Relationships between
Myocardial Perfusion, Myocardial Necrosis, and Technetium-99m Pyrophosphate Uptake in Dogs Subjected to Sudden Coronary Occlusion

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SUMMARY The quantitative relationship between abnormalities seen on technetium-99m pyrophosphate (99mTc-PYP) infarct scintigrams and the size of the myocardial infarction is unclear. We evaluated two possible determinants of 99mTc-PYP accumulation: myocardial perfusion measured with 7–10 μ microspheres and the extent of necrosis determined histologically. Hemodynamics and myocardial perfusion to small segments of the left ventricle were measured prior to, 5–10 min, and 44–48 hours following sudden occlusion of the left anterior descending coronary artery in ten awake dogs. 99mTc-PYP was injected i.v. following the third injection of microspheres and the animals were killed 2 hours later. The important findings were as follows: 1) there is a close relationship between the extent of myocardial necrosis observed and the perfusion of segments 5–10 min following coronary occlusion; and 2) that segmental myocardial perfusion is an important determinant of 99mTc-PYP accumulation by myocardial segments which contain areas of necrosis. Although the present data preclude statistical analysis of the relationship between the level of necrosis in a segment and the accumulation of 99mTc-PYP by that segment, the two do not appear to be related, a finding which would discourage use of intensity of 99mTc-PYP images for infarct size. The distribution of an abnormality on the scintigram may provide an estimate of infarct size. However, the geometry of the infarct and the resolving power of the scanning equipment will significantly limit this in many clinical situations.

INFARCT SCINTIGRAMS have been shown to be a highly specific and sensitive qualitative method of diagnosing acute myocardial infarction. The scintigrams would be of further value if a quantitative relationship between the abnormalities observed on the scintigrams and the size of myocardial infarction could be established. Thus far, two studies have shown a high correlation between the size of the abnormality on the scintigram and infarct size in experimentally-induced transmural anterior infarctions. Another investigation has shown a poor correlation between the intensity of the scintigraphic abnormality and the size of an experimentally-induced myocardial infarction. The quantitative aspects of these scintigrams is dependent on a comparison of the concentration of the scanning agent in the infarcted versus noninfarcted area.

Several studies have suggested that myocardial perfusion may significantly affect the accumulation of 99mTc-PYP by necrotic myocardium. To evaluate the importance of myocardial perfusion to 99mTc-PYP accumulation by necrotic myocardium, the three critical variables involved (99mTc-PYP tissue concentrations, myocardial perfusion, and the extent of necrosis) must be quantified with techniques that have a high degree of precision. This was done in this study.

Methods

Surgical Procedures

Twelve adult mongrel dogs of both sexes weighing between 20 and 25 kg were operated on under sterile conditions. With sodium pentobarbital anesthesia (25 mg/kg i.v.), the chest was opened and cannulas were placed in the left atrium and descending aorta via the left internal mammary artery and a snare was placed around the left anterior descending coronary artery just distal to the first lateral branch. The cannulas were filled with heparin (7,000 units/ml) and the proximal ends were capped and placed subcutaneously along with the proximal end of the snare device. Antibiotics were administered during the first three postoperative days. The animals were studied seven to ten days after surgery.

Experimental Protocol

Day 1: A cannula was placed percutaneously in a foreleg vein and the animals were given 10 mg of morphine sulfate i.v. They were then acclimated for 1 hour to a retaining harness which permitted them to remain in the upright position. Xylocaine was injected into the skin overlying the catheters, an incision was made, and the catheters and snare device were exposed. Blood was withdrawn from the catheters, they were flushed with saline and attached to Statham P23db strain gauges placed at the level of the mid-chest. An electrocardiogram using standard limb leads and pressure signals was recorded on a multichannel direct writing recorder.

