Detection of Acute Myocardial Infarction by ^{99m}Tc-Labeled D-Glucaric Acid Imaging in Patients with Acute Chest Pain

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Definitive diagnosis of acute myocardial infarction early in the process is often difficult. An imaging agent that localized quickly and specifically in areas of acute necrosis could provide this critical diagnostic information. To determine whether imaging with ^{99m}Tc-labeled D-glucaric acid (GLA) could provide this information, we imaged a group of patients presenting with symptoms suggestive of acute infarction. **Methods:** Twenty-eight patients presenting to the emergency department with symptoms highly suggestive of acute infarction were injected with ^{99m}Tc-GLA and imaged about 3 h later. **Results:** The sensitivity of lesion detection was remarkably time dependent. Fourteen patients with acute infarction injected within 9 h of onset of chest pain had positive scans, even in the presence of persistent occlusion. The remaining 14 patients had negative scans. Nine patients with negative scans had acute infarction but were injected more than 9 h after onset of chest pain. The final diagnosis in the remaining 5 patients was unstable angina (3 injected <9 h and 2 injected >9 h after onset of chest pain). Six patients were reinjected with ^{99m}Tc-GLA 4–6 wk after their initial study to determine whether persistent positive scans occurred with this agent. All 6 had negative scans. **Conclusion:** This study suggests that ^{99m}Tc-GLA localizes in zones of acute myocardial necrosis when injected within 9 h of onset of infarction.

Key Words: acute myocardial infarction; scintigraphic imaging; ^{99m}Tc labeling; D-glucaric acid; perfusion imaging

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Early, definitive, diagnosis of acute myocardial infarction (AMI) is necessary to initiate therapy to salvage myocardium at risk (*1*) and to avoid the risk of unnecessary thrombolytic therapy (*2*). Difficulty of diagnosing acute infarction was documented in 1984 by Kannel and Abbott (*3*) in the Framingham study. Unrecognized infarction associated with atypical symptoms or the absence of chest pain was found in 14% of patients (708/5127) (*3*). Even today, the diagnosis is difficult to make because 15%–20% of patients present to the emergency department with symptoms other than chest pain (*4*), and about 6%–21% of patients with acute infarction have normal electrocardiograms (ECGs) (*5*). Even after detailed clinical and laboratory evaluation, including rapid tests for creatine phosphokinase (CPK) MB subunit, myoglobin and cardiac troponin T and I, uncertainty about the diagnosis remains in a significant fraction of patients (*6,7*).

As early as 1976, myocardial perfusion scans were used to detect acute infarction (*8*). The seminal study of Wackers et al. (*8*) with ^{201}Tl identified two major problems with the technique: A zone of decreased perfusion could be associated with necrosis or ischemia, and it was impossible to differentiate an acute infarct from an event that occurred in the past. Recently, myocardial perfusion imaging has been advocated in the emergency department as part of a program to reduce the overall cost of care in patients presenting with ambiguous symptoms, because a negative perfusion scan defines a population with a very low risk for cardiac events (*9*). A positive scan, however, still remains problematic.

Infarct-avid agents such as ^{99m}Tc-labeled pyrophosphate (*10*) or ^{111}In-antimyosin (*11*) have been used to identify, localize and estimate the size of AMI. Unfortunately, the cellular changes required for localization of these agents are not present in the initial moments of acute necrosis, limiting the use of this approach in an emergency department situation (*12,13*).

^{99m}Tc-labeled D-glucaric acid (GLA), a six-carbon dicarboxylic acid that is the physiologic end-product of uridine diphosphoglucose metabolism (*14,15*), was found to localize in zones of cerebral and myocardial necrosis shortly after occlusion in animals (*16–19*). Surprisingly, when the tracer was injected 24 h or more after the acute event, localization was markedly reduced or absent.

This study was performed to determine whether ^{99m}Tc-GLA imaging could be used to identify myocardial necrosis in the early hours after onset of chest pain in patients

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admitted to the coronary care unit of a major metropolitan hospital. The results of ^{99m}Tc-GLA imaging were compared with those of serial ECGs, CPK, echocardiography, perfusion scintigraphy and coronary arteriography when clinically indicated.

MATERIALS AND METHODS

Patients

Twenty-eight patients (22 men, 6 women; average age 61.7 y; median age 65 y) admitted to the coronary care unit because of symptoms and signs highly suggestive of AMI, and whose clinical condition was judged stable, were enrolled in the study. All patients presented with typical prolonged chest pain unresponsive to nitrates, associated with persistent S-T segment changes on ECG. In 21 patients with a satisfactory acoustic window, echocardiograms were recorded on admission and on at least one additional occasion during hospitalization and at 2 mo after discharge. Informed consent for the injection of tracer and radionuclide imaging was obtained from all subjects, as approved by the institutional review board. Therapy to restore perfusion was performed at the discretion of the patient's cardiologist and was not delayed by administration of tracer or subsequent imaging.

