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Significance of the hydrogen ion concentration in synovial fluid in rheumatoid arthritis

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ABSTRACT. *The hydrogen ion (H^+) concentration and pCO_2 were measured in the synovial fluid (SF) from the knee joints of 130 patients with arthritis by an acid-base analyser (ABL_2 Acid-Base Laboratory), using a simple technique which prevented contact with air.*

H^+ concentration was significantly higher in SF from 60 RA patients (mean 64.4 n mol/l; range 38-142 n mol/l) compared with patients with OA (mean 44 n mol/l; range 29-56 n mol/l), and 40 with other arthritides (mean 52 n mol/l). The H^+ concentration in the SF showed a significant association with other variables of local inflammation-platelet, total leucocyte and polymorph counts, 5-nucleotidase, acid phosphatase and IgA levels in the SF and the clinical knee score, but not with the volume of the effusion. A similar relationship between these variables of inflammatory activity and SF pCO_2 was also established. A higher SF H^+ concentration was also found in systemically active disease, but no difference in SF pH between seropositive and seronegative patients. Whilst the pH of SF approximated to that of the blood in OA, it was significantly lower in the SF in RA.

SF pH is a useful marker of local inflammatory activity, and its measurement is simple, reliable and rapid. It is relevant because changes in pH influence many of the processes involved in inflammation and the pH difference between SF and blood influences the transfer of drugs into the joint.

Key words: hydrogen ion (H^+) concentration, pH, synovial fluid, rheumatoid arthritis.

Introduction

Analysis of synovial fluid (SF) adds to the clinical assessment of a joint particularly in relation to local disease activity. Intrasynovial events should give more relevant information about a particular joint than general measurements made on the blood such as the erythrocyte sedimentation rate (ESR). The degree of inflammatory activity in a joint has been assessed by total leucocyte, polymorph and platelet counts in SF (1, 2), and by the levels of SF lysosomal enzymes, 5-nucleotidase and other cytoplasmic enzymes (3, 5). Since tissue acidosis is a consequence of inflammation (6), a change in SF pH might offer a simple alternative way of recognizing an inflammatory arthropathy and of grading its severity.

The aim of this study was to investigate the relationship of the SF pH with other variables of local and general disease activity to evaluate whether it offers a realistic alternative for assessing inflammatory activity in a joint and secondly to determine its relevance in SF.

Patients

Sixty patients with classical or definite rheumatoid arthritis (RA) (8), who had knee effusions were studied and compared with 30 patients with osteoarthrosis (OA) and 40 patients with other arthropathies. The diagnoses in the latter included gout, Reiter's disease 5 (7 joints) Crohn's

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disease 4, psoriasis 7 (11 joints), Whipple's disease 2 (6 joints), septic arthritis 1, chondrocalcinosis 1, inflammatory monoarthritis 6 and ankylosing spondylitis 3. All patients were taking at least one non-steroidal anti-inflammatory drug, and 32% of the rheumatoid patients were taking a second line agent - sulphazalazine. All attended the morning research clinic (9.30-11.30 am).

A detailed history and full clinical examination was carried out with appropriate radiological examination. The knee with the effusion was examined and the knee score calculated based on a semi-quantitative assessment of pain, stiffness, swelling, tenderness, heat and redness of the joint before aspiration of synovial fluid (7). In addition to the knee score, the total articular index (TAI) was calculated. This was similarly based on a semi-quantitative assessment of pain on movement, stiffness, swelling, tenderness, heat and redness of the peripheral joints. Each clinical parameter was given a score 0-3 and the total articular index was calculated by totalling these scores for each joint.

