Estimation of myocardial infarct size in man using ^{99m}Tc polyphosphate

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SUMMARY We have critically evaluated the use of ^{99m}Tc polyphosphate to estimate myocardial infarct size. Optimum conditions were first defined with respect to infarct edge definition, and relative activity over infarct and bone and in the blood pool. The scintigrams of 53 patients with acute transmural myocardial infarction were recorded under these defined constant conditions and analysed in various ways. Visual grading of infarct area or intensity correlated poorly with other indices of infarct severity. Computer-assisted measurements of above-background infarct uptake area or of total infarct activity correlated well with clinical, electrocardiographic, and enzymatic measurements of infarct severity.

The observation that ^{99m}Tc technetium stannous pyrophosphate accumulates in a developing myocardial infarct has led to its use with the scintillation camera in clinical practice (Bonte *et al.*, 1975). Animal work has shown that there is good correlation between infarct uptake on surface scintigrams and actual infarct size (Botvinick *et al.*, 1975; Stokely *et al.*, 1976). There has, however, been little attempt to correlate scintigraphic estimates of infarct size with other evidence of infarct severity in man (Willerson *et al.*, 1977). ^{99m}Tc polyphosphate has also been used for infarct imaging (McLaughlin *et al.*, 1975) but less extensively. It has the potential advantage of a higher infarct/bone uptake ratio as indicated from animal experiments (Bonte *et al.*, 1974).

We have therefore critically evaluated the use of ^{99m}Tc polyphosphate to estimate infarct size. In particular we examined the time course of relative infarct, bone, and blood pool activity, and measured the sharpness of infarct edge definition, with a view to obtaining optimal conditions for this technique. ^{99m}Tc polyphosphate scintigrams were then obtained under these defined and precisely constant conditions in 53 patients with acute transmural infarction. The infarct image was measured in various ways and correlated with clinical, electrocardiographic, and biochemical indices of infarct severity. Visual estimates correlated poorly but computer-assisted measurements of infarct area

correlated well with these other criteria of infarct severity.

Methods

Seventy-one patients were studied: 57 men and 14 women aged between 35 and 72 years.

Group 1 consisted of 53 patients who fulfilled all 3 criteria for acute myocardial infarction: (i) typical cardiac pain lasting 1 hour or longer and starting within 8 hours of admission; (ii) 12 lead surface electrocardiographic abnormalities of 'very probable' acute myocardial infarct (WHO criteria), and (iii) serum total CK level >220 IU/l (normal <110 IU/l) in the initial or the next two daily measurements done routinely in every patient.

Group 2 consisted of 18 patients who had acute coronary insufficiency fulfilling criterion (i) but not (ii) or (iii), and showing ischaemic T wave changes or transient ST segment shift (>2 mm) on the electrocardiogram.

CLINICAL CLASSIFICATION (GROUP 1)

Class 1: no clinical or radiological evidence of pulmonary oedema or circulatory disturbance.

Class 2: mild pulmonary oedema, with basal crepitations, a diastolic filling sound, and radiological upper-zone pulmonary venous dilatation.

Class 3: severe pulmonary oedema with or without cardiogenic shock (systolic BP <90 mmHg, peripheral coldness, sweating, urine volume <20 ml/h).

ELECTROCARDIOGRAPHIC CLASSIFICATION (GROUP 1)

Anterior infarct

Class 1: localised, with pathological Q waves in only V2 and/or V3. *Class 2:* extensive, with pathological Q waves in 4 or more of chest leads. *Class 3:* extensive, with bifascicular block in addition.

Inferior infarct

Class 1: localised, with pathological Q waves only in leads II and/or III and/or aVF. *Class 2:* extensive, with lateral and/or posterior extension, that is with pathological Q waves also in the lateral chest leads and/or increase in R wave voltage in chest leads V1-3.

