

Lymphatic clearance rates in rheumatoid arthritis

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In rheumatoid arthritis recurrent oedema of the lower limbs frequently occurs. In some subjects this may be due to an inflammatory exudate around an acutely involved joint, but, in many, there is no clearly defined cause. In a previous study, a generalized increase in capillary filtration was demonstrated in rheumatoid arthritis with greater changes in those subjects that develop oedema (Jayson and Barks, 1971). The present investigation has been performed in order to determine whether there is any abnormality in lymphatic clearance from the subcutaneous tissues. The disappearance rates of isotopically-labelled iodinated albumin has been established as a standardized technique for this purpose (Hollander, Reilly, and Burrows, 1961; Cavill and Jacobs, 1971) and the half-life of subcutaneously injected ¹²⁵I albumin has been used in the present study.

Subjects studied

The lymphatic clearance rates were measured in 22 control subjects and 20 patients with definite or classical rheumatoid arthritis (Ropes, Bennett, Cobb, Jacox, and Jessar, 1959). Eleven of the rheumatoid patients had no history of oedema and the remainder had a history of recurrent bilateral pitting oedema of the lower limbs without any cardiac, renal, or other identifiable cause.

Experimental method

25 μl. ¹²⁵I labelled albumin (Radiochemical Centre, Amersham), containing not more than 1.0 μCi ¹²⁵I, was injected intradermally into the volar aspect of the forearm. The ¹²⁵I remaining at the site of injection was counted by surface monitoring over a 2-day period. Constant counting geometry was achieved by placing a perspex jig between two marks on the skin surface. This jig was then located in the collimator of a 2 × 2 in. thallium activated sodium iodide crystal. Activity was measured for two successive periods of 100 seconds on a scaler/timer (Panax). The count rate was of the order of 1,000,000 counts per 100 sec., giving a coefficient of variation of less than 0.5 per cent. The background count was approximately 1 per cent. of the arm count rate. All results were corrected for the physical decay of the ¹²⁵I and for fluctuations in the sensitivity of the apparatus by the simultaneous counting of an ¹²⁵I standard source.

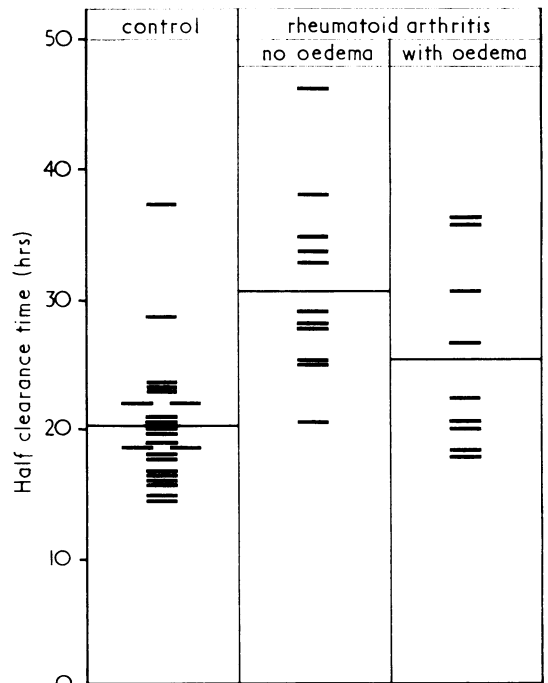
The ¹²⁵I remaining at the site of injection decreased as an exponential function of time. The fractional rate of clearance (*k*) was calculated by regression analysis of the

logarithm (*ln*) of the activity with time. A half clearance time (*t*_½) in hours was calculated from the relationship

$$t_{\frac{1}{2}} = \frac{\ln 2}{k} \text{ hrs}$$

Results (Figure)

The mean (±SD) half-clearance time in the controls was 20.4 ± 5.1 hrs. There was no difference in the mean values between male and female controls and no correlation with age. In the patients with rheumatoid arthritis, the mean (±SD) half-clearance time was 28.3 ± 7.5 hrs, and this was significantly different (*t* = 4.03, *P* < 0.001) from that of the



FIGURE

*T*_½ values in control subjects (C), and in patients with rheumatoid arthritis without oedema (RA - O) and with oedema (RA + O).

C v. All R.A. *t* = 4.03 *P* < 0.001

C v. R.A. - O *t* = 4.88 *P* < 0.001

C v. R.A. + O *t* = 2.10 *P* < 0.05

R.A. + O v. R.A. - O *t* = 1.77 *P* > 0.05

control series. There was no significant difference in mean half-clearance times between the rheumatoid patients without oedema (30.9 ± 7.1 hrs) and those with oedema (25.2 ± 7.2 hrs). Clearance rates were the same for both male and female patients.

Discussion

Recurrent limb oedema is a common finding in patients with rheumatoid arthritis. In some of these patients the cause of the oedema is easily seen, but in many there is no consistent abnormality.

Lymphadenopathy in rheumatoid arthritis is well recognized, and has been postulated as the cause of rheumatoid oedema (Kalliomäki and Vastamäki, 1968). On lymphangiography, Robertson, Hart, White, Nuki and Boardman (1968) confirmed that lymphadenopathy was common, but they found no evidence of lymphangiectasia or lymphatic blockage. The present study indicates that there is a delay in lymphatic clearance rates in rheumatoid arthritis. This would be consistent with slowed passage through the enlarged lymphatic glands. It is perhaps surprising that the lymphatic clearance rate was faster in those patients with oedema than in those without, although the difference was not of statistical significance. Many of the oedema patients had $T\frac{1}{2}$ values similar to those of the controls. Clearly, lymphatic obstruction alone will not account for oedema in rheumatoid arthritis.

Conflicting evidence is available regarding the protein content of oedema fluid in rheumatoid arthritis. Park and Swinburne (1964) and Swinburne (1964) found this to be less than 1 g. per cent. with a relative increase in the concentration of small protein molecules and a decrease in that of the larger molecules. These results suggested that the capillary endothelium has a normal selective permeability in rheumatoid arthritis and that the

fluid is not of inflammatory or allergic origin but is due to some alteration in venous function. On the other hand, Gandy, Ansell, and Bywaters (1965) and Consden and Smith (1965) found this protein concentration to be relatively higher especially in active disease. In active arthritis, the differential protein pattern matched that of the serum more closely than in inactive disease.

Jayson and Barks (1971) found a generalized increase in the coefficient of capillary filtration in rheumatoid arthritis and thought that this indicated a generalized capillary defect. The coefficient of capillary filtration was even greater in the patients who developed oedema. When there is excess production of tissue fluid, a relative insufficiency of interstitial fluid evacuation can lead to the appearance of oedema (Jue, Entrup, Hughes, Narang, and Wégria, 1970). The more rapid rate of tissue fluid formation in patients who develop oedema leads to an increased rate of lymphatic clearance, but this is insufficient to cope with the problem.

Summary

Measurements of the clearance rate of intradermal ^{125}I albumin have been performed as an index of lymphatic drainage in control subjects and in rheumatoid patients with and without oedema. There was a significant slowing in clearance in the rheumatoid patients. This change was more marked in those without than in those with oedema. The results suggest that there is some obstruction to lymphatic clearance in patients with rheumatoid arthritis, but that this is not primarily responsible for the appearance of oedema.

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