Dual Radionuclide Study of Myocardial Infarction

Relationships between Myocardial Uptake of Potassium-43, Technetium-99m Stannous Pyrophosphate, Regional Myocardial Blood Flow and Creatine Phosphokinase Depletion

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SUMMARY The dual radionuclide myocardial distributions of imaging agents potassium-43 (43K) and technetium-99m stannous pyrophosphate (99mTc-PYP) were studied in a 24-hour closed chest canine infarct preparation. In multiple myocardial biopsies in 20 dogs, tissue levels of both radionuclides were compared to either an index of tissue viability (myocardial creatine phosphokinase [CPK] depletion), or to estimates of regional myocardial blood flow as measured by the microsphere technique.

Myocardial 43K uptake in the ischemic and infarcted zone correlated well with both CPK depletion (r = 0.73) and microsphere estimates of relative blood flow. The correlation with microspheres was excellent in the transmural sample (r = 0.93) as well as endocardial (r = 0.97) and epicardial (r = 0.86) portions.

On the other hand, 99mTc-PYP myocardial uptake did not correlate with the extent of CPK depletion. Maximal uptake was frequently noted in border zones with only moderate CPK depletion, while lesser degrees of 99mTc-PYP uptake were noted in the central infarct zone where CPK activity was lowest. The relationship of 99mTc-PYP uptake to microsphere regional flow estimates demonstrated that 99mTc-PYP uptake was maximal at flows of 0.3 to 0.4 of normal. At lower flows, 99mTc-PYP uptake fell toward normal levels. A similar relationship was noted between the distributions of 99mTc-PYP and 43K. In relatively high flow border segments (≥0.80 of normal), abnormal 99mTc-PYP uptake of five to six times normal persisted. The transmural distribution of 99mTc-PYP demonstrated that in low flow regions 99mTc-PYP uptake was primarily epicardial, while in the higher flow ischemic periphery of the infarct endocardial uptake predominated. Thus, while there is a direct correlation between cationic 43K myocardial uptake and regional myocardial viability and blood flow, no such direct relationship exists for 99mTc-PYP. This is in part based on the necessity for delivery of the radioactive tracer to the infarct zone.

NONINVASIVE RADIONUCLIDE IMAGING techniques can visualize acute myocardial infarction in two general ways. On the one hand, a myocardial radionuclide distribution may be obtained with maximal incorporation in normal myocardium and minimal uptake in the region of the infarct. Imaging of such a distribution would demonstrate the zone of infarction and/or ischemia as a "cold spot," or region of relatively reduced myocardial radioactive tracer accumulation. Radioactive potassium and its analogs, rubidium, cesium, and thallium have been utilized for such studies.1-13 Alternatively, certain radioactive tracers maximally concentrated in infarcted and/or ischemic myocardium, such that the region of infarction is visualized as a "hot spot," or "positive" zone of increased radionuclide accumulation. Prototype "positive" infarct imaging radionuclides include technetium-99m labelled stannous pyrophosphate, tetracycline, and glucoheptonate.14-18 Simultaneous assessment of an infarction with both types of externally detected radionuclide myocardial distributions might allow more precise definition of regions of infarction and associated peri-infarction ischemia.

If this noninvasive approach is to be utilized to quantify gradations of abnormality within the infarcted left ventricle, then the pathophysiologic correlates of myocardial radionuclide uptake must be defined. With this purpose, dual radionuclide myocardial distributions of potassium-43 (43K) and technetium-99m stannous pyrophosphate (99mTc-PYP) were studied in a canine model of acute myocardial infarction. These radionuclide distributions were related to an index of tissue viability (myocardial creatine phosphokinase concentration), and to an index of regional myocardial blood flow as measured by radioactive microspheres.