All patients were continuously monitored for arrhythmia for at least 3 d and had serial determinations of CPK on at least five occasions over the first 2 d and daily thereafter for the following week.

The charts were reviewed by an attending cardiologist who arrived at a final diagnosis of acute infarction based on serial ECGs, on the presence of wall motion abnormalities on echocardiogram and on serial CPK values (peak levels more than twice the upper normal limit of 190 mU/mL).

Radiopharmaceuticals and Protocol of Scintigraphic Imaging

^{99m}Tc-GLA was prepared from a lyophilized kit containing 12.5 mg of D-glucaric acid and 0.15 mg stannous chloride (*20*) by adding 1480 MBq (40 mCi) freshly eluted ^{99m}Tc-pertechnetate. Labeling efficiency was checked by ascending chromatography and was always >98%. ^{99m}Tc-GLA (900–1110 MBq [25–30 mCi]) was injected as an intravenous bolus in the coronary care unit.

A computerized gamma camera (Elscint SP6 or Elscint Apex-409; Elscint Ltd., Haifa, Israel) equipped with a high-resolution or an all-purpose parallel-hole collimator was used to perform planar imaging of the chest in the anterior, 45° left anterior oblique (LAO) and left lateral projections (80°–90°). Each view required 5–10 min to record 2–3 million counts. An electronic zoom was used to exclude most of the liver and kidneys, sites of high physiologic accumulation of ^{99m}Tc-GLA, from the images. Tomographic imaging was not performed for this trial because of logistics.

^{99m}Tc-GLA images were recorded >2 h after injection to permit blood clearance of the radiopharmaceutical. Preliminary human pharmacokinetic studies indicated that activity in the blood decreased to <30% of initial activity at 2 h and <20% at 4 h (*21*).

About 2 d after ^{99m}Tc-GLA imaging, perfusion images were recorded after injection at rest. Either ^{201}Tl (111 MBq [3 mCi]) or ^{99m}Tc-sestamibi (555–740 MBq [15–20 mCi]) was used for the perfusion studies. Planar images were recorded with a high-resolution collimator in the anterior, 45° LAO and lateral positions using a 20% window set around the 80-keV mercury x-ray of ^{201}Tl or the 140-keV photopeak of ^{99m}Tc. A minimum of 800 counts/cm was recorded in the myocardium in each view.

Patients were asked to volunteer for repeat ^{99m}Tc-GLA scanning 4–6 wk after their acute scanning. This late imaging was performed to determine whether "persistent positive" uptake occurred with this agent.

Image Interpretation

The images were independently interpreted by three physicians who were unaware of the clinical and laboratory information. Zones of unequivocal, focally increased tracer concentration in the region of the myocardium were identified. ^{99m}Tc-GLA uptake was visually scored from zero (no focal uptake) to 3 (distinct focal uptake), with a scale that was a combination of both intensity and extent of uptake. The results of separate readings were compared, and a consensus was reached in the few cases with discordant interpretations. In addition to the subjective evaluation, myocardium showing ^{99m}Tc-GLA uptake was quantified as a percentage of the total myocardial circumference in the view showing the largest lesion extent. This was done by dividing the area (number of pixels) of a region of interest (ROI) manually drawn around the site of focal ^{99m}Tc-GLA uptake by the area of the total myocardium circumference estimated by combining the ^{99m}Tc-GLA scan (where, in addition to the area of focal ^{99m}Tc-GLA uptake corresponding to the infarct, most of the noninfarcted myocardium was detectable as a negative halo surrounding the left ventricle chamber) with the perfusion scan (where noninfarcted myocardium was neatly delineated). The site of uptake was compared with the location of the lesion estimated on ECG and with wall motion abnormalities detected on echocardiograms, combining the different echocardiographic views (lateral, intercostal view and apical, four-chamber view) to derive segmental wall motion abnormalities in a similar manner as performed when comparing planar perfusion scans with echocardiographic evaluation.

The intensity of ^{99m}Tc-GLA accumulation in the acutely infarcted myocardium and that in normal myocardium were calculated. The zone of normal myocardium, defined from the perfusion scan, was transposed to the ^{99m}Tc-GLA scan. In cases in which the ^{99m}Tc-GLA scan was negative, the zone of diminished perfusion was designated as the infarct zone. The count density of equal-sized ROIs over the AMI and the non-AMI regions of the ^{99m}Tc-GLA scan were used to calculate the uptake ratio.