Hemodynamic measurements (arterial pressure, left atrial pressure and heart rate) were recorded and the first bolus of microspheres (see below) was injected into the left atrium (flow I). The electrocardiogram was continuously recorded, starting before injection of the microspheres and continuing until completion of the withdrawal of the arterial reference sample. Fifteen minutes later in ten of the 12 animals, the left anterior descending coronary artery was suddenly occluded with the snare. Five to ten minutes after the occlusion a second set of hemodynamic measurements was recorded and then a second bolus of differently labeled microspheres was injected into the left atrium (flow II).
the other two animals, the left anterior descending coronary artery was not occluded but repeated measurements of hemodynamics and myocardial perfusion were made. Thereafter, the cannulas were filled with heparin, placed subcutaneously along with the snare device, and the skin was closed. The animals were returned to their kennel and brought back to the laboratory 44–48 hours later.

Day 3: Hemodynamics were recorded and a third bolus of differently labeled microspheres was injected (flow III). Immediately after collection of the arterial reference sample in nine of the ten dogs subjected to coronary occlusion and in the two control dogs, between 2 and 15 mCi of $^{99m}$Tc-PYP ($\bar{X} = 5.1 \pm 1.7 \text{ se}$) were injected i.v. Two hours following injection of the $^{99m}$Tc-PYP or microspheres the animals were anesthetized with sodium pentobarbital (25 mg/kg, i.v.) and subsequently killed with potassium chloride.

Measurement of Myocardial Perfusion

Microspheres 7–10 $\mu$m in diameter labeled with $^{51}$Cr, $^{46}$Sc, or $^{85}$Sr were used. In six studies $^{125}$I microspheres, 15 ± 5 $\mu$m in diameter, rather than $^{51}$Cr 7–10 $\mu$m microspheres were used to measure control perfusion (flow I). For each flow measurement between $1.0 \times 10^6$ and $1.1 \times 10^6$ tracer microspheres were suspended in saline and injected into the left atrium. Before injection the vial containing the microspheres and one drop of Tween-80 was mechanically agitated for at least 4 min. Microscopic examination of microspheres prepared in this manner showed dispersion of at least 98% of the spheres. Occasionally, small groups of three to five spheres were observed. The microspheres were injected slowly over a 30 sec period, and the cannula was flushed over a 60 sec period with 5 ml of saline at 37°C. Starting 1 min before injection and continuing until 3 min after injection, blood was withdrawn from the cannula in the descending aorta at a rate of 2.06 ml/min with a Harvard pump.

Following completion of the study, the heart was excised and the free walls of the right ventricle, left atrium, great vessels, valves, surface vessels, and epicardial fat were removed. Using the posterior descending coronary artery as the starting point, the left ventricle was divided into four levels of eight segments each and each segment was divided into three layers — endocardium, mid-wall, and epicardium. The thickness of these layers was approximately equal. Thus, the left ventricle was divided into 96 segments (fig. 1). The relative geometric position of each segment was constant from animal to animal. The myocardial segments were weighed (to the nearest milligram), placed in glass tubes containing 10% formalin, and counted for 5 min in a 3 inch well sodium iodide gamma counter. The average weight of the segments was $1.0 \pm 0.06$ (se) g. Reference blood samples were divided so that their counting geometry was similar to that of the myocardial samples. In eight animals the $^{99m}$Tc-PYP emissions from a rib were also analyzed. The bone to normal myocardium ratios averaged 29 ± 7, which indicates that the binding of the $^{99m}$Tc to PYP was adequate. Energy windows utilized were $^{46}$Sc 700–1500 Kev, $^{85}$Sr 400–600 Kev, $^{51}$Cr 270–370 Kev, $^{99m}$Tc 125–155 Kev, and $^{125}$I 20–50 Kev. Isotope separation was done using standard techniques. The $^{99m}$Tc-PYP counts in each sample (half life = 6.0 hours) were corrected for radioactive decay during the 10–18 hour counting period necessary to count all of the samples.

Myocardial blood flow was calculated using the formula: $MBF = C_m \times 100 \times RBF / C_r$, where $MBF = \text{myocardial blood flow in ml per min} \times 100$, $C_m = \text{counts per gram of myocardium}$, $RBF = \text{reference blood flow} = \text{rate of withdrawal from the reference artery}$, and $C_r = \text{total counts in the reference blood}$.

