used, and the reaction was carried out at 30°C. The protein content of the homogenate was estimated by the biuret method, and myocardial CPK level expressed in international units per milligram of protein.

Analysis of data. In each of our experiments, seven myocardial samples were obtained from the anterior left ventricular wall, two from the normal zone, two from the border zone, and three from the infarcted zone. A further sample was taken from the anterior left ventricular wall. From each sample, the data was collected with respect to: (*a*) MBF at 15 min and 24 h after coronary occlusion, (*b*) myocardial CPK at 24 h, and (*c*) electrocardiographic features at 15 min and 24 h after ligation from two contiguous electrode positions. ST-segment elevation over each myocardial sample was obtained by averaging the changes in the two ECG positions. Since the microspheres were injected after epicardial ECG maps had been taken, possible effects of microspheres on ST-segment elevation could be discounted. Late Q-waves were considered to be present in a myocardial sample if they were found in the records from at least one of the two electrode positions.

Correlative analyses of these data were performed using the correlation of linear regression and the Student's *t* test; results were considered statistically significant when $2P < 0.05$.

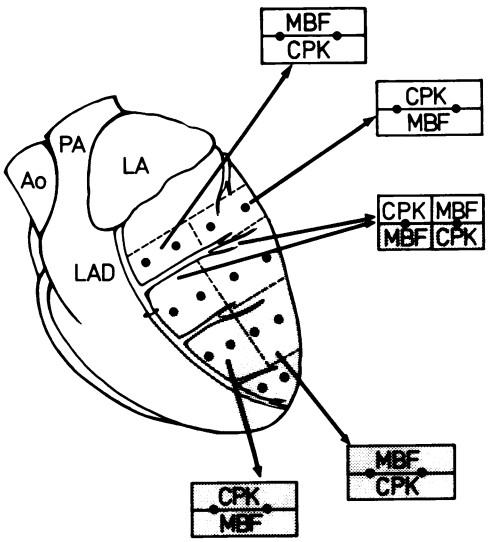

FIGURE 1 Schematic illustration of the experimental preparation used to study regional distribution of MBF and its relationship to epicardial ECG changes and myocardial CPK depletion after LAD artery occlusion in the dog. The stippled area distal to the ligature (center of the diagram) represents the ischemic zone. The closed circles in the diagram represent electrode positions: they are numbered consecutively from 1 to 14 from left to right (see text). Inserts illustrate the method of tissue sampling for the measurement of MBF and CPK activity from the normal (electrode areas 1–4), border (electrode areas 5–8), and center (electrode areas 9–14) zones. An additional biopsy was also taken from the back of left ventricle (LV). The method of randomization illustrated was necessary because tissue CPK and MBF could not be measured in the same samples. The mean values of CPK and MBF could thus be correlated with the mean value of ST-segment elevation from two consecutive electrode positions.

RESULTS

The data showing the effects of LAD occlusion on regional MBF, acute epicardial ST-segment elevation, and myocardial CPK depletion are presented in Table I.

TABLE I

Effect of Coronary Occlusion on Average ST-Segment Elevation, Regional Myocardial Blood Flow and Myocardial Creatine Phosphokinase Depletion

	MBF		Myocardial CPK at 24 hours	Mean ST at 15 min
	15 min	24 h		
	ml/min/100 g		*IU/mg protein*	*mV*
Normal zone (Anterior LV: Areas 1–4)	123.4±14.2	133.0±15.7	26.9±1.03	0
Border zone (Areas 5–8)	62.9±8.7*	63.7±8.2*	15.2±2.6*	4.2±0.8
Center zone (Areas 9–14)	9.6±1.7*	14.9±3.6*	6.7±0.6*	3.7±0.8
Control zone (Posterior LV)	118.6±17.4	103.6±12.4	24.4±1.1	—

The data shown are means±SEMs; those for MBF and myocardial CPK were obtained from eight animals. In three other animals MBF was measured, but absolute flows for 15 min could not be calculated because of technical factors relating to reference sample. In another animal, epicardial mapping and MBF at 15 min were not measured. The data relative to ST-segment elevation are from 11 animals.

* Significantly different from the values in the normal zones ($2P < -0.001$).