Because this study was designed to test the feasibility of imaging with ^{99m}Tc-GLA in a selected population of patients, no statistical analysis of sensitivity, specificity, diagnostic accuracy or predictive values of the ^{99m}Tc-GLA scan was performed.

RESULTS

The clinical characteristics, ECG findings, site of echocardiographic wall motion abnormality, site of uptake of ^{99m}Tc-GLA and final diagnosis are summarized in Table 1. In addition, coronary angiography was performed within 20 d of AMI in 18 patients. The vascular territories with the most severe stenoses are also summarized in Table 1. Eighteen patients received thrombolytic therapy within 8 h of onset of chest pain. Five of the remaining 10 patients received heparin and 5 had no anticoagulant or thrombolytic therapy.

A final diagnosis of AMI was made in 23 of the 28 patients. In 3 of the remaining patients (patients 17, 21 and

TABLE 1
Main Clinical Characteristics of 28 Patients Included in ^{99m}Tc-GLA Imaging Study

Patient no.	Sex	Age (y)	Territory of critical stenosis*	Final diagnosis	ECG findings: S-T elevation	Site of echocardiographic abnormality	Site of ^{99m}Tc-GLA uptake
1	M	63	LAD	AMI	V1–6, VL	Anteroseptal	Anterolateral-septal
2	M	58	LAD	AMI	V1–4	Anterior	Anteroapical
3	M	44	LAD	AMI	V1–6, VL	Anterolateral	Anteroapical-septal
4	M	55	RCA	AMI	III, II, VF	Posteroinferior	Posteroinferior
5	M	68	—	AMI	V1–6, VL	Not recorded	Anterolateral-septal
6	M	64	RCA	AMI	III, II, VF	Posteroinferoapical	Inferoapical
7	M	57	LAD, RCA	Post-AMI angina†	III, II, VF	Inferior	No uptake
8	M	73	RCA, LAD	AMI	III, II, VF	Posteroseptal	No uptake
9	M	62	LAD, RCA	AMI	V1–6, VL	Not recorded	Anterolateral
10	M	68	—	AMI	III, II, VF	Posteroinferior	No uptake
11	F	24	None	AMI	III, II, VF	Inferior	Inferoapical
12	F	48	LAD	AMI	V1–3	Not recorded	Apical
13	M	52	LAD	AMI	V1–4	Anterior	Anterolateral
14	F	69	—	AMI	V1–4	Not recorded	No uptake
15	M	68	LAD, RCA	AMI	V1–6, VL	Anterolateral	Anterolateral
16	M	57	LAD, LCx	AMI	I, VL	Posterolateral	No uptake
17	M	68	—	Unstable angina	V1–6, VL	Anterolateral	No uptake
18	M	47	LCx, LAD	AMI	III, II, VF	Inferior	Inferior
19	M	70	LAD	AMI	V5–6, I, VL	Inferolateral	No uptake
20	M	66	—	AMI	V1–6	Not recorded	No uptake
21	F	64	RCA	Unstable angina	III, II, VF	None	No uptake
22	M	67	—	AMI	III, II, VF	Inferior	No uptake
23	M	67	LAD	Post-AMI angina†	V1–4	Anteroseptolateral	No uptake
24	M	62	LAD	AMI	III, II, VF	Inferior	Inferoapical
25	F	69	—	AMI	III, II, VF	Not recorded	Inferoapical
26	M	73	—	AMI	V1–4	Septal	No uptake
27	M	73	—	AMI	V1–5	Not recorded	No uptake
28	F	73	—	Unstable angina	V6, VL	Inferoseptal	No uptake

*Most severe stenosis site listed first.
†Within 48 h before hospital admission.
GLA = D-glucaric acid; ECG = electrocardiogram; LAD = left anterior descending artery; AMI = acute myocardial infarction; RCA = right coronary artery; LCx = left circumflex artery.
Patients 3, 9, 15, 21, 22 and 23 had histories of prior AMI 1.5, 3, 5, 1.5, 9 and 5 y earlier, respectively.

28), the final diagnosis was unstable angina, whereas it was postinfarct angina in 2 patients (patients 7 and 23).

^{99m}Tc-GLA imaging was generally acquired 2–4.5 h after tracer injection. In patient 18, imaging was postponed until 24 h after injection of ^{99m}Tc-GLA because of recurrent chest pain and clinical instability.

Initial ^{99m}Tc-GLA images were obtained in all patients within 44 h of onset of chest pain (Table 2). Eighteen patients were injected within 9 h of the onset of chest pain. Of these 18 patients, 14 patients with a final diagnosis of acute infarction had positive scans (Table 2 and Figs. 1 and 2), whereas 3 patients with unstable angina and 1 with postinfarct angina had completely negative scans (Table 2). Conversely, scintigraphic imaging was negative in the 9 patients with acute infarction and in 1 patient with postinfarct angina who were injected with ^{99m}Tc-GLA >9 h after the onset of chest pain (Figs. 1 and 3).

