Apparent Improvement in Canine Collateral Myocardial Blood Flow during Vasodilation Depends on Criteria Used to Identify Ischemic Myocardium

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SUMMARY We measured epicardial S-T segment elevation and blood flow to the subjacent myocardium in 8-12 samples from anesthetized, open-chest dogs with coronary occlusion. The response to iv adenosine of blood flow to "ischemic" myocardium/mean aortic pressure depended on which criterion (among criteria I-V) was used to select samples as "ischemic": I—(S-T ≥ 3 mV), 125 ± 47% increase (P < 0.05); II—(S-T ≥ 4 mV), 58 ± 48% increase [not significant (NS)]; III—(myocardial blood flow < 50% of control zone), 8 ± 19% decrease (NS); IV—(flow < 25% of control), 13 ± 16% decrease (NS); V—(< 2% normal zone tissue, labeled by a special microsphere technique), 46 ± 8% decrease (P < 0.03). Peripheral coronary pressure and retrograde flow/mean aortic pressure decreased by 23 and 28%, respectively (P < 0.05), to suggest that criterion V was correct in identifying as ischemic a group of samples in which adenosine decreased collateral flow. The higher apparent control collateral flow values (criteria I-III) and unchanged or increased flow to samples of supposedly ischemic myocardium (criteria I-IV) could be explained by their larger fractions of normal zone tissue mixed in with ischemic tissue: absolute flow change during adenosine = 3.85 (fraction of normal zone tissue in sample)—0.158 ml/min per g, r = 0.94, n = 64. We conclude that criteria which fail to exclude contamination of supposedly ischemic samples by normal zone tissue can lead to misinterpretation of the direction and/or magnitude of changes in collateral flow to ischemic myocardium during vasodilation. Changes in flow to samples containing mixtures of normal and ischemic tissue may not be relevant to attempts to salvage truly ischemic myocardium by increasing actual collateral myocardial blood flow. Cir Res 47:108-116, 1980
experimental problems with this method (Heymann, 1977). In the use of microspheres and other indicator methods to estimate collateral myocardial blood flow, there has been no study of the possible influence of problems in the identification of ischemic myocardium on the results of interventions.

Thus, this study tests two hypotheses: (1) the use of different criteria to identify samples as ischemic for microsphere counting may influence the apparent response of collateral myocardial blood flow to vasodilation, and (2) criteria to identify ischemic myocardium which fail to exclude normal zone tissue from the supposedly ischemic samples may permit the blood flow increase in normal tissue during vasodilation to obscure the actual flow decrease in the ischemic component of the mixed sample. The potential importance of the latter problem is that agents designed to improve survival of ischemic myocardium by increasing collateral blood flow should be tested for their effects on ischemic myocardium, not on mixtures of ischemic and normal tissue. Our specific objective was to test the effects of adenosine on collateral flow to ischemic myocardium estimated by the tracer microsphere technique.

Methods

Experimental Preparation

Twelve mongrel dogs weighing 18-27 kg were anesthetized with sodium pentobarbital (30 mg/kg, iv). Additional pentobarbitol was given as required to maintain anesthesia. After tracheostomy with a cuffed endotracheal tube, the dogs received intermittent positive pressure respiration with 100% oxygen. A thoracotomy was performed in the 4th left intercostal space. A pericardiotomy was performed and the heart suspended in a pericardial cradle. We inserted two polyvinyl catheters, through a stab wound in the left atrial appendage, advancing one into the left ventricle for pressure measurements and leaving the other in the atrium for radioactive microsphere injections. Polyvinyl catheters also were placed in one femoral vein for drug infusions and in one femoral artery, from which it was advanced into the thoracic aorta. The aortic catheter was used to monitor pressure and to withdraw a reference arterial blood sample at a known rate during microsphere injections. Left ventricular pressure was measured by a Statham P23Gb transducer with a short, stiff, polyvinyl catheter, while aortic pressure was measured by a Statham P23Db transducer. The pressures were recorded continuously on a Beckman type SII multichannel oscillograph.

A large-bore cannula attached to polyvinyl tubing was inserted into the left carotid artery after administration of heparin, 5000 units, iv (Fig. 1). The left anterior descending coronary artery (LAD) branch was isolated, dissected free, and ligated distal to the first one or two diagonal branches. A steel cannula attached to the carotid tubing was inserted and tied into the LAD, distal to the ligature. Within 1-2 minutes, LAD perfusion was restored from the carotid, and perfusion continued during a 15- to 20-minute recovery period.

