Distribution of Deoxyglucose and Technetium-99m-Glucarate in the Acutely Ischemic Myocardium

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The regional myocardial distribution of ^{99m}Tc-glucarate was compared to ^{3}H-deoxyglucose in 22 rabbits with left circumflex marginal artery occlusion. In 12 rabbits, tissue radioactivity measurements were compared to the results of triphenyl tetrazolium chloride staining and light microscopy. In 10 additional rabbits, the myocardial sodium space (^{24}NaCl), an indicator of tissue edema induced by injury, was compared to the distribution of deoxyglucose and glucarate. Technetium-99m-glucarate accumulated in injured myocardium within 6 hr after coronary ligation and myocardial concentration was greatest in the most severely injured zones (TTC unstained). Hydrogen-3-deoxyglucose behaved as a marker of ischemia but concentrated in tissue with injury ranging from mild ischemia (TTC stained) to transmural infarction (TTC unstained). Both ^{99m}Tc-glucarate and ^{3}H-deoxyglucose concentrated in acute, severely injured myocardial tissue. These studies suggest that ^{99m}Tc-glucarate is a useful tracer for evaluating myocardial injury. In addition, it appears that ^{99m}Tc-glucarate and ^{3}H-deoxyglucose demarcate different points in the spectrum of myocardial injury.

J Nucl Med 1993; 34:1303–1308

Preservation of ischemic, viable myocardium is a major goal of therapy for myocardial infarction and unstable angina. Altered substrate utilization (*1,2*) is a particularly promising indicator of viability. Positron emission computed tomography (PET) can detect ischemia as focally enhanced myocardial uptake of ^{18}F-deoxyglucose (*3–6*) in zones of diminished perfusion. Recently, a new ^{99m}Tc-labeled sugar analog, ^{99m}Tc-glucaric acid, was found to concentrate in areas of acute cerebral and myocardial injury (*7–10*). Although ^{99m}Tc-glucarate concentrates in ischemic brain, the mechanism of accumulation appears to be different from FDG (*8*). Also, it has been demonstrated that glucarate can act as a fructose analog under some conditions (*8*). In a canine model of myocardial infarction and ischemia, it was demonstrated that ^{99m}Tc-glucarate accumulates in infarcted but not ischemic myocardium (*10*). However, only three animals were studied and ischemia was produced by a single occlusion with reflow. Thus, it is possible that ^{99m}Tc-glucarate accumulates in myocardium when ischemia is more severe. This hypothesis was tested in the present study.

Since it is unclear which point in the spectrum of myocardial injury is demarcated by glucarate accumulation, we compared the tissue distribution of ^{99m}Tc-glucarate to ^{3}H-deoxyglucose (DG) in reperfused myocardium. In all experiments, tissue damage was verified by triphenyl tetrazolium chloride (TTC) staining, a histochemical method which measures mitochondrial dehydrogenase activity (*11*). Also, as an independent measure of myocardial injury, the sodium space (which increases with tissue injury), was measured in some of the animals (*12,13*).

MATERIALS AND METHODS

Animal Model

Myocardial ischemia and reperfusion injury was induced in 5 (fasting) and 17 (fed) New Zealand white rabbits weighing about 3 kg. Under ketamine/xylazine anesthesia, a 2.5-F endo-tracheal tube was inserted and respirator-assisted ventilation was started. Following left thoracotomy, the left circumflex marginal artery (LCXMA) was occluded with 4.0 silk (Ethicon, Somerville, NJ).

Three groups of animals were studied to determine the relative distribution of glucarate in zones of injury; Group 1: acute necrosis; Group 2: recurrent ischemia; and Group 3: relation between tissue edema and glucarate uptake.

Group 1. The LCXMA of six fed animals was occluded for 60 min followed by reperfusion for 5 hr. At the fourth hour of reperfusion, ^{3}H-DG (1 mCi) and ^{99m}Tc-glucarate (15 mCi) were injected and the animals were sacrificed 1 hr later.

Group 2. Six fed animals had multiple short episodes of occlusion/reperfusion. The LCMXA was occluded for 20 min followed by 5 min of reperfusion and this process was repeated three times over 70 min. At 4 hr after the last reperfusion, ^{3}H-DG (1 mCi) and ^{99m}Tc-glucarate (15 mCi) were injected and the animals were killed 1 hr later.