Image contrast between the zone of infarction and normal myocardium remained high even when images were recorded hours after tracer administration. In fact, the ^{99m}Tc-GLA scan was positive in patient 18, in whom imaging was postponed to about 24 h after tracer injection. Furthermore, in patient 25, imaging was performed both 3 and 23 h after a single injection of ^{99m}Tc-GLA to determine how long ^{99m}Tc-GLA remains at the site of acute necrosis. Localization was still visible at the site of infarction on the late scan. ROI analysis of myocardial counts in this patient (corrected for physical decay) showed a decrease of ^{99m}Tc-GLA in the AMI region of about 26% over 20 h.

The site of ^{99m}Tc-GLA uptake was compared with the zone of infarct on ECG, abnormal wall motion on echocardiography and the site of decreased perfusion on myocardial perfusion scan (Fig. 4). Perfusion imaging was not performed in patient 27, who died 24 h after hospitalization because of arrhythmia. The site of ^{99m}Tc-GLA uptake corresponded with the site of decreased perfusion (except in patients with prior AMI) and with the general location of ECG abnormality in all positive cases. Echocardiographic wall motion abnormalities were usually larger than the extent of ^{99m}Tc-GLA uptake, and echocardiographic abnormalities were also seen in patients without acute infarction.

Although AMI patients with negative scans had lower peak serum CPK levels than did the patients with positive scans (1015 ± 498 versus 3190 ± 1809 mU/mL, $P < 0.01$), there was no correlation between peak serum CPK levels and the intensity of ^{99m}Tc-GLA uptake as defined by the AMI to non-AMI uptake ratio. Furthermore, there was wide overlap in the peak serum CPK levels among AMI patients with uptake scores of 1 (2337 ± 1814 mU/mL, range 434–4223 mU/mL), uptake scores of 2 (3364 ± 1856 mU/mL, range 1800–5415 mU/mL) and uptake scores of 3 (3603 ± 1897 mU/mL, range 1263–5584 mU/mL). Despite the variability in peak serum CPK levels induced by thrombolysis (22), there was a significant correlation between this parameter and the fraction of myocardium showing ^{99m}Tc-GLA uptake (Fig. 5A); however, such correlation was not very close ($r = 0.53$; $P = 0.0495$), so that the 95% confidence intervals would be quite wide.

TABLE 2
Scintigraphic Results Observed on ^{99m}Tc-GLA Imaging Study in 28 Patients Enrolled in Study

Patient no.	Peak CPK mU/mL	Peak CPK Time (h)	Time to rTPA (h)	Time to ^{99m}Tc-GLA injection (h)	Acute imaging result*	AMI to non-AMI ^{99m}Tc-GLA uptake ratio
1	5584	18	3	5	3	2.18
2	1184	14	3/14	4	1–2	1.41
3	4223	10	2	9	1–2	1.33
4	2876	18	2.5	4	2–3	1.52
5	2995	11	7.5	8.5	3	1.59
6	1454	15	2.5	3	3	1.33
7	124		8	9	0	—
8	733	8	1	41	0	1.05
9	5509	5	2.5	3.5	3	2.22
10	957	8	4	13	0	1.13
11	3507	12	(Heparin)	1	1	1.59
12	434	7	(Heparin)	4.5	1	1.56
13	5398	11	5	6.5	3	1.48
14	564	13	(No therapy)	14	0	1.26
15	1263	10	2	4	3	2.41
16	1686	12	5.5	25	0	0.98
17	179		(Heparin)	6	0	—
18†	5415	4	4	7	2	1.37
19	1470	23	(Heparin)	17	0	1.01
20	676	13	4	17	0	0.86
21	33		(No therapy)	6	0	—
22	326	15	(No therapy)	19	0	0.98
23	106		3.5	11	0	—
24	1800	7	4.5	6	2	1.61
25‡	3021	25	7	7	3	2.20
26	1038	21	(No therapy)	16	0	1.06
27	1689	8	(Heparin)	37	0	0.94
28	91		(No therapy)	4	0	—

*Visual score of intensity of ^{99m}Tc-GLA uptake: 0 = no focal uptake; 3 = distinct focal uptake.

†Imaged 23 h after ^{99m}Tc-GLA injection.

‡Imaged both 3 and 23 h after single ^{99m}Tc-GLA injection.

GLA = D-glucaric acid; CPK = creatine phosphokinase; rTPA = recombinant tissue plasminogen activator; AMI = acute myocardial infarction.