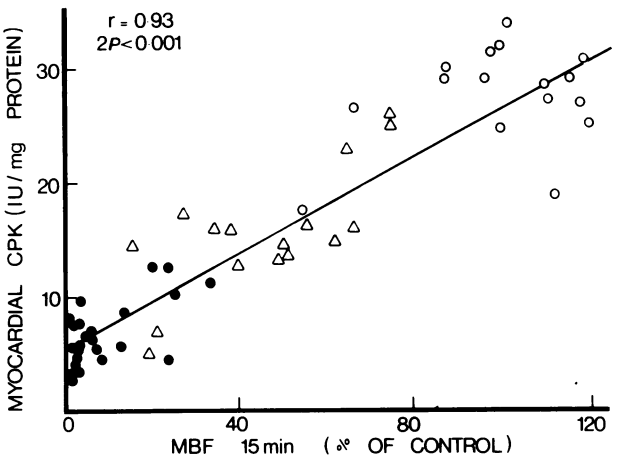

FIGURE 2 Relationship between regional MBF (% of control) at 15 min after LAD occlusion and CPK activity obtained at the same site 24 h later. Open circles represent individual control samples from normally perfused areas, open triangles represent areas with moderate reduction in MBF (border zone), and closed circles represent areas with severe reduction in MBF (center zone). Regression line: $y = 5.25 + 0.21\,x$; $r = 0.93$; eight dogs, 56 biopsies.

15 min after LAD occlusion, MBF in the center of the territory of the ligated artery fell to 8% of that of the normally perfused myocardium. At the border of the infarct, the flow was reduced to 51% of normal. 24 h later, the flow in the center of the infarct was 11% of normal, and it was 48% of normal in the border zone. Corresponding values for the myocardial CPK activity were 25 and 56%, respectively. At 15 min after LAD occlusion the mean heart rate for the whole series of dogs was 116±7 beats/min (mean ±SEM), mean arterial pressure was 113±8 mm Hg, and the mean left atrial pressure was 8.3±1.2 mm Hg. 24 h later, the mean heart rate was 162±7 beats/min, mean arterial pressure was 80±8 mm Hg, and mean left atrial pressure was 6±1 mm Hg.

TABLE II

A Comparison of the Correlations between Epicardial ST-Segment Elevation on MBF and Myocardial CPK Activity after Linear and Logarithmic Plots

	Number of biopsies	r_1 or r_2	Significance, r_1 vs. r_2*
ST-elevation‡ (15 min) vs. myocardial CPK	48	$r_1 = -0.358$ $r_2 = -0.338$	$2P < 0.25$
MBF (15 min) vs. myocardial CPK	56	$r_1 = 0.926$ $r_2 = 0.886$	$2P < 0.22$
MBF (24 h) vs. myocardial CPK	56	$r_1 = 0.880$ $r_2 = 0.839$	$2P < 0.04$

* The statistical analysis for difference between r_1 and r_2 according to (38). r_1 = correlation coefficient using myocardial CPK on linear scale and r_2 = correlation coefficient using myocardial CPK on logarithmic scale.

‡ The ST-segment elevation here was measured at 60 ms after end of QRS complex.

Since ST-segment elevation may be influenced by the development of focal intraventricular conduction block, areas with abnormal QRS prolongation were excluded in the analysis of ST-segment changes. Before coronary ligation, the mean QRS duration of 154 epicardial ECG complexes from 11 dogs was 41.6 ±6.3 ms (mean±SD, range 30–50 ms). The upper limit of the normal QRS interval was taken to be 60 ms (mean±3 SD). After coronary occlusion, 13 of the 154 (8.4%) epicardial ECG sites were found to have abnormal QRS prolongation. These 13 sites, from 7 animals, were all from the center zones, and 4 had ST-segment elevation 0.5 mV or greater. The mean ST-segment elevation of 3.7±0.8 mV for the center zones (11 animals) having normal QRS duration was not significantly different from the value, 4.2±0.8 mV, for the border zone. No ST-segment elevation was found over the normally perfused myocardium (areas 1–4).

Relationship between myocardial CPK and regional transmural MBF. Correlations involving myocardial CPK activity were examined with myocardial CPK activity expressed in international units per milligram of protein on linear as well as logarithmic scales. In every instance, a higher correlation coefficient was found when myocardial CPK levels were expressed on a linear scale than when they were expressed

on a logarithmic scale (Table II). Correlative data are, therefore, presented here with levels expressed on a linear scale.