Methods

Adult mongrel dogs of either sex weighing 20-35 kg were utilized for all studies. Closed chest myocardial infarction was created by a modification of the catheter plug embolization technique of Cohen and Eldh.19 Animals were lightly anesthetized with sodium pentobarbital. A #7 Sones catheter was introduced into the aortic root via a right carotid artery cutdown. Following fluoroscopic subselective positioning of the catheter in the left anterior descending coronary artery, a guidewire impaled plug present at the catheter tip was dislodged into the coronary artery. The plug was solid, 2-4 mm in length, and was made from the tip of a polyethylene angiographic catheter. This plug usually lodged in the distal one-third of the coronary artery at the point of origin of the last large diagonal branch from the anterior descending artery. Animals were pretreated with xylocaine prior to infarction and a xylocaine infusion (2 mg/min) was continued.
for one hour postinfarction. ECG monitoring was maintained throughout. Short bursts of ventricular ectopy were common immediately following the embolic infarction and were treated with bolus injections of xylcaine (50–100 mg i.v.). Precordial ST-segment elevation was noted in all animals. This preparation resulted in infarction which appeared grossly to be small to medium in size. Once the animals appeared electrically stable, the cutdown was closed and the dog was allowed to recover.

In eight dogs the following protocol was followed. Twenty-four hours following infarction, the conscious animal received 10 mCi of \(^{99m}\)Tc-PYP (Mallinkrodt) intravenously. One hour later a second intravenous injection of 0.5 mCi \(^{42}\)K was administered. One minute after the injection of \(^{42}\)K the dogs were again anesthetized, the trachea intubated, respiration maintained with a Harvard respirator, and a lateral thoracotomy performed at the level of the left fourth intercostal space. Following adequate exposure, the beating heart was immediately removed, washed and placed on iced saline. In all instances the site of plug embolization could be identified and epicardial demarcation of the site of infarction was evident. Approximately 20 full thickness myocardial samples weighing 40–80 mg were obtained with either a cylindrical core biopsy instrument or by direct scalpel dissection. In each heart, approximately 6–8 of the twenty samples were obtained from a normal left ventricular region remote from the infarct. Infarct samples were obtained in sequence from center to periphery of the visually discernible region of infarction. Topographical maps were drawn for each animal relating the biopsy sites to coronary anatomy and site of infarction (fig. 1).

Samples were immediately quick frozen in liquid nitrogen, placed in pre-weighed, chilled tubes and transferred on ice to be weighed and assayed for radioactivity. Samples were counted in a well type scintillation counter. Utilizing differential spectrometry, \(^{42}\)K activity was counted at a window from 560–660 KeV and \(^{99m}\)Tc-PYP at a window of 100–140 KeV. By employing a ratio obtained by counting a \(^{42}\)K standard in both the \(^{42}\)K and \(^{99m}\)Tc window, appropriate correction was made for higher activity \(^{42}\)K in the \(^{99m}\)Tc window. Sample activity was obtained as counts per minute per gram of tissue. Infarct sample activity was expressed as an activity ratio between that of the sample and the mean value of the 6–8 normal samples obtained in each animal. Samples were kept on ice throughout, except for the brief period when placed in the well counter. All samples remained frozen.

Immediately following radioactivity counting, the biopsies were homogenized in 2 ml of 0.01M phosphate buffer (pH 7.2) containing 0.01 M sodium EDTA, 0.01 Tris HCl, and 0.01M glutathione. Homogenization was performed in an ice bath. The homogenizer was rinsed with 2 ml of the homogenizing medium and this was combined with the homogenate. The homogenate was then centrifuged at 10,000 RPM at 0°C for ten minutes, the supernatant removed and frozen. One milliliter of the supernatant was used for creatine phosphokinase (CPK) assay. Dilution was made when appropriate. CPK was measured by the method of Rosalki, utilizing Stat-Paks obtained from Calbiochem, La Jolla, California.21

