Original Article

Application of contrast-enhanced ultrasonography and ultrasonography scores in rheumatoid arthritis

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Abstract: Objective: To investigate diagnostic value of ultrasonography scores (US) and contrast-enhanced ultrasonography (CEUS) in evaluating rheumatoid arthritis (RA) activity. Methods: 39 patients with RA were included and the metacarpophalangeal, proximal interphalangeal, wrist, elbow and knee joints of them were examined by high frequency ultrasound. The severe joints and the related indexes (synovial thickness, synovial blood flow, joint effusion and bone erosion) were exposed. Then scores (0~3) were obtained and the sum was calculated. For 12 patients of the 39, 2.4 ml SonoVue was intravenously injected with observation of synovial enhancing. ROIs time-intensity curve (TIC) was obtained and the parameters including area under curve (AUC), peak intensity (PI) and time to peak (TTP) were analyzed. For 39 patients, the relationships among each parameters, ultrasonography scores, DAS28 scores and biochemical examinations (ESR, CRP, RF, anti-CCP) were analyzed. Results: The US were significantly correlated with DAS28 Scores (r=0.823, P<0.01). The correlation between US and CRP was better than that between DAS28 scores and CRP (rUS =0.692, rDAS28=0.526, P<0.01). The synovial thickness in US were correlated with DAS28 Scores and biochemical examinations (ESR, CRP) (rDAS28=0.852, rESR=0.779, rCRP=0.587, P<0.01). The AUC and PI in CEUS were significantly correlated with US (rAUC=0.832, rPI=0.809, P<0.01). The correlations among AUC, PI and ESR were better than that between US and ESR (rAUC=0.907, rPI=0.851, rUS=0.836, P<0.01). The correlations among AUC, PI and CRP were better than that between US and CRP (rAUC=0.855, rPI=0.854, rUS=0.692, P<0.01). Conclusions: US was almost identical with DAS28 Scores and biochemical examinations (ESR, CRP) in diagnosis of RA activity, while CEUS was almost identical with DAS28 Scores and biochemical examinations (ESR, CRP). In diagnosis of RA, US may be better than DAS28 Scores, while CEUS better than US. Both of them were useful for evaluation of RA activity.

Keywords: Rheumatoid arthritis, Contrast-enhanced ultrasonography, ultrasonography scores, Joint, synovial

Introduction

RA is a kind of chronic autoimmune disease, whose incidence is 0.5%~1% [1]. RA, with high disability rate, symmetry, persistence and invasiveness, appears mainly around joints, including shoulders, wrists, fingers, knees and so on [2]. RA induces the inflammation changes of synovial membrane firstly, then invades cartilage and bones, finally leads to the broken of joints, with the adjacent tissue injury of tendons, sheath and the bursal. Previous research [3] found that there was irreversible arthritis in the first year, then the narrowing of the joint space and bone substance damage happened in the following year. The average life of the RA patients decreased 5 years, even to 10 years. Although RA appears in any ages, the main onset age is between 40 and 50, increasing as the aging. Some studies [4] showed that early intervention treatment improved RA prognosis and changed the development. Therefore, how to evaluate the activity degree of the patients draws more and more attentions.

Clinically, high frequency ultrasound develops rapidly, with 91% diagnostic specificity [5]. High frequency ultrasound resolves tissue fine structure, which is suitable to observe the lesions of joints and soft tissue. Color doppler ultrasound shows the blood flow signal in proliferative synovial membrane, which is more suitable for the dynamic observation of proliferative vessels in synovial membrane and hemodynamic changes. As the development of contrast agent,
Table 1. Ultrasonography scores of the indexes in RA patients