One side-arm of the LAD perfusion line was used to measure LAD perfusion pressure on a P23Db transducer. After occlusion of the LAD perfusion line, this transducer measured peripheral LAD pressure. Also, after occlusion, another side-arm allowed timed collections of retrograde flow from the distal LAD.

Two other side-arms led to a two-chambered reservoir, as described in detail previously (Hirzel et al., 1976, 1977). By adjusting clamps, one chamber of this reservoir could perfuse the LAD at aortic pressure to minimize flow through interarterial anastomoses. Thus, the LAD could be perfused independently with blood which contained no microspheres during left atrial injection of radioactive microspheres. Microspheres destined for the LAD were trapped instead in the other chamber of the reservoir, in order to exclude these microspheres from myocardium which is ordinarily perfused by the LAD. The microspheres injected under these conditions label tissue that is normally perfused by patent vessels other than the LAD. Within a myocardial sample, one can identify the presence of tissue normally perfused by interdigitating branches from arteries other than the LAD by the presence of this label. Collateral flow should contribute negligibly to microsphere distribution under these conditions because the LAD is perfused at the same pressure (aortic) as are the other coronary branches. Thus, from a given sample in the vicinity of the LAD, one can estimate an index of the
fraction of tissue in the sample which is normally perfused by the other patent arteries. This fraction is calculated by comparing the radioactivity due to this label in the sample with the radioactivity due to this label in the normal zone remote from the LAD.

Microsphere Estimates of Myocardial Blood Flow

Standard carbonized microspheres 9 ± 1 μm in diameter, labeled with the nuclides, 141Ce, 85Sr, 51Cr, and 58Nb (3M Company), were used to measure regional myocardial blood flow and cardiac output as described previously (Hirzel et al., 1976; Hirzel et al., 1977). A few drops of Tween 80 were added to the microspheres which then were suspended in a 63% sucrose solution. Prior to injection, they were dispersed by mechanical agitation and sonication for 10 minutes in an ultrasonic bath. Ten milliliters of the suspension containing 1–2 × 10⁶ beads were injected over 20–25 seconds through the left atrial catheter which was flushed with 10 ml of saline. Only occasionally did the injections alter hemodynamics, decreasing aortic systolic pressure 10–15 mm Hg for 10–15 seconds. Arterial blood was withdrawn starting just before and continuing for 30–60 seconds after the microsphere injection, at 19.4 ml/min by a calibrated pump (Harvard Apparatus). At the conclusion of each experiment, the dogs were killed and the hearts were frozen for later sectioning.

The sites of the electrograms were designed to represent the entire region near the LAD in each animal and to be easily reproducible because of their locations near branching points of arteries. Thus, each biopsy allowed correlation of myocardial blood flow with the epicardial electrogram overlying that sample. Each sample of tissue (0.4–0.6 g) and blood was subjected to γ spectrometry (Searle Analytic 2-channel model 1085). Samples were not divided into endocardial and epicardial sections so as to maintain a precise relationship between the areas of the electrogram and the blood flow measurement without reducing the number of microspheres per sample. The count rates were corrected for background and crossover counts on a Wang Laboratories model 2200S computer. Standard indicator dilution formulas were used to calculate myocardial blood flow per unit weight of tissue and cardiac output (Heymann et al., 1977).

Epicardial Electrograms

Epicardial electrograms were recorded from eight to 12 sites on the surface of each heart, in the vicinity of the LAD, as described previously (Maroko et al., 1971; Cohen et al., 1976). Sites were selected to be near branching points of vessels, and a map was drawn to allow reproducible positioning. An atraumatic saline-soaked cotton-tip electrode was attached to the V lead of a standard capacitor-coupled electrocardiograph. Evaluation of the S-T segment was measured from the baseline to a plateau, 0.04 second after the end of the QRS complex. The ECG standardization was 1.0 mV/mm paper. Pre-occlusion control S-T segments were rarely elevated, and the values never exceeded 1.0 mV. Epicardial QRS durations were always noted because of the suggested effect of conduction delay on S-T segments. Electrograms from three sites in three dogs indicated conduction block (QRS ≥ 0.08 second) and were excluded from the study without influencing results.