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** Diagrammatic presentation of the method used to divide the left ventricle. The left ventricle was divided into four levels (A–D), apex to base. The left ventricle is pictured as being opened as a book between the B and C levels. This gives the diagram a three-dimensional appearance. Each level is divided into eight subsections and each subsection was divided into three layers (epicardium, mid-wall, and endocardium). The ischemic segments are clustered together in the region perfused by the left anterior descending coronary artery. Normally perfused segments with increased $^{99m}$Tc-PYP concentrations were usually immediately adjacent to ischemic segments.
Identification of Ischemic and Normally Perfused Segments

The method of classifying myocardial segments as ischemic or nonischemic has previously been described in detail. Briefly, the method estimates the heterogeneity of perfusion to normally perfused segments (segments with flow greater than 50% of mean left ventricular perfusion) and uses these data to separate normally perfused and hypoperfused (ischemic) myocardium utilizing statistical techniques. The average perfusion of segments classified as ischemic or hypoperfused was 40 ± 5% (SEM) of the perfusion to normal myocardium.

Determination of \(^{99m}\text{Tc-PYP}\) Ratios

The mean normal \(^{99m}\text{Tc-PYP}\) concentration was determined by averaging the \(^{99m}\text{Tc-PYP}\) concentration of all normally perfused segments (flow II) that were remote from the ischemic area. A segment was considered "remote" from the ischemic area if the three-dimensional perfusion map based on flow II (see fig. 1) demonstrated that the segment was not immediately adjacent to the ischemic area. This was done to eliminate normally perfused segments adjacent to the ischemic area which contain small areas of necrosis and increased concentrations of \(^{99m}\text{Tc-PYP}\) from the group segments used to calculate the mean normal \(^{99m}\text{Tc-PYP}\) concentration. In each dog a \(^{99m}\text{Tc-PYP}\) ratio was calculated for each segment using the following formula:

\[
\text{\(^{99m}\text{Tc-PYP}\) ratio} = \frac{(i) \text{\(^{99m}\text{Tc-PYP}\)}}{(X) \text{\(^{99m}\text{Tc-PYP}\)}}
\]

where \((i)\) is the concentration of the isotope in an individual segment and \((X)\) is the mean concentration of the isotope in all segments remote from the ischemic area.

Histology

Selected myocardial segments obtained from the ten dogs subjected to coronary occlusion were embedded in paraffin. In two of the ten animals only a single histological section of each segment was examined histologically. In the other eight animals, three pairs of serial sections were obtained from three locations within each segment approximately 1–1.3 mm apart. One section of each pair was stained with periodic acid Schiffs stain and the other was stained with hematoxylin-eosin.

The investigator who evaluated the histological sections did not know the perfusions or \(^{99m}\text{Tc-PYP}\) ratios of the segments. The sections were classified as either normal or abnormal on the basis of histological criteria for myocardial infarction. These criteria include pyknosis, karyorrhexis, karyolysis, fiber fragmentation, and polymorphonuclear cell infiltration. Classification as infarction required that at least two of the above criteria be fulfilled. After examining the sections from each segment, the area of infarction within each segment was subjectively rated according to the following size classification: class 0, no infarction; class 1, 1–20% infarction; class 2, 21–40% infarction; class 3, 41–60% infarction; class 4, 61–80% infarction; class 5, greater than 81% infarction. In 90% of the segments examined the range of histological classes of the sections from each segment did not exceed one class.

The total number of segments available for histological examination was 960 (10 × 96). These segments were divided into three major subgroups as follows: 1) segments with myocardial perfusion (flow II) which were classified as ischemic; 2) normally perfused segments with abnormally elevated \(^{99m}\text{Tc-PYP}\) uptake ratios (greater than 2); and 3) normally perfused segments with normal \(^{99m}\text{Tc-PYP}\) ratios (less than 2). The number of segments selected for histological examination from each of these three groups was 104, 54, and 47, respectively.

The number of necrotic segments and the distribution of these segments with respect to histological class varied from dog to dog (table 2). This is not unexpected since the size of the ischemic area varied from dog to dog (18 ± 10.1% [SD] of left ventricular mass) and the range of the perfusion defects in the ischemic segments within a dog was also variable. The complex composition of the ischemic areas in our preparation have previously been described in detail.

