DETECTION OF SUBCHONDRAL BONE MICROCIRCULATORY PERFUSION IN ADULTS WITH EARLY OSTEONECROSIS OF THE FEMORAL HEAD USING CONTRAST-ENHANCED ULTRASOUND: A PROSPECTIVE STUDY

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Abstract—The aim of this study was to quantitatively assess subchondral bone microcirculation perfusion in adults with early osteonecrosis of the femoral head (ONFH) using contrast-enhanced ultrasound (CEUS) and to evaluate its correlation with the Association Research Circulation Osseous (ARCO) stage. We investigated 97 adult patients with definite ONFH by imaging a total of 155 hips, performing CEUS, storing images of CEUS processes at different ARCO stages and generating CEUS time–intensity curves (TICs) to obtain perfusion parameters. Differences in CEUS parameters at different ARCO stages were analyzed, and correlations were explored. A logistic regression model was constructed by incorporating the meaningful CEUS indicators. The CEUS parameters time to peak (TTP), peak intensity (PI), enhanced intensity (EI), ascending slope (AS), descending slope (DS) and area under the receiver operating characteristic curve (AUC) were significantly different in ARCO stage Ⅰ compared with stage ⅢA, and the same results were obtained in stage Ⅱ compared with stage ⅢA. However, there were no significant differences between stages Ⅰ and Ⅱ. The MTT (mean transit time) assay was not significantly different between the different stages. The receiver operating characteristic curve analysis of TTP, PI, EI, AS, DS and AUC in stages Ⅰ and ⅢA had a certain diagnostic efficacy, similar to the results in stages Ⅱ and ⅢA. The diagnostic performance of DS was less accurate in stages Ⅰ and ⅢA, while the diagnostic performance of TTP was less accurate in stages Ⅰ and ⅢA. ARCO stage was independently and negatively correlated with TTP and DS and independently and positively correlated with PI, EI, AS and AUC. The MTT assay was not correlated with ARCO stage. Logistic regression models containing statistically significant TTP, EI and AUC values were constructed, and all three values were closely related to the ARCO stage. In patients with different ARCO stages of ONFH, CEUS can effectively assess subchondral bone perfusion of the femoral head and is expected to become an effective imaging method for the diagnosis of early ONFH. (E-mail: pingzhao1499@126.com)

Key Words: Contrast-enhanced ultrasound, Microcirculation perfusion, Osteonecrosis, Association Research Circulation Osseous stage.

INTRODUCTION

Osteonecrosis of the femoral head (ONFH) is caused by various pathogenic factors, such as lipid embolus, intravascular thrombus and elevated intraosseous pressure, which affect the local microcirculatory hemodynamic changes in the femoral head (Li et al. 2020; Zhao et al. 2020), resulting in local ischemia in the femoral head, which in turn leads to necrosis (Narayanan et al. 2017). A large number of arteries and veins supply the deep cartilage in the subchondral bone of the femoral head, where microcirculatory disorders play an important role in the development of ONFH (Burr 2004; Li et al. 2013; Petek et al. 2019). Impaired blood supply to the subchondral bone of the femoral head is the initiating factor in ONFH (Petek et al. 2019). Microcirculation disorders and hemodynamic alterations in the femoral head are always accompanied by the progression of ONFH
Contrast-enhanced ultrasound (CEUS) has unique hemodynamic advantages and is widely used to assess microcirculation perfusion within various tissues and organs (Piscaglia et al. 2012; Bamber et al. 2013; Pitre-Champagnat et al. 2015; Loffler et al. 2016; Li et al. 2018). Furthermore, it provides a new and complementary test for diagnosing and treating orthopedic diseases (Krammer et al. 2018; Back et al. 2020; Liu et al. 2021). The ultrasound contrast agent SonoVue is a lipid-coated microbubble of sulfur hexafluoride with a diameter of approximately 2.5 \( \mu \text{m} \), which has hemodynamic characteristics similar to those of red blood cells and can be widely distributed in the systemic capillary network. Transvenous injection of contrast agents confines it within the vessel, giving it high reflectivity and a low mechanical index, allowing dynamic detection of microvessels up to 100 \( \mu \text{m} \) in diameter. Moreover, it is a good blood pool tracer for the clinical application (Stramare et al. 2014; Ran et al. 2017; Jäschke et al. 2018; Fischer et al. 2020). Some scholars have quantified perfusion of tibial discontinuity using the CEUS technique (Krammer et al. 2018; Doll et al. 2019), evaluated neovascularization of bone scabs (Pozza et al. 2018), and observed neovascularization of graft bone neovascularization (Jin et al. 2019). Therefore, accurate detection of local hemodynamic changes in the femoral head prior to the onset of osteonecrosis is essential for early diagnosis and treatment of ONFH. The team’s previous animal experiments (Chen et al. 2020) confirmed the feasibility of using CEUS in detecting blood supply changes in hormonal osteonecrosis of the femoral head in rabbits; however, no quantitative studies have been conducted on the subchondral microcirculation of human ONFH. This study aimed to quantitatively study the local microcirculation perfusion of ONFH patients in different Association Research Circulation Osseous (ARCO) stages using contrast-enhanced ultrasound and to explore whether contrast-enhanced ultrasound could be an effective imaging tool for predicting ONFH.