<table>
<thead>
<tr>
<th>Scores</th>
<th>Synovial thickness</th>
<th>Joint effusion</th>
<th>Bone erosion</th>
<th>CDFI or PDUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
<td>Smooth bone surface</td>
<td>Without color doppler signal in synovial membrane</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Synovial thickened mildly; small joint synovitis were lower than the line connecting of two highest bone points; synovial thickness of large joints &gt;2 mm, &lt;5 mm</td>
<td>Little</td>
<td>Smooth bone surface but without bony defect</td>
<td>Punctate flow signals in synovial membrane</td>
</tr>
<tr>
<td>2</td>
<td>Synovial thickened moderately; small joint synovitis were higher than the line connecting of two highest bone points but not reached at the shaft; synovial thickness of large joints &gt;5 mm, &lt;9 mm</td>
<td>Moderate</td>
<td>Slight bone defect</td>
<td>More punctate or liner flow signals in synovial membrane</td>
</tr>
<tr>
<td>3</td>
<td>Synovial thickened seriously; small joint synovitis reached at the shaft; synovial thickness of large joints &gt;9 mm</td>
<td>Large</td>
<td>Bone defect and wide damage</td>
<td>Dendritic or reticular flow signals in synovial membrane</td>
</tr>
</tbody>
</table>

Inclusion criteria

According to American College of Rheumatology (ACR) in 1987, the diagnosis criteria were followed: ① morning stiffness sustained more than 1 hour each day with course of 6 weeks; ② the number of swollen joints were more than or equal to 3 with course of weeks; ③ swollen wrist, metacarpophalangeal and proximal interphalangeal sustained more than 6 weeks; ④ swollen joints with symmetry sustained more than 6 weeks; ⑤ there were subcutaneous nodules; ⑥ the x-ray on hands appeared changes (osteoporosis and narrowing joint space); ⑦ rheumatoid factors appeared positive (titer >1:20).

The patients with more than or equal to 4 mentioned above were diagnosed as RA.

Exclusion criteria

① The patients had swollen joints induced by other causes including gouty arthritis, osteoarthritis and systemic lupus erythematosus; ② the patients were with congenital articular dysplasia; ③ the patients had a history of trauma leading to swollen joints.

Materials and methods

Subjects

39 patients with RA, 10 males and 29 females, age 27 to 76 (average age 45.4 ± 4.6), hospitalized in Ultrasonography Department of Zhangzhou Municipal Hospital (Fujian Province, China). The patients were examined by color ultrasound. The onset time of the RA patients was from 6 months to 21 years, average 32 ± 4.1 months.

Instruments and methods

Instruments

By color doppler imaging (Philips iU22, Esaote, Italy), we detected the patients’ body with 5~12 MHz of transducer frequency and selected the musculoskeletal condition of low-velocity blood flow.
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Methods

Calculating DAS28 scores: ① the number of tenderness joints (t28): examined metacarpophalangeal, proximal interphalangeal, wrist, elbow and knee joints, totally 28 joints, and calculated the t28 with joint tenderness or passive motion; ② the number of swollen joints (sw28): examined the 28 joints mentioned above and calculated sw28; ③ according to DAS28=[0.56 X sqrt(t28) + 0.28 X sqrt(sw28) + 0.70 X Ln(ESR)] X 1.08 + 0.16 by ESR, calculated DAS28. DAS28>5.1 meant RA activity; DAS28<3.2 meant low RA activity; DAS28<2.6 meant RA remission [10].

Calculating ultrasonography scores: According to Hartung [11] et al and Szkudlarek [12] et al, observed the lesions of metacarpophalangeal, proximal interphalangeal, wrist, elbow and knee joints in RA patients by high frequency ultrasound, including synovial thickness, synovial blood flow, joint effusion and bone erosion. Due to RA severity, scored the indexes mentioned above (0~3) (Table 1). Selected the highest scores of metacarpophalangeal and proximal interphalangeal as the represents and summed the both sides.

CEUS

The patients were in the supine or sitting position, the severe joints were exposed and the related indexes (synovial thickness, synovial blood flow, joint effusion and bone erosion) were recorded. Ultrasound contrast agent was SonoVue and obtained from Bracco, Italy. 5.0 mlnormal saline was mixed with the agent completely until the powder dissolved totally. CEUS: scanned under normal modal, observed and recorded the positions and boundaries of synovial thickness. Selected the clear sections and changed into CEUS modal. 2.4 ml SonoVue was injected and synovial enhancing was observed with timing (Figure 1). Observing time was more than 2 min and the images were obtained.