Statistical Analysis

The analysis of the data was designed so that the relationship between two of the three dependent variables (extent of necrosis, \(^{99m}\text{Tc-PYP}\) ratios, and myocardial perfusion) could be examined while the third was held constant.

Student's \(t\)-test for paired and unpaired data was used where appropriate to assess statistical significance of the observed differences. Results are expressed as the mean ± 1 standard error unless otherwise indicated.

Results

Hemodynamic Effects of Coronary Occlusion

The hemodynamic effects of sudden coronary occlusion are shown in table 1. The only significant change following sudden coronary occlusion was an increase in heart rate.

Myocardial Perfusion Following Coronary Occlusion

The effects of coronary occlusion on perfusion and coronary vascular resistance to the ischemic and nonischemic myocardium are shown in figures 2A and 2B. Sudden coronary occlusion was associated with a marked decrease in perfusion and a marked increase in total coronary vascular resistance to the ischemic myocardium. Two days later, perfusion was increased and coronary vascular resistance

| Table 1. Hemodynamic Effects of Sudden Coronary Occlusion |
|---------------------------------|----------|----------|----------|
|                                | HR (beats/min) | MSP (mm Hg) | MLAP (mm Hg) |
| Control (flow I)               | 76 ± 3    | 93 ± 5    | <5        |
| 5-10 min following occlusion (flow II) | 108 ± 9  | 97 ± 6    | <5        |
| 44-48 hr following occlusion (flow III) | 108 ± 8  | 87 ± 4    | <5        |

Values are given in mean ± standard error. 
\(N = 10\). The hemodynamics of two animals not subjected to coronary occlusion were similar to the control values shown here.

\(HR\) = heart rate; \(MSP\) = mean systemic pressure; \(MLAP\) = mean left atrial pressure.
A 99mTc-PYP ratios to decreased collateral onary size of the segments of these mass. 2 than greater of the grams ratios greater than 2. Therefore, 99mTc-PYP ratios greater than 2 were assumed to be abnormal.* In 79.8% of the 693 normally perfused segments (based on flow II) in all the dogs subjected to coronary occlusion the 99mTc-PYP ratios were less than 2 (mean = 1 ± 0.26 [SD]). Forty-seven of these segments were examined histologically, and in 94% no infarcted muscle was present. In the remaining 20.2% of the normally perfused segments in the dogs subjected to coronary occlusion 99mTc-PYP ratios exceeded 2 (mean = 6.72 ± 0.4). Three-dimensional perfusion maps (based on flow II) showed that 92% of these segments were adjacent to ischemic segments (fig. 1). Fifty-five of these normally perfused segments with 99mTc-PYP greater than 2 were examined histologically and 85% of them contained small areas of infarcted myocardium (average histological class = 1.3 ± 0.1). The average 99mTc-PYP ratio in the ischemic myocardial segments (based on flow II) was 13.7 ± 0.6.

Relationship Between the Extent of Myocardial Necrosis and Myocardial Perfusion Following Coronary Occlusion

The extent of necrosis in individual segments was inversely related to their perfusion flow II (fig. 3). The average perfusion of the segments showing no necrosis was 98 ± 4% of mean perfusion to the nonischemic segments; in contrast, the average perfusion of segments showing greater than 80% necrosis was 12 ± 2% of the mean perfusion to nonischemic myocardium.

The absolute increase in perfusion 44-48 hours following coronary occlusion to myocardial segments with necrosis was inversely related to the extent of necrosis (fig. 3). Perfusion to segments with extensive necrosis (class 5) changed very little; in contrast, perfusion to segments with minimal necrosis (class 1) increased substantially.

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<tr>
<th>Dog</th>
<th>Histological Class</th>
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<td>1</td>
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<td>4.9</td>
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<td>9</td>
<td>12.7</td>
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| Total segments | 53 | 25 | 29 | 28 | 23 |

*This does not imply, however, that if a small group of adjacent myocardial segments contained twice the normal concentration of 99mTc-PYP that a scintigram would reveal a clear-cut abnormality. Studies with a ventricular phantom performed in our laboratory suggest that if a 9.5 g segment of myocardium contains two times the normal concentration of 99mTc-PYP, scintigrams of the phantom will clearly show the abnormal area. However, this represents optimal sensitivity which is probably not achieved in man.