Experimental Protocol

After preparation of each dog had been completed, the first set of microspheres was injected to label tissue perfused by other arteries during independent LAD perfusion. Hemodynamic and epicardial electrogaphic data were obtained, and the LAD cannula was occluded to render ischemic the tissue supplied by the LAD after pretreatment with lidocaine, 3 mg/kg iv bolus. Seven to 8 minutes after LAD occlusion, hemodynamic recordings were made at faster paper speed (50 mm/sec), and retrograde LAD flow was collected for 60 seconds. Ten minutes after occlusion, a second set of radioactive microspheres was injected to measure regional myocardial blood flow. Eleven to 14 minutes after occlusion, epicardial electrograms were recorded at 50 mm/sec, and the site of each electrogram was noted on a map based on the coronary arterial anatomy. Fourteen to 18 minutes after occlusion, an intravenous infusion of adenosine was begun at 0.01-0.03 μmol/kg per minute to reduce systolic aortic pressure by 20–35 mm Hg. After hemodynamics had remained stable for 1–2 minutes, radioactive microspheres were injected to estimate flows. Retrograde flow was collected an average of 2.8 minutes after completion of microsphere injection and collection of the reference arterial blood sample (range, 1.3–5.0 minutes). The dogs were killed with KCl.

Criteria to Identify Ischemic Myocardium

Eight to 12 samples from each of six dogs were taken from the vicinity of the ischemic LAD region. Five criteria were used to identify a sample as ischemic. Any given sample might have been selected by all, a few, or none of the five criteria. Samples were selected as ischemic by the following criteria: (1) if the overlying electrogram showed S-T elevation ≥ 2.0 mV (Maroko et al., 1971); (2) if S-T ≥ 4.0 mV; (3) if myocardial blood flow 10 minutes after coronary occlusion ≤ 50% of normal zone flow (Becker, 1976; Marcus et al., 1975; Vatner et al., 1976); (4) if myocardial blood flow ≤25% of normal zone flow; and (5) if the first set of microspheres labeled ≤2% normal zone tissue mixed in with the supposedly ischemic sample (Hirzel et al., 1976, 1977).
Data Analysis

The mean ± SE of the myocardial blood flow values during control and adenosine infusion periods were determined for samples selected as “ischemic” by each criterion. The mean change in flow and standard error of the difference between control and adenosine periods were also determined for the samples selected as ischemic by each criterion. The significance of the flow change between control and adenosine periods was evaluated by the paired Student’s t-test. Regression lines were calculated by the least squares fit, including the 95% confidence limits of the lines and the correlation coefficient.

Results from six dogs are used in this study. Six other dogs failed to fulfill the only criterion for inclusion in the study: ≥100% increase in myocardial blood flow to the normal zone during adenosine.

Hemodynamic Effects of Adenosine

Administration of adenosine, 0.01-0.03 µmol/kg per minute, iv, 14-18 minutes after LAD occlusion, caused the hemodynamic changes shown in Figure 2. Adenosine caused a 12% decrease in heart rate, a 30% decrease in mean aortic pressure, an insignificant decrease in left ventricular end-diastolic pressure LVEDP, a 29% increase in cardiac output, and a 362% increase in blood flow to normal myocardium.

The apparent effects of intravenous adenosine on myocardial blood flow to the ischemic region depended on the criteria used to identify the samples as “ischemic,” as indicated in Figure 3A. Criterion I, S-T ≥ 2.0 mV, identified 24 of the samples in six dogs as “ischemic” in which adenosine caused an increase in flow from 0.63 to 6.03 ml/min per g, which was at the borderline of significance (0.05 > P > 0.06). As indicated by the bargraphs, criterion II, S-T ≥ 4.0 mV was more stringent and selected only 13 samples in five dogs as ischemic. The flow increase during adenosine in these samples was not significant. Deleting the three sites with QRS ≥ 0.08 sec did not change any of the results. Criterion III, flow ≥50% of the normal zone, identified 28 samples as ischemic in six dogs. Control flow was lower in these samples than in those selected by criteria I and II, and there was no change during adenosine. Criterion IV, flow ≤25% normal zone, was more selective and identified as ischemic only 16 samples in five dogs in which flow decreased insignificantly during administration of adenosine. Criterion V, ≤2.0% normal zone tissue labeled in the sample, identified 22 samples in six dogs as ischemic. After LAD occlusion, average control flow to samples selected by their having ≤2% normal zone tissue before adenosine administration was lower than was flow to samples identified as “ischemic” by criteria I or II and was similar to flows to samples identified by criterion III. Control flow to samples with ≤2% normal tissue was higher than in samples identified as “ischemic” by criterion IV. Adenosine caused a 51% decrease in myocardial blood flow to the ischemic zone selected by criterion V (P < 0.005).