CK CLASSIFICATION (GROUP 1)

The serum total CK was measured one hour after admission and at 9 am on each of the first 3 days (but excluding the first day when admission was between 3 and 8 am). The sum of the first 3 measurements of serum total CK levels was used as a crude enzymatic index of infarct size: *class 1:* <1000 IU/l; *class 2:* 1000-2000 IU/l; *class 3:* 2000-2500 IU/l; *class 4:* >2500 IU/l.

TECHNIQUE OF RECORDING SCINTIGRAMS

Scintigrams were recorded $\frac{3}{4}$ to 1 hour and 2 to $2\frac{1}{2}$ hours after intravenous injection of 10 mCi ^{99m}Tc polyphosphate. Scintigrams were recorded

on day 1 and on day 2 or 3, each day representing a 24-hour period with reference to the onset of chest pain. A General Electric Radicamera II was used with a 20 per cent window centred upon 140 Kev. Each scintigram consisted of a total of 300 000 counts and was stored in frame mode as a 64×64 matrix on high density disc (BASF systems HD8). A Nuclear Data (ND812) digital computer was used for subsequent data analysis with constant display size.

Records were obtained with the patient in the supine projection, or in patients with severe pulmonary oedema in the 45° head-up tilt position. In each case scintigrams were recorded in the anteroposterior (AP), 45° left anterior oblique (LAO), and left lateral (LL) projections (with the patient's arms above the head in the last two of these projections).

CLEARANCE OF ^{99m}Tc POLYPHOSPHATE

Serial blood samples were taken from 10 minutes to 4 hours after the isotope injection. Each sample was immediately divided into two, one being stored as whole blood, and the other immediately centrifuged and stored as plasma. Samples were subsequently counted at the same time in a well scintillation detector.

INFARCT/BONE RATIO

Scintigrams were recorded in the identical left lateral projection in each patient. Measurements were made in two representative rectangular areas

Fig. 1 Horizontal and vertical markers enclosing rectangular areas of interest over the infarct image and spine image for measurement of infarct/bone uptake ratio.

(A)

(B)

Fig. 2 Definition of infarct edge. (A) ^{99m}Tc polyphosphate scintigram (LAO projection). Horizontal marker (Y2) crosses the infarct edge in its traverse between vertical markers, X1 and X2. (B) Profile of increasing activity across infarct edge. Computer read-out of counts over successive points along Y2 between X1 and X2 (Fig. 2A). Line is best fit through 4 adjacent points of steepest slope. Its slope represents sharpness of definition of infarct edge.

within the region of the 'infarct' uptake and in the two corresponding areas at the same horizontal level over the spine (Fig. 1). The average count density over the infarct was compared with that over the spine to give the infarct/bone ratio.

INFARCT EDGE DEFINITION

Scintigrams were recorded as above. Count density was plotted along a profile selected as passing through the infarct edge (in an intercostal space). An index of the sharpness of definition of the infarct

edge was obtained from steepness (estimated peak slope) of the change in counts across the edge (Fig. 2A and B). In each scintigram the average peak slope derived from two parallel profiles was calculated. In each patient it was clearly critically important that corresponding scintigrams recorded at different times represented identical profiles as nearly as possible. In order to achieve this the camera position and angle were maintained constant relative to the floor. The patient was positioned to lie supine on a hard table of constant height from the floor and in an identical place on the table with respect to the position of the head and feet. A protruding rigid arm from the camera was related to a constant anatomical landmark on each patient further to ensure precisely constant positioning.

Profiles were horizontal, through lung, heart, infarct, and spine, and as they were in the LAO projection the anterior portion of these profiles avoided rib activity. Activity along the profile fell to a low plateau anteriorly, presumably over normal heart and lungs, and the level of this plateau was taken to represent 'background activity'.

ELECTROCARDIOGRAPH GATING

A synchronising unit was used, triggered by the leading edge of the R wave—derived 'SYNC' output of a Hewlett Packard 7807B patient electrocardiograph monitor. The 'dwell' period was fed to the 'GATE' input of the gamma camera analogue computer module which, in the absence of the signal, was held off. Thus data were acquired only during the 'dwell' period. To facilitate setting up, a duplicate of the 'dwell' signal was applied to the second channel of the patient monitor oscilloscope. Scintigrams were recorded consisting of 300 000 counts with and without electrocardiograph gating. Edge analysis was performed as described above.