In an additional 12 animals, the same infarction protocol was followed and \(^{99m}\)Tc-PYP and \(^{42}\)K were administered in the same manner. In these experiments following thoracotomy, the left atrial appendage was cannulated and approximately 4.4–6.0 million 15 ± 5μm diameter carbonized microspheres labelled with chromium-51 (3M Corporation) were administered following constant agitation in an ultrasonic bath for at least 15 minutes. The microspheres were suspended in a volume of 1–2 cc 10% Dextran and had a specific activity of 10.8 mCi/g. This relatively large number of microspheres was employed to improve overall counting statistics. Injection of a similar number of microspheres has been shown by Fortuin et al. not to significantly alter coronary blood flow or peak reactive hyperemic coronary blood flow.22 Two minutes following injection of microspheres, the heart was removed and washed. The atria, right ventricle and interventricular septum were dissected free from the left ventricle. Samples were obtained from the left anterior descending distribution of the free wall of the left ventricle (infarct zone) and from the normal circumflex distribution of the lateral wall. Approximately 12–16 2g myocardial samples were obtained from each heart. The topography of each sample in relation to the infarct zone and coronary anatomy was again recorded. Samples were trimmed of epicardial fat and blood vessels. Each sample was divided into approximately equal 1g endocardial and epicardial portions.

**Figure 1.** Diagrammatic representation of the topography of dual radionuclide distribution in an individual study. The stippled area indicates the visually appreciated zone of infarction. The plug embolus is situated in the left anterior descending coronary artery just proximal to the last large diagonal branch. The numbers in circles correspond to sample biopsy sites in the individual experiment. Sample activities for \(^{99m}\)Tc-PYP, \(^{42}\)K and CPK are expressed as activity ratios between the infarct sample and mean of 6–8 normal biopsies obtained from a left ventricular region remote from the infarct. Abnormality in \(^{42}\)K uptake generally parallels the extent of CPK depletion. Highest \(^{99m}\)Tc-PYP activity is noted in sample 10, which is located near the margin of the infarction and is associated with only moderate reduction in tissue CPK and tissue uptake of \(^{42}\)K. Relatively low \(^{99m}\)Tc-PYP activity is noted in sample 12, which is associated with lowest CPK and \(^{42}\)K levels.

\(^{42}\)K kindly supplied by Dr. J.K. Poggenburg, Oak Ridge National Laboratory, Oak Ridge, Tennessee.
Samples were then immediately counted for radioactivity using differential spectrometry and the previously described 43K and 99mTc windows and a 300–340 KeV 51Cr window. 51Cr and 43K activity was recounted approximately four days following study. This afforded a more optimal condition for counting 51Cr following physical decay of the major portion of the overlapping higher energy 43K. From these data utilizing ratios obtained from known standards, appropriate correction for the absolute amounts of 43K, 99mTc, and 51Cr in each sample was determined. Infarct sample radioactivity for each of the three radionuclides was again expressed as an activity ratio of the sample to the mean of all samples obtained from a distant normal left ventricular site.

Four sham infarcted animals receiving both 43K and 99mTc-PYP served as controls for initial studies involving dual radionuclide and CPK determinations. Following administration of radioactive tracers the heart was removed, multiple biopsies obtained, and both differential counting and enzyme analysis performed. Two additional sham infarcted animals served as controls for the microsphere studies. In these studies following intravenous administration of the soluble radioactive tracers and left atrial microsphere injection, the heart was removed and samples obtained and analyzed as outlined above.

Results

In all animals studied, significant abnormality was demonstrated in the myocardial uptake of 43K and 99mTc-PYP within the infarct zone. In the initial eight dogs in which small sample biopsies (40–80 mg) were obtained, infarct:normal myocardial radioactivity ratios averaged 0.39 ± 0.03 (mean ± SEM) for 43K with a range from 0.07:1 to 0.88:1. 99mTc-PYP infarct:normal ratios averaged 23:1 ± 3 (range 3:1–68:1). In the subsequent 12 animals (microsphere studies), in which larger myocardial samples (1–2 g) were obtained, infarct:normal ratios for 43K were 0.53:1 ± 0.03, and for 99mTc-PYP were 11:1 ± 2.0. In each experiment, values for infarct zone radioactivity were significantly different (P < 0.001) from those obtained in normal zones. In sham infarct control animals, from which 60 myocardial samples were obtained, the standard deviation of the mean and standard error for 43K samples averaged 6% and 3%, respectively, and for 99mTc-PYP 4% and 2%, respectively.

