

Isotopic indices as a measure of inflammation in rheumatoid arthritis

H. BERRY AND E. C. HUSKISSON
From St. Bartholomew's Hospital, London

Assessment of inflammation in rheumatoid arthritis (RA) has been studied in several different ways. Hart and Huskisson (1972) considered morning stiffness to be a reflection of inflammation with the disadvantage of being subjective. Boardman and Hart (1967) used proximal interphalangeal joint circumference which is at least objective, but may not be responsive to anti-inflammatory therapy, for example in patients with long-standing or 'burnt-out' disease.

Dick, Neufeld, Prentice, Woodburn, Whaley, Nuki, and Buchanan (1970) found that external count rates over single inflamed joints were greater than those over normal joints. They used technetium 99 (^{99}Tc), an isotope with a half-life of 6 hours, and showed reduction in counts after treatment with anti-inflammatory drugs. In a previous study, Huskisson, Berry, Browett, and Balme (1973) showed, no relationship between technetium count over a single joint and any other measurement, arguing that reduction in count rate over a single joint could not be equated with anti-inflammatory effect. These authors also used an index based on counts over both wrists and knees, and in a small study there was a significant correlation with articular index.

Though highly protein bound, ^{99}Tc is presumably distributed to some extent in the extravascular extracellular space. Huskisson and others (1973) showed, by simultaneous counting of a blood sample and of soft tissues over the forearm, that ^{99}Tc tended to remain more within the vascular compartment in patients with rheumatoid arthritis than in normals. Since most authors have suggested that ^{99}Tc measures 'vascularity', an isotope which remains entirely within the circulation might be more useful for this purpose. In this study, Indium 113 (^{113}In), a gamma emitter with a half-life of 99.5 minutes, was used. It is believed that it remains almost entirely within the circulation (Stern, Goodwin, Scheffel, Wagner, and Kramer, 1967). The ^{113}In and ^{99}Tc indices have been compared and their responsiveness to anti-inflammatory therapy assessed.

Methods

1 INJECTION OF ISOTOPE AND MEASUREMENTS

In all studies approximately 200 μCi isotope was injected intravenously. The syringe was counted before and after injection; the dose of isotope was obtained by subtracting the counts for the syringe after injection from the counts before injection. ^{99}Tc and ^{113}In indices were calculated by dividing the total counts for four joints by the dose of isotope given. In a preliminary study, peak count rates over joints were reached within 15 mins after injection of both ^{99}Tc and ^{113}In . External counts were therefore carried out 15 mins after injection of isotope. Both knees and both wrists were counted, each joint for 20 sec, with the patient supine and the counter just touching the skin. Repositioning error was 2.3% compared to a counting error of 0.8%.

2 STUDY OF NORMAL PATIENTS

^{113}In and ^{99}Tc indices were measured in seven normal volunteers.

3 STUDY OF PATIENTS WITH RA

^{113}In index was measured in twenty-nine patients, and ^{99}Tc index in thirty patients with classical or definite RA by the A.R.A. criteria (Committee of the American Rheumatism Association, 1959). The patients were taking only placebo or simple analgesics, all anti-inflammatory therapy having been stopped at least 1 week before the start of the study. Articular index was measured at the same time using the method of Ritchie, Boyle, McInnes, Jasani, Dalakos, Grievesson, and Buchanan (1968).

4 DOUBLE BLIND CROSS-OVER STUDY OF PREDNISOLONE AND PLACEBO IN PATIENTS WITH RA

Twelve patients with active rheumatoid arthritis were admitted to this study. Details of these patients are shown in Table I. In the 1st week they received either prednisolone 15 mg daily or identical placebo. At the end of the first week there was a 'wash-out' period of 1 week to allow for full excretion of the drug. During the third week, the patients crossed over to the second treatment. The ^{99}Tc and ^{113}In indices were measured at the end of the first and third weeks of the study, at the same time as conventional measures of disease severity, including joint size (Boardman and Hart, 1967), articular index (Ritchie and others, 1968), morning stiffness, and pain by means of the visual analogue scale (Berry and Huskisson, 1972). During the study, the patients were also allowed paracetamol and tablets returned were counted. Patients were asked at the end of the study which treatment period they preferred.