A high degree of correlation existed between myocardial CPK at 24 h and MBF, expressed as a percentage of normal at 15 min (Fig. 2; $r = 0.93$, $t = 18.027$ ($2P < 0.001$) and that at 24 h (Fig. 3; $r = 0.88$, $t = 13.63$, $2P < 0.001$) after coronary occlusion. It will be apparent that the values for myocardial CPK and MBF for the normal zones and those for the center zones are clustered at the opposite ends of the graphs (Figs. 2 and 3), whereas the values for the border-zones are intermediate in position.

Relationship between acute epicardial ST segment and myocardial CPK and regional transmural MBF. In 8 dogs, a weak but statistically significant negative correlation was demonstrated between the height of early epicardial ST-segment duration (measured at 60 ms after the end of S-wave) and subsequent levels of myocardial CPK. The linear regression of method of least squares between these parameters is shown in Fig. 4 ($r = -0.36$, $t = 2.600$, $2P < 0.02$). A correlative analysis between myocardial CPK levels and early epicardial ST-segment elevation measured at 20 ms after the S-wave was also performed. The regression was: $y = 3.94 - 0.13x, r = -0.51, 2P < 0.001$, $n = 45$ biopsies. 7 of the 16 biopsy sites from the center zones of the infarct which had no ST-segment elevation at 15 min after coronary occlusion had severe depression of myocardial CPK activity (less international units per milligram of protein) 24 h later.

Similarly, the degree of early ST-segment elevation in 11 dogs, correlated inversely but weakly with regional MBF both at 15 min (Fig. 5; $r = -0.41$, $t = 3.68$, $2P < 0.001$) and at 24 h (Fig. 6; $r = -0.35$, $t = 2.284$, $2P < 0.05$) after coronary occlusion. The relationship between early ST-segment elevation and early as well as late measurements of regional MBF was somewhat closer when values for ST-segment elevation measured at 20 ms after S-wave were used in

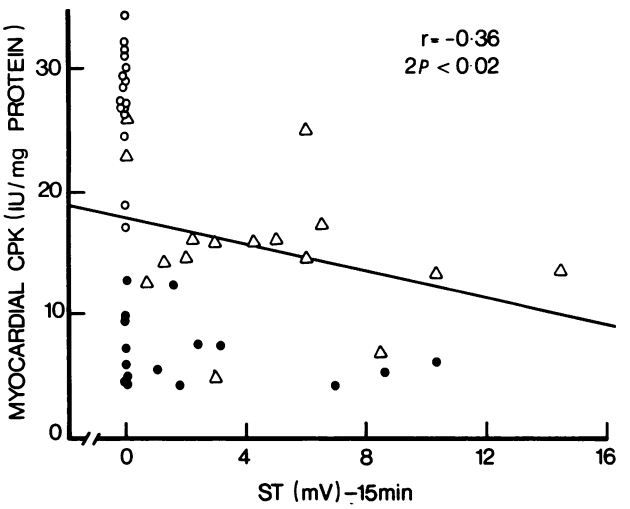

FIGURE 4 Comparison between epicardial ST-segment elevation 15 min after LAD occlusion and myocardial CPK activity obtained at the same electrode sites 24 h later. Symbols in the graph are the same as in Fig. 2. Regression line: $y = 18.8 - 0.97\,x$; $r = -0.36$, eight dogs, 48 biopsies. ST-segment elevation was measured at 60 ms after the end of QRS complex.

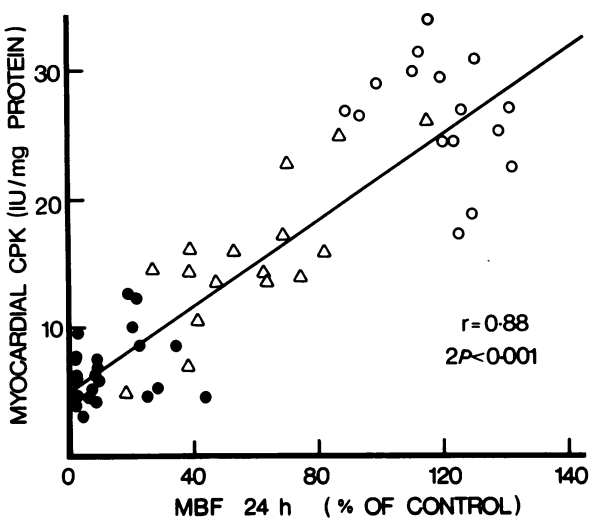

FIGURE 3 Relationship between regional MBF (% of control) and myocardial CPK activity at 24 h after LAD occlusion. Symbols in the graph are the same as in Fig. 2. Regression line: $y = 5.0 + 0.17\,x$; $r = 0.88$, eight dogs, 56 biopsies.