All the images were analyzed by QLAB imaging analysis software. TIC (Figure 2) was obtained and quantified the AUC, PI and TTP.

Figure 1. There was clear flow perfusion of synovial proliferation by CEUS. The left arrow indicated that SonoVue was injected into the synovium with joint proliferation by CEUS. The right one indicated the synovial proliferation by high frequency ultrasound.

Figure 2. The rising branch was steep but the declining branch was flat in TIC. The red region in the upper indicated ROI of synovium, while the red region in the lower indicated TIC.
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The average score of bone erosion was 0.77 ± 1.14 with the range of 0~3 (Figure 5). The average score of CDFI or PDUS was 5.08 ± 1.84 with the range of 0~20 (Figure 6). The average US was 12.79 ± 5.10 with the range of 3~25.

**CEUS**

Average AUC was 830.08 ± 412.80 db/s with the range of 114.49~1370.9 db/s. Average PI

**Results**

**Clinical date of the 39 patients**

**Clinical index**

DAS28 average score was 3.931 ± 1.10 with the range of 0~10.

**Biochemical examination**

The average ESR was 32.00 ± 30.05 mm/h with the range of 2~104 mm/h; average CRP was 21.01 ± 41.21 mg/L with the range of 0.168~115 mg/L; average RF was 9.19 ± 0.40 IU/ml with the range of 7.0~41.2 IU/ml; average Anti-CCP was 6.96 ± 4.38 RU/ml with the range of 0.9~39.2 RU/ml.

**US**

The average score of synovial thickness was 5.77 ± 1.99 with the range of 0~24 (Figure 3). The average score of joint effusion was 1.77 ± 1.69 with the range of 0~6 (Figure 4).

The average score of bone erosion was 0.77 ± 1.14 with the range of 0~3 (Figure 5). The average score of CDFI or PDUS was 5.08 ± 1.84 with the range of 0~20 (Figure 6). The average US was 12.79 ± 5.10 with the range of 3~25.

**Detecting serum indexes**

Peripheral blood was obtained from all the RA patients. The ESR, CRP, Anti-CCP and RF were detected.

**Statistical analysis**

All the data were input in Excel 2003 software and analyzed by SPSS 17.0 software, represented as mean ± standard deviations (M ± S).
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AUC and PI and ESR were better than between ultrasound and ESR ($r_{AUC} = 0.907$, $r_{PI} = 0.832$, $r_{ESR} = 0.587$, $P < 0.01$). The correlation among AUC, PI and CRP were better than between US and CRP ($r_{AUC} = 0.855$, $r_{PI} = 0.854$, $r_{CRP} = 0.692$, $P < 0.01$). There were not significant correlations among TTP, biochemical indexes and US ($P > 0.05$), the same to the correlations among CEUS, US, RF and Anti-CCP ($P > 0.05$).

Correlation among US, DAS28 scores and biochemical indexes

From Table 2, there was significant correlation between US and DAS28 score ($r = -0.823$, $P < 0.01$). The correlation between US and CRP was better than between DAS28 and CRP ($r_{US} = 0.692$, $r_{DAS28} = 0.526$, $P < 0.01$). There were no significant correlations among US, DAS28 score, RF and Anti-CCP ($P > 0.05$).

The correlation among every subproject in US, DAS28 and clinical indexes

From Table 4, in the subprojects of US, synovial thickness, synovial flow and joint effusion appeared correlation with DAS38, ESR and CRP ($P < 0.05$). The correlation coefficient of synovial thickness was the highest ($r_{DAS28} = 0.852$, $r_{ESR} = 0.779$, $r_{CRP} = 0.587$, $P < 0.01$). There were no significant correlations among bone erosion, DAS28 and 4 kinds of biochemical indexes ($P > 0.05$).

Side effect of CEUS

SonoVue was safe and liable, which was easy to be metabolized and without side effect or allergy. Observed the patients for 30 min after the examination. All the patients were without adverse reaction.