SCINTIGRAPHIC ASSESSMENT OF INFARCT SIZE

Scintigrams recorded between 2 and 2½ hours after isotope injection on day 2 or 3 were used. Assessment was made (a) by subjective grading of one projection, (b) by subjective grading of three projections, and (c) by computer-assisted measurement of above-background counts within the subjectively delineated area of the infarct in one projection.

Assessment was blind, without knowledge of related clinical, electrocardiograph, or enzyme data. Infarcts were subjectively graded from 1 to 3 according to increasing area and from 1 to 3 according to increasing density of isotope uptake, the sum of the two giving an index of infarct size. The index was assessed in each case (a) from the

Fig. 3 Profile of counts along a horizontal marker through infarct for estimation of background activity immediately surrounding infarct. Line is drawn through ventral background only, because dorsal background is influenced by activity over spine. Average of 3 different profiles is used in each case.

single LAO projection, and (b) from the sum of the indices in the AP, LAO, and LL projections. (c) Three different horizontal profiles were plotted to give 'background activity' (Fig. 3) which was subtracted from total activity over the infarct to give a clearer image of specific 'infarct activity'. By projecting the resultant specific 'infarct activity', the area of the infarct was more easily outlined with a light pen, extrapolating across overlying ribs between intercostal spaces. The total 'infarct activity' within this area was analysed with the aid of the computer to give the number of points (computed area) showing 'infarct activity' and the total number of counts (total activity) within the delineated infarct area, from which was also derived the average number of counts/point (computer average uptake density). Rib uptake will, therefore, contribute to total infarct activity, but it will not influence measurement of 'infarct area', nor should it seriously affect estimates of relative 'intensity', 'total computed infarct activity', or 'average uptake density' compared at different times and in different patients.

STATISTICAL ANALYSIS

This was by Student's *t* test for paired data except as otherwise indicated. Results are expressed as mean $\pm$ standard deviation, and considered significantly different when $P < 0.05$.

Results

CLEARANCE OF ^{99m}Tc POLYPHOSPHATE

Fig. 4 shows the clearance curves which are

Fig. 4 Clearance of ^{99m}Tc polyphosphate from whole blood and plasma. Samples were taken at times indicated, and measured at the same time later, so that the curves represent biological clearance and not radioactive decay. (Mean $\pm$ SD, $n = 5$). $\circ$ = whole blood; $\bullet$ = plasma.

biexponential with half-times in whole blood of 18.5 minutes and 7 hours 45 minutes, and in plasma of 16.5 minutes and 5 hours.

INFARCT/BONE RATIO

Infarct/bone ratio was significantly higher ($P < 0.02$) 1 hour after isotope injection (0.960 ± 0.139 , $n = 20$) than $2\frac{1}{2}$ hours after injection (0.848 ± 0.132) in scintigrams recorded on day 2 or 3.

Infarct/bone ratio $2\frac{1}{2}$ hours after injection was significantly higher ($P < 0.001$) on day 2 ($n = 7$) or day 3 ($n = 3$) (1.101 ± 0.292 , $n = 10$) than on day 1 (0.898 ± 0.111).

INFARCT EDGE DEFINITION

The infarct edge was significantly more sharply defined 2 to $2\frac{1}{2}$ hours after isotope injection than 1 hour after injection. The mean peak slope of difference in count density along profiles through the infarct edge was 16.162 ± 11.568 counts/interval between adjacent points at 2 to $2\frac{1}{2}$ hours compared with 10.219 ± 4.12 counts/interval at 1 hour, $n = 24$, $P < 0.001$.

The infarct edge was significantly more sharply defined on day 2 ($n = 17$) or 3 ($n = 7$) than on day 1. On day 2 or 3 the slope was 22.915 ± 15.271 , compared with 11.0 ± 7.139 on day 1, $n = 10$, $P < 0.001$.