Time values refer to period elapsed from onset of chest pain.

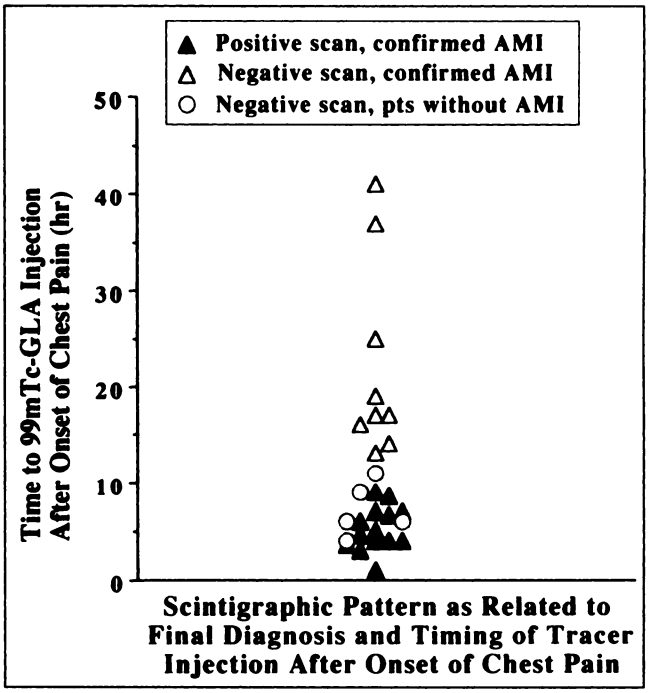

FIGURE 1. Diagrammatic representation of ^{99m}Tc-labeled D-glucaric acid (GLA) imaging results obtained in terms of final diagnosis and time delay between onset of chest pain and tracer injection. Nine-hour delay is clearly turning point between positive and negative scan on patients with confirmed acute myocardial infarction (AMI). Imaging was negative on patients without AMI, regardless of time delay between onset of chest pain and tracer injection.

Finally, there was a significant inverse correlation between time delay after onset of chest pain and ^{99m}Tc-GLA injection and the AMI to non-AMI uptake ratio (Fig. 5B). This correlation is best described by a power equation and therefore appears to indicate the presence of at least two subpopulations in the patients evaluated.

Six patients volunteered for restudy 4–6 wk after their initial images were obtained. Four patients had acute infarction and positive scans initially (patients 1, 6, 9 and 12). In these 4 patients, the previously positive scan became negative. In the remaining 2 patients (patients 7 and 23), whose initial scan was negative during the acute phase of AMI, the scan remained negative also at follow-up.

DISCUSSION

This study indicates the feasibility of imaging the site and extent of AMI in patients with ^{99m}Tc-GLA when the tracer is injected within 9 h of the onset of chest pain. ^{99m}Tc-GLA scintigraphy permits direct visualization of AMI before serum CPK has reached peak levels. Conversely, scans were negative when ^{99m}Tc-GLA was injected >9 h after the onset of chest pain in patients with acute infarction. In patients with unstable angina or postinfarct ischemia, even when

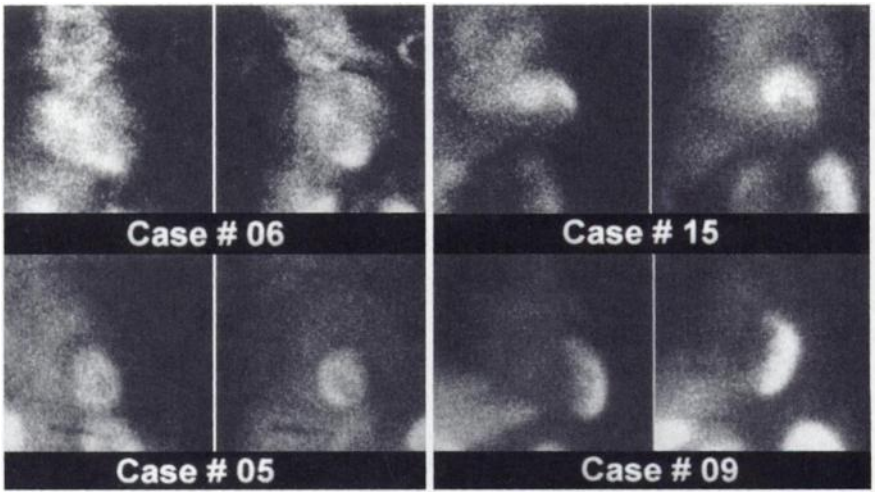

FIGURE 2. Representative examples of ^{99m}Tc-GLA scans with positive imaging of AMI. In each patient's scan, anterior and the 45° LAO views are shown. Top left: patient 6, with small inferoapical AMI. Top right: patient 15, with anterolateral infarct. Bottom left: patient 5, with anterolateral AMI. Bottom right: patient 9, with anterolateral AMI. In patients 5 and 15, ^{99m}Tc-GLA uptake in infarcted area tends to "doughnut"-type shape (also observed in other patients with large infarct), although this particular pattern (higher uptake at periphery versus center of infarct) cannot be easily ascertained solely on basis of planar images of heart.

injected earlier than 9 h after onset of chest pain, scans were negative.