Table I *Details of patients studied after one week of therapy with paracetamol only*

Case no.	Age (yrs)	Sex	Duration of disease (yrs)	Articular index*
1	64	M	23	20
2	62	M	5	45
3	74	M	9	14
4	64	M	16	8
5	69	M	2	20
6	35	M	1	27
7	58	F	3	10
8	69	F	16	30
9	45	F	3	36
10	62	F	3	14
11	45	F	16	36
12	50	F	6	24

* Ritchie and others (1968).

Results

Fig. 1 shows the ⁹⁹Tc indices obtained from seven normal controls and twenty-nine patients with rheumatoid arthritis. There was a significant difference between the two groups studied ($t = 2.6$; $P < 0.02$).

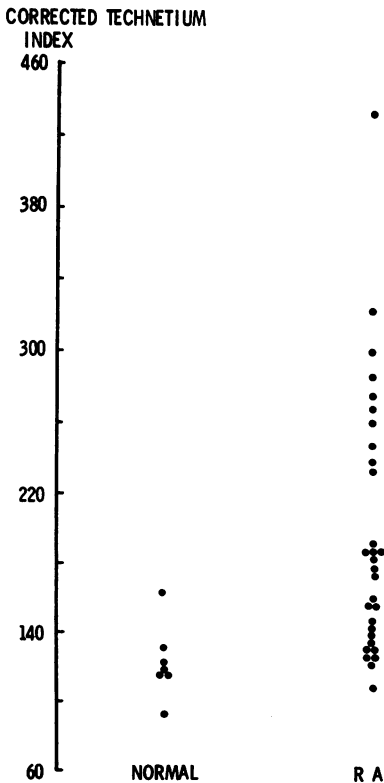


FIG. 1 *Corrected ⁹⁹Tc index in patients with RA and normal controls*

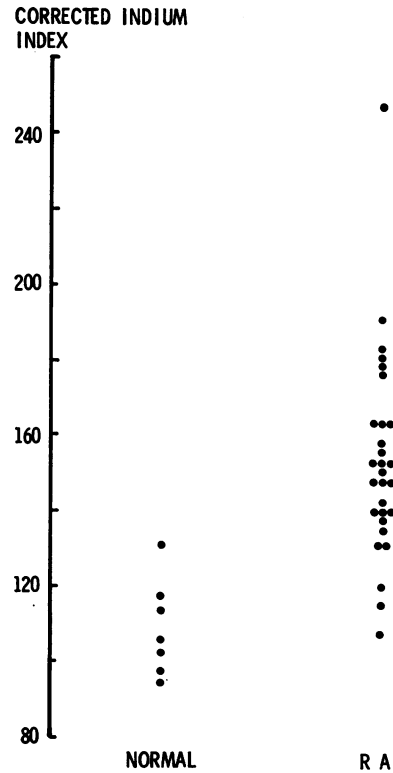


FIG. 2 *Corrected ¹¹³In index in patients with RA and normal controls*

Fig. 2 shows the ¹¹³In indices obtained from seven normal controls and thirty patients with RA. There was a highly significant difference between the two groups studied ($t = 4.1$; $P < 0.01$).

A highly significant correlation was found between articular index and ⁹⁹Tc index ($r = 0.6$; $t = 4.0$; $P < 0.01$). No such correlation was found between articular index and ¹¹³In index ($r = -0.15$; $t = 0.8$; $P < 0.1$).

Table II shows changes in pain, duration of morning stiffness, articular index, paracetamol consumption, joint size, and the two isotope indices at the end of the placebo and prednisolone weeks. There was a highly significant reduction in pain and joint size and a significant reduction in articular index on prednisolone. Changes in paracetamol consumption, duration of morning stiffness, ⁹⁹Tc index, and ¹¹³In index were not statistically significant. Ten patients preferred prednisolone, one preferred placebo, and one had no preference, a significant difference ($P < 0.02$).