METHODS

Ethics

This prospective study was approved by the National Clinical Trial Registry under Registration No. ChiCTR 2000034754. Ethical approval was granted by the local institutional review board under ZYYECK [2020]016. All procedures were performed in accordance with the ethical standards of the World Medical Association’s Declaration of Helsinki. All participants voluntarily signed an informed consent form.

Participants

Patients who attended inpatient or outpatient clinics in our orthopedic hip preservation ward between May 2020 and April 2021 were recruited. On the basis of clinical and imaging examinations, all patients were diagnosed as adult patients with early ONFH. A total of 99 patients with 157 hips were included, of which 2 hips were excluded because the patients were unable to externally rotate and abduct because of hip pain and inability to cooperate with CEUS. Therefore, we investigated 97 patients with 155 hips, with a mean age of 34.9 ± 8.7 y. Inclusion criteria: According to the latest version of the ONFH stage criteria of the 2019 ARCO guidelines (Yoon et al. 2020), early and late ONFH staging was based on whether the collapsed femoral head exceeded 2 mm in ARCO stage IIIA as the threshold value. The staging criteria were as follows: (i) 13 cases of 13 hips diagnosed as stage \( \gamma \), with a mean age of 37.5 ± 7.4 y and X-ray and MRI revealing normal and abnormal results, respectively; (ii) 38 cases of 65 hips diagnosed as stage II, with a mean age of 36.3 ± 9.4 y, and both X-ray and MRI revealing normalcy and abnormalities; (iii) 46 cases of 77 hips diagnosed as stage IIIA (early), with a mean age of 33.3 ± 8.1 y and femoral head collapse ≤2 mm. Exclusion criteria were a combination of serious primary diseases of the cardiovascular system, liver, kidney and hematopoietic system; allergy to ultrasound contrast agents; concomitant other bone metabolic diseases; rheumatic diseases; and pregnancy or lactation.

CEUS inspection

Instruments. We used Mindray’s (Shenzhen, China) Resona8 ultrasonic diagnostic instrument, with a Model L9-3U linear array probe, frequency 3–9 MHz, and a Model SC5-1U convex array probe, frequency 1–5 MHz, with CEUS time–intensity curve software. The US contrast agent SonoVue was purchased from Bracco Suisse SA, Milan, Italy (Import Drug Registration No. H20171213) was selected. Each bottle of contrast agent was injected with 5 mL of 0.9% sterile sodium chloride injection diluted according to the instructions, shaken thoroughly for 20 s and configured into a sulfur hexafluoride microbubble suspension for backup.