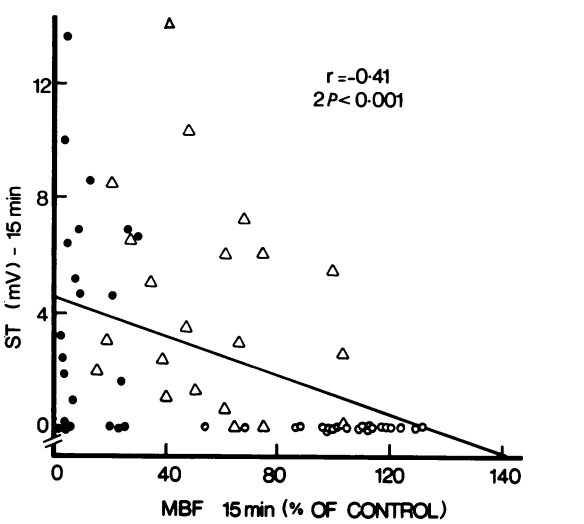

FIGURE 5 The relation between epicardial ST-segment elevation and regional MBF (% of control) 15 min after LAD occlusion. Symbols in the graph are the same as in Fig. 2. A weak but highly significant negative correlation is shown: $y = 4.52 - 0.034\,x$; $r = -0.41$, 11 dogs, 69 biopsies. ST-segment elevation was measured 60 ms after the end of QRS complex.

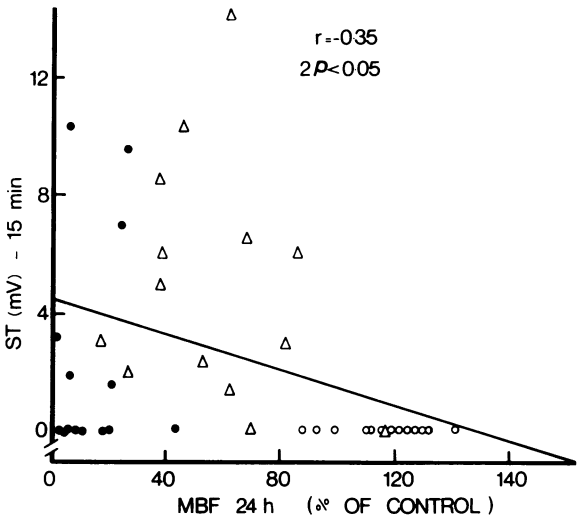

FIGURE 6 The relation between epicardial ST-segment elevation at 15 min after LAD occlusion and regional MBF (% control) at the same times 24 h later. Symbols in the graph are the same as in Fig. 2. Regression: $y = 4.49 - 0.029\ x$; $r = -0.35$, seven dogs, 42 biopsies. ST-segment elevation was measured 60 ms after the end of QRS complex.

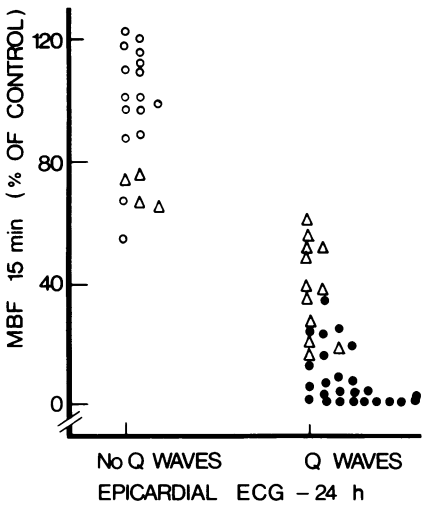

FIGURE 8 The frequency of Q-wave development in epicardial ECGs at 24 h in relation to changes in regional MBF (% of control) at 15 min after LAD occlusion. Symbols in the graph are the same as in Fig. 2. Data from eight dogs, 56 biopsies. As can be seen, areas with 50% or greater reduction in MBF 15 min after coronary occlusion invariably developed significant Q-waves 24 h later.