Because of the known effects of aortic pressure on collateral blood flow (Gregg, 1974), we normalized the flows to “ischemic” myocardium by calculating vascular conductance (Fam and McGregor, 1964). We divided each flow by the simultaneously measured value of mean aortic pressure. Despite this normalization, the results of adenosine infusion shown for ischemic myocardial vascular conductance in Figure 3B were similar to those for ischemic myocardial flow. The apparent response of ischemic myocardial vascular conductance to adenosine depended on the criteria used to identify ischemic myocardium. Criterion V identified as ischemic a group of samples in which adenosine caused a significant decrease in myocardial vascular conductance. The other four criteria identified as ischemic those samples in which adenosine caused insignificant increases or no changes in ischemic myocardial vascular conductance.
Adenosine decreased three hemodynamic indices of collateral perfusion: LAD diastolic peripheral coronary pressure (PCP), 23%; LAD retrograde flow, 48%; and retrograde flow/mean aortic pressure (collateral conductance), 28% (Fig. 4). These hemodynamic indices do not require identification of ischemic myocardium because they depend on the cannula inserted into the distal LAD (Gregg, 1974). The change in these indices of collateral perfusion is similar in direction and magnitude to the change in blood flow and vascular conductance to ischemic myocardium identified by criterion V, but the hemodynamic indices which indicate a significant decrease in collateral flow and conductance differ from flow results with criteria I-IV.

The different criteria identified groups of samples as "ischemic" which contained variable fractions of normal zone tissue labeled by the first set of microspheres. The supposedly ischemic samples which had the largest average increase in myocardial flow during adenosine also showed the largest average...
Figure 5 Effects of labeled normal zone tissue in a sample on MBF to the sample. Figure 5 (top) shows control MBF 10 minutes after LAD coronary occlusion, and Figure 5 (bottom) shows the absolute change in MBF comparing adenosine infusion to the control occlusion. The horizontal (x) axis of each graph depicts the percent normal zone tissue in the sample labeled by the first set of microspheres during independent LAD perfusion (see Fig. 1 and text for details). The vertical (y) axis of Figure 5 (top) depicts the control MBF in ml/min per g to each sample, 10 minutes after LAD occlusion. The vertical axis of Figure 5 (bottom) depicts the absolute change in MBF, in ml/min per g due to adenosine, by subtracting control from adenosine values of MBF. The best-fit least-squares regression line and its 95% confidence limits are drawn on each graph. The regression equation (y = mx + b), correlation coefficient (R), and number of samples considered (N) are indicated above each graph. As the percent labeled normal zone tissue in each sample increased, the control MBF (A, top) and change in MBF during adenosine (B, bottom) also increased. Note that the most ischemic samples (those with the smallest percent labeled normal zone tissue) show the lowest control MBF (5, top) and an absolute decrease in MBF during adenosine, indicated by the negative y intercept, b (5, bottom). In Figure 5 (bottom), the regression line estimates a decrease in MBF when no normal zone tissue is labeled in the sample, no change in MBF when there is 4% normal zone tissue contamination by the normal zone tissue label as follows: criterion I, 21.6 ± 6.0%; II, 13.0 ±6.0%; III, 6.5 ± 2.2%; IV, 6.1 ± 3.5%; and criterion V, 1.2 ± 0.3%. Indeed, when all samples were considered, as in Figure 5 (bottom), the percent normal zone tissue in a sample appears to be the major determinant of the magnitude of the change which occurred in myocardial blood flow during adenosine infusion. Samples containing a large percent normal zone tissue indicated by the first set of microspheres showed a large increase in myocardial blood flow during adenosine, whereas samples that contained no normal zone tissue showed a decrease in myocardial flow. Samples containing mixtures of normal and ischemic tissue showed intermediate changes. The regression lines indicate a decrease in flow during adenosine when no normal zone tissue is present, and no change in flow when 4% normal zone tissue is present.