Methods

Aspiration of synovial fluid

A small amount of local anaesthetic (2% procaine) was injected into the skin at the medial aspect of the knee joint with care not to penetrate beyond the subcutaneous tissues. Fluid was then aspirated using a No 1 needle by free flow into a 2 ml sterile syringe via a 3-way tap with caution to avoid contact with air. The air bubble filling the dead space was found not to influence the result if removed immediately following aspiration. The tap was closed after aspiration to seal the syringe. This was then removed with the tap attached, leaving the needle in the joint so that aspiration of the synovial fluid for other tests could be completed. The acid base analysis was performed within half an hour of aspiration. Control studies were carried out and measurements of the H^+ concentration were made: 1) immediately after aspiration; 2) after half an hour, 4 hours and 12 hours stored at either room temperature or 4°C. There was no significant difference in the H^+ concentration of the specimens analysed up to 4 hours after aspiration.

Analysis of synovial fluid

Acid base analysis was carried out using H^+ and CO_2 electrodes in an acid base analyser (ABL_2 Acid Base Laboratory). On the remainder of the fluid, total and differential white cell counts and platelet counts were carried out. Acute phase proteins - C-reactive protein and orosomucoids were estimated by radial immunodiffusion. Immunoglobulin IgG, IgM, IgA levels were determined by Fahey's method (9). Acid phosphatase activity was measured on the whole and supernatant fractions of SF by Roy's method (10) and 5-nucleotidase by Persijn's method (11).

Analysis of blood

Acid base analysis was carried out on arterialized capillary blood obtained from the thumb at the same time. A venous sample was obtained for full blood count including ESR (Westergren), biochemical profile (Technicon SMA 12/60), acute phase proteins, immunoglobulin levels and Rose-Waaler titre.

Statistical methods

Pearson's correlation coefficients (r values) were calculated and the significance between means obtained by applying the Student 't' test.

Results

The H^+ concentration of synovial fluid showed large and highly significant differences between the 3 groups of patients (Fig. 1). The mean H^+ concentration for the rheumatoids was 64.42 n mol/l (range 38-142 n mol/l), ie. pH mean was 7.19 (pH range 7.41-6.85); the mean H^+ concentration for the OA group was 44 n mol/l (range 29-56 n mol/l), ie. pH was 7.38 (pH range 7.54-7.25); and the mean H^+ concentration for the miscellaneous group was 52 n mol/l (range 39-86 n mol/l) ie. pH mean was 7.28 (pH range 7.41-7.06).

There was no significant difference between the blood pH in RA and OA patients (Table I). No rela-

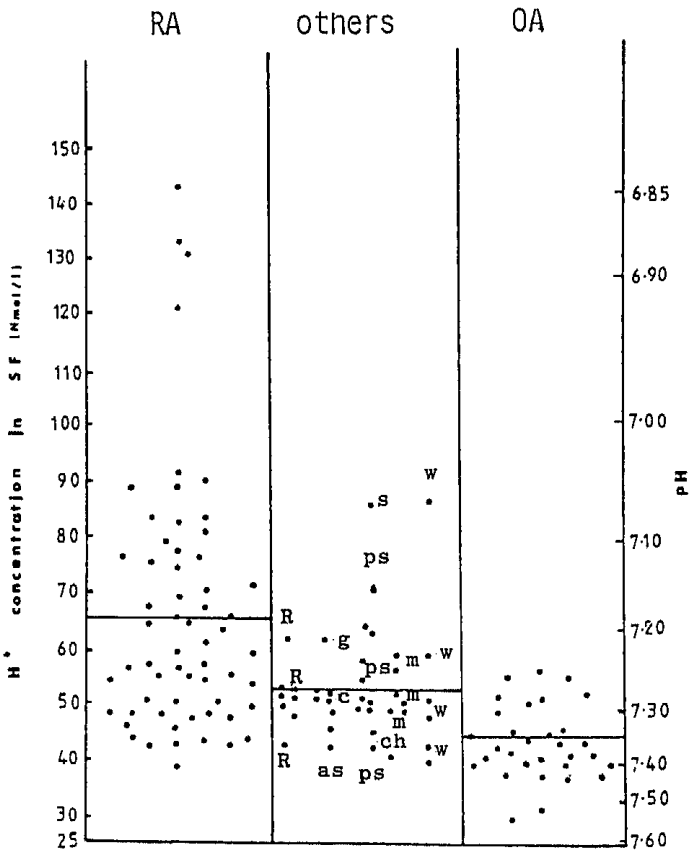

Fig. 1 - Scattergram of the hydrogen ion concentration in the synovial fluid of patients with rheumatoid arthritis (RA), osteoarthrosis (OA) and other forms of arthritis (others).
as ankylosing spondylitis; c Crohn's disease; g gout; r Reiter's syndrome; w Whipple's disease; m inflammatory monoarthritis; ps psoriatic arthropathy; ch chondromalacia; s septic.