the regression analysis: $y = 4.00-0.03\ \bar{x}$, $r = -0.51$, $2P < 0.001$, $n = 63$ biopsies (early) and $y = 3.32-0.025\ \bar{x}$, $r = 0.43$, $2P < 0.01$, $n = 38$ biopsies (late). Fig. 5 shows that ST-segment elevation was absent in 8 of 23 areas (34.8%) in the center zone (MBF about 10 ml/min per 100 g) but in only 3 of 23 areas (13.6%) of those in the border zones (MBF about 65 ml/min per 100 g) of the infarct. The correlation between epicardial ST-segment elevation, measured at 60 ms after S-wave, and regional MBF was not improved by substituting epicardial flow for the total flow; when epicardial blood flow was used in place of total transmural MBF for the data shown in Figs. 5 and 6 the correlation coefficients were $r = -0.42$ (15-min epicardial flow vs. 15-min epicardial ST-segment elevation) and $r = -0.31$ (24-h epicardial flow vs. 15-min epicardial ST-segment elevation).

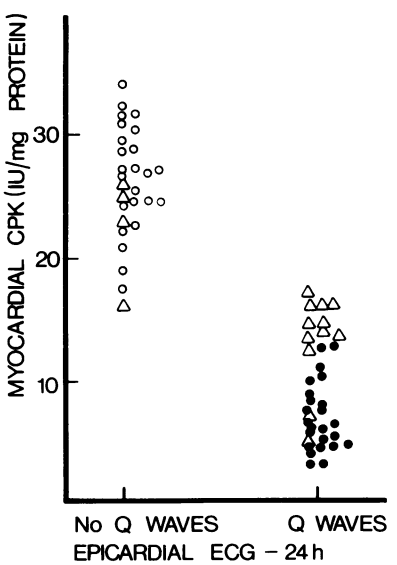

FIGURE 7 Relationship between myocardial CPK activity and the development of abnormal Q-waves in the epicardial ECG 24 h after LAD occlusion. Symbols in the graph are the same as in Fig. 2. As can be seen, the evolution of abnormal Q-waves is associated with severe depletion of tissue CPK. Data from nine dogs, 63 biopsies.

Relationship between late development of epicardial Q-waves and other indices of myocardial ischemia. A close relationship between the presence of epicardial Q-waves and the levels of myocardial CPK at 24 h after coronary occlusion was demonstrated (Fig. 7); with only exception, abnormal Q-waves were present in areas with myocardial CPK of 16 IU/mg protein or less. The development of abnormal Q-waves could also be predicted by the severity of reduction in MBF 15 min after coronary ligation (Fig. 8); areas with 50% or greater reduction in MBF, 15 min after coronary occlusion invariably developed significant Q-waves 24 h later. In contrast, the development of late Q-waves could not be predicted reliably from early ST-segment changes (Fig. 9). About 44% of the electrode areas, particularly from the center of the infarct, that developed late abnormal epicardial Q-waves had demonstrated no early ST-segment elevation. Furthermore, for the areas which had early ST-segment elevation, no simple relationship was found

between the magnitude of ST-segment deviation and the subsequent development of abnormal Q-waves.

The data from an animal in which early ST-segment changes after coronary occlusion did not correlate systematically with changes in myocardial CPK activity and regional blood flow or the late evolution of epicardial Q-waves are summarized in Fig. 10. In electrode areas 5 and 9, a relatively small difference in the degree of ST-segment elevation 15 min after coronary ligation was associated with widely divergent tissue enzyme activity, late electrocardiographic changes, and MBF (at 15 min and 24 h). In area 14, however, no ST-segment elevation was present despite severe reduction in MBF or myocardial CPK level. The severity of ischemia was further confirmed by the loss of R-wave voltage and the development of abnormal Q-waves 24 h later.