Figure 5. Bone erosion appeared in RA. The arrow indicated bone defect with the US of 2.

Figure 6. Blood supplying was abundant in RA patients. The arrow indicated flow signals in synovial membrane with the US of 3.
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**Table 2. Correlation analysis among CEUS parameters, US and biochemical indexes**

<table>
<thead>
<tr>
<th>Biochemical indexes and US</th>
<th>AUC</th>
<th>PI</th>
<th>TTP</th>
<th>Total score</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR</td>
<td>0.907▲▲</td>
<td>0.851▲▲</td>
<td>0.182</td>
<td>0.836▲▲</td>
</tr>
<tr>
<td>CRP</td>
<td>0.855▲▲</td>
<td>0.854▲▲</td>
<td>0.245</td>
<td>0.692▲▲</td>
</tr>
<tr>
<td>RF</td>
<td>-0.243</td>
<td>-0.243</td>
<td>-0.330</td>
<td>0.032</td>
</tr>
<tr>
<td>Anti-CCP</td>
<td>-0.0286</td>
<td>-0.476</td>
<td>-0.048</td>
<td>-0.102</td>
</tr>
<tr>
<td>Total US</td>
<td>0.832▲▲</td>
<td>0.809▲▲</td>
<td>0.074</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Note: ▲P<0.05, ▲▲P<0.01.

**Table 3. Correlation among US, DAS28 scores and clinical indexes**

<table>
<thead>
<tr>
<th>Ultrasound and clinical examination</th>
<th>DAS-28</th>
<th>ESR</th>
<th>CRP</th>
<th>RF</th>
<th>Anti-CCP</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>0.823▲▲</td>
<td>0.836▲▲</td>
<td>0.692▲▲</td>
<td>-0.110</td>
<td>-0.102</td>
</tr>
<tr>
<td>DAS28</td>
<td>1.000</td>
<td>0.963▲▲</td>
<td>0.526▲▲</td>
<td>-0.096</td>
<td>-0.226</td>
</tr>
</tbody>
</table>

Note: ▲P<0.05, ▲▲P<0.01.

**Discussions**

RA is a kind of autoimmune disease. RA appears around joints with multiple system, inflammation and symmetry. Clinically, the characteristics of RA involved joint pain, swollen joints, function decrease, sustainable lesions and repeated attack. The main pathologies included chronic synovitis, invading the cartilage and bone, leading to joint damage [13]. RA happened in all age but the onset was with 3 times in females than in males [14].

The mechanism of RA is complicated, which might relate to gene, infection, cold, moisture, endocrine, smoking, mental stimulation, generation of autoantigens or antibodies and so on. All the factors acted on the immune system and led to the disorder of immune function including cellular immunity and humoral immunity [15].

X-ray examination easily detected swollen joints, narrowing joint space, dislocation, hyperosteogeny, marginal nature bone erosion and so on, but not sensitive to RA early lesions including synovial hyperplasia, cartilage destruction and joint effusion [16], which were with significant changes after 6 months to 1 year [17].

MRI could show a relatively comprehensive image of joint including all the articular surfaces (synovial membrane and tendon), which could quantitatively measure the synovial membrane and help to early diagnosis, activity judgment and prognosis [18]. However, MRI needed longer time and more expensive cost with complicated detecting process and potential motion artifacts. It could not to be examined if there was metal in the patients' body. There was out releasing after injection of contrast agent in MRI, which would influence the flow perfusion of synovial membrane.

Ultrasound had the real-time dynamic, noninvasive and repeated advantages [19]. For the soft tissue lesions and joint damage, ultrasound and MRI were better than X-ray, while for synovial membrane, ultrasound was more sensitive than MRI. Mathiesen [20] et al found that the 10 MHz high frequency probe could accurately measure the defect area of cartilage and cartilage thickness.

