

Value of contrast-enhanced ultrasonography in assessing the activity of idiopathic retroperitoneal fibrosis: a prospective study

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Abstract

Objective

We aimed to evaluate changes in the contrast-enhanced ultrasound (CEUS) parameters in patients with idiopathic retroperitoneal fibrosis (RPF) before and after treatment, and to analyse the value of CEUS to assess RPF activity.

Methods

We performed a prospective study that included patients with idiopathic RPF who were treated for RPF at our hospital from April 2016 to April 2019. All patients underwent CEUS examination and some of them underwent positron emission tomography/computed tomography (PET/CT) examination simultaneously. CEUS parameters included tube wall and peripheral thickness, arterial wall intensity, and lumen intensity. The changes in CEUS parameters before and after treatment were evaluated, and their correlations with the standardised uptake value (SUVmax), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were analysed.

Results

Thirty-one active idiopathic RPF patients were enrolled, of whom 11 underwent PET/CT examination before treatment. Tube wall and peripheral thickness ($r=0.743$, $p<0.01$) and arterial wall intensity ($r=0.702$, $p<0.05$) both correlated significantly with SUVmax. Lumen intensity did not correlate significantly with SUVmax ($r=0.544$, $p=0.084$). The correlation coefficients between lesion thickness and ESR levels were 0.508 ($p=0.037$), between lesion thickness and CRP levels were 0.575 ($p=0.016$). Arterial wall intensity and lumen intensity were not significantly correlated with ESR or CRP levels. Tube wall and peripheral thickness, arterial wall intensity, decreased significantly after treatment ($p=0.001$), while the lumen intensity was not significantly changed after treatment.

Conclusion

Our findings suggest that CEUS, a radiation-free and repeatable detection method, is effective for assessing idiopathic RPF disease activity.

Key words

retroperitoneal fibrosis, contrast-enhanced ultrasonography, disease activity, positron emission tomography/computed tomography (PET/CT), acute phase reactant

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Introduction

Retroperitoneal fibrosis (RPF) is a group of diseases characterised by the proliferation of inflammatory fibrosclerotic tissues surrounding the blood vessels. The proliferative tissues around the abdominal aorta and iliac artery may compress the surrounding ureter and inferior vena cava, resulting in corresponding clinical manifestations (1). At present, the diagnosis of RPF mainly depends on imaging examinations, including ultrasound, computed tomography (CT) scans, and magnetic resonance imaging (MRI). Glucocorticoids are the main medication used for treating RPF (2). Disease activity needs to be regularly evaluated during the course of treatment. At present, acute phase reactants (APRs), CT, and MRI are the most commonly used methods evaluating RPF disease activity. Positron emission tomography (PET) can also assess RPF disease activity, by monitoring the volume and 18F-FDG uptake of retroperitoneal masses (3); however, PET/CT has been limited in clinical applications due to its high cost and radiation exposure.

Contrast-enhanced ultrasound (CEUS) is an economical and convenient radiation-free imaging technique. In recent years, CEUS has been shown to evaluate wall inflammation in large vessel vasculitis and inflammatory bowel disease by assessing vascularisation (4). Considering that RPF is also characterised by inflammatory lesions around the abdominal aorta and iliac artery, the purpose of our study was to investigate the value of applying CEUS to detect idiopathic RPF disease activity.

Materials and methods

Patients

A prospective idiopathic RPF patient cohort was created and a total of 31 patients at the rheumatology department of our hospital from April 2016 to April 2019 who met the Scheel diagnostic criteria were enrolled. Scheel criteria include: (A) soft-tissue mass surrounding the infrarenal aorta and/or iliac vessels detected via CT or MRI; (B) absence of intraabdominal or pelvic masses aside from the periaortitis; (C) lack of clinical suspicion of ma-

lignancy from the patient's history and physical examination; and (D) negative age appropriate cancer screening.

All 31 patients were active when enrolled. Among these patients, 25 patients were first-time treated, while 6 were recurrent RPF patients.

There was a total of 24 men and 7 women, aged 34–77 years, with an average age of 54.6±11.4 years. The included patients had the following characteristics: CT or MRI examination that indicated soft tissue masses surrounding the lower abdominal aorta and/or iliac vessels; no abdominal and pelvic masses were found except for aortic inflammation; and exclusion of malignancy through patient history, laboratory, and imaging studies (5). Patient demographics, clinical manifestations, previous medical history, and medication use were recorded. This study was approved by the ethics committee of our hospital, and all patients provided written informed consent.