CEUS inspection. The patient was placed in a supine position with the affected lower limb in an
abducted and externally rotated position, with the toes facing upward, exposing the anterolateral region of the femoral head to the probe directly below. The L9-3U high-frequency line array probe was used to visualize the articular cartilage on the surface of the femoral head, with the probe parallel to the line between the anterior superior iliac spine and the lesser trochanter. The acetabular labrum, a triangular hyperechoic structure, was visible between the femoral head and acetabulum. Following the clear display of the acetabular lip, the body surface was marked with the probe position and direction, and an SC5-1U low-frequency convex array probe was selected. In the image, the acetabular labrum was positioned on the most lateral part of the femoral head, and the anterolateral area of the femoral head was below the probe. The probe was kept stable and pressure was avoided while advising the patient to breathe peacefully. During the CEUS procedure, 2.4 mL of SonoVue was administered through the elbow vein, followed by 5 mL of a saline push to flush the tube. The instrument’s built-in timer was used to observe the process of ultrasound contrast agent perfusion and decompensation in real time for approximately 2 min, and the dynamic images were collected and stored in the background of the instrument for analysis using self-contained software. We performed CEUS on both femoral heads of the same patient at intervals >15 min. CEUS screening was conducted by an attending physician with more than 5 y of experience who had no access to patient information.

Image processing. The quantitative assessment of subchondral bone microcirculation perfusion was performed with time–intensity curve (TIC) analysis using the Mindray Resona8 system. The femoral head was manually traced, and the region of interest (ROI) within the subchondral bone of the femoral head surface was outlined, starting from the acetabular lip, wrapping around the femoral head’s anterolateral cartilage and bone plate, and terminating at the femoral neck, with an anterior–posterior spacing of approximately 5 mm, avoiding interfering areas such as the acetabulum, joint capsule, soft tissues around the femoral head and abnormally high echogenicity. The system automatically generated the time–intensity change curve and used a gamma fitting curve for quantitative analysis. Peak intensity (PI), enhanced intensity (EI), time to peak (TTP), ascending slope (AS), descending slope (DS), area under the receiver operating characteristic curve (AUC) and mean transit time (MTT) were calculated by curve analysis. Two other attending physicians with more than 5 y of experience, who did not participate in the contrast-enhanced ultrasound examination, independently evaluated the contrast-enhanced imaging process using a single-blind method, in which the analyzing physician did not know the specific information of the participant such as ARCO stage. All data acquired by each of the two physicians were measured three times consecutively, and the average value was obtained as the ultimate statistic.

Statistical analysis

Data were analyzed using SPSS Statistics (version 25.0; IBM Corp., Armonk, NY, USA). The Shapiro–Wilk normality test was performed on measures, where normally distributed measures were expressed as the mean ± standard deviation (SD) and non-normally distributed measures were expressed as medians (upper and lower quartiles). One-way analysis of variance (ANOVA) was used for the comparison of multiple samples that conformed to a normal distribution, and Levene’s test for the test. The least significance difference (LSD) method was applied for the two-way comparison of multiple groups, and the Kruskal–Wallis H-test was used for comparison of multiple data groups that did not conform to a normal distribution. Correlation analysis of grade data was performed using the Spearman rank correlation. Logistic regression models were constructed by incorporating statistically different CEUS parameters, and the differences were considered statistically significant at \( p < 0.05 \). ROC curves were plotted, and an AUC of 0.7 was considered to have a detectable value for evaluating the detection efficacy of each parameter. \( p \) values \( < 0.05 \) were considered to indicate a statistically significant difference.