Group 3. Ten animals (5 fasting and 5 fed) were subjected to the same occlusion-release protocol used in Group 2. Regional tissue edema was measured with ^{24}NaCl in this group. To assure adequate mixing of ^{24}Na chloride (^{24}NaCl) in the extracellular fluid space, 10 μCi of ^{24}NaCl was administered 24 hr prior to the

Received Sept. 4, 1992; revision accepted Apr. 1, 1993.

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Note: Review of this manuscript was made under the supervision of Guest Editor Michael J. Welch, Mallinckrodt Institute of Radiology, Washington University Medical Center, St Louis, MO.

ischemic insult. Technetium-99m-glucarate and ^{3}H-DG were injected at 4 or 22 hr after the last reperfusion.

TTC Staining and Tissue Radioactivity Measurements of ^{99m}Tc-Glucarate, ^{3}H-Deoxyglucose and ^{24}NaCl

After death, the heart was removed and sliced breadloaf (6-mm sections). Two slices (chorda and papillary muscle level) were divided into 14 radial segments. The segments were classified into seven zones based on the results of histopathology: zones 1–3 (septum); zones 4, 5, 13 and 14 (normal); zones 6 and 12 (surrounding); and zones 7 and 11 and 8–10 (center). Each segment was further divided into three transaxial layers of equal thickness. The upper and lower layers were incubated with 2% TTC solution for 30 min at 37°C. The staining of the radial segments was scored as follows: unstained—no staining in both the upper and lower layers; stained—staining in both the upper and lower layer; and partial staining—staining in only one of the layers. The medial layer was weighed and stored frozen. Tissue radioactivity was measured with a well-type gamma counter. All measurements were corrected for crossover. The slices were then minced and solubilized (Solvable, New England Nuclear) for 48 hr. Twenty ml of Aquasol (New England Nuclear, N. Billerica, MA) was then added and the samples were stored in the dark for 24 hr. Tritium radioactivity was measured with a liquid scintillation counter.

Histopathology

Following TTC staining, the upper and lower transaxial layers of each segment were prepared for histopathological examination. After 5 days of fixation in 10% neutral buffered formalin, the samples were embedded in a plastic resin blocks using a JB-4 Plus embedding kit (Polyscience, ICN, Costa Mesa, CA). Sections of 2-μm thickness were stained with hematoxylin-eosin (H & E) and paratungstanoic acid hematoxylin (PTAH).

Data Processing

Tissue concentrations of ^{99m}Tc, ^{3}H and ^{24}Na were expressed as percent injected dose per gram of tissue (%ID/g). Segments of the posterior interventricular septum were considered to be normal and target-to-normal ratios (T-to-N) were calculated. To facilitate assessment of tracer localization in the myocardium, the concentration of each tracer in each segment was compared to the concentration in blood and was called the tissue-to-blood ratio (T-to-B). One-way and two-way analysis of variance followed by the Scheffe test was used for statistical analysis.

RESULTS

Histopathology

The antero-lateral wall of all Group 1 animals had no TTC staining and H & E and PTAH staining showed severe contraction band necrosis (Fig. 1A and B). Most of the cells in zones with contraction bands had eosinophilic changes indicative of cell death. In the edematous interstitial tissue, neutrophil infiltration and bleeding were observed.

In Groups 2 and 3, the appearance of their anterolateral wall on TTC staining was: complete staining in 6/16, partial staining (nontransmural) in 6/16 and no staining in 4/16. Contraction band cells were observed focally in areas of absent TTC staining (Fig. 1C) and no hemorrhage was observed. At 24 hr, greater numbers of neutrophils were seen (Fig. 1D).