There is not a linear relationship between 99mTc-PYP accumulation and the extent of necrosis.

*Mean 99mTc-PYP ratio.
†Number of segments analyzed.
tent of necrosis and \textsuperscript{99m}Tc-PYP accumulation (table 2). The small size of the various subgroups of segments analyzed within each dog does not allow statistical analysis.

Relationship Between the Extent of Myocardial Necrosis, Myocardial Perfusion, and \textsuperscript{99m}Tc-PYP Ratios

The \textsuperscript{99m}Tc-PYP ratios were lower in segments with extremely limited perfusion (flow III) even though the extent of necrosis in these segments was greatest (fig. 4). In addition, within histological classes 3, 4, and 5, \textsuperscript{99m}Tc-PYP ratios were generally greater in the segments with greater perfusion (fig. 5). With myocardial perfusion held at the same level, increases in histological class tended to be associated with increases in \textsuperscript{99m}Tc-PYP ratios (fig. 5).

Discussion

The most important finding in this investigation is that myocardial perfusion is one important determinant of \textsuperscript{99m}Tc-PYP accumulation by myocardial segments which contain areas of necrosis. In addition, it appears that the magnitude of \textsuperscript{99m}Tc-PYP accumulation does not provide a dependable assessment of the extent of necrosis.

The intensity of the abnormalities on an infarct scintigram will be affected by the transmural extent of the infarct and the relationship between the location of the infarct and the scintigram projection. Thus, regardless of the extent of necrosis, subendocardial infarcts will yield less intense abnormalities than transmural infarcts and posterior infarctions will be associated with less intense scintigraphic abnormalities than anterior infarctions, particularly if the scintigram is taken in the anterior projection. As stated above, the perfusion of the involved myocardium will also affect the

\begin{figure}
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\includegraphics[width=\textwidth]{fig3}
\caption{Relationship between the extent of myocardial necrosis and myocardial perfusion following coronary occlusion.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig4}
\caption{Relationship between myocardial perfusion and \textsuperscript{99m}Tc-PYP accumulation. Segments with the lowest myocardial perfusion accumulated the least amount of \textsuperscript{99m}Tc-PYP, even though the extent of necrosis in these segments was the greatest. The number in parentheses refers to the average histological class of the segments in each perfusion subgroup. All of the myocardial segments included in this figure and in figure 5 contained areas of necrosis.}
\end{figure}
A second problem is created by the complete three-dimensional geometry of myocardial infarctions. Because of this, determining the size of an infarct from the distribution of the scintigraphic abnormalities will be dependent on integration of information from scintigrams of an irregularly shaped area of infarction; these scintigrams are taken in multiple projections at different distances from the infarcted myocardium. Particular difficulties will probably be encountered in subendocardial infarctions where the scintigraphic abnormalities are diffuse and in true posterior infarcts which are not well seen with the currently available projections.

Still another problem is that the resolving power of current scanning equipment is limited: 3–5 g infarcts are not detectable even though the infarcted myocardium contains a large concentration of \(^{99m} \text{Tc-PYP}\). Thus, although almost the entire infarct contains a high concentration of \(^{99m} \text{Tc-PYP}\), problems related to the complex three-dimensional geometry of infarction and the resolving power of current scanning equipment will probably make it difficult to precisely quantitate the size of all infarcts by analyzing the distribution of the scintigraphic abnormalities. However, when some of these problems are minimized (e.g., by utilizing of computer-processed anterior scans of transmural anterior infarctions) a high correlation between the distribution of the scintigraphic abnormalities and the size of the infarct can be obtained.

In addition to the \(^{99m} \text{Tc-PYP}\) data obtained in this investigation, the myocardial perfusion data confirm two important relationships with respect to coronary collateral flow which have been suggested previously. They are 1) following sudden coronary occlusion in awake dogs, within 44–48 hours there is a substantial increase in perfusion to the involved segment which contains mild to moderate sized areas of necrosis; and 2) there is a close relationship between the extent of myocardial necrosis observed 44–48 hours following coronary occlusion and the relative perfusion of ischemic myocardium 5–10 min following the occlusion. Finally, this study provides additional support for the concept that the “marginally perfused zone of myocardium” which surrounds and separates severely ischemic myocardium from normally perfused myocardium is not geometrically well defined and in some areas may not be definable at all. The presence of small areas of necrosis in one gram left ventricular segments with normal perfusion precludes the existence of a large marginally perfused zone in these segments.