tionship existed between the blood pH and SF pH in either condition, although there was a highly significant difference between the pH of the blood and SF in rheumatoids but not in OA (Table I).

Table I. Comparison of the H+ concentration in the blood and synovial fluid of patients with RA and OA.

	RA Mean ± SD	OA Mean ± SD	p
Blood	37.47 ± 2.29	40.0 ± 2.16	NS
Synovial fuid	64.62 ± 21.25	44.0 ± 5.8	< 0.001
Difference p	< 0.001	< 0.05	

The rheumatoid patients were divided into those with a 'high' H^+ concentration (> 55) and those with a 'low' H^+ concentration (< 55) in SF. There was no difference in age, sex, duration of the disease or volume of the effusion, between 'high' and 'low' H^+ groups. High H^+ concentration occurred in patients with locally active disease shown by the high clinical knee scores and the factors reflecting local inflammation in the SF-total leucocyte, polymorph and platelet counts, acid phosphatase and 5-nucleotidase activity, glucose, IgA and orosomucoid levels (Table II). Furthermore the SF H^+ concentration significantly correlated with these variables of local disease activity. The strongest correlations were seen with platelet, total leucocyte and polymorph counts and 5-nucleotidase activity. Acid phosphatase, IgA and IgM also correlated (Table III). In addition there was an association with systemic disease activity as shown by significant correlations with the ESR and C-reactive protein levels in the blood. There was no correlation however with the Rose-Waaler titre.

pCO_2 showed a similar positive correlation to the hydrogen ion concentration with local and systemic disease activity (Table IV).

Discussion

Early studies of SF from normal joints showed that the pH was between 7.4 and 8.4 (12) but these studies had the disadvantage of being on post-mortem specimens and joints of cattle. Subsequently *in vivo* studies demonstrated that pH decreased with age, but was higher in normal SF than in injured or OA joints (13). In the SF from a small number of normal and RA patients in whom a hydrogen electrode was inserted into the joint space, the pH of normal SF did not significantly differ from the blood pH, but in RA, the SF pH dropped while the blood pH did not (14). Since then further studies have shown that SF of RA and other proliferative synovitides has a low pH and a high pCO_2 and lactate concentration compared with control patients (15, 17).

The present study showed that the pH of the SF in OA approximated to that of the blood, whereas in RA and other forms of inflammatory arthritis the pH was much lower in SF. Furthermore the SF pH became more acidic as the intensity of the inflammatory reaction increased. All SF samples were aspirated during the morning clinic (9.30-11.30 am) so that changes in pH due to diurnal variation were minimised (18). The findings in this study were in contrast to those of Falchuk *et al.* in 1970 (15) and Goetzl *et al.* in 1974 (17) in which a low pH and high pCO_2 were not associated with severity of the joint disease or the total WCC in the SF. In the present study the pH of the SF correlated with selected variables of inflammation in SF-acid phosphatase and 5-NT activity, total leucocyte, polymorph and platelet counts, glucose and IgA levels and the clinical index - the knee score. pCO_2 in the SF showed a similar relationship to the local inflammation of the joint as did the H^+ concentration. The strength of the correlation between the pH and the total WCC in SF, although significant, was not sufficiently strong to suggest that the cells in SF accounted for all or even most of the fall in intra-articular pH. Thus the pH may be a better reflection of events within the synovial membrane itself than is the WCC in SF. This view is supported by the work of Falchuk *et al.* (15) in which the pH, pO_2, pCO_2 and lactate concentration correlated with proliferation of synovial cells, focal necrosis and focal obliterative microangiopathy in the SM. There was not a strong association between SF pH and acute phase proteins measured in this study, suggesting that changes in H^+ concentration do not directly influence SM permeability. However there was a significant correlation between SF pH and enzyme (5-NT and acid phosphatase) activity and Ig (M and A) levels in SF, suggesting that the release of enzymes and the synthesis of immunoglobulins locally in the SM are influenced by changes in the H^+ concentration.