Tomographic images were not recorded in this study because of equipment location and staffing. Although a 2-h interval between ^{99m}Tc-GLA injection and detection of the acute infarct by planar imaging as performed in this study was judged by the cardiologists as also being suitable for diagnostic purposes in an emergency situation, the added contrast of SPECT imaging should shorten this interval. In fact, tomographic images have already revealed better contrast at earlier imaging times with another infarct-avid radiopharmaceutical, ^{99m}Tc-pyrophosphate (*23*).

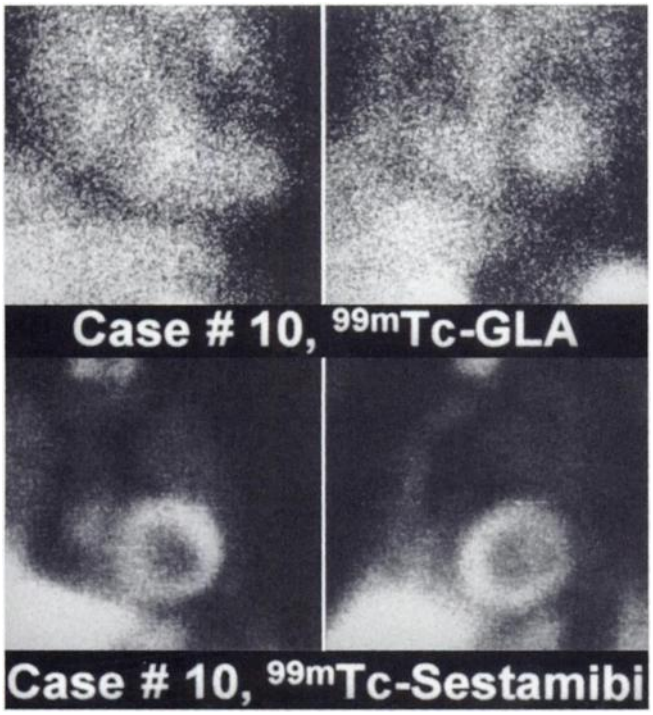

FIGURE 3. ^{99m}Tc-labeled D-glucaric acid (GLA) scan of patient 10 with confirmed inferior AMI, in whom tracer was injected 13 h after onset of chest pain (peak serum CPK levels had already been attained 8 h after onset of chest pain). Myocardium appears as uniform negative halo surrounding left ventricle cavity, showing obvious blood-pool effect, despite fact that imaging was recorded about 4 h after ^{99m}Tc-GLA injection.

Patients with large infarcts usually have more severe symptoms, leading to earlier hospitalization, which in this study resulted in earlier injection of ^{99m}Tc-GLA and a higher likelihood of a positive scan. Although AMI patients with negative ^{99m}Tc-GLA scans tended to have smaller infarcts, there was no correlation between the extent of infarcted myocardium and the intensity of ^{99m}Tc-GLA uptake at the site of AMI. However, a significant inverse correlation was found between the interval chest pain to ^{99m}Tc-GLA injection and intensity of uptake at the site of AMI. This finding indicates that timing of tracer injection is a critical factor determining positivity or negativity of the ^{99m}Tc-GLA scan on patients with AMI (Figs. 1 and 5B).

Localization of ^{99m}Tc-GLA in this study correlates well with the site of acute necrotic injury as determined by abnormal wall motion, ECG localization and decreased perfusion, although echocardiography tended to show larger regions of abnormal wall motion than the lesion extent on the ^{99m}Tc-GLA scan. In this regard, impaired wall motion caused by an acute infarct frequently involves not only the frankly necrotic myocardium (directly imaged by ^{99m}Tc-GLA) but also the adjacent myocardial regions, usually suffering from severe, though noncritical ischemia. In 4 patients with ^{99m}Tc-GLA-positive AMI who had repeat ^{99m}Tc-GLA scans, the area of increased uptake disappeared in the chronic phase.