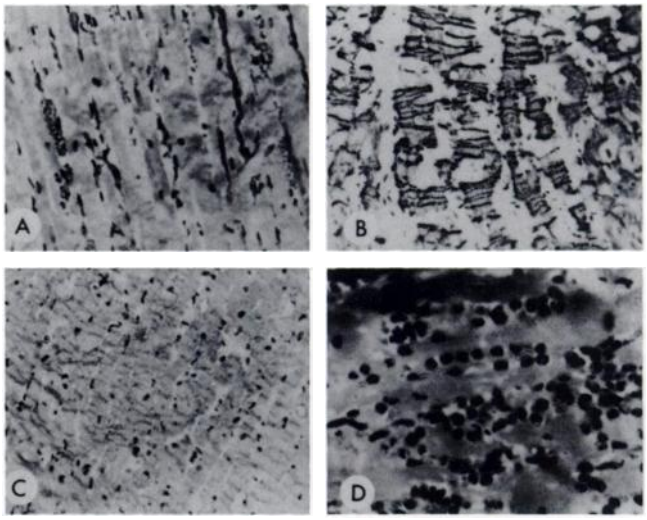

FIGURE 1. Histopathological findings in Group 1, 2 and 3 animals. (A) Section of myocardium (TTC unstained) of a Group 1 animal, illustrating contraction band necrosis and interstitial bleeding (H & E stained, 400 ×). (B) Similar section to A demonstrating contraction band cells (PTAH stained, 400 ×). (C) Section of myocardium (TTC stained) of a Group 2 animal, illustrating contraction band cells without obvious cell disruption (H & E stained, 400 ×). Interstitial bleeding was uncommon in Group 2. (D) Section of myocardium (TTC unstained) of a Group 3 animal at 24 hr after ischemia, illustrating marked neutrophil infiltration (H & E stained, 400 ×).

Relationship Between Tissue Concentrations of ^{99m}Tc-Glucarate, ^{3}H-Deoxyglucose and ^{24}NaCl in Normal Myocardium

At 1 hr postinjection, tracer concentrations (%/ID/g) in normal myocardium were 0.016 ± 0.006 for ^{99m}Tc-glucarate in fed animals and 0.07 ± 0.016 for ^{99m}Tc-glucarate in fasted animals ($p < 0.01$); and 0.021 ± 0.003 for ^{3}H-DG in fed animals and 0.015 ± 0.001 for ^{3}H-DG in fasted animals ($p < 0.01$). Residual blood activities were 0.041 ± 0.017 for ^{99m}Tc-glucarate in fed animals and 0.18 ± 0.03 for ^{99m}Tc-glucarate in fasted animals; and 0.009 ± 0.0003 for ^{3}H-DG in fed animals and 0.007 ± 0.001 for ^{3}H-DG in fasted animals. The extracellular fluid space calculated from the plasma and tissue ^{24}NaCl concentrations was 0.22 ml/g of tissue in normal myocardium.

Distribution of Tracers in Ischemic Myocardium

The pattern of tracer distribution in ischemic myocardium varied with the number of contraction band cells. In Group 2, ^{99m}Tc-glucarate had a myocardial distribution similar to ^{3}H-DG, however differences were detected in Group 1. Group 2 animals showed a gradient of increasing ^{99m}Tc-glucarate and ^{3}H-DG concentrations from the periphery to the center of the ischemic zone (surrounding zone < marginal zone < center zone). In contrast, Group 1 animals with extensive necrosis and hemorrhage tended to have focally increased ^{3}H-DG concentration in marginal zones (marginal > center and surrounding zones). However, the differences were not statistically significant. In the central region, the concentration of ^{99m}Tc-glucarate was significantly higher than ^{3}H-DG ($p < 0.001$) (Fig. 2).