Discussion

These data confirm our first hypothesis; the choice of different criteria to identify a myocardial sample as “ischemic” exerts an important influence on the apparent level of collateral myocardial blood flow and, especially, on the apparent response of collateral flow to adenosine. The quantitative difference in the value of myocardial blood flow to the ischemic zone is considerable, with values ranging from 0.43 to 0.08 ml/min per g for criteria I and IV, respectively. Even more striking were the qualitative or directional differences in the apparent responses of collateral or ischemic zone myocardial blood flow to adenosine. Depending only on the criterion defined prospectively to identify samples as “ischemic,” the effect of adenosine on blood flow to ischemic myocardium in these same experiments might have been reported as an increase (P < 0.06) (criterion I, ST <2.0 mV), no change (criteria II, III, and IV), or a decrease (P < 0.005) (Criterion V, NZT < 2%).

Evidence that Adenosine Decreases Collateral Blood Flow to Ischemic Myocardium

Several lines of evidence from this and other studies indicate that adenosine decreases blood flow to ischemic myocardium, as shown for samples selected as ischemic by criterion V in this study. First, in these experiments, adenosine decreased the hemodynamic indices of collateral coronary blood flow, retrograde LAD flow (RF), and peripheral coronary pressure (PCP). These hemodynamic indices do not depend on identification of ischemic myocardium because they reflect hemodynamics labeled, and a large increase in MBF during adenosine as the percent normal zone tissue labeled increased above 4%.
distal to the occlusion of the LAD. Several workers have concluded that retrograde flow measurements offer a valid index of at least the direction of changes in coronary collateral function (Gregg, 1974; Schaper, 1971; Fam and McGregor, 1964).

Other data also indicate that arteriolar vaso-dilators such as adenosine can decrease collateral coronary blood flow. First, aortic pressure is the most important determinant of collateral coronary perfusion (Gregg, 1974), and the 30% decrease in aortic pressure in our experiments would lead one to expect a decrease in collateral flow unless the vasodilator had selective effects on large coronary arteries. In fact, there is considerable evidence that adenosine exerts its major action selectively on small arteriolar resistance vessels (Rubio and Berne, 1975). Drugs that selectively dilate small coronary arterioles are thought to cause a greater decrease in vascular resistance in normal than in ischemic myocardium because of the nearly maximal decrease in vascular resistance which results from the process of ischemia, per se (Fam and McGregor, 1964), and thus precipitate a "coronary steal." Our data cannot prove the occurrence of "coronary steal" during adenosine infusion, however, because of the decrease in aortic pressure.

Effects of Mixed Samples of Ischemic and Normal Zone Tissue on Myocardial Blood Flow Responsiveness of Supposedly "Ischemic" Samples

The results also support our second hypothesis: criteria to identify ischemic myocardium which fail to exclude samples that contain small amounts of normal zone tissue, permit the directionally different blood flow response of normal zone tissue to obscure the actual effect of adenosine on blood flow to ischemic myocardium. Criteria I-IV (S-T and myocardial blood flow to the sample as a percent of the normal region) do not identify as ischemic those groups of samples in which adenosine decreases the mean value of ischemic myocardial flow for the group. The data indicate that criteria I-III were less specific than criterion V, in that they failed to reject supposedly "ischemic" samples which contained mixtures of ischemic and normal zone tissue, labeled by the first set of microspheres. The blood flow response to adenosine of normal zone tissue is directionally opposite to the response of blood flow to ischemic tissue (identified by criterion V) and the hemodynamic indices of collateral flow. Thus, Figure 5 (bottom) indicates that the myocardial blood flow response to adenosine is directly proportional to the percent normal zone tissue component in the sample, labeled by the first set of microspheres. With less than 4% normal zone tissue, the regression line estimates that adenosine causes a decrease in myocardial blood flow, whereas, for a sample with about 8% normal zone tissue, the regression line and confidence limits estimate a significant increase. Even the control flows measured 10 minutes after coronary occlusion were higher in samples selected as ischemic by criteria I-III than in those selected by criterion V (<2% of normal zone tissue). The higher control blood flows to samples of myocardium identified by criteria I-III appear to result from the failure of these criteria to reject supposedly "ischemic" samples which were contaminated by mixtures of a percentage of normal zone tissue (21.6 to 6.5%, respectively).