Electrocardiograph gating did not significantly improve the definition of the infarct edge. In

scintigrams recorded 2 hours after isotope injection on the 2nd day in hospital, the slope across the infarct edge was 15.729 ± 6.641 counts/interval without electrocardiograph gating, and 18.114 ± 8.425 with gating, $n = 7$, $P > 0.05$.

SCINTIGRAPHIC FINDINGS RELATED TO CLINICAL DIAGNOSIS

Of the 53 patients with myocardial infarction (group 1), 52 had positive scintigrams and 1 was equivocal. This was in a patient whose scintigram was recorded only at 18 hours after the onset of chest pain and who had a localised (class 1) inferior infarct.

Of 10 patients with scintigrams recorded within the first 12 hours, 8 had positive scintigrams and 2 were negative. The patients with negative scintigrams at this time (one with an anterior, class 1, infarct, measured at 6 hours, the other with an inferior, class 1, infarct, measured at 5 hours) both showed positive scintigrams on day 3. Of 24 patients where scintigrams were recorded during the first 24 hours after the onset of chest pain, 20 had positive scintigrams, 2 were equivocal, and 2 (detailed above) were negative. Of the 2 patients with equivocal scintigrams, one is detailed above; the other was recorded at 14 hours in a patient with a class 3 anterior infarct, and a repeat scintigram at 5 days was positive. Of 30 patients studied on day 2 or 3, all showed positive scintigrams. Of 9 patients studied on days 4 and 5, 8 had positive scintigrams, and 1 (studied on day 4, class 1, inferior infarct) was equivocal.

Of the 18 patients with acute coronary insufficiency (group 2), 13 had positive scintigrams, 2 were equivocal, and 3 were negative. Of the 13 positive scintigrams, 4 were recorded on day 1, 5 on day 2, 3 on day 3, and 1 on day 5. Three patients with positive scintigrams experienced continuing angina despite medical treatment and 3 patients developed acute myocardial infarction (fulfilling the diagnostic criteria described above), 2 during the same admission (day 5 and day 6) and 1 three months later. In the other 10 patients with positive scintigrams, continued serial electrocardiograph monitor recordings and measurements of serum CK showed no changes of myocardial infarction. All 3 patients with negative scintigrams became asymptomatic on treatment with oxprenolol.

CORRELATION OF INDEXED SEVERITY OF INFARCT FROM SCINTIGRAMS WITH CLINICAL, ELECTROCARDIOGRAPHIC, AND CK CLASSIFICATION

Table 1 shows that from the LAO projection alone, the indexed area of uptake (see Methods, scinti-

Table 1 Visual analysis: scintigraphic index of severity of infarct (LAO projection)

Clinical class	No.	Area log index	Intensity log index	Area and intensity log index
1	17	0.272 ± 0.133	0.230 ± 0.213	0.565 ± 0.136
2	12	0.349 ± 0.082*	0.307 ± 0.121	0.620 ± 0.100
3	10	0.389 ± 0.093*	0.371 ± 0.091*	0.686 ± 0.066*†
<i>Electrocardiogram class</i>				
Anterior	1	0.301 ± 0.100	0.366 ± 0.167	0.635 ± 0.098
	2	0.389 ± 0.093	0.354 ± 0.085	0.676 ± 0.071
	3	0.366 ± 0.079	0.336 ± 0.079	0.612 ± 0.107†
Inferior	1	0.274 ± 0.165	0.219 ± 0.180	0.560 ± 0.136
	2	0.371 ± 0.096*	0.251 ± 0.240	0.626 ± 0.140
<i>CK class</i>				
	1	0.255 ± 0.134	0.263 ± 0.199	0.566 ± 0.116
	2	0.306 ± 0.115	0.287 ± 0.185	0.603 ± 0.132
	3	0.360 ± 0.088*	0.340 ± 0.078*	0.654 ± 0.066*†
	4	0.389 ± 0.096*	0.389 ± 0.096*	0.672 ± 0.116*

For definition of clinical, electrocardiogram, and CK classes see Methods.