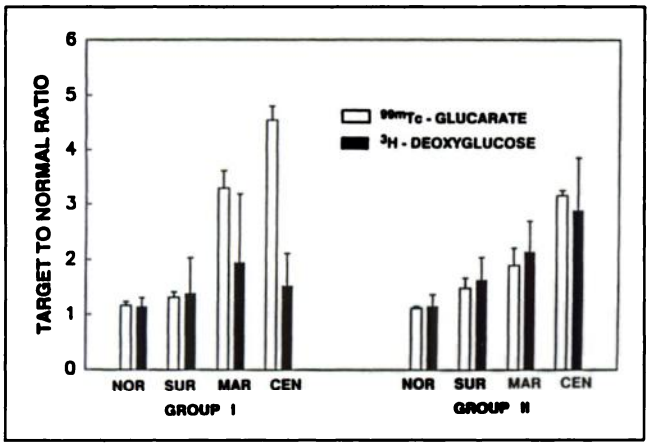

FIGURE 2. Target-to-normal myocardial ratios of ^{99m}Tc-glucarate and ^{3}H-DG in Group 1 and Group 2 animals (mean ± s.e.m.). Myocardial zones: NOR—normal (distal to ischemia), SUR—surrounding, MAR—marginal and CEN—central zone. Significant ($p < 0.001$) regional differences in level of accumulation were detected for ^{99m}Tc-glucarate in Groups 1 and 2 and ^{3}H-DG in Group 2. In the central zone of Group 1, accumulation of ^{99m}Tc-glucarate was significantly greater ($p < 0.001$) than ^{3}H-DG.

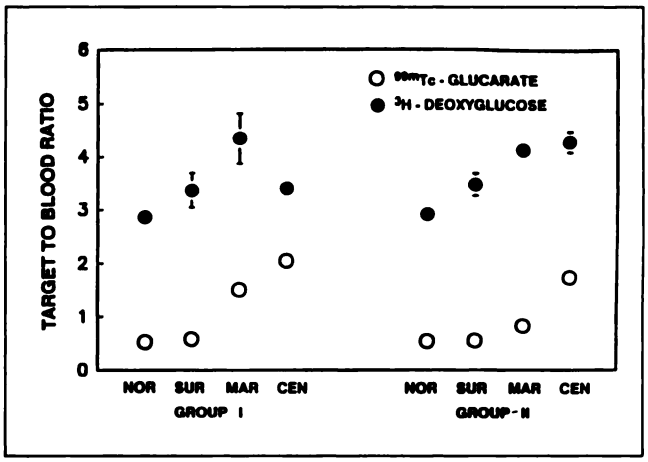

FIGURE 4. Myocardium-to-blood ratios (mean ± s.e.m.) of ^{99m}Tc-glucarate and ^{3}H-DG in Group 1 and Group 2 animals. Myocardial zones: NOR—normal, SUR—surrounding, MAR—marginal and CENT—central zone. TTC staining: S—stained, PS—partially stained and NS—nonstained. Open circles: ^{99m}Tc-glucarate, filled circles: ^{3}H-DG. Significant regional differences in level of accumulation were detected for ^{99m}Tc-glucarate in Groups 1 and 2 ($p < 0.001$) and ^{3}H-DG in Group 2 ($p < 0.05$). In all regions of both groups, accumulation of ^{99m}Tc-glucarate was significantly greater ($p < 0.001$) than ^{3}H-DG. Error bars smaller than the diameter of the symbols are not indicated.

The T-to-B of ^{99m}Tc-glucarate increased from 0.2 in normal myocardial tissue to 1.78 in sections with the highest ^{24}Na distribution space (DS_{Na}) at 6 hr after the onset of ischemia ($T\text{-to-}B_{GLU} = 1.19 * DS_{Na} + 0.16$; $r = 0.52$ and $p < 0.05$ in fasted animals and $T\text{-to-}B_{GLU} = 2.50 * DS_{Na} - 0.23$; $r = 0.94$ and $p < 0.01$ in fed animals, Fig. 3). This linear relationship did not change significantly at 24 hr after the ischemic insult ($T\text{-to-}B_{GLU} = 1.81 * DS_{Na} - 0.05$, $r = 0.70$, $p < 0.01$ in fasted animals and $T\text{-to-}B_{GLU} = 2.77 * DS_{Na} - 0.37$, $r = 0.94$, $p < 0.01$ in fed animals). In both fed and fasted animals, the T-to-B of ^{3}H-DG increased nonlinearly from a minimum value of 0.60 in normal tissue to a maximum of 5.54 in ischemic zones at 6 hr after the onset of ischemia. In contrast, at 24 hr after the ischemic insult, the T-to-B of ^{3}H-DG tended to decrease.

Target-to-Blood Ratio of ^{99m}Tc-Glucarate, Target-to-Normal Ratio of ^{3}H-Deoxyglucose and TTC Staining Results

In Group 1 animals, the T-to-B ratios of ^{99m}Tc-glucarate were higher than 1 in marginal and central zones of infarction (Fig. 4). The T-to-B ratios for ^{3}H-DG were maximal in the marginal zones, but were also greater than 1 in normal areas. Thus, there were significant increases in the T-to-B ratios for both radiopharmaceuticals, indicating that the T-to-B ratio for ^{99m}Tc-glucarate and the T-to-N ratio for ^{3}H-DG are useful for the detection of myocardial damage in the experimental model under investigation.