Criterion IV, <25% normal zone flow, was more specific in that it identified samples with a very low average myocardial blood flow, 0.08 ml/min per g, but it lacked sensitivity because it excluded samples with high true collateral flows (26-50% of the simultaneous control zone flow) which decreased during adenosine infusion. Thus, the usefulness of criterion IV was limited because it lacked sensitivity to detect a significant decrease in collateral flow which was detected by criterion V and the hemodynamic indices.

Significance of Normal Zone Tissue Label in Myocardial Samples

A question which arises from these results is whether the differential responsiveness of blood flow is caused by a gradient of severity of ischemia in samples selected by the different criteria, e.g., least severely ischemic myocardium responding to adenosine with the greatest increase in blood flow. The normal zone tissue-labeling technique indicates that a lateral border zone or gradient of severity of ischemia within the LAD zone is not necessary to explain these results because the intermediate values of blood flow and the response of blood flow to adenosine seem to be accounted for by the amount of normal zone tissue mixed with ischemic myocardium in the sample (Fig. 5). The background and implications of the concept of a gradient of severity of ischemia within the LAD zone require careful consideration of the methods used to analyze this possibility. The technique to label normal zone tissue with the first set of microspheres is not simply measuring collateral flow because the LAD zone is not ischemic during the labeling. The LAD is perfused at aortic pressure through a large-bore cannula with blood free of microspheres during injection of the first set of microspheres into the left atrium. Under these conditions, flow through interarterial anastomoses was minimized and the microspheres labeled tissue which was normally perfused by vessels other than the LAD distal to its cannula (Hirzel et al., 1976). In fact, there was an occasional slight (2-3 mm Hg) pressure gradient present between aortic and LAD coronary perfusion system pressures during the balloon perfusion. To account for the small number of microspheres which might enter the LAD zone during the labeling procedure, an upper limit of this "contaminating" radioactivity for defining ischemic samples was chosen prospec-


The concept of a lateral border zone in which there is a gradient of severity of ischemia is built on the finding of intermediate values of the following variables from center to peripheral border of the ischemic zone: blood flow reduction (Rees and Redding, 1969; Vokonas et al., 1978; Judgutt et al., 1979), histological evidence of infarction (Edwards, 1969), histochemical evidence of metabolic abnormalities (Cox et al., 1968), tissue metabolite concentration and ST segment elevation in epicardial electromograms (Maroko et al., 1971; Hearse et al., 1977), and local contractile activity (Hood, 1975; Vatner et al., 1976; Helfant et al., 1978). The results of the present study and other work from this laboratory confirm intermediate values of blood flow in dogs (Hirzel et al., 1976) and pigs (Patterson and Kirk, 1978), myocardial creatine kinase in dogs (Hirzel et al., 1977), and histological evidence of necrosis (Factor et al., 1978). The current study and the other work in this laboratory seem to explain the findings of others by accounting for the contribution to the intermediate values which result from the overlap between native circumflex and LAD vascular distributions.

The mixed tissue in the border zone has major implications for assessing the effects of interventions designed to salvage ischemic myocardium. In testing the effects of agents on collateral blood flow to ischemic myocardium, selection of samples for microsphere measurements by criteria which fail to exclude normal zone tissue can cause confusing results because of different responses of normal and ischemic tissue. Thus, agents such as adenosine, which increase blood flow to normal myocardium and normal components of mixed samples but decrease blood flow to ischemic myocardium and ischemic components of mixed samples, would be expected to aggravate the severity of ischemia and eventual infarction. Mixed samples might not indicate the potential harmful effects of an agent such as adenosine because the increased blood flow to the normal component of the mixed sample might obscure the decreased blood flow to the ischemic component. This problem of mixed tissue samples appears to explain the observation that myocardial blood flow during vasodilation may increase considerably in the normal zone, moderately in the lateral “border zone,” and little or not at all in the central ischemic zone (Becker, 1976; Linder and Sieman, 1967; Henry et al., 1978; Vatner et al., 1978).

Our results with adenosine do not indicate that dipyridamole and nifedipine cannot increase collateral flow, but our data demonstrate a potential problem which might have influenced these or other studies. Contamination of supposedly ischemic samples by small fractions of normal zone tissue was shown in this study to cause serious misinterpretation of the direction, as well as the magnitude, of the apparent response to adenosine. Thus, this qualitative problem may be more important than some of the quantitative problems with estimation of blood flow by the radioactive microsphere technique (Heymann et al., 1977).


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