Footnote: Data are analysed by logarithmic transformation to compare geometric means, and are given as mean ± SD of log 10 index.

*Indicates P < 0.05 compared with respective class 1.

†Indicates P < 0.05 compared with preceding class, where this is not class 1.

graphic assessment of infarct size, method (a) was significantly greater in clinical class 2 or 3 than class 1, significantly greater in electrocardiogram class 2 than class 1 inferior infarcts, but not significantly different in different electrocardiogram classes of anterior infarcts or different CK classes. The indexed intensity of uptake showed no significant differences between adjacent clinical electrocardiogram or CK classes but distinguished between clinical class 1 and 2 and also between CK classes 3 or 4 compared with 1. The combined index of area and intensity was greater in clinical class 3 than 1 or 2, and significantly greater in CK classes 3 or 4 compared with 1 or 2.

Table 2 shows that, from the combination of AP, LAO, and LL projections, the indexed area of uptake was significantly greater in clinical class 3

than classes 2 or 1 and in clinical class 2 than class 1. The area was greater in electrocardiogram class 2 than class 1 inferior infarcts, though not significantly different in the different electrocardiogram classes of anterior infarct. It was greater in CK class 4 than in classes 3, 2, or 1. The indexed intensity of uptake was greater in clinical class 3 than 2. It did not correlate positively with electrocardiogram classes of severity or between adjacent CK classes although the index was significantly greater in CK classes 3 and 4 compared with 1. The combined index of area and intensity was greater in class 3 than classes 2 or 1. It was greater in extensive than in localised inferior infarcts, but did not distinguish between anterior infarcts of differing severity. It was greater in CK class 4 than classes 3, 2, or 1, and in CK class 3 than class 1.

Table 2 Visual analysis: scintigraphic index of severity of infarct (combined AP, LAO, and LL projections)

Clinical class	No.	Area log index	Intensity log index	Area and intensity log index
1	17	0.686 ± 0.177	0.716 ± 0.135	1.009 ± 0.133
2	12	0.774 ± 0.130*	0.667 ± 0.125	1.028 ± 0.114
3	10	0.876 ± 0.068*†	0.791 ± 0.146†	1.147 ± 0.042*†
<i>Electrocardiogram class</i>				
Anterior	1	0.715 ± 0.143	0.777 ± 0.131	1.049 ± 0.133
	2	0.848 ± 0.091	0.792 ± 0.117	1.129 ± 0.069
	3	0.846 ± 0.111	0.705 ± 0.180†	1.088 ± 0.078
Inferior	1	0.658 ± 0.172	0.703 ± 0.149	0.989 ± 0.136
	2	0.769 ± 0.098*	0.721 ± 0.177	1.032 ± 0.134*
<i>CK class</i>				
	1	0.701 ± 0.164	0.682 ± 0.165	0.992 ± 0.137
	2	0.757 ± 0.150	0.726 ± 0.162	1.048 ± 0.138
	3	0.768 ± 0.099	0.759 ± 0.101*	1.060 ± 0.083*
	4	0.888 ± 0.076*†	0.817 ± 0.141*	1.156 ± 0.080*†

For definition of clinical, electrocardiogram, and CK classes see Methods.

Footnote: Data are analysed by logarithmic transformation to compare geometric means, and are given as mean ± SD of log 10 index.

*Indicates P < 0.05 compared with respective class 1.

†Indicates P < 0.05 compared with respective preceding class, where this is not class 1.