The secondary SonoVue, with the advantages of safety, cycling by lung, but not free transmission through vascular wall, was the kind contrast agent [21]. SonoVue could fill the microvesSEL even capillary, reflecting the synovial proliferation. Synovitis is the pathological changes of RA, while the proliferation of microvessel is the important factor for forming and sustaining synovitis. High frequency ultrasound and CEUS were used for determining and evaluating the synovitis severity. CEUS reflected the proliferation in synovial membrane, which represented the activity of synovitis [22].

Chang S [23] et al found that when judging RA activity, CEUS was more sensitive, accurate and objective than high frequency ultrasound, which could find the flow signals high frequency ultrasound could not.

AUC was positive correlated to ESR, CRP and IgG in TIC, while PI was positive correlated to CRP. In our study, AUC and PI of CEUS were significantly correlated to US (r<sub>u</sub>=0.832, r<sub>u</sub>=0.8-09, P<0.01=). The correlations among AUC, PI and ESR were better than between US and ESR (r<sub>AUC</sub>=0.907, r<sub>PI</sub>=0.851, r<sub>us</sub>=0.836, P<0.01=). The
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was parallel to ESR, but appeared more early and disappeared faster than ESR [27]. ESR was influenced by many factors and lacked of specificity, but not the age, lipid, hemoglobin (Hb) and erythrocytes. CRP in RA patients was related to the RA activity after comprehensive evaluation including arthritis index, morning stiffness, grip and Hb. CRP was sensitive in RA with the linear correlation between the increase and RA activity [28]. There was no specificity about the diagnosis of CRP on RA. But when the tissue damage and inflammation were led by many factors, CRP was a sensitive index, whose lever was positively correlated to tissue damage degree [29]. Therefore, we presumed that CRP was more accurate than ESR in RA activity judgement. US was better than DAS28, with better reflecting RA activity.

RF is the autoantibody of degenerative IgG, which reacts only with degenerative IgG but not normal IgG. The positive rate of RF in RA was 60%~80% in health people [30]. But the specificity of RF was low, appearing in other autoimmune disease and chronic infectious disease. Anti-CCP was the specific antibody of RA, as the early diagnosis index [31]. The earliest found was 10 years before the first patients with RA. The sensitive rate of Anti-CCP to RA was 40%~85%, with specificity of 94%~98% [32]. In the meantime, Anti-CCP had the predictive effect for RA, for that the erosive arthritis appeared more in patients with positive Anti-CCP than the negative [33]. But in our study, US and DAS28 were not significantly correlated to RF and Anti-CCP (P>0.05), which indicated that RF and Anti-CCP were not related to RA activity.

Additionally, the subprojects of US including synovial thickness, synovial flow and joint effusion were related to DAS28, ESR and CRP

Table 4. The correlation among every subproject in US, DAS28 and clinical indexes

<table>
<thead>
<tr>
<th>Clinical and biochemical examination</th>
<th>Synovium thickness</th>
<th>Joint effusion</th>
<th>Bone erosion</th>
<th>CDFI or PDUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS-28</td>
<td>0.852**</td>
<td>0.843**</td>
<td>0.215</td>
<td>0.687**</td>
</tr>
<tr>
<td>ESR</td>
<td>0.779**</td>
<td>0.585**</td>
<td>0.237</td>
<td>0.584**</td>
</tr>
<tr>
<td>CRP</td>
<td>0.587**</td>
<td>0.397*</td>
<td>0.245</td>
<td>0.432**</td>
</tr>
<tr>
<td>RF</td>
<td>-0.202</td>
<td>0.146</td>
<td>0.007</td>
<td>-0.128</td>
</tr>
<tr>
<td>Anti-CCP</td>
<td>-0.136</td>
<td>-0.025</td>
<td>-0.161</td>
<td>-0.249</td>
</tr>
</tbody>
</table>

note: *P<0.05, **P<0.01.

The correlations among AUC, PI and CRP were better than between US and CRP (r_{AUC}=0.855, r_{PI}=0.854, r_{US}=0.692, P<0.01). AUC and PI reflected the proliferation of vessels in synovial membrane, while CEUS showed the perfusion in synovial membrane. Therefore, we presumed that CEUS was better than US on better reflecting RA activity. Damjanov [24] et al found that US was highly related to DAS28, ESR and CRP. Some researches found that doppler ultrasound and CEUS were correlated to RA activity and more sensitive than clinical indexes [25]. Comparing to previous researches, we analyzed the correlation among CEUS, US, ESR, CRP, RF and Anti-CCP and presumed that CEUS was better than US on evaluating RA activity.