Myocardial CPK activity in the infarct zone in 68 samples from eight animals averaged 0.43 ± 0.03 of normal. This was significantly different (P < 0.01) from normal samples. In forty samples obtained from four sham infarcted dogs, mean tissue CPK averaged 487 milliunits/mg wet weight of tissue, with a standard deviation of 121, and a standard error of 20 milliunits/mg.

The greatest CPK depletion was most frequently noted in the center of the grossly evident infarct zone, with lesser degrees of enzyme depletion noted as the periphery of the infarct was approached. Generally, the magnitude of decrease in 43K uptake paralleled the extent of enzyme depletion. On the other hand, frequently 99mTc-PYP uptake was maximal in border zones where CPK depletion was only moderate, while lesser degrees of 99mTc-PYP uptake were noted in the central infarct zone where CPK activity was lowest (fig. 1). When the results of studies in all eight animals were analyzed, a linear relationship was noted between the extent of abnormality in 43K uptake and CPK depletion (r = 0.73) (fig. 2). Comparison of the relationship between 99mTc-PYP uptake and CPK depletion yielded no such linear relationship (fig. 3).

When the relationships between 99mTc-PYP and 43K uptake were compared in the same samples, again no simple linear relationship existed. 99mTc-PYP uptake was maximal in regions associated with 43K uptake of approximately 0.4 of normal. A positive relationship existed in samples in which 43K uptake was less than 0.4 of normal, such that 43K uptake increased, 99mTc-PYP uptake similarly increased (r = 0.73). In infarct regions with 43K uptake greater than 0.4 of normal, a negative linear relationship existed, such that as 43K uptake increased and approached normal, 99mTc-PYP uptake fell (r = −0.75) (fig. 4).

![Figure 2. Relationship between myocardial 43K and CPK activities in 74 biopsy samples obtained from eight dogs with infarction. Activities are expressed as ratios between infarct sample and mean of 6–8 normal samples in each individual study.](image1)

![Figure 3. Relationship between myocardial 99mTc-PYP and CPK activities in 67 biopsy samples from eight dogs with infarction. No significant correlation was noted (r = −0.17).](image2)
while at regional myocardial blood flow rates greater than 0.4 of normal, PYP uptake decreased as flow approached normal. However, in relatively high flow border segments (≥ 0.80 of normal) significant 99mTc-PYP uptake of approximately 5–6 times normal persisted. Similar trends were noted in comparison of endocardial and epicardial samples.

Of note as well was the transmural distribution of 99mTc-PYP uptake within the infarct zone (fig. 7). In low flow regions, pyrophosphate myocardial uptake was primarily epicardial, with endo-epicardial ratios of 0.4–0.5. As the regional flow profile increased toward normal, transmural distribution became equivalent between endocardium and epicardium. In the highest flow border zones of the infarct, 99mTc-PYP uptake was primarily endocardial with endo-epicardial ratios of 3–3.5.

Discussion

If radionuclide imaging techniques are to be utilized to detect ischemia and infarction as well as to quantify their respective sizes, then the factors governing individual radionuclide myocardial uptake must be clearly understood. Such insights may be obtained from animal models, recognizing that direct comparison of results obtained in different species can be difficult since variation in coronary anatomy and collateral pathways may be significant.