RESULTS

As illustrated in Figure 1a, in the stage I group, when the contrast agent was injected for approximately 23 s, the contrast microbubbles were diffusely perfused from the head–neck junction area to the femoral head. The contrast agent perfusion in the subchondral bone area of the femoral head peaked at approximately 39 s after injection and gradually subsided at 72 s. The contrast agent exhibited uniform perfusion and fading. The time–intensity (TIC) curve revealed an AS of 0.63 and DS of 0.06, with an overall "slowly ascending and descending" pattern (Fig. 2a). The stage II group had higher contrast perfusion intensity and faster contrast perfusion and fading rates than the stage I group (17-s contrast agent entry, 32-s peak arrival, 55-s fading). The distribution of contrast microbubbles in the subchondral bone region of the femoral head was uniform (Fig. 1b). The ascending and descending slopes of the TIC curve were faster in the stage II group than in the stage I group (Fig. 2b). In the stage IIIA group, the contrast microbubbles rapidly entered the femoral neck and gathered in large quantities in the subchondral bone area of the
femoral head surface and the round ligament of the femoral head. Moreover, the contrast agent exhibited rapid perfusion and fading (12-s contrast agent entry, 18-s peak arrival, 46-s fading), and the microbubbles were not uniformly distributed (Fig. 1c). The TIC curve of the stage IIIA group had significantly higher ascending and descending slopes than that of the stage II group (AS = 2.09, DS = 0.23). The peak of the TIC curve was slightly sharper and exhibited an overall "rapid ascending and descending" pattern (Fig. 2c).

The most interesting aspect of Table 1 and Figures 3 and 4 is that the differences in TTP, EI, AS, DS, PI and AUC were all statistically significant ($p < 0.05$) in the stage $y$ group compared with the stage IIIA group. In addition, the differences in TTP, PI, EI, AS, DS and AUC between the stage II and stage IIIA groups were statistically significant ($p < 0.05$). Surprisingly, no significant difference between the stage $y$ and stage II groups was evident. The MTT (mean transit time) assay was not statistically significant in the comparison of ARCO stages ($p > 0.05$).

Unfortunately, the previous results indicated that the differences in CEUS parameters were not statistically significant when comparing the stage $y$ group with the stage II group. Therefore, ROC curve analysis was
Table 1. Comparison of CEUS parameters in different ARCO stages

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>TTP (s)</th>
<th>PI (dB)</th>
<th>EI (dB)</th>
<th>MTT (s)</th>
<th>AS (dB/s)</th>
<th>DS (dB/s)</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>13</td>
<td>15.30 (14.58, 16.01)</td>
<td>7.24 (6.18, 8.09)</td>
<td>24.49 (22.87, 26.11)</td>
<td>7.31 (6.28, 8.34)</td>
<td>11.54 (10.32, 12.76)</td>
<td>6.63 (5.11, 8.16)</td>
<td>63.44 (51.11, 75.81)</td>
</tr>
<tr>
<td>Stage II</td>
<td>65</td>
<td>10.82 (9.17, 12.48)</td>
<td>6.38 (5.10, 7.65)</td>
<td>10.97 (9.20, 12.74)</td>
<td>5.60 (4.41, 6.89)</td>
<td>56.94 (44.11, 65.59)</td>
<td>0.95 (0.51, 1.86)</td>
<td>405.67</td>
</tr>
<tr>
<td>Stage III A</td>
<td>77</td>
<td>8.78 (7.24, 11.60)</td>
<td>32.78 (29.64, 36.92)</td>
<td>31.98 (28.12, 35.84)</td>
<td>5.73 (4.32, 7.14)</td>
<td>55.90 (43.11, 68.69)</td>
<td>2.04 (1.28, 2.80)</td>
<td>0.79</td>
</tr>
<tr>
<td>Stage III B</td>
<td>2 = 17.48</td>
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<tr>
<td>Stage IIIA</td>
<td>84 (84.4%)</td>
<td>10.5 (10.5, 10.5)</td>
<td>23.5 (23.5, 23.5)</td>
<td>15.1 (15.1, 15.1)</td>
<td>2.2 (2.2, 2.2)</td>
<td>2022.4 (2022.4, 2022.4)</td>
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<td>4.98</td>
</tr>
<tr>
<td>Stage I vs. Stage II</td>
<td>0.801 (p &lt; 0.001)</td>
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<tr>
<td>Stage I vs. Stage III A</td>
<td>0.011 (p &lt; 0.001)</td>
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</tr>
<tr>
<td>Stage I vs. Stage IIIA</td>
<td>0.007 (p &lt; 0.001)</td>
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<tr>
<td>Stage II vs. Stage III A</td>
<td>0.005 (p &lt; 0.001)</td>
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<td></td>
<td></td>
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<tr>
<td>Stage II vs. Stage IIIA</td>
<td>0.014 (p &lt; 0.001)</td>
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<tr>
<td>Stage IIIA vs. Stage III B</td>
<td>0.040 (p &lt; 0.001)</td>
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<tr>
<td>Stage III A vs. Stage III B</td>
<td>0.047 (p &lt; 0.001)</td>
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</tbody>
</table>