Table 3 *Quantitative analysis: left anterior oblique projection*

<i>Clinical class</i>	<i>No.</i>	<i>Area log no. of points</i>	<i>Total activity</i> <i>Total no. of counts</i>	<i>Average uptake density</i> <i>Log counts/point</i>	
	1	17	1·639 ± 0·291	3·574 ± 0·368	1·935 ± 0·281
	2	12	2·032 ± 0·296*	3·932 ± 0·206*	1·900 ± 0·155
	3	10	2·386 ± 0·163*†	4·228 ± 0·149*†	1·843 ± 0·148
<i>Electrocardiogram class</i>					
<i>Anterior</i>	1	5	1·705 ± 0·345	3·726 ± 0·281	2·021 ± 0·220
	2	10	2·215 ± 0·135*	4·077 ± 0·120*	1·862 ± 0·138
	3	5	2·402 ± 0·083*†	4·221 ± 0·116*†	1·819 ± 0·113*
<i>Inferior</i>	1	14	1·613 ± 0·239	3·593 ± 0·384	1·980 ± 0·264
	2	5	1·990 ± 0·237*	3·964 ± 0·236*	1·974 ± 0·143
<i>CK class</i>					
	1	15	1·608 ± 0·237	3·595 ± 0·318	1·986 ± 0·255
	2	12	1·856 ± 0·337*	3·711 ± 0·517	1·854 ± 0·274
	3	9	2·069 ± 0·294*†	3·980 ± 0·253*	1·911 ± 0·144
	4	6	2·317 ± 0·148*†	4·125 ± 0·190*	1·808 ± 0·109*

For definition of clinical, electrocardiogram, and CK classes see Methods.

Footnote: Data are analysed by logarithmic transformation to compare geometric means, and are given as mean $\pm$ SD of log 10 points, counts, or counts/point.

*Indicates $P < 0.05$ compared with respective class 1.

†Indicates $P < 0.05$ compared with respective preceding class, where this is not class 1.

CORRELATION OF COMPUTED 'INFARCT ACTIVITY', WITH CLINICAL, ELECTROCARDIOGRAM, AND CK CLASSIFICATION

Only the LAO projection was used in this analysis. Table 3 shows that the *computed infarct area* (number of points showing 'infarct activity') differed significantly between all clinical classes, all electrocardiographic classes of severity, and all CK classes. If *total computed infarct activity* (total number of counts) is considered, the discrimination is not quite so good though the differences between clinical classes and between electrocardiographic classes of severity remain significant. The average uptake density (counts/point) did not differ significantly between any adjacent clinical, electrocardiogram, or CK class. The average count density was in fact significantly less in anterior electrocardiogram class 3 compared with class 1 and in CK class 4 compared with class 1.

Discussion

The accuracy of any assessment of infarct size from surface scintigraphy will be related to the density of the uptake over the infarct relative to the surrounding area and to the sharpness with which it can be defined. Precise constancy of recording technique is obviously essential. The first part of this study is concerned with establishing optimum conditions for measuring infarct size, using ^{99m}Tc polyphosphate (as distinct from the more commonly used ^{99m}Tc pyrophosphate).

Background blood pool activity declined rapidly

after injection of the isotope. Infarct/bone uptake ratio also declined, partly because blood pool activity will contribute to total activity measured over the infarct. The infarct edge, however, was more sharply defined at the later time, probably also because of declining blood pool and therefore background activity. We therefore chose to use the later time (2½ hours) after isotope injection. Scintigrams were compared on day 1 and on day 2 (or 3) after the clinical onset of the myocardial infarct. Both infarct/bone uptake ratio and the sharpness of the infarct edge were better on day 2 (or 3) than on day 1. This finding is in keeping with the observation of improved image quality obtained after the first 24 hours by other workers (Bonte *et al.*, 1975) using Tc pyrophosphate and probably indicates increasing tracer concentration in the infarct over the first few days.

We recorded ^{99m}Tc polyphosphate scintigrams 2½ hours after injection on day 2 (or 3) in patients with transmural infarcts. Subjective grading of infarct severity from scintigrams in terms of infarct area, or density, or a combination of area and density correlated poorly with the other clinical, electrocardiographic, and enzymatic criteria of infarct severity. This remained true whether a single left anterior oblique projection was used or a combination of the three projections. With the aid of computer analysis, however, a highly significant correlation was demonstrated with all the different clinical, electrocardiographic, and enzyme criteria.

This study establishes a relation between myocardial infarct size and the size of the image of the infarct obtained from surface scintigrams in man.

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