Acidosis is one of the consequences of inflammation (19), being localised to the inflammatory site and is due to accumulation of lactic acid. In RA there is an inverse relationship between SF lactate and glucose (15). Glucose is metabolised to pyruvic acid and then to lactic acid under anaerobic conditions. Low pH and high pCO_2 and lactate levels are associated with low pO_2 in SF (16, 20).

Table II. Comparison of the local and systemic characteristics of patients with a 'high' and 'low' SF hydrogen ion concentration.

PARAMETERS	'High' H+ in SF Mean ± SD	'Low' H+ in SF Mean ± SD	t	°F	p
A SYNOVIAL FLUID & JOINT					
White cell count (per cu mm)	13612 ± 7264	5712 ± 3705	4.99	43	< 0.001
Polymorph count (per cu mm)	10331 ± 6095	5068 ± 4411	3.412	40	< 0.01
Lymphocyte count (per cu mm)	2218 ± 1743	1219 ± 728	2.611	40	< 0.02
Acid phosphatase					
— whole (iu/1)	2.98 ± 1.87	1.37 ± .76	3.045	28	< 0.01
— supernatant (iu/1)	0.82 ± .66	0.37 ± .29	2.641	36	< 0.02
5-nucleotidase (iu/1)	71.63 ± 33.49	27.17 ± 14.90	4.314	24	< 0.001
Glucose (m mol/1)	3.11 ± 1.1	4.19 ± 0.74	—5.70	26	< 0.001
IgG (g/1)	7.69 ± 3.33	9.07 ± 8.35	— .498	40	NS
IgM (g/1)	.95 ± .34	0.72 ± .30	2.123	40	< 0.05
IgA (g/1)	1.84 ± .87	1.07 ± 0.57	3.306	40	< .01
C-reactive protein (mg/1)	33.9 ± 23.2	22.5 ± 16.4	1.696	49	NS
Orosomucoids (g/1)	1.51 ± .40	1.2 ± 0.51	3.802	35	< .001
Knee score	7.4 ± 1.8	5.8 ± 2.2	2.847	57	< .01
B SYSTEMIC					
Total articular index	26.5 ± 11.0	23.3 ± 11.5	0.752	36	NS
ESR (mm/h)	67 ± 36.2	43.7 ± 21.7	2.800	51	< 0.01
C-reactive protein (mg/1)	78.3 ± 58.6	50.1 ± 43.9	1.904	51	NS
Orosomucoids (g/1)	1.82 ± .43	1.71 ± 0.67	1.710	46	NS

Table III. Correlation of SF H^+ with local and systemic indices of activity.

PARAMETERS	n	r	p
A SYNOVIAL FLUID AND JOINT			
Total white cell count (/cu mm)	54	0.515	< 0.001
Polymorph count (/cu mm)	49	0.451	< 0.001
Lymphocyte count (/cu mm)	49	0.195	NS
Synovial cells (/cu mm)	49	0.132	NS
5-nucleotidase (iu/1)	25	0.566	< 0.01
Acid phosphatase			
Whole (iu/1)	27	0.442	< 0.02
Supernatant (iu/1)	40	0.426	< 0.01
Glucose (m mol/1)	32	0.425	< 0.01
Platelets (/ cu mm)	20	0.691	< 0.001
IgG (g/1)	40	—0.098	NS
IgA (g/1)	40	0.461	< 0.01
IgM (g/1)	40	0.306	< 0.05
C-reactive protein (mg/100 ml)	49	0.238	NS
Orosomucoids (g/1)	34	0.250	NS
Amount of fluid (ml)	33	—0.178	NS
Knee score	56	0.386	< 0.01
B SYSTEMIC			
Total articular index	37	0.213	NS
ESR (mm/h)	51	0.553	< 0.001
C-reactive protein (mg/100 ml)	51	0.357	< 0.01
Orosomucoids (g/1)	51	0.019	NS

n = number of patients studied
r = correlation coefficient
p = statistical significance

Table IV. Correlation of SF PCO_2 with local and systemic indices of activity.