43K was chosen as the cold spot radionuclide for this study because of previous clinical experience with this tracer, and its energy spectrum which allowed simultaneous radioactivity counting of the high energy 43K and the lower energy 99mTc and 67Cr. Although 43K was utilized in this study, its long-term widespread utilization is limited by cost and mode of production, and physical characteristics which make routine scintillation camera imaging difficult. For these reasons, rubidium-81 (81Rb) and thallium-201 (201T1) have been developed as alternative monovalent cation imaging radionuclides. 5–7, 11–13 These radioactive tracers possess more favorable physical properties and have a more feasible commercial means of production. It is clear, however, from previous studies that physiologic statements concerning 43K are generally applicable to potassium analogs 81Rb and 201T1, both of which are currently available from commercial sources. 5, 11 Differences between myocardial uptake of potassium and thallium have been noted at high flow situations such as reactive hyperemia, but this would not be relevant to the model of acute infarction reported in this study. 11.

FIGURE 4. Relationship between myocardial 43K and 99mTc-PYP activities in 91 samples from 12 dogs. Note that maximum 99mTc-PYP activity occurs at 43K levels of between 0.3 – 0.4 of normal. Two significant linear relationships are evident. At 43K levels below 0.4 of normal, 99mTc-PYP levels increase as 43K activity increases. At 43K levels greater than 0.4 of normal, 99mTc-PYP decreases as 43K increases toward normal.

Microsphere studies based upon 91 samples from 12 animals demonstrated an excellent linear correlation between regional myocardial uptake of the flow related particles and ionic 43K (fig. 5). This relationship existed for transmural samples (r = 0.93) as well as endocardial (r = 0.97) and epicardial (r = 0.86) portions. In extremely low flow regions, the radioactive cation uptake was generally greater than that of microspheres.

On the other hand, the relationship between flow related microsphere distribution and that of 99mTc-PYP was by no means linear. The relationship rather closely resembled that demonstrated between 43K and 99mTc-PYP. Again, 99mTc-PYP uptake was maximal at relative microsphere flow distributions between 0.30 and 0.40 of normal (fig. 6). At regional myocardial blood flow less than 0.40 of normal, 99mTc-PYP myocardial uptake increased as flow increased;
FIGURE 6. Relationships between myocardial °mTc-PYP and microsphere distributions in the transmural sample. Note the similarity in distributions to the relationships between °K and °mTc-PYP. °mTc-PYP uptake is again maximal at relative flows of between 0.3-0.4 of normal. Note the frequent finding of abnormal °mTc-PYP uptake in relatively high flow border zones.

Our data demonstrate an excellent correlation between myocardial radioactive cation uptake as manifest by °K distribution and both myocardial viability as assessed by regional myocardial CPK depletion, and regional myocardial blood flow as estimated by the radioactive microsphere technique. The correlation between °K uptake and regional blood flow existed in both endocardial and epicardial samples as well as across the entire wall thickness. These studies in a 24-hour infarct preparation are similar to data obtained in more acute open chest canine preparations by Prokop et al. and Becker et al. In our study, as in that of Becker in the very low flow regions, radioactive cation uptake was somewhat greater than that of microspheres.

Compared to the regional topography of myocardial cation uptake in experimental infarction, that of °mTc-PYP appears more complex. A definitive statement concerning myocardial necrosis is difficult in the absence of histologic confirmation. However, no linear relationship existed between pyrophosphate uptake and the extent of presumed myocardial necrosis as defined by regional CPK depletion. Specifically, relative reduction in the extent of abnormal °mTc-PYP uptake was frequently encountered in myocardial segments associated with maximal depletion of CPK. Highest myocardial levels of °mTc-PYP frequently occurred in regions associated with only mild to moderate CPK depletion. This lack of correlation between an index of myocardial viability and °mTc-PYP myocardial uptake can in part be explained by a demonstrated flow dependence. °mTc-PYP uptake within the infarct would appear to be governed by at least two factors: 1) regional radionuclide extraction dependent upon myocardial necrosis or ischemia, and 2) regional flow to the involved area which allows delivery of the radioactive tracer. Microsphere data would suggest that the maximal uptake occurs at a regional blood flow profile within the infarct of between 0.30 and 0.40 of normal. Similar data are obtained when °K and °mTc-PYP distributions are compared. The "doughnut" appearance of reduced central °mTc-PYP accumulation noted in images of canine infarction involving occlusion of the proximal left anterior descending coronary artery would be an in vivo imaging manifestation of this observation.