ARCO = Association Research Circulation Osseous; AS = ascending slope; AUC = area under the receiver operating characteristic curve; CEUS = contrast-enhanced ultrasound; DS = descending slope; EI = enhanced intensity; MTT = mean transit time; PI = peak intensity; TTP = time to peak.

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Table 2 summarizes the results of the logistic regression analysis of the CEUS parameters and ARCO stage. Logistic regression models were constructed by including CEUS parameters such as TTP, PI, EI, AS and AUC with univariate screening for significance, considering stage IIIA as the reference category. At the TTP level, the regression coefficients were −0.182, $\chi^2 = 14.262$ and $p < 0.001$, implying a negative relationship between TTP and ARCO stage. The OR value was 0.8336, suggesting that the predicted increase in the ARCO stage for every 1-s decrease in TTP was 0.8336 times (95% confidence interval [CI]:...
0.7588—0.9167). Furthermore, EI and AUC had the same statistical significance as TTP. Surprisingly, the PI and AS regression coefficients were \( -0.054 \) (\( p = 0.411 \), >0.05) and \( 0.061 \) (\( p = 0.843 \), >0.05), respectively, and there was no statistical difference between them in predicting ARCO stage. The results are outlined in Figure 7.

Fig. 3. Contrast-enhanced ultrasound parameters AS, DS, EI and TTP in different Association Research Circulation Osseous stages CEUS parameters (violin plots). AS = ascending slope; DS = descending slope; EI = enhanced intensity; TTP = time to peak.

Fig. 4. Contrast-enhanced ultrasound parameters AUC and PI in different Association Research Circulation Osseous stages (histograms). AUC = area under the receiver operating characteristic curve; PI = peak intensity.
DISCUSSION

Traditionally, orthopedic diseases are considered a blind zone for ultrasound inspection because of the opaque nature of the bone. The resolution of ultrasound on soft tissues has gradually improved with the development of high-frequency ultrasound imaging technology, penetrating joint gaps, articular cartilage and destroyed bone tissue, allowing the continuous and dynamic observation of skeletal joints' anatomical structure, sonographic characteristics and lesion process. Research (Aula et al. 2010; Geis et al. 2013; Kiyan et al. 2018) has confirmed the ability of CEUS to detect subchondral bone microstructural properties and variations. The European Federation of Biomedical Ultrasound Societies (Sidhu et al. 2018) has highlighted that CEUS can better assess the degree of vascularization in inflammatory joint diseases. Previous animal experiments by our group revealed that CEUS could be an effective tool for the quantitative evaluation of microcirculation perfusion in rabbits with SIONFH (Chen et al. 2020). Therefore, CEUS has become a non-negligible test for detecting musculoskeletal disorders (Sconfienza et al. 2018).

