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Serial changes in the T_1 magnetic relaxation parameter after myocardial infarction in man

M BEEN,* M A SMITH,†‡ J P RIDGWAY,‡ R H B DOUGLAS,†
D P DE BONO,* J J K BEST,† A L MUIR*

*From the Nuclear Magnetic Resonance Imaging Unit (Departments of *Medicine; †Medical Radiology, and ‡Medical Physics and Medical Engineering, University of Edinburgh), Royal Infirmary, Edinburgh*

SUMMARY A low field resistive nuclear magnetic resonance imaging system (0·08 Tesla) was used to study the in vivo changes in the relaxation parameter T_1 of the left ventricular myocardium from the first day to six months after acute myocardial infarction in 41 consecutive patients admitted to a coronary care unit. T_1 maps were constructed from transverse and coronal images at various times after infarction. Thrombolytic treatment had been successful in 28 patients. Thirty three of the 34 patients studied within two weeks of infarction had a significantly increased T_1 value but this developed only after the third day in four. At day 1–3 the mean (1 SD) maximum T_1 was 413 (29) ms (n = 23) compared with 430 (41) ms (n = 22) at day 4–7, 433 (35) ms (n = 24) at day 8–14, 420 (34) at one month (n = 22), 388 (39) (n = 20) at three months, and 361 (24) (n = 14) at six months. The number of regions of interest with an increased T_1 followed a similar time course. Although the increase in T_1 measured at three months correlated with the initial maximum creatine kinase and with the left ventricular ejection fraction measured at one month, the number of regions with abnormal T_1 from day 4 through to one month correlated best with left ventricular ejection fraction. There was no significant difference in T_1 between patients with or without reperfusion. The rise in T_1 over the first few days together with the prolonged time course of T_1 increase suggests that the increase in T_1 may reflect cellular infiltration as much or more than tissue oedema.

It has been suggested that the magnetic relaxation parameters T_1 and T_2 which are associated with an increase in free water content may be used to demonstrate tissue abnormalities.[1] After experimental canine myocardial infarction in vitro T_1 and T_2 were prolonged, and these changes correlated well with increases in tissue water content.[2 3] In vivo prolongation of both T_1 and T_2 after myocardial infarction has been confirmed in dogs[4 5] and recently in human beings.[6 7] In dogs the changes begin within 30 minutes of coronary occlusion[2] and become more pronounced with occlusions of one, two, and three hours.[2 5] Recently, Pflugfelder *et al* described the serial changes in the intensity of the in vivo signal in canine myocardial infarction[8] but similar studies in human beings have not been reported.

The purpose of the present study was primarily to define the time course of changes in T_1 after acute myocardial infarction in human beings.

Patients and methods

We studied 41 patients with transmural myocardial infarction that was confirmed by both electrocardiographic and creatine kinase changes. Whenever possible, imaging was carried out on day 1–3, day 4–7, day 8–14 and one month, three months, and six months after infarction. Serial imaging was performed on 2–6 occasions (mean 3·4 per patient); however, in two patients adequate images were obtained on one occasion only. Consecutive patients were selected provided that the imager was available, the patient consented, and none of the following exclusion criteria was present: current symptomatic pulmonary oedema, continuing chest pain, major

Requests for reprints to Dr A L Muir, Department of Medicine, Royal Infirmary, Edinburgh EH3 9YW.

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arrhythmia within 12 hours, previous infarction in the same electrocardiographic territory, or any myocardial infarct in the preceding year.

The study was approved by the local ethics review committee and all patients gave written informed consent.

Ten patients did not have thrombolytic treatment and in a further three thrombolysis was found to be unsuccessful at subsequent coronary angiography (group 1). The remaining 28 patients (group 2) had successful coronary thrombolysis with intravenous anisoylated plasminogen streptokinase complex[9] (n = 23) or recombinant tissue type plasminogen activator (n = 5) (table 1).