PARAMETERS	n	r	p
A SYNOVIAL FLUID AND JOINT			
Knee score	55	0.336	< 0.02
Total white cell count (/cu mm)	53	0.564	< 0.001
Polymorph count (/cu mm)	31	0.475	< 0.01
5-nucleotidase (iu/1)	25	0.541	< 0.01
Acid phosphatase			
whole	29	0.633	< 0.01
supernatant	36	0.409	< 0.02
Glucose (m mol/1)	29	—0.401	< 0.05
B BLOOD			
ESR (mm/h)	51	0.588	< 0.001
C-reactive protein (mg/1)	51	0.487	< 0.001

Although regional blood flow is increased in RA it is insufficient to meet the increase in demands imposed by disease. Rheumatoid villi utilise more oxygen and glucose (21) and so produce more lactic acid and a lower pH than non-RA synovial membrane. This could explain the fall in pO2 found in the previous studies and the increase in pCO_2 and fall in pH with increased inflammatory activity found in this study. It is also consistent with the pH of the juxta-synovial region being lower than in the

general joint cavity (14). Diffusion of lactic acid into the general joint cavity from these synovial acid producing areas would result in subsequent buffering. The results of this study are consistent with this, in that there was no correlation between the SF pH and volume of the effusion. Lactate and H^+ concentrations correlate with the cellular picture during an inflammatory reaction (19). Polymorphs are unable to survive below pH 7.0 and this explains why large numbers of polymorphs in the SF in this study were dead and disintegrating when the SF pH fell to 6.89 and 6.85.

Lactate concentration in SF has been used to differentiate septic from non-septic arthritis (22), but its measurement is not as simple as the pH. Nevertheless it has been found to be a useful marker of bacterial infection (33). In this study one patient with septic arthritis had a low SF pH of 7.06, but several RA patients with active joints without infection had a lower pH in the SF - 7.05, 7.05, 7.04, 6.92, 6.89, 6.89 and 6.85. A low pH therefore appeared to be a marker of inflammation and not sepsis. Lactate concentrations and pH have also been measured in cerebro-spinal fluid (CSF) and found to be useful in distinguishing bacterial from aseptic meningitis (24, 25, 26). In the same way that the pH of CSF approximates to the surface pH of the brain (27), the pH of the SF may approximate to that of the synovial membrane.

Changes in the local pH of the joint influence many of the processes involved in inflammation. When the pH of SF is low, fibrin is deposited leading to the persistence of synovitis (28). A low pH also activates the lysosomal system by labilising the lysosomal membranes increasing the activity of acid hydrolases in synovial membrane and synovial fluid (29). It also contributes to chemotaxis (30) and possibly to enhancement of proteolysis and formation of neo-antigenic sites in proteins (31, 32). A low pH enhances the generation of toxic oxygen radicals (33) which degrade hyaluronic acid resulting in decreased viscosity of SF. Although toxic oxygen radicals are generally suspected of contributing to joint lesions in RA, their formation may be suboptimal in severe hypoxia, possibly explaining the increased incidence of infections in non-specific synovitides (34). It has also been suggested that acidosis may stimulate mitogens and antigens to activate lymphoid tissues (35). Inflammatory cells and fibroblasts in the joint have different degrees of sensitivity to acidosis which may alter their presence and funtion in synovitis.

This study has shown that the pH in SF correlates with other variables of inflammation in SF. Its measurement is simple, reliable and rapid. We propose that it is a valuable index of local inflammation in the joint and furthermore changes in the concentration of hydrogen ions and pCO_2 might contribute to the persistance of synovitis and development of erosions.

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