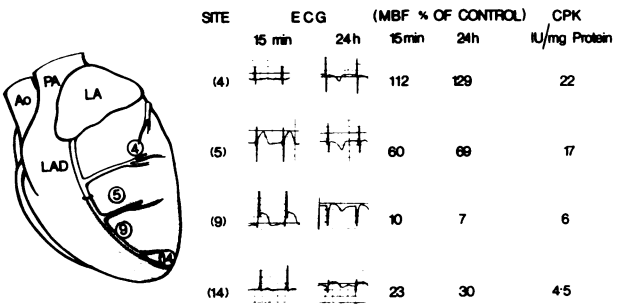

FIGURE 10 An example of an experiment in a dog with LAD occlusion in which QRS width was unaltered but acute epicardial ST-segment elevation did not occur in the center of the infarct where there was profound reduction in regional MBF and CPK activity. Abnormal Q-waves developed in this zone (area 14) as well as in the adjacent myocardium (area 9) in which early ST-segment elevation was present. The data illustrates the potential error in using the magnitude of early ST-segment elevation in predicting the severity of ultimate myocardial damage after coronary occlusion.

DISCUSSION

The results of the present study have demonstrated a high degree of correlation between reduction in regional MBF at 15 min after coronary ligation and the severity of myocardial CPK depletion 24 h later. The values for measured regional flow at 15 min were not significantly different from those at 24 h; thus, the intensity of tissue CPK depletion also correlated well with regional flow at 24 h as reported previously (20). The limitations of the microsphere technique for quantifying regional tissue perfusion have been discussed previously by others (21) with a particular reference to errors inherent in measuring MBF in tissue samples containing relatively small numbers of microspheres as might occur in the center zones of experimental infarcts. The accuracy of such measurements is improved substantially by using a larger number of spheres and most investigators have, therefore, used over 1,000,000 spheres per injection (21–23). The number of spheres in individual tissue samples in our studies were not measured. However, the absolute values of regional MBF for ischemic as well as nonischemic areas in our preparations, also with 1,000,000 spheres per injection, were very similar to those reported by others (22–23). MBF in the center of the infarct in the experimental canine model usually falls to about 10% of normal (14, 22). This degree of ischemia in the present experiments was associated with a reduction in tissue CPK level to about 25% of the concentration in the normal myocardium, which is in close agreement with the value (22%) first reported by Shell et al. (18) and subsequently confirmed by others (7, 9). The extent and severity of CPK depletion at 24 h after coronary occlusion have also been found to parallel the degree of histological alterations (9) and our results, therefore, strongly support tissue CPK depletion as a reliable index of the extent and severity of ischemic damage (24).

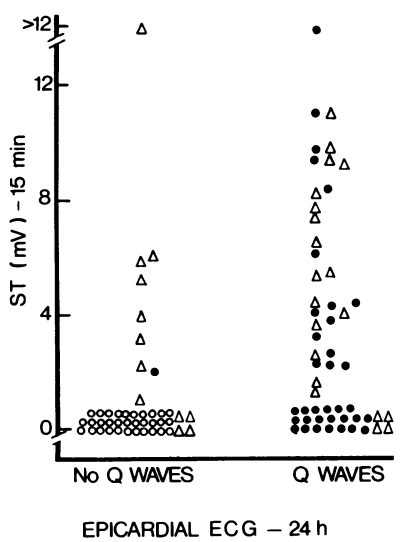

FIGURE 9 The frequency of Q-wave development in epicardial ECGs at 24 h in relation to ST-segment elevation at 15 min after LAD ligation. Symbols in the graph are the same as in Fig. 2. It is apparent that the occurrence of Q-waves could not be predicted reliably by the magnitude of each ST-segment elevation. Data from 11 dogs; 100 electrode areas.

The main object of the present study, however, was to evaluate the reliability of acute epicardial ECG changes after coronary occlusion in predicting the severity of the ultimate myocardial damage as reflected in the degree of CPK depletion in relation to the early and late alterations in regional MBF. It was found that early ST-segment changes over the developing infarct after proximal LAD ligation correlated relatively poorly both with regional MBF as well