To draw a conclusion, CEUS could objectively reflect RA activity and was better than US, which was an effect method for early RA diagnosis, therapeutic evaluation and condition monitoring.

DAS28 is the comprehensive evaluation index. According to t28, we28 and ESR, DAS28 could objectively evaluate RA activity, which was the best comprehensive evaluation index for monitoring RA activity and evaluating medical treatment effectiveness in clinical [26]. However, RA was the chronic inflammatory disease with repeated illness. Some patients, who were called clinically negative patients, were without obvious symptoms, joint tenderness and swelling, leading to low DAS28. The joint deformity and dysfunction would appear as time went by, and the patients would lose working and living ability. Therefore, early diagnosis, treatment and intervention are very important.

In our study, US was significantly correlated to DAS28 (r=0.823, P<0.01). For involving ESR in calculation formula, the correlation coefficient between DAS28 and ESR (r=0.963) was better than between US and ESR (r=0.8-36). However, the correlation between US and CRP was better than between DAS28 and CRP (r_{US}=0.692, r_{DAS28}=0.526, P<0.01).

ESR and CRP were the examining indexes reflecting RA activity. In RA activity, CRP increased significantly, which was parallel to ESR, but appeared more early and disappeared faster than ESR [27]. ESR was influenced by many factors and lacked of specificity, but not the age, lipid, hemoglobin (Hb) and erythrocytes. CRP in RA patients was related to the RA activity after comprehensive evaluation including arthritis index, morning stiffness, grip and Hb. CRP was sensitive in RA with the linear correlation between the increase and RA activity [28]. There was no specificity about the diagnosis of CRP on RA. But when the tissue damage and inflammation were led by many factors, CRP was a sensitive index, whose lever was positively correlated to tissue damage degree [29]. Therefore, we presumed that CRP was more accurate than ESR in RA activity judgement. US was better than DAS28, with better reflecting RA activity.

RF is the autoantibody of degenerative IgG, which reacts only with degenerative IgG but not normal IgG. The positive rate of RF in RA was 60%~80% in health people [30]. But the specificity of RF was low, appearing in other autoimmune disease and chronic infectious disease. Anti-CCP was the specific antibody of RA, as the early diagnosis index [31]. The earliest found was 10 years before the first patients with RA. The sensitive rate of Anti-CCP to RA was 40%~85%, with specificity of 94%~98% [32]. In the meantime, Anti-CCP had the predictive effect for RA, for that the erosive arthritis appeared more in patients with positive Anti-CCP than the negative [33]. But in our study, US and DAS28 were not significantly correlated to RF and Anti-CCP (P>0.05), which indicated that RF and Anti-CCP were not related to RA activity.

Additionally, the subprojects of US including synovial thickness, synovial flow and joint effusion were related to DAS28, ESR and CRP.
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(P<0.05). The highest correlation coefficient was the r of synovial thickness ($r_{\text{DAS28}}=0.852$, $r_{\text{ESR}}=0.779$, $r_{\text{CRP}}=0.587$, P<0.01), which indicated that synovial thickness reflected RA activity and accorded to the mainly pathological changes. Bone erosion was not correlated to DAS28 and other 4 indexes (P>0.05). Bone erosion was the repeated action result of bone damaging and repairing. RA activity would change as time went by, which was less correlated to bone erosion [34].

To draw a conclusion, high frequency ultrasound got more and more attention in early RA diagnosis and monitoring therapy, which was sensitive to exam synovial thickness, joint effusion and pannus formation. High frequency ultrasound helps to find the lesion range and degree in early RA and provides medication with references and evidences. Therefore, US is a kind of simple, effective and sensitive method to evaluate RA activity.

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Disclosure of conflict of interest

None.

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