In Group 3, 164/171 (96%) of TTC stained segments had

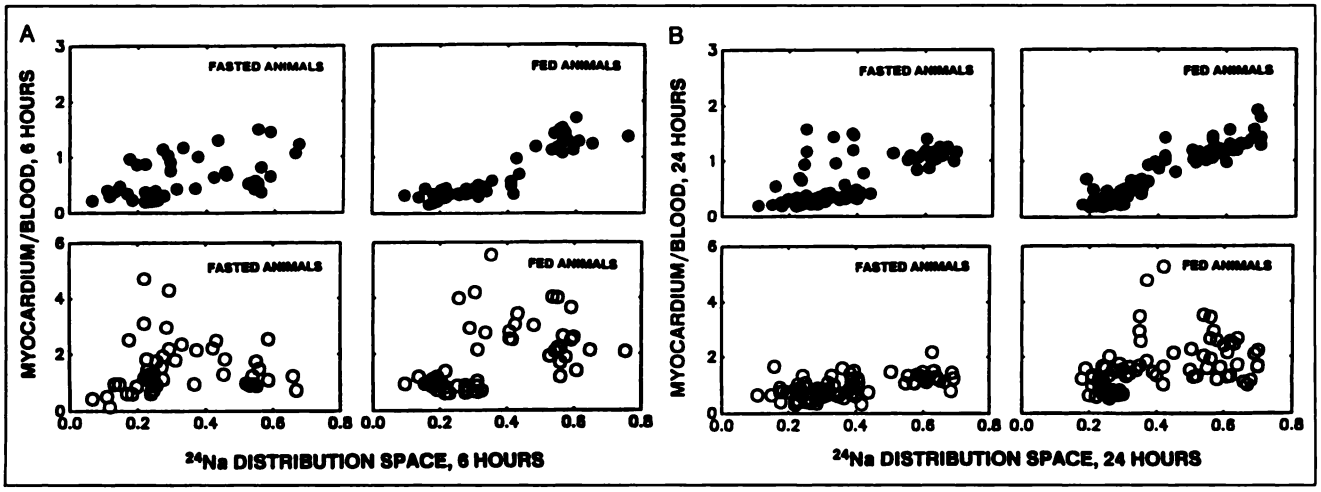

FIGURE 3. Myocardial tissue-to-blood ratio of ^{99m}Tc-glucarate and ^{3}H-DG at 6 hr (A) and 24 hr (B) after initiation of myocardial ischemia in fed and fasted animals. Filled circles—^{99m}Tc-glucarate and open circles—^{3}H-DG.

TABLE 1
Relationship Between Target-to-Blood Ratios of ^{99m}Tc-Glucarate and Target-to-Normal Myocardial Ratios of ^{3}H-Deoxyglucose to the Results of TTC Staining

Target-to-blood (T-to-B) or target-to-normal (T-to-N) ratios		Results of TTC staining		
		Staining	Partial staining	No staining
^{99m}Tc-glucarate	T-to-B > 1	7	56	50
	T-to-B < 1	164	3	0
^{3}H-deoxyglurose				
Fasted animals	T-to-N > 1	83	35	22
	T-to-N < 1	0	0	
Fed animals	T-to-N > 1	88	24	26
	T-to-N < 1	0	0	2

^{99m}Tc-glucarate T-to-B ratios of less than 1, and 106/109 (97%) minimally TTC stained specimens had ratios > 1 (Table 1, Fig. 5). In fasted animals, all segments had ^{3}H-DG T-to-N ratios of >1 regardless of the results of TTC staining, while in fed animals, 2/29 (7%) of TTC unstained specimens had ^{3}H-DG T-to-N ratios of <1 (Table 1, Fig. 6).