Early thrombolytic therapy may enhance localization of ^{99m}Tc-GLA by providing a patent conduit to deliver the tracer to the zone of necrosis. However, ^{99m}Tc-GLA is a small molecule that diffuses rapidly, allowing the agent to come in contact with tissue that has very low flow. In fact, 2 AMI patients injected earlier than 9 h after the onset of chest pain had positive scans (patients 11 and 12, with ^{99m}Tc-GLA score 1) in the absence of administration of recombinant tissue plasminogen activator. (However, that intrinsic thrombolysis could have been activated by heparin administration in these patients.) These results support previous studies of

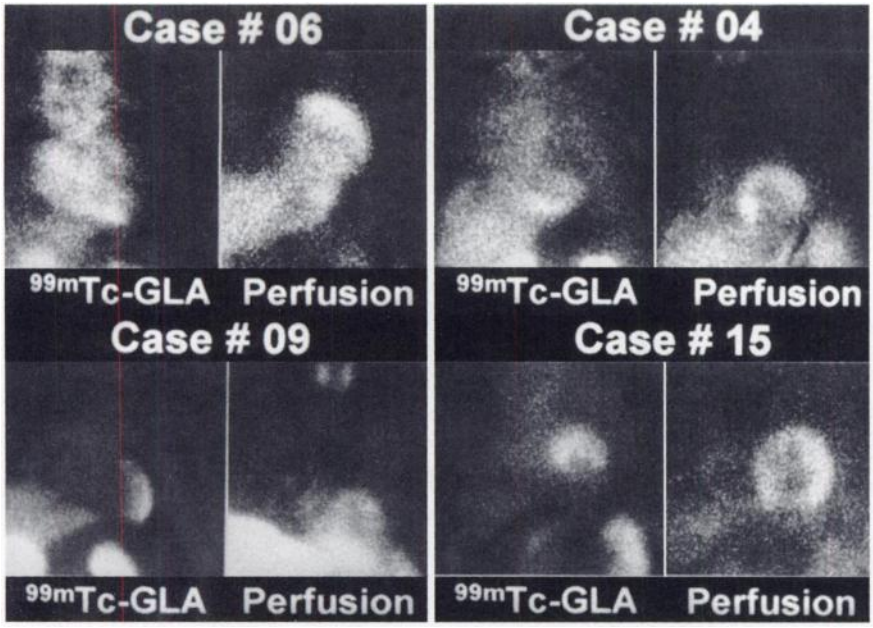

FIGURE 4. Examples of ^{99m}Tc-labeled D-glucaric acid (GLA) scans and corresponding perfusion scans of 4 patients. All scans show quite close match between uptake of positive infarct indicator and perfusion defect associated with AMI. Perfusion scan of patient 15 (with anterolateral AMI leading to this hospitalization) also shows perfusion defect associated with inferior AMI suffered by patient about 18 mo before this AMI evaluation.

myocardial necrosis in animals with persistent coronary occlusion (*24–26*).

Timely, objective diagnosis of AMI is difficult in the early hours of infarction because of the relatively slow evolution of objective markers. Classical clinical symptoms are absent in 20%–60% of patients (*4,6,27–29*), and ECG sensitivities as low as 49%–69% have been reported at the time of presentation (*7,30–32*). To avoid missing patients with acute infarction, emergency department physicians admit about 90% of patients presenting with symptoms suggestive of ischemic heart disease (*5*), even though only <30% of patients will have acute infarction (*33*) and only 6% will be in the low-risk group (*34*). Although the introduction of rapid assays for measuring the levels of cardiac enzymes or cardiac proteins (or both) in circulating blood has resulted in considerable improvements in early diagnosis (*35*), the search for better objective markers and procedures for accurately identifying and localizing the area of infarcted myocardium is ongoing (*26,36*). In this respect, ^{99m}Tc-GLA imaging offers another approach to identify and localize AMI.

Both ^{99m}Tc-pyrophosphate and ^{111}In-labeled monoclonal antimyosin Fab, advocated for direct scintigraphic imaging of infarcted myocardium, rarely identify lesions <9 h old. These agents generally require an interval of at least 12 h from the onset of chest pain for lesion visualization (*10–12,37*).

The exact mechanism(s) of intracellular accumulation of ^{99m}Tc-GLA and the exact structure of the radiolabeled compound are not known. Although glucarate can be enzymatically converted to pyruvate in vitro, it is not clear whether the radiolabeled form of the molecule behaves in a similar manner. Previous studies have shown competitive inhibition of fructose uptake by ^{99m}Tc-labeled glucarate in vitro (*17*), suggesting that the likely dimeric form of the molecule retains some metabolic activity.