The transmural distribution of °mTc-PYP within the infarct zone again illustrates the role of regional blood flow in determining radionuclide uptake. In regions of lowest flow within the center of the infarct, °mTc-PYP uptake is predominantly epicardial, with endo-epicardial ratios of 0.4-0.5. This occurs despite the fact that the more intense local region of necrosis would involve the endocardial surface of the infarcted segment. On the other hand, in higher flow regions, uptake becomes primarily endocardial. These observations of pyrophosphate uptake stand in direct contrast to those recently obtained with radioactive labelled myosin specific antibodies. With this radioactive tracer, uptake in the central infarction zone is primarily endocardial, and maximal uptake occurs in the lowest flow regions.

Of further interest, the microsphere data show significant myocardial °mTc-PYP uptake (approximately 5.3:1) in regions where flow is minimally if at all reduced (greater than 0.80 of normal). This would imply either uptake in ischemic but not irreversibly damaged cells or uptake by a small population of infarcted myocardial cells interspersed with a normal population within the border zone. Discrimination between these alternative possibilities will require the use of techniques such as autoradiography. A possible clinical correlate of this phenomenon might be the finding of positive myocardial images of abnormal pyrophosphate uptake in patients with unstable angina who demonstrate neither serum enzyme nor electrocardiographic evidence of infarction.

The biochemical mechanisms governing °mTc-PYP uptake once it has been presented to the infarcted cell have not yet been resolved. Initial thoughts concerning influx into mitochondria with resultant hydroxy apatite crystal formation have been questioned by recent observations.
Although intracellular calcium influx appears to occur in the presence of increased pyrophosphate uptake, no quantitative relationship between the two is immediately evident, suggesting that the two events may not be causally related.

Our data concerning the relationships between pyrophosphate uptake and other radioactive cationic myocardial distributions are in agreement with other preliminary reports utilizing either radioactive potassium, cesium, or ammonium ion.\textsuperscript{9-10} The relationship shown between \textsuperscript{99m}Tc-PYP uptake and CPK depletion, however, contrasts with the reports of Botvinick et al.\textsuperscript{11} and Shames et al.\textsuperscript{12} who demonstrated a significant linear relationship between loss of tissue CPK and \textsuperscript{99m}Tc-PYP myocardial accumulation. These authors used a 48-hour rather than the 24-hour infarction preparation used in this study. Moreover, if the infarction produced in their study was less severe, regions in which flow reduction was maximal may not have been encountered. Our correlative data with both \textsuperscript{42}K and microspheres indicate that if flow is significantly reduced, then a fall off in maximal pyrophosphate uptake would be expected. The earlier studies of Kjekshus and Sobel demonstrated a linear relationship between blood flow and CPK depletion, with lowest tissue CPK levels in regions of lowest flow.\textsuperscript{30} Therefore, maximal \textsuperscript{99m}Tc-PYP uptake would not be expected in the lowest flow, maximally CPK depleted region.

Results of correlative studies between pathologic and \textsuperscript{99m}Tc-PYP radionuclide assessment of infarct size in animal models have been somewhat variable and await further confirmation.\textsuperscript{31, 34-36} What extrapolations can be made from these data, obtained at the tissue level, to external detection of myocardial radionuclide distributions in the patient with myocardial infarction? If computer generated isocount contour maps were utilized, one would expect radioactive cation distributions to correspond well with both flow related and viability related parameters of infarcted and ischemic myocardium. \textsuperscript{99m}Tc-PYP uptake might well be lower in central infarction zones and excessively high in the perimeter or margin zone, such that over-all infarct size might be overestimated. If cold and hot spot tracers were used together, subtraction of the isocount distribution of one radionuclide from that of the other might allow definition of a region of mismatch or nonalignment. This zone might correspond to an ischemic peri-infarction zone.