Relationship Between Tissue Tracer Concentration, Tissue Edema and TTC Staining Results

At 6 hr after ischemia in fasted animals, the ^{24}Na concentration (%ID/g) significantly increased ($p < 0.01$) with the development of myocardial injury evaluated by TTC staining; 0.026 ± 0.001 (staining), 0.049 ± 0.003 (partial staining) and 0.093 ± 0.008 (no staining).

There was a linear relationship between the %ID/g of ^{99m}Tc-glucarate and ^{24}Na at 6 hr ($\%ID_{GLU} = 2.46 * \%ID_{Na} + 0.03$; $r = 0.76$ and $p < 0.01$ in fasted animals and $\%ID_{GLU} = 2.13 * \%ID_{Na} - 0.02$; $r = 0.94$ and $p < 0.001$ in fed animals) and 24 hr ($\%ID_{GLU} = 3.08 * \%ID_{Na} + 0.02$; $r = 0.76$ and $p < 0.01$ in fasted animals and $\%ID_{GLU} = 2.13 * \%ID_{Na} - 0.02$; $r = 0.94$ and $p < 0.001$) after the onset of ischemia. In contrast, the relationship between the %ID/g of ^{3}H-DG and ^{24}Na at 6 hr and 24 hr after the onset of is ischemia was nonlinear. At 24 hr after the onset of ischemia, the %ID/g for ^{3}H-DG tended to be less than at 6 hr.

DISCUSSION

The results of this study indicate that normal myocardium had minimal accumulation of ^{99m}Tc-glucarate (44% of residual blood activity) at 1 hr after intravenous administration. Although the concentration of ^{99m}Tc-glucarate in myocardial lesions was higher than in normal tissue, the relatively high concentration in blood could limit early visualization of lesions. In contrast, ^{3}H-DG accumulation in corresponding regions was higher than residual blood activity. These observations suggest that ^{99m}Tc-glucarate is not a preferred substance in normal myocardium.

The observations of the present study were similar to the results of our previous study of ^{99m}Tc-glucarate in acute cerebral injury (*8*). As in the previous study, the greatest concentrations of ^{99m}Tc-glucarate were detected in the central zone of infarcted tissue. In the current study, the average concentration of ^{3}H-DG was not significantly different between normal tissue and the central zone of infarcted myocardium, however, a high level of variability was detected. In contrast, in the previous study, decreased FDG accumulation was detected in the central zone of cerebral infarction, however, only three rats with infarction were studied. In both studies, increased concentrations of the glucose analogs were detected in regions of severe ischemia. Overall, these observations indicate that accumulation of ^{99m}Tc-glucarate is not species specific and is equally applicable to the evaluation of brain and myocardial injury.