According to the results of this study, the contrast agent revealed more rapid and higher perfusion and faster clearance as the ARCO stage progressed during CEUS. In the quantitative analysis of TICs, TTP and AS reflected the speed of contrast agent perfusion in the region of interest, PI was related to the concentration of microbubble aggregation and EI referred to the intensity of enhancement of contrast agent microbubbles into the microvasculature, reflecting the total amount of microvasculature; MTT and DS indicated the speed of contrast agent clearance in the vasculature. The AUC is the area under the curve that responds to the overall contrast agent filling volume. PI, EI, AUC, and the absolute values of DS were greater in group IIIA than in group y, whereas TTP was lower than that in group y, indicating that the contrast agent perfusion was faster and more intense in the microvasculature and that vascular clearance was faster. Additionally, there was a greater abundance of contrast agents in the ONFH area, and the local blood supply was richer. A comparison of stages IIIA and II also revealed the aforementioned results. Unfortunately, there was no significant difference between the
stage y and II groups in all parameters, considering that the sample size of the stage y group may be too small to reflect the significant difference between them. The CEUS parameters such as TTP, PI, EI, AS, DS and AUC were moderately correlated with ARCO stages, but no correlation was found for MTT. This is consistent with the previous comparison of MTT between different stages, which also revealed no difference, considering the possible reason for the poor sensitivity of MTT in the evaluation of microcirculatory perfusion. The logistic regression results indicated that the EI and AUC values increased and the corresponding ARCO stage was higher. Nevertheless, the corresponding ARCO stage decreased with increasing TTP. The parameters AS, DS and PI were not included in the final regression model, and a well-fitting regression equation was constructed after assessing the clinical value of the CEUS parameters, considering the influence of multiple covariates.

These findings were consistent with those of Chan et al. (2011), who found that as ONFH progressed, the necrotic femoral head was hyperperfused. The author evaluated idiopathic ONFH femoral head perfusion with DCE-MRI, finding that the peak signal intensity and the percentage of blood volume in the femoral head increased with an increase in the degree of osteonecrosis. This may be due to reactive congestion and vasodilation of the arteries supplying the femoral head following ischemia in the femoral head, resulting in a gradual increase in the peak signal intensity of femoral perfusion. We hypothesized that ONFH begins with the repair of the normal blood supply around the necrotic area and gradually extends toward the center of necrosis, with revascularization, new bone formation and resorption of dead bone. However, these usually occur at the marginal portion of the necrotic area, leading to incomplete repair and resulting in granulation tissue with abundant blood supply. Therefore, as ONFH progresses and the ARCO stage escalates, the rate of blood perfusion and clearance of the subchondral bone on the femoral head surface is faster than in normal femoral heads, and perfusion increases significantly, especially in stage IIIA.

The femoral head, however, is 3-D and spherical, and two-thirds of its area is accommodated in the acetabular labrum. The location of neovascularization in the

<table>
<thead>
<tr>
<th>ARCO</th>
<th>TTP</th>
<th>PI</th>
<th>EI</th>
<th>MTT</th>
<th>AS</th>
<th>DS</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.00</td>
<td>-0.548*</td>
<td>1.00</td>
<td>-0.471*</td>
<td>0.006</td>
<td>0.506*</td>
<td>-0.328*</td>
<td>0.556*</td>
</tr>
<tr>
<td>0.598*</td>
<td>0.562*</td>
<td>0.712*</td>
<td>0.042</td>
<td>0.521*</td>
<td>0.486*</td>
<td>0.839*</td>
<td>0.692*</td>
</tr>
<tr>
<td>0.634*</td>
<td>-0.694*</td>
<td>0.708*</td>
<td>-0.044</td>
<td>0.521*</td>
<td>0.471*</td>
<td>0.862*</td>
<td>0.674*</td>
</tr>
<tr>
<td>0.006</td>
<td>0.339*</td>
<td>-0.042</td>
<td>0.05</td>
<td>0.712*</td>
<td>0.486*</td>
<td>1.00</td>
<td>-0.432*</td>
</tr>
<tr>
<td>0.556*</td>
<td>0.328*</td>
<td>0.712*</td>
<td>0.741*</td>
<td>1.71</td>
<td>0.692*</td>
<td>1.00</td>
<td></td>
</tr>
</tbody>
</table>

ARCO = Association Research Circulation Osseous; AS = ascending slope; AUC = area under the receiver operating characteristic curve; CEUS = contrast-enhanced ultrasound; DS = descending slope; EI = enhanced intensity; MTT = mean transit time; PI = peak intensity; TTP = time to peak.