as the degree of tissue enzyme depletion. For example, epicardial ST-segment elevation which has been used extensively in experimental studies to monitor the extent and severity of myocardial ischemic injury (7–9, 25, 26), was absent in about 35% of the electrode areas in which ischemia was severe as judged by reduction in myocardial flow and CPK level or the subsequent development of abnormal Q-waves. Furthermore, a wide range of values for epicardial ST-segment elevation was found for a given level of regional MBF or myocardial CPK even though a significant elevation of ST segment was usually associated with measurable abnormalities of perfusion and tissue enzyme activity. Of particular interest in this context are the studies of Kjekshus et al. (20) who also investigated the relation between ST-segment alterations at 15 min after coronary occlusion and myocardial CPK depletion as well as regional MBF measured by radioactive microspheres 24 h later in a limited number of animals. They found that although local CPK depletion was directly related to reduction in blood flow both in deep and superficial layers of the left ventricle, ST-segment elevation at 15 min after coronary ligation was not. There was a linear relationship between acute ST-segment elevation and the reduction in the subepicardial flow. However, a disproportionately less ST-segment elevation for a comparable reduction in perfusion was found for the subendocardium. Kloner et al. (23) recently reported that the peak ST-segment elevation showed a significant but a weak negative correlation ($r = -0.53$, $2P < 0.05$) with epicardial blood flow but there was no correlation between peak ST-segment elevation and the inner wall flow. Such a difference was not apparent in our own studies in which measurements of regional MBF were made at 15 min as well as 24 h after coronary occlusion in a larger series of animals. A relatively weak correlation was found between epicardial as well as endocardial flow vs. peak epicardial ST-segment elevation.

Our observations are thus in direct conflict with those in which summated ST-segment elevation from multiple epicardial electrograms was found to be a reliable index of the extent and severity of myocardial ischemic injury (7–9). The reasons for these differences in experimental data are not completely certain. They are clearly of clinical significance, however, since the results of epicardial mapping techniques in animals have provided the basis and stimulus to evaluate precordial mapping as an atraumatic means of assessing changes in myocardial ischemic injury in response to therapeutic interventions designed to limit infarct size in man (11, 27, 28).

It has recently been emphasized that epicardial ST-segment elevation in the center of large infarcts may be minimized or abolished if focal intraventricular block supervenes (29). It is noteworthy that this occurred in fewer than 10% of the electrode areas in our own studies, and all such epicardial sites were excluded from analysis of ST-segment elevation. Focal conduction block is, however, seldom pronounced in the early stages of myocardial ischemia (4) and even 1 h after LAD ligation in dogs Samson and Scher (4) reported an average conduction delay of only 2.5 ms, maximum 18 ms. Thus, the absence of ST-segment elevation over a significant number of severely ischemic sites in our preparations could not be accounted for by the presence of associated conduction anomaly. Similarly, it is unlikely that the measurement of ST-segment change at somewhat varying intervals after the end of the QRS complex explains the discrepancies between our findings and those of Maroko and his associates (7, 8, 29). They measured ST-segment elevation 20 ms after the end of the QRS complex (i.e., approximately 60 ms from the onset of QRS). Previously (14) we adopted the method of Reid et al. (10), who, like Redwood et al. (30), quantitated ST-segment shifts at about 60 ms after the end of the QRS (or about 100 ms from the onset of QRS). The duration of the ST segment in the dog is approximately 150 ms (4) and so the results of the ST-segment measurements at an interval 60 or 100 ms after the end of the QRS complex are not expected to be seriously divergent. In the current series of experiments, ST-segment elevations were measured 20 ms as well as 60 ms after the end of the QRS complex. Although somewhat higher correlation coefficients ($r = -0.36$ vs. $r = -0.51$) were obtained when the values for ST-segment elevation measured at 20 ms after the end of QRS were used, the relationship demonstrated was nevertheless of little value for a quantitative prediction of the degree of tissue damage for a given level of ST-segment deviation. The limitations of ST-segment elevation as a predictive index is also emphasized by studies in patients with acute myocardial infarction in whom no significant correlation was found between the summated peak precordial ST-segment elevation and ultimate infarct size calculated from the fractional disappearance curves of serum CPK activity (31).