The nutritional condition of the animals had a significant

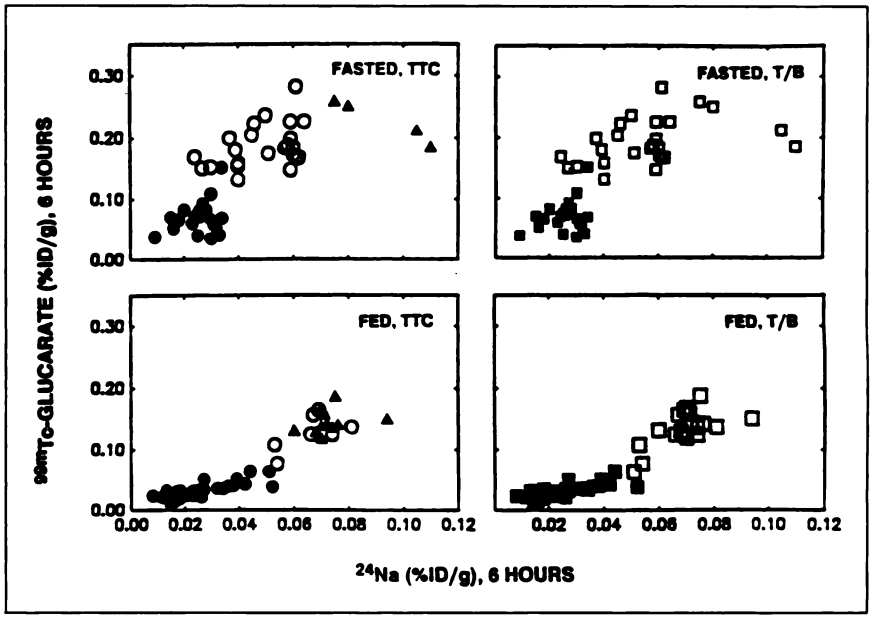

FIGURE 5. Myocardial concentration of ^{99m}Tc-glucarate (%ID/g) versus sodium concentration (%ID/g) in fasted (upper panels) and fed (lower panels) rabbits at 6 hr after the onset of ischemia; TTC staining status (left panels) and T-to-B ratio (right panels) are indicated. Filled circles—normal TTC staining; open circles—partial TTC staining; filled triangles—no TTC staining; filled squares—T-to-B ratio < 1; and open squares—T-to-B ratio > 1. Similar results were obtained at 24 hr.

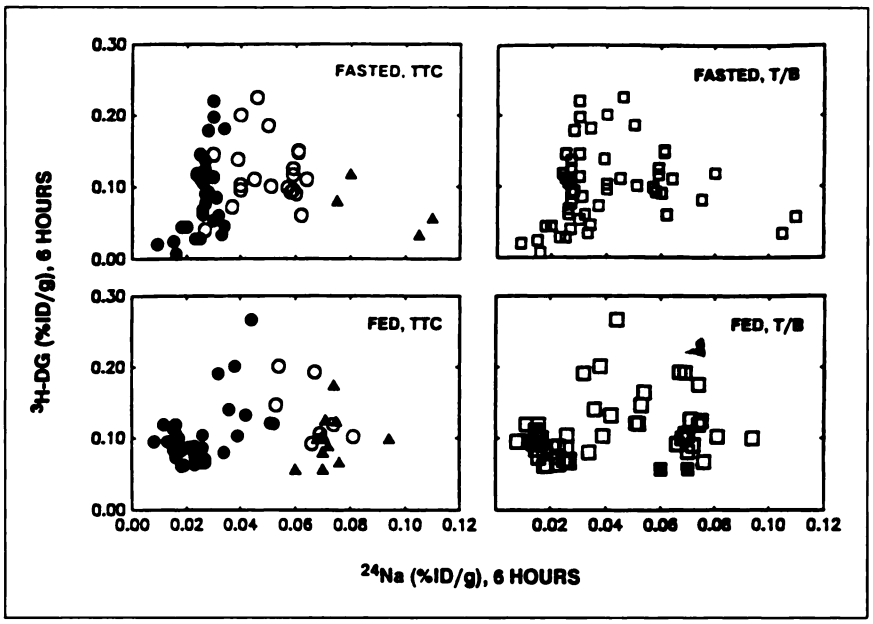

FIGURE 6. Myocardial concentration of ^{3}H-DG (%ID/g) versus sodium concentration (%ID/g) in fasted (upper panels) and fed (lower panels) rabbits at 6 hr after the onset of ischemia; TTC staining status (left panels) and T-to-N ratio (right panels) are indicated. Filled circles—normal TTC staining; open circles—partial TTC staining; filled triangles—no TTC staining; filled squares—T-to-N ratio < 1; and open squares—T-to-N ratio > 1. Similar results were obtained at 24 hr.

effect on ^{99m}Tc-glucarate and ^{3}H-DG accumulation. In general, fasted rabbits tended to have higher levels of ^{99m}Tc-glucarate accumulation than fed animals. Likewise, nutritional state is also important when ^{3}H-DG is used to evaluate myocardial viability. In the present study, lower levels of ^{3}H-DG accumulation in normal myocardium of fasted animals resulted in higher T-to-N ratios for ischemic segments; even some severely injured segments had ^{3}H-DG T-to-N ratios of greater than 1. In contrast, higher accumulation of ^{3}H-DG in the normal myocardium of fed animals led to the identification of some segments with T-to-N ratios less than 1 in histochemically infarcted zones. This phenomenon was most frequently observed in fed animals at 6 hr after ischemia. Fed animals at 24 hr after ischemia were probably "nearly fasted" because of decreased food intake in the post-thoracotomy state. Levels of plasma fatty acids, insulin and other nutritional factors that were not controlled in our study may have affected the results.