Laboratory data collection

The following CEUS parameters were recorded before and after treatment: tube wall and peripheral thickness, arterial wall intensity, lumen intensity, and levels of concurrent acute reactants (APR), including ESR and CRP, were also recorded. Some of the patients underwent PET/CT (Positron Emission Tomography/Computed Tomography) examination before treatment, and SUVmax (Standardised Uptake Value) values were recorded.

Contrast-enhanced ultrasonography (CEUS)

CEUS was performed using a Philips IU-22 or EPIQ7 ultrasound system (mechanical index, <0.08) with a 1–5 MHz convex array transducer and contrast agent SonoVue (Bracco Imaging, Geneva, Switzerland). Before CEUS was performed, the B-mode was used to scan the retroperitoneal organs, ranging from the pancreas to the iliac fossa (including the abdominal aorta, iliac vessels, kidney, ureter, and others). The instrument's gain, image depth, and flow gain were adjusted to ensure optimal image quality. After standard US, Sono Vue lyophilised powder was dis-

Competing interests: none declared.

solved in a 5 ml 0.9% sodium chloride solution, then 2.0~2.4 ml of the contrast agent was rapidly injected via the median cubital vein followed by a 5-mL saline flush. The images were observed and stored. The whole process was recorded dynamically. Parameters such as the enhancement intensity of the lesion, and the lumen enhancement intensity were measured using software. Since the examination was a routine diagnostic procedure, the sonographers were aware of the patients' clinical data. The above examinations were determined and measured by two experienced sonographers under the same examination protocol.

Positron emission tomography/computed tomography (PET/CT)

PET/CT scans were performed at the PET/CT center of the Chinese PLA General Hospital using a PET/CT machine (Biograph Truepoint, Siemens). Blood glucose levels were ≤ 8.3 mmol/L before tracer injection. All participants were instructed to fast for at least six hours before injection of ^{18}F -FDG (5.55 MBq/kg), and the mean time to acquire the whole-body emission scans was 60 min after the intravenous injection. For the first CT scan, voltage was 110 kV, current was 90 mA, 0.9 s/s/week, and layer thickness was 3.8 mm. Whole-body PET scans were performed from the pelvis to the chin with 5–7 bed positions in 3-dimensional mode for 2.5 min/bed, using a CT protocol (90 mAs, 110 kV, 0.9 pitch). PET images were reconstructed using the True X method.

Statistical methods

All analyses were performed using SPSS v. 22.0. The CEUS parameters before and after treatment were compared using a paired sample t-test, and the correlations between CEUS parameters and SUVmax, ESR, and CRP levels were determined by Pearson correlation analysis. A p -value < 0.05 was considered significant.

Results

Clinical data

Among the 31 patients in this study, 26 (83.9%) had abdominal pain and low back pain as the first symptoms,

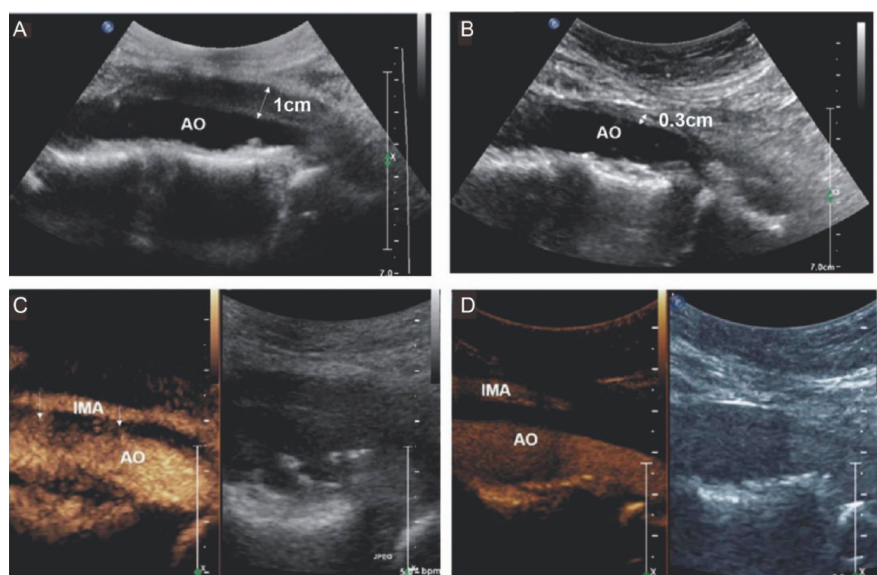


Fig. 1. Ultrasound and contrast-enhanced images of retroperitoneal fibrosis.