Discussion

Oka, Rekonen, and Ruotsi (1971) showed a correlation between articular index and ⁹⁹Tc index; we

Table II Mean measurements made after one week of treatment with either 15 mg prednisolone daily or identical placebo

	Prednisolone	Placebo	t	P
Pain	6.42	11.83	4.091	<0.01
Duration of morning stiffness	27.91	39.58	0.695	>0.1
Articular index	13	23.67	2.67	<0.05
Joint size	579.67	595.58	5.655	<0.01
Paracetamol consumption	17.58	31.08	1.795	>0.1
Tc Index	23,075	25,113	1.026	>0.1
In index	7,088	6,683	0.3322	>0.1

were again able to confirm this observation. Thus, ^{99}Tc index may be a useful measure of disease severity. Such a correlation was not found between articular index and ^{113}In index, even though ^{113}In appeared to have theoretical advantages as a measure of vascularity.

Neither isotope index was responsive to steroid therapy. It appears from these observations that joint scanning using these two isotopes has little value in the assessment of an anti-inflammatory compound, being less sensitive than conventional methods.

It was of interest that ^{99}Tc index proved to be a better index of inflammation than ^{113}In index. ^{99}Tc appears to reflect not only vascularity but other

features, possibly related to its distribution in the extravascular space.

Summary

Technetium and indium indices are higher in RA than in normals. There is a significant correlation between articular index and technetium index but not indium index. Neither technetium nor indium indices were responsive to treatment with prednisolone. These indices did not therefore represent an advantage over conventional methods.

We would like to thank Dr. H. W. Balme for permission to study patients under his care.

References

- BERRY, H., AND HUSKISSON, E. C. (1972) *Clin. Trials J.*, **9**, 13 (Treatment of rheumatoid arthritis: a trial of meprothixol)
- BOARDMAN, P. L., AND HART, F. D. (1967) *Brit. med. J.*, **4**, 264 (Clinical measurement of the anti-inflammatory effects of salicylates in rheumatoid arthritis)
- COMMITTEE OF THE AMERICAN RHEUMATISM ASSOCIATION (1959) *Ann. rheum. Dis.*, **18**, 49 (Diagnostic criteria for rheumatoid arthritis, 1958 revision)
- DICK, W. C., NEUFELD, R. R., PRENTICE, A. G., WOODBURN, A., WHALEY, K., NUKI, G., AND BUCHANAN, W. W. (1970) *Ibid.*, **29**, 135 (Measurement of joint inflammation: a radio-isotopic method)
- HART, F. D., AND HUSKISSON, E. C. (1972) *Lancet*, **1**, 28 (Measurement in rheumatoid arthritis)
- HUSKISSON, E. C., BERRY, H., BROWETT, J. P., AND BALME, H. W. (1973) *Ann. rheum. Dis.*, **32**, 99 (Measurement of inflammation. 2. Comparison of technetium clearance and thermography with standard methods in a clinical trial)
- OKA, M., REKONEN, A., AND RUOTSI, A. (1971) *Acta rheum. scand.*, **17**, 27 (Tc-99m in the study of systemic inflammatory activity in rheumatoid arthritis)
- RITCHIE, D. M., BOYLE, J. A., MCINNES, J. M., JASANI, M. K., DALAKOS, T. G., GRIEVESON, P., AND BUCHANAN, W. W. (1968) *Quart. J. Med.*, **37**, 393 (Clinical studies with an articular index for the assessment of joint tenderness in patients with rheumatoid arthritis)
- STERN, H. S., GOODWIN, D. A., SCHEFFEL, U., WAGNER, H. N., AND KRAMER, H. H. (1967) *Nucleonics*, **25**, 62 (In ^{113}m for blood-pool and brain scanning)