Some of the discrepancies in the ST-segment data in myocardial ischemia may possibly be related to the differences between the pattern of ST-segment changes which occur after LAD branch ligation and that which follows proximal occlusion of the main vessel. Such variations, which have generated much interest recently (15, 29) were not apparently considered in the earlier studies of experimental ischemia, in which a close relationship was found between epicardial ST-segment elevation at 15 min after coronary branch occlusion and the severity of subsequent myocardial CPK depletion or cell necrosis (7, 8). This relationship was very much less precise in our model of ischemia produced by proximal LAD occlusion which was considered to be more clinically relevant

than branch occlusion. Of particular importance thus are the observations of Cohen and Kirk (15) who recently reported that local ST-segment elevation may be minimized by a maneuver which increases both the area and depth of myocardial ischemia. Specifically, they demonstrated that ST-segment elevation caused by the ligation of a branch of LAD was diminished, often dramatically, after proximal LAD ligation in dogs. This was found to be related to the presence of an identifiable boundary to the ischemic area, across which injury currents flow from normal into the ischemic myocardium during electrical diastole. Since the magnitude of such currents is likely to diminish as the distance from the transition zone increases, it is possible that ST-segment elevation over the center of large infarcts may be minimal or even absent as found in our previous (14) as well in the present studies.

Other preliminary studies have also questioned the reliability of epicardial ST-segment mapping in predicting the severity of myocardial ischemia (32, 33). For example, reperfusion after a 2-h LAD occlusion in pigs was associated with loss of ST-segment elevation but the development of abnormal Q-waves and impaired mitochondrial function indicating persisting severe ischemia (32). Similarly, reperfusion after a 1-h coronary occlusion in dogs produced a significant reduction in epicardial ST-segment elevation with either no change or actual decrease in zonal contraction as measured by Walton-Brodie strain gauges sutured over the territory of the occluded artery (33). With solid angle analysis (34) in the porcine model of experimental infarct, Holland and Brooks (35) have recently shown that a reduction in epicardial ST-segment elevation does not necessarily indicate a decrease in the extent of ischemic injury and that ST-segment changes are strongly influenced by the placement and orientation of the recording electrode in relation to the geometry of the ischemic region, as well as by the size, severity, and duration of the ischemic process. Such an analysis has not been done in the canine model but the theoretical and experimental findings of Holland and Brooks (35) do raise serious doubts about the usefulness of ST-segment elevation in predicting the severity or trends in ischemic injury. Further limitations of the ST-segment mapping technique are indicated by the clear demonstration of the considerable spontaneous decay in ST-segment elevations which occurs as early as 15 min after coronary occlusion and which persists for many hours (36).

It must, however, be emphasized that these findings do not invalidate the observation that acute ST-segment elevation is a frequent and indeed usual accompaniment of acute myocardial ischemia in experimental animals and man and may therefore be used to identify fresh episodes of ischemic injury, provided nonischemic causes of ST-segment deviations are excluded on other grounds. The experimental evidence discussed here does, however, raise serious doubts regarding the use of ST-segment elevation from multiple epicardial electrograms as an index to monitor trends in the extent and severity of myocardial ischemic injury. It is clear than even when allowance is made for QRS prolongation which is known to reverse the direction of the ST-segment vector, over 30% of severely ischemic areas, especially in the center of large infarcts, do not exhibit ST-segment elevation. The measurement of the number of sites with respect to the presence or absence of ST-segment elevation, therefore, does not constitute a reliable guide to the overall extent of ischemic injury. Furthermore, our data have not revealed a simple quantitative relationship between the early ST-segment elevation and the severity of ultimate myocardial damage as judged by tissue CPK depletion. In this regard, our findings are consistent with those of Karlsson et al. (37) who showed that, although areas of myocardium which had abnormally high concentrations of lactate also showed ST-segment elevation, a precise quantitative relationship did not exist between the magnitude of ST-segment change and the absolute levels of lactate in the ischemic myocardium.

We suggest, therefore, that while ST-segment elevation implies acute ischemic injury, the lack of ST-segment change over an area of the myocardium does not necessarily permit the conclusion that ischemia is absent. Similarly, as indicated elsewhere (14), a reduction in the magnitude of ST-segment elevation may result either from an improvement in the degree of ischemic injury or alternatively from progression of an acute ischemic lesion to necrosis and cell death with loss of electrophysiological functions of the myocardial membrane. Unless these alternative possibilities can be resolved unequivocally in individual instances by more specific and nonelectrocardiographic markers of cell injury and necrosis, the limitations of the ST-segment mapping technique in the assessment of myocardial ischemic injury should be clearly recognized.

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