Subcellular distribution studies in experimental AMI have shown that about 75% of incorporated ^{99m}Tc-GLA is in the nuclear fraction, the remainder being nearly equally distributed between the cytosol and the mitochondrial fractions (*24*). About 83% of the nuclear-incorporated ^{99m}Tc-GLA is associated with nucleoproteins (histones), with about 17% associated with DNA of the nonviable cells (*38*). On the basis of this finding, the hypothesis has been made that intracellular accumulation of ^{99m}Tc-GLA is simply associated with disruption of the cell and nuclear membranes (an event occurring early after irreversible hypoxic insult), allowing free intracellular diffusion and electrochemical binding of the negatively charged ^{99m}Tc-GLA to the positively charged histones. This chain of events would also explain the lack of ^{99m}Tc-GLA uptake by frankly necrotic cells because nuclear histones are washed out rapidly on full cell death.

CONCLUSION

^{99m}Tc-GLA localizes in zones of acute myocardial necrosis when injected within 9 h of the onset of chest pain in patients with acute infarction. Visualization of necrosis occurred in patients both with and without reflow of the infarct region. When 4 patients with initially positive scans were reinjected at 4–6 wk, their scans were negative, suggesting that persistent positive scans will be less frequent than those observed with ^{99m}Tc-pyrophosphate.

This study determined feasibility for this infarct-avid radiopharmaceutical and does not permit any firm conclusion about the diagnostic accuracy of ^{99m}Tc-GLA imaging in the broad spectrum of patients with suspected ischemic syndromes. The patients enrolled in this investigation had a clinical presentation and S-T segment changes with a very high predictive value for AMI, even in the absence of additional tests. In these patients, ^{99m}Tc-GLA imaging

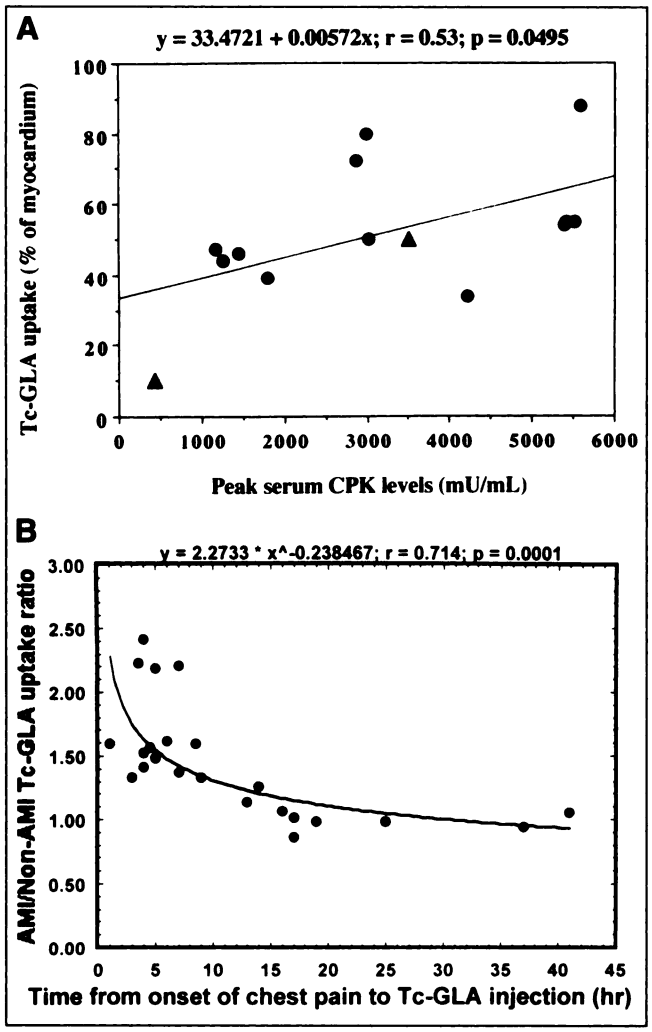

FIGURE 5. (A) Direct correlation between peak serum creatine phosphokinase (CPK) levels and extent of infarcted myocardium visualized by ^{99m}Tc-labeled D-glucaric acid (GLA) imaging, estimated as fraction of total myocardium circumference in best view. This fraction refers only to myocardium that is scintigraphically visualized on planar scans (perfusion imaging and ^{99m}Tc-GLA imaging), corresponding virtually to left ventricle. Patients who received thrombolytic therapy with recombinant tissue plasminogen activator (rTPA) (●); patients who received only heparin (▲). (B) Correlation between time delay from onset of chest pain and ^{99m}Tc-GLA injection (on x-axis) and ratio of ^{99m}Tc-GLA uptake in infarcted to noninfarcted myocardium (on y-axis). AMI = acute myocardial infarction. Uptake ratios <1 obviously indicate negative scan; such ratios are observed only in patients injected with ^{99m}Tc-GLA >9–12 h after onset of chest pain.

proved capable of identifying AMI, provided tracer injection was performed within 9 h from the onset of symptoms.

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