† At the level of 0.01 (two-tailed), the correlation is significant.
* At the level of 0.05 (two-tailed), the correlation is significant.

Table 2. Correlation of CEUS parameters with ARCO stage

<table>
<thead>
<tr>
<th>β</th>
<th>SE</th>
<th>Wald</th>
<th>p Value</th>
<th>OR</th>
<th>Lower limit</th>
<th>Upper limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ARCO = 1]</td>
<td>0.089</td>
<td>1.477</td>
<td>0.004</td>
<td>0.952</td>
<td>1.0931</td>
<td>0.0604</td>
</tr>
<tr>
<td>[ARCO = 2]</td>
<td>4.182</td>
<td>1.47</td>
<td>8.089</td>
<td>0.004</td>
<td>65.4967</td>
<td>3.6693</td>
</tr>
<tr>
<td>TTP</td>
<td>-0.182</td>
<td>0.048</td>
<td>14.262</td>
<td>0.000</td>
<td>0.8336</td>
<td>0.7588</td>
</tr>
<tr>
<td>PI</td>
<td>-0.054</td>
<td>0.066</td>
<td>0.677</td>
<td>0.411</td>
<td>0.9474</td>
<td>0.8319</td>
</tr>
<tr>
<td>EI</td>
<td>0.15</td>
<td>0.062</td>
<td>5.761</td>
<td>0.016</td>
<td>1.1618</td>
<td>1.0284</td>
</tr>
<tr>
<td>AS</td>
<td>0.061</td>
<td>0.31</td>
<td>0.039</td>
<td>0.843</td>
<td>1.0629</td>
<td>0.5793</td>
</tr>
<tr>
<td>AUC</td>
<td>0.002</td>
<td>0.001</td>
<td>6.160</td>
<td>0.013</td>
<td>1.0020</td>
<td>1.00019</td>
</tr>
</tbody>
</table>

ARCO = Association Research Circulation Osseous; AS = ascending slope; AUC = area under the receiver operating characteristic curve; β = regression coefficient (>1 indicates risk factor); CEUS = contrast-enhanced ultrasound; EI = enhanced intensity; PI = peak intensity; SE = standard error; TTP = time to peak; 95% CI = 95% confidence interval of OR.

WALD is a hypothesis test commonly used for regression coefficients; OR reflects the dominant ratio of the degree of correlation between the dependent variable (ARCO stage) and the independent variable (CEUS parameters).
subchondral bone area of patients with ONFH was deep, and it was difficult to clearly reveal the vascular structure with a high-frequency line array probe. The ultrasonic probe used in our examination of the femoral head was a low-frequency probe, and the sound beam emitted by the transducer made a certain angle of sector scanning, which could only reveal the image of a certain surface of the anterolateral area of the femoral head. Furthermore, it was difficult to explore the acoustic image characteristics of the head end of the femoral head; thus, there was a lack of evaluation of the overall situation of the femoral head. This is one of the limitations of this study. In addition, the insufficient sample size of the stage $y$ group failed to present definite conclusions. In the future, a multicenter study with a large sample size is needed. The quantitative study of local microcirculation perfusion not only enhances imaging technology and machine performance but also improves the performance of the ultrasound contrast agent. Therefore, in the future, we will further apply 3-D CEUS to assess microcirculation perfusion and study the application of nano-targeted contrast agents in the precise diagnosis and treatment of ONFH.

CONCLUSIONS

Contrast-enhanced ultrasound could be used effectively to assess subchondral bone perfusion of the femoral head in patients with different ARCO stages of ONFH and is expected to become an effective imaging method for the diagnosis of early osteonecrosis of the femoral head.

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