Technetium-99m-glucarate showed T-to-B ratios of greater than 1 in segments with partial or absent TTC staining (Figs. 4 and 5), but ratios of less than 1 in most segments with complete TTC staining. In a previous study, an autoradiographic comparison of the extent of ^{99m}Tc-glucarate and ^{111}In-antimyosin accumulation in the myocardium of rats with permanent occlusion of left anterior descending artery demonstrated that the area of ^{99m}Tc-glucarate localization was about 20% larger than that of ^{111}In-antimyosin at 24 hr after coronary occlusion (*14*). This excess ^{99m}Tc-glucarate accumulation disappeared at 3 days after occlusion. These findings suggest that ^{99m}Tc-glucarate accumulates in severely injured but viable myocardium. In the present study, many ischemic segments failed to attain greater concentration of this agent than residual blood-pool activity. Thus, although ^{99m}Tc-glucarate accumulates in mildly damaged myocardium, only zones of severe injury will be visible on in vivo images recorded 1 hr after intravenous injection.

Increased sodium concentration in ischemic or infarcted myocardium is probably related to three factors: (1) Increase in amount of extracellular fluid due to vascular permeability changes; (2) Influx of sodium from extracellular to the intracellular space due to altered permeability of the cell membrane of the ischemic cells and failure of the sodium/potassium pump; and (3) Increased distribution space of sodium in dead cells after loss of membrane integrity. The increased vascular permeability induced by ischemia raises the extra cellular fluid content from approximately 20% of the total water space in normal rat muscle (*12*) to about 60% in severely damaged tissue. Also, intracellular edema occurs in ischemic myocytes with intact cell membranes (*15–17*). Overt membrane damage, indicative of cell death (*18*), causes a further increase in tissue sodium concentration.

The concentration of ^{3}H-DG was not linearly related to tissue sodium concentration, but rather peaked at ~0.045% NaCl ID/g, suggesting a relationship of enhanced ^{3}H-DG accumulation to mild and moderate ischemic injury with initial development of edema. Enhanced ^{3}H-DG accumulation was frequently observed in segments with partial TTC staining. In most segments with partial TTC staining, accumulation of ^{3}H-DG and ^{99m}Tc-glucarate were similar. In contrast, severely injured segments (no TTC staining) showed discrepancies in ^{3}H-DG and ^{99m}Tc-glucarate accumulation, suggesting that these tracers demarcate different points in the spectrum of myocardial injury. In addition, the nonlinear relationship between myocardial ^{3}H-DG accumulation and the degree of injury suggests that this tracer is a qualitative marker of myocardial ischemia.

There are several possible explanations for increased ^{3}H-DG accumulation in severely damaged tissue. First, histochemistry and histopathology may have limited value

in identifying complete tissue death in the acute phase of infarction. An electron microscopic study of ischemic brain tissue revealed that zones of absent TTC staining might retain significant numbers of intact mitochondria (*19*). Also, some contraction band cells without eosinophilic change observed in the acute phase may survive for a significant time. In a previous study it was demonstrated that 25% of underperfused areas, including the lateral border zone, survived (*20*) after coronary reperfusion following 1 hr occlusion of the left anterior descending artery in rabbits. In our study, segments with retained ^{3}H-DG uptake with no TTC staining had extremely high sodium concentrations, suggesting extremely severe tissue injury. In this situation, ^{3}H-DG may have identified surviving islands of viable tissue in infarcted zones. Second, the results of TTC staining depend on the status of mitochondrial enzyme activities, whereas accumulation of deoxyglucose assesses metabolic processes that are localized to the cytosol. Third, ^{3}H-DG enters dead myocytes in the acute phase after infarction. A recent microautoradiographic study has demonstrated a poor correlation between localization of viable myocytes and exogenous ^{14}C-DG accumulation in acutely ischemic rabbit myocardium; frequently high ^{14}C-DG concentrations were observed in zones of necrotic myocytes. Since a threefold to fourfold increase in the sodium space of tissue indicated severe damage in the present study, ^{3}H-DG (MW = 164.2) may enter the intracellular and extracellular space of irreversibly injured edematous tissue by diffusion.

Since the acute setting of our experiments might have affected the results, further studies at later times after ischemia will be required to better characterize ^{99m}Tc-glucarate and deoxyglucose accumulation in ischemic myocardium.

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