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References

Left Ventricular End-Diastolic Pressure Volume Relationships with Experimental Acute Global Ischemia

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SUMMARY The mechanism of elevation of left ventricular end-diastolic pressure during acute global ischemia was evaluated by examination of the relative contributions of a decrease in contractility and an alteration of the pressure-volume relationship. The external circumference (mercury-in-silastic gauge) pressure relationship, as an index of the pressure-volume relationship, was studied in beta adrenergic and ganglionic blocked, open chest dogs on right heart bypass at constant heart rate and aortic pressure. Ischemia of one and two hours' duration was produced by reducing total coronary blood flow in cannulated left and right coronary arteries until left ventricular end-diastolic pressure rose significantly. At a constant stroke work, left ventricular end-diastolic pressure rose from 5.0 ± 0.5 to 15.0 ± 0.5 cm H2O in the experiments of one hour of ischemia, and from 7.0 ± 1.0 to 17.0 ± 1.0 cm H2O in experiments of two hours of ischemia. Ischemia was followed by one hour of restoration of coronary blood flow. Ischemia produced a marked depression of ventricular function: stroke work, considered at a left ventricular end-diastolic pressure of 15 cm H2O, decreased from 21.0 ± 3.0 to 3.5 ± 0.5 gm-m, and from 15.0 ± 2.0 to 2.5 ± 0.5 gm-m, in the experiments of one and two hours, respectively. Neither ischemia nor reflow changed the pressure-volume relationship. Thus, the elevation of left ventricular end-diastolic pressure during ischemia in an otherwise normal canine myocardium is due to a decrease in systolic performance of the heart rather than to an alteration of the pressure-volume relationship.

LEFT VENTRICULAR END-DIASTOLIC PRESSURE (LVEDP) is determined by volume and pressure load conditions, systolic performance of the heart, and diastolic pressure-volume relationships. Left ventricular end-diastolic pressure increases during angina in some patients with coronary artery disease.1-7 The mechanism of this increase, whether a decrease in left ventricular contractility or an alteration in pressure-volume relationship, 1-4 remains controversial.

The present experiments were designed to examine the mechanism of elevation of end-diastolic pressure during acute left ventricular ischemia in an otherwise normal heart. A canine model was employed. Pressure-external circumference relationships were studied before, during, and after left ventricular ischemia. Global left ventricular ischemia, produced by a controlled reduction in flow in both coronary arteries, was used because local ischemia may obscure the relative contribution of normal and ischemic myocardium to the overall pressure-circumference relationship, when the circumferential gauge surrounds both ischemic and nonischemic myocardium. Also, overall intracavitary pressure may not reflect end-diastolic tension of a local ischemic area.

Methods

1. Right Heart Bypass

Right heart bypass preparation (fig. 1) experiments were conducted in 13 open chest mongrel dogs weighing between 17 and 20 kg. The dogs were anesthetized intravenously with a mixture of chloralose (60 mg/kg) and urethane (600 mg/kg). The trachea was intubated and ventilation was maintained with a Harvard respiratory pump using 100% oxygen. Details of the right heart bypass preparation have been previously reported.5,6 Both left main and right coronary arteries were cannulated and total coronary blood flow was controlled by means of a separate calibrated roller pump. Total coronary venous blood flow was measured directly from the cannulated right ventricle.

Heart rate was maintained constant throughout the experiments by means of atrial pacing after sinoatrial node crush. The aorta was cannulated at the junction of thoracic and abdominal segments. Mean aortic pressure in the

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