A–B: Ultrasound images show the thickness of the blood vessel wall before (A) and after treatment (B) in two-dimensional grey-scale ultrasound mode. The double-sided arrows measure the thickness of the vessel wall.

C–D: contrast-enhanced images show that neovascularisation is indicated inside the microbubbles before (C) and after treatment (D).

IMA: inferior mesenteric artery; AO: abdominal aorta.

11 (35.5%) had urinary symptoms, and 18 (58.1%) were smokers. Treatment plans included hormones in nine patients (29.0%), hormone combined with leflunomide in 14 (45.2%), hormone combined with mycophenolate mofetil in 3 (14.3%), hormone combined with rituximab in 2 (9.5%), hormone plus cyclophosphine amide in 1 (3.2%), and no treatment in two patients (6.5%).

Ultrasound images before treatment

All 31 patients had retroperitoneal abnormalities, and seven had hydronephrosis. Conventional ultrasound findings revealed that the lesions were covered from the lower part of the abdominal aorta to the wall of the bilateral common iliac artery, showing low level echoes. The contrast agent in the lesion was enhanced after injection of the ultrasound contrast agent sulfur hexafluoride as microbubbles in suspension (Fig. 1).

Correlation between contrast-enhanced ultrasound parameters and SUVmax

Eleven patients underwent an ^{18}F -FDG PET/CT examination. The CT images showed that all 11 patients had irregular

soft tissue density in retroperitoneum that surrounded the abdominal aorta to varying degrees. All involved the front or both sides of the abdominal aorta, of which six (54.5%) involved the ureter. PET images showed an average SUVmax value of 7.39 ± 3.54 for the 11 patients. Correlation analysis between the SUVmax value and contrast ultrasound parameters showed that the tube wall and peripheral thickness ($r=0.743$, $p=0.009$) as well as the arterial wall intensity ($r=0.702$, $p=0.016$) were significantly correlated with the PET/CT SUVmax value. There was no statistically significant correlation between the lumen intensity and the SUVmax value ($p=0.084$) (Fig. 2).

Correlation between ultrasound parameters and levels of acute phase reactants

Tube wall and peripheral thickness were moderately correlated with ESR ($r=0.508$, $p=0.037$) and CRP ($r=0.575$, $p=0.016$) values. The lumen intensity had no significant correlation with ESR ($p=0.548$) or CRP ($p=0.062$) values. Similarly, arterial wall intensity had no significant correlation with the ESR value ($p=0.307$) or CRP value ($p=0.828$).

Correlation between the PET/CT SUVmax and acute phase reactants values

The correlation analysis between PET/CT SUVmax and acute phase reactants values revealed no significant correlation between SUVmax and ESR ($p=0.53$) or CPR ($p=0.718$).

Comparison of ultrasound images before and after treatment

Sixteen patients were followed up with CEUS after treatment. In these patients, the thickness of the lesion ($p=0.001$), and the enhancement intensity of the lesion ($p=0.013$) decreased significantly after treatment. There was no significant change in lumen intensity after treatment ($p=0.158$) (Fig. 3).

Discussion

RPF is characterised by chronic, non-specific and non-purulent inflammation of the retroperitoneal tissue with fibrous tissue hyperplasia, and most patients with RPF have a chronic disease course (6). Glucocorticoids are the main drugs for such disease. Multiple studies have shown that the disease is prone to relapse after discontinuation of glucocorticoids. Since long-term use of glucocorticoids can easily lead to a variety of complications and RPF patients have high rate of recurrence after inappropriate discontinuation of medication, close follow-up and evaluation of RPF patients is needed for rational use and withdrawal of drugs (7). Therefore, it is necessary to find a suitable and effective assessment method for disease activity.

Studies have shown that the disease activity of RPF can be evaluated by PET tracer uptake (8, 9). RPF patients, having normal levels of inflammatory markers, were reported having active lesions as shown by PET/CT, suggesting that PET/CT is more sensitive to RPF activity than inflammatory markers. Bertagna *et al.* (10) have found that the SUVmax value was significantly lower in RPF patients with complete remission, and they speculated that PET/CT examination is helpful in evaluating the efficacy of early treatment in RPF. Thuermel *et al.* (11) found that the volume of retroperitoneal mass as