**Acknowledgments**

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**References**


**Figure 5. Relationship between the extent of myocardial necrosis, myocardial perfusion, and \(^{99m} \text{Tc-PYP}\) accumulation. In histological classes 3, 4, and 5 \(^{99m} \text{Tc-PYP}\) accumulation tended to increase as perfusion increased. The zero values in the class 5 and class 1 and 2 panels signify that no segments occurred in these categories.**

The distribution of the abnormality of an infarct scintigram is dependent on the presence of a high concentration of \(^{99m} \text{Tc-PYP}\) in the infarct, the three-dimensional geometry of the infarction, and the resolving power of the scanning equipment. In this study, almost all segments that contained infarcted myocardium had a large concentration (average = 13 \times control) of \(^{99m} \text{Tc-PYP}\). Other studies have noted similar results. An important exception was two severely necrotic segments (<2% of all infarcted segments studied) which had \(^{99m} \text{Tc-PYP}\) ratios in the normal range. It is likely that the very low perfusion (3% of normal left ventricular perfusion) in these segments blunted the anticipated distribution of \(^{99m} \text{Tc-PYP}\) in infarcted myocardium. The presence of necrotic segments with markedly decreased perfusion, and hence, very little \(^{99m} \text{Tc-PYP}\) accumulation, accounts for the “doughnut-like appearance” of some infarct scintigraphic abnormalities.
Effect of Coronary Thrombus Age on Fibrinogen Uptake

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With the Technical Assistance of Amparo Escobinas and Ashwinkumar Gandhi

SUMMARY A study was carried out to define the time limits during which an experimental coronary thrombus remains capable of incorporating fibrinogen. 125I-fibrinogen was given to intact anesthetized dogs at different time intervals, up to 67 hours, following the formation of a coronary thrombus by catheter-electrode. Radioactivity of the recovered thrombus as a whole and segmentally divided, was determined following variable time intervals of exposure to circulating fibrinogen and was expressed as thrombus/blood ratio. The results indicate that coronary thrombi formed in a normal coronary vessel remain capable of incorporating fibrinogen for at least eighteen hours, with no significant differences in the segmental distribution of radioactivity. These findings do not support the view that the recovery of isotopic fibrinogen, which was given after the onset of coronary symptoms, in thrombi from patients with myocardial infarction establishes that the thrombus was initiated after the ischemic process.

RADIOIODINATED FIBRINOGEN remains at the present time the most commonly used agent for pathophysiologic studies of the thrombotic process and for noninvasive diagnosis of a formed thrombus. Although data are available on the incorporation of fibrinogen in human and experimental venous thrombi, information regarding the length of time during which a thrombus formed in the coronary artery remains actively capable of incorporating fibrinogen is scanty. Regional determinants of the thrombotic process might be quite different. A systemic vein is a part of a low pressure system whereas a systemic artery is exposed to high pressures with pulsatile flow. In addition, the coronary arteries constitute the location with the highest incidence of atherosclerosis and thrombosis in the adult human subject. Therefore, extrapolating to coronary arteries data obtained from observations on systemic vessels regarding the initiation, duration and organization of the thrombotic process is not warranted.

The objective of the present study has been to expand our initial observations1 to define the time limits during which a coronary thrombus, once formed, remains capable of incorporating fibrinogen. Such information would be useful for studies concerned with the pathogenetic role of coronary artery thrombosis in myocardial infarction as well as the development of techniques for its detection.

Methods

Intact mongrel dogs weighing 22–26 kg and fasting for 18 hours were anesthetized with morphine (3 mg/kg) and nembutal (20 mg/kg). Coronary thrombus was induced by a catheter-electrode as described previously.5,10 Histo-
Relationships between myocardial perfusion, myocardial necrosis, and technetium--99m pyrophosphate uptake in dogs subjected to sudden coronary occlusion.
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