The study population was heterogeneous in terms of the site of infarct, rise in creatine kinase, and the use and success of thrombolytic treatment (table 1). Patients on thrombolytic treatment underwent early coronary angiography to determine whether the infarct related vessel was patent, and left ventricular function was assessed by gated blood pool scan.[10] In all patients creatine kinase activity was measured twice a day during their stay in the coronary care unit.

The number of patients in group 1 (n = 13) was smaller than that in group 2 (n = 28) because the use of thrombolytic treatment increased during the study and because non-reperfused patients tended to be less well and were therefore more likely to be excluded from this study.

MAGNETIC RESONANCE IMAGING TECHNIQUE

Patients were imaged with a 0·08 T vertical field resistive magnetic resonance imaging system, manufactured by M & D technology, installed in the Edinburgh Royal Infirmary,[11] and situated between the coronary care unit and the angiography laboratory. Calculated T_1 maps were obtained by an interleaved saturation-recovery and inversion-recovery pulse sequence with a time from inversion (TI) of 200 ms. Inversion was obtained with an adiabatic fast passage inverting pulse rather than the usual 180° pulse; this is particularly suitable for precise T_1 calculation because it efficiently inverts all the nuclei within the section. In addition, it is not slice selective which means that it inverts all the nuclei within the heart and therefore does not have to be synchronised with the cardiac cycle.

Table 1 *Data (mean (1 SD)) on the study population*

	Group 1	*Group 2*
	Coronary occlusion (proven or assumed)	*Coronary reperfusion (proven vessel patency)*
No of patients	13*	28
Anterior infarction	5	19
Inferior infarction	8	9
Age (years)	57 (10)	53 (10)
Peak creatine kinase (U/l)	1889 (800)	1947 (1334)

*Confirmed at angiography[3] or assumed because thrombolysis was not used.

The patient's electrocardiogram was used to trigger the imager such that the 90° pulse in both the saturation-recovery and inversion-recovery sequences occurred in the same part of the cardiac cycle.[12] A field gradient echo of 20 ms was used. The minimum time from the R wave trigger at which imaging can be performed is 230 ms, principally because of the time from inversion (TI) values used. Partly as a consequence of this, but also to obtain tomographic sections of maximum myocardial thickness, images were obtained towards end systole. The pixel size was 3·5 mm × 3·5 mm.

In an attempt to obtain comparable sections on serial studies for individual patients we used the following routine. After attachment of the electrocardiographic leads we used an alignment marker to position the patient on the couch. The lower edge of the xiphisternum was used as the reference level. The distance of subsequent couch movements was recorded from the digital readout provided by the system. Initial images were obtained with a 16 s ungated saturation-recovery sequence as an anatomical guide for the sections to be scanned. Having optimised the image position and recorded its distance from the xiphisternum we performed a gated scan with a slice thickness of 16 mm. To encompass the whole left ventricle, further scans were performed at two or three 15 mm levels cranial or caudal to this or both, and the position was noted to allow equivalent sections to be obtained at subsequent imaging.

A single coronal section through the left ventricle was obtained. The most suitable imaging slice was again selected from rapid ungated images, but in this case the position was adjusted by slightly altering the strength of the magnetic field. Despite the measures described above, it is likely that changing left ventricular geometry over the six month period prevented serial imaging of exactly the same portion of myocardium. For this reason we used the area of highest T_1 found in any region of interest in the infarct territory for analysis.

The imager was triggered by each R wave for heart rates <75/min and by alternate R waves for faster heart rates. Patients who were scanned during the first 48 hours while in the coronary care unit were moved on a trolley equipped with a defibrillator, and electrocardiographic monitoring was continued throughout.

DATA ANALYSIS

For analysis of T_1 values, the myocardium was divided into six sections for each image containing the left ventricular myocardium and cavity. Figure 1 shows the areas into which the myocardium was divided. T_1 values for each of the six sections of every image were obtained by using the computer to draw circular regions of interest within the myocardium. The largest circle that could be placed clearly within the myocardium was used. The area of interest selected was either 0·26 or 0·51 cm^2, but where wall thinning was considerable the smallest available region of interest (0·08 cm^2) was used. This gives a T_1 value of the full thickness of the ventricular wall but with a greater contribution from the central portion of the myocardium. In nine patients there was considerable thinning of the myocardium in the infarct region (eight anterior, one inferior). To avoid the possibility that measurements of myocardial T_1 from this region might be rendered inaccurate by inclusion of intracavitary signal (from blood or thrombus) or extramyocardial signal (from pericardial fat or connective tissue) the region of interest was modified where necessary to encompass the closest lateral position which lay clearly within the myocardium. Attempts at obtaining a T_1 value from the narrowed segment illustrated the necessity for this modification since minor inward or outward adjustment of position resulted in major alterations in T_1.

The maximum T_1 value for each patient investigation was noted as was the number of areas with a T_1 value >390 ms, the value previously identified as the cut off between normal and infarcted tissue.[7] Values for non-affected myocardium were then obtained as follows. On the first image showing an increased T_1 value (>390 ms) we selected the T_1 value from an area anatomically remote from the site of infarction to control for and give information about the variability of T_1 measurements with our system. T_1 values for this selected non-affected region were noted for subsequent examinations.

The data were analysed in both a cross sectional and longitudinal manner. In the cross sectional analysis the maximum T_1 for all patients at each time period after infarction is presented as a mean and 1 SD. The variation in T_1 with time since infarction was studied by fitting a gamma variate curve to the mean maximum T_1 values at each time period and calculating the regression coefficient. The maximum T_1 at day 1–3 was compared with the value obtained from the non-affected region on the same scan by means of a paired Student's *t* test. Linear regression analysis was used to correlate the maximum T_1 values and the number of areas of increased T_1 with left ventricular ejection fraction and peak creatine kinase activity.

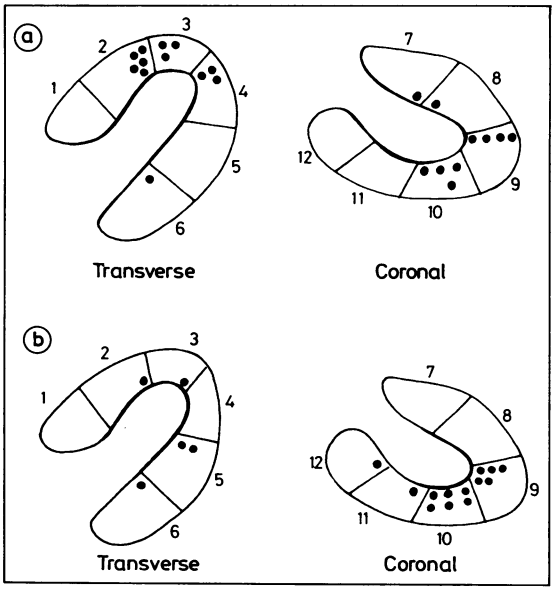

Fig 1 *(a) Regions of myocardium with greatest T_1 value in patients with anterior infarction. Each dot represents the region with the maximum value for a single patient. (b) Regions of myocardium with greatest T_1 value in patients with inferior infarction.*

Longitudinal analysis of the data was performed by noting the change in T_1 at each study interval.

Results

T_1 VALUES IN THE NON-AFFECTED AREA

For the group as a whole the mean T_1 of the non-affected myocardium at day 1–3 was 320 (19) ms. There was no significant difference in the measured T_1 at any time in the non-affected region, the highest mean value being 326 (18) ms at one month. The range of T_1 values in the 41 patients over all time periods was 274–382 ms, confirming our previous observation that a cut off of 390 ms differentiates between normal and infarcted myocardium.[7]

T_1 VALUES IN THE AFFECTED AREA

Maximum T_1 values

Table 2 shows the results for each patient at the six times after infarction. Maximum T_1 values always occurred in an anatomical position consistent with the electrocardiographic changes (fig 1a and b). But the highest T_1 was not always seen in the same region on serial imaging.

Cross sectional analysis of the data (fig 2) showed that at day 1–3 T_1 was significantly higher in the infarct region than in the non-affected area

Table 2 *Patient details, maximum creatine kinase (CK) and T1 values at intervals shown*

Patient No	Age	Site of infarct	Successful thrombolysis	Max CK	T_1 maximum					
					Day 1–3	Day 4–7	Day 8–14	1 mnth	3 mnth	6 mnth
1	39	Lateral	Yes	717	480	—	476	462	397	399
2	45	Inferior	Yes	1261	—	435	443	374	—	—
3	64	Inferior	No	1395	—	—	—	476	427	—
4	58	Inferior	No	1230	415	404	447	454	410	378
5	70	Anterior	Yes	1169	371	—	539	—	—	348
6	55	Anterior	Yes	2624	—	475	—	452	400	389
7	37	Anterior	Yes	3117	366	—	409	399	377	—
8	49	Inferior	No	1529	—	389	468	439	322	356
9	56	Inferior	Yes	2076	—	—	—	—	430	353
10	54	Anterior	Yes	4578	428	507	455	451	408	366
11	60	Anterior	Yes	789	414	472	483	402	—	364
12	46	Inferior	Yes	2361	—	400	379	—	—	344
13	60	Inferior	Yes	1030	435	—	—	—	—	356
14	67	Inferior	Yes	799	378	386	—	—	357	—
15	57	Anterior	Yes	513	—	452	—	—	—	—
16	48	Anterior	Yes	2743	—	—	—	391	—	361
17	53	Anterior	Yes	4565	414	402	420	453	478	372
18	61	Anterior	Yes	3602	—	—	474	—	—	—
19	57	Inferior	No	1301	392	—	397	470	363	344
20	56	Inferior	No	3156	410	—	—	—	—	—
21	73	Anterior	No	699	431	469	468	—	346	385
22	49	Anterior	No	2215	—	—	400	358	358	—
23	42	Lateral	Yes	3719	441	439	438	425	392	—
24	33	Anterior	Yes	1736	442	502	—	405	—	412
25	57	Anterior	Yes	247	429	387	—	—	—	—
26	62	Anterior	Yes	881	—	397	—	—	371	359
27	40	Inferior	No	—	—	460	390	—	360	350
28	42	Anterior	Yes	1652	—	—	396	—	423	338
29	56	Anterior	No	3025	—	—	—	—	—	412
30	63	Inferior	Yes	814	—	—	—	—	364	343
31	52	Inferior	Yes	1286	—	—	—	—	393	347
32	58	Anterior	No	2869	426	—	—	—	—	—
33	61	Anterior	Yes	1701	—	—	408	—	—	—
34	58	Anterior	Yes	4372	435	396	—	424	438	376
35	58	Anterior	Yes	—	—	—	—	—	—	374
36	58	Anterior	Yes	203	402	428	372	429	—	—
37	61	Inferior	Yes	1303	390	365	393	390	346	—
38	44	Anterior	No	2138	404	465	456	427	472	—
39	58	Inferior	No	1216	374	394	469	387	383	—
40	73	Inferior	No	1890	443	—	442	410	355	—
41	62	Anterior	Yes	2723	371	441	443	384	392	—

($p < 0{\cdot}0001$). T_1 continued to rise, reaching a peak at day 8–14 before falling gradually towards normal. Fig 3a–d shows images from one patient at increasing intervals after infarction. The gamma variate curve fitted to the change in peak T_1 gave a significant correlation coefficient ($r = 0{\cdot}95$, $p < 0{\cdot}001$).

The results of longitudinal analysis, which combined the changes in individual patients, supported the trend shown in fig 2.

Area of raised T_1 (fig 4)

In this study 38 of the 41 patients had a maximum T_1 of >390 ms. Of the 23 patients who had their first scan between the first and third day after the onset of infarction, five had no regions of interest with a T_1 above 389 ms. In four of these, however, the T_1 subsequently rose to more than 390 ms by the time of the second scan on day 4–7. Only one patient did not demonstrate a T_1 value above 390 ms on at least one scan; the maximum T_1 value in this patient was 386 ms.

The number of areas with significantly increased T_1 varied greatly both between patients and at different times. The same general pattern to that of the peak T_1 values was found. By six months only two patients had any areas of T_1 >390 ms.

COMPARISON OF REPERFUSED AND NON-REPERFUSED GROUPS

The maximum T_1 and number of areas of increased T_1 (above 390 ms) were not significantly different between the two groups at any time period. Neither was there any significant difference in T_1 values between those patients in the reperfused group who were treated early (within two hours) and those who were treated later, although there was a trend towards a more rapid fall in the number of areas of raised T_1 in the group treated early.

IDENTIFICATION OF INFARCT SITE

For inferior infarcts the maximum T_1 was most commonly seen on the coronal image (fig 1a) but

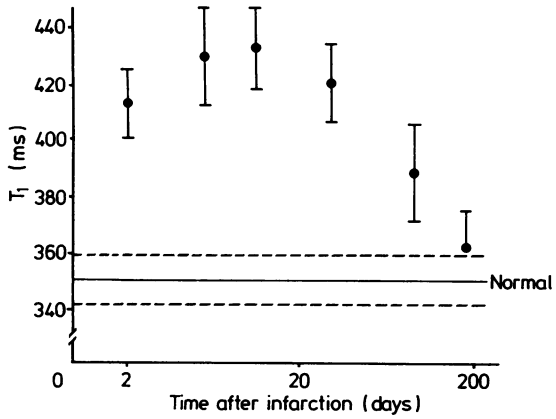

Fig 2 *Mean maximum T_1 values (2 SE) after myocardial infarction. Values were greater than the normal mean maximum T_1 (SE) at first imaging (day 1–3) and tended to increase until the third imaging sequence (day 8–14); values only returned to the mean maximum T_1 values seen in normal subjects six months after infarction.*

maximum T_1 values were more commonly seen on the transverse views when there was an anterior infarct (fig 1b).

CORRELATION OF T_1 WITH OTHER MEASURED VARIABLES

Creatine kinase

Because inferior infarcts tended to have a smaller peak activity of creatine kinase (1471 (581) *vs* 2162 (428) U/l) and left ventricular function was better preserved (52 (7)% *vs* 32 (11)%), they were first considered separately from anterior infarcts. There was no significant difference in maximum T_1 values between anterior and inferior infarction, however. There was a correlation ($r = 0{\cdot}59$, $p < 0{\cdot}01$) between the peak activity of creatine kinase and the maximum T_1 found at three months in the combined groups.

Left ventricular ejection fraction

There was a correlation between ejection fraction and peak T_1 values at one month ($r = -0{\cdot}57$, $p < 0{\cdot}05$). The number of areas of increased T_1 (>390 ms) correlated with ejection fraction at 4–7 days ($r = -0{\cdot}63$, $p < 0{\cdot}01$), 8–14 days ($r = -0{\cdot}53$, $p < 0{\cdot}05$), and at one month ($r = -0{\cdot}6$, $p < 0{\cdot}02$).

Discussion

After myocardial infarction T_1 rises in the area of infarction in almost all patients. There is no significant change in T_1 in the unaffected myocardium. This confirms reports of in vitro[2 3] and in vivo[5 6] experimental studies and those in human infarction.[7 8] The changes may not appear or be appreciable before four days after the onset of infarction, and they reach a peak by the end of the first week. While it is likely that there was some increase in T_1 during the early stages of infarction in all our patients, the magnitude of this increase was not sufficient to permit reliable identification of abnormal myocardium in every case. The values in the five patients who did not have a T_1 >390 ms on their initial scan ranged from 366 to 378 ms compared with a mean 320 (9) ms in the normal myocardium and they were within our previously reported range for normal myocardium.

Our finding that maximum T_1 values occurred at about two weeks was unexpected. The reported close correlation between T_1 and water content[2] suggests that a more uniform and rapid increase in T_1 would be expected, because myocardial interstitial oedema and mitochondrial swelling occur early after the onset of infarction.[13] The dissociation between the timing of the peak T_1 and the expected peak of myocardial oedema formation may partly be explained by the fact that T_1 depends not simply on the total myocardial water content but also on the binding or interaction of water with biological macromolecules.[1]

The difference between our findings and previous in vitro studies of early changes in T_1 is likely to reflect the major differences between ischaemic human myocardium and excised heart muscle. Not only will the quantity of blood in the intramyocardial vessels differ, as does the coronary anatomy, but in addition there are differences in the state of binding of water within cells. In living systems metabolic processes continuously produce water and its biological state is regulated by cellular processes. That such differences affect T_1 has been demonstrated by comparative in vivo and in vitro T_1 measurements in rabbits.[14]

Our results accord with the in vivo experimental work of Pflugfelder *et al* who studied the serial changes in relaxation parameters and signal intensity in eight dogs after myocardial infarction.[8] In one animal the increase in signal intensity was only seen 4–6 days after infarction. The timing of peak signal intensity was dependent on the pulse sequence used but occurred between the fourth and thirteenth day. Furthermore, these workers frequently found an area of increased signal intensity on day 20 (the final image) and they commented that the affected area seemed to get smaller. Similarly in our study T_1 values remained raised at one month and even in some patients at three and occasionally six months, but the number of areas of increased T_1 fell more rapidly.

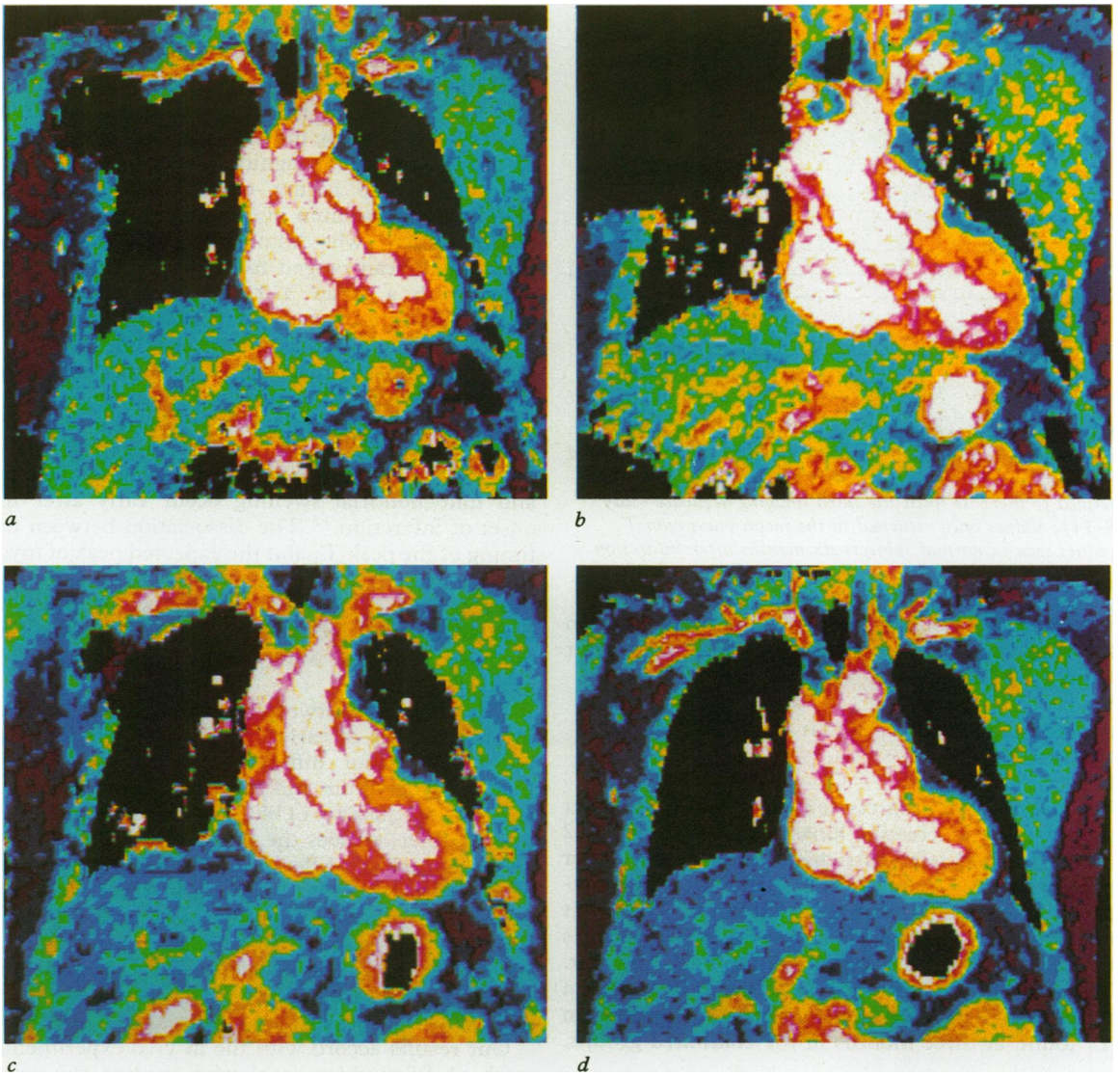

Fig 3 *Sequential coronal images in a patient with inferior infarction: (a) 3 days, (b) 14 days, (c) 1 month, and (d) 3 months after infarction.*

The presence of T_1 prolongation for up to three months confirms that factors other than myocardial oedema are responsible. The classic histological findings[15 16] after myocardial infarction indicate that neutrophils appear after about six hours and increase rapidly after 24 hours, reaching a peak between the third and fifth day.[15 17] Thereafter the number of large mononuclear macrophages increases, reaching a maximum at six weeks and subsequently declining. Other cellular infiltrates also occur, as does proliferation of capillaries which reaches a peak between 3–6 weeks. The histological changes may vary in the same patient at various times.[17] These cellular changes may influence magnetic resonance variables but, as yet, precise histological correlations are not possible. The possibility that T_1 and T_2 changes may provide a method of obtaining in vivo information about pathogenesis is exciting and has received some support from the recent finding that T_2 correlates with the histological severity of rejection in

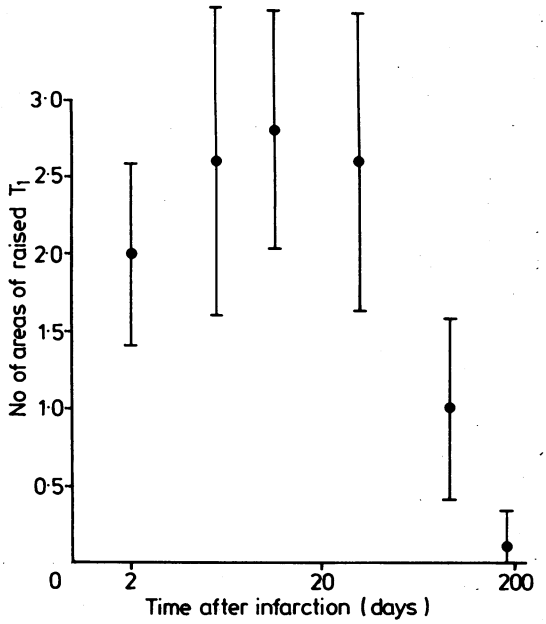

Fig 4 *Number of areas (mean (1 SE)) of myocardium with raised T_1 (>390 ms) after myocardial infarction. The changes with time follow the same pattern as the changes in maximum T_1.*

heterotopic cardiac transplantation in dogs.[18]

Some studies have suggested that T_2 is better than T_1 for the identification of infarcted tissue, but this may reflect different imaging sequences where the pulse sequence combination used was more appropriate for T_2 measurements than for T_1. Spin echo sequences with a short time to recovery do not contain as much T_1 weighting as an inversion-recovery sequence. In addition, variation in a patient's RR interval can influence time to recovery in the spin echo sequence causing a variable T_1 weighting and, as a consequence, error in the T_1 value. The constant time for inversion used in our technique, coupled with a non-slice selective efficient inverting pulse, minimises the error in T_1 caused by variation in the RR interval.[12]

Ratner *et al* measured endocardial and epicardial T_1 and T_2 and correlates these variables with perfusion measured after 30 and 60 minutes of coronary occlusion.[19] They suggested that the magnitude of change in T_1 and T_2 correlates with the extent of the ischaemic insult. The magnitude of the ischaemic insult is dependent not only on the duration of vessel occlusion but also on vessel size, collateral flow, and the rate of oxygen consumption which all modify the response and determine the infarct size. In this clinical study our means of assessing infarct size were limited. We used the peak creatine kinase activity as a crude assessment of infarct size. There was a correlation with maximum T_1, but only at one month. Thus the maximum level of T_1 seems to correlate poorly with infarct size in clinical practice. Because the kinetics of creatine kinase release are altered by reperfusion we also measured left ventricular ejection fraction at 8–10 days. All patients included in this analysis presented with a first infarct and so the reduction in left ventricular function provides some information about infarct size. The number of areas of increased T_1 did correlate with the ejection fraction at 4–7 days, 8–14 days, and at one month. No correlation was expected at day 1–3 or at three and six months because some patients did not develop changes until after the third day and by three months the area of increased T_1 was considerably reduced. This correlation presumably reflects the amount of myocardium affected by the ischaemic event. Thus the extent of the area with abnormal T_1 values seems a better guide to infarct size than the magnitude of changes in T_1. When this study was undertaken we were unable to perform multiple slice acquisitions but with this capability a precise determination of the volume of infarcted tissue should be possible.

Studies of changes in T_1 in dogs after coronary occlusion and reperfusion have suggested that T_1 is further prolonged by reperfusion,[20] and an increase in cellular swelling after reperfusion has been reported.[13] None the less, we found no significant difference in maximum T_1 between our reperfused and non-reperfused patients. This may reflect a balance between beneficial and harmful[21] effects of reperfusion; however, further analysis of our data in which those given early and late thrombolytic treatment were compared gives no evidence of this. Because time to reperfusion is critically important[22] to the effect of reperfusion, it might be expected that the T_1 values would be different in these groups. There was no significant difference in maximum T_1 or the number of areas showing raised T_1 between those treated within two hours and those treated more than two hours after the onset of symptoms. We noted a trend towards a more rapid fall in the number of areas with a raised T_1 in those treated early. The small numbers in these subgroups and the heterogeneity of the patients (in terms of the vessel affected, the position of the lesion, rate of reperfusion, extent of residual stenosis, collateral flow, disease of other vessels and therefore of infarct size and degree of continuing ischaemia) may be masking real differences.

The factors which produce these alterations in T_1 are complex and as yet we do not know whether changes in T_1 values reflect specific histological

findings. If the demonstrated changes reflect healing then alterations in T_1 may provide an important method for studying a neglected area in our understanding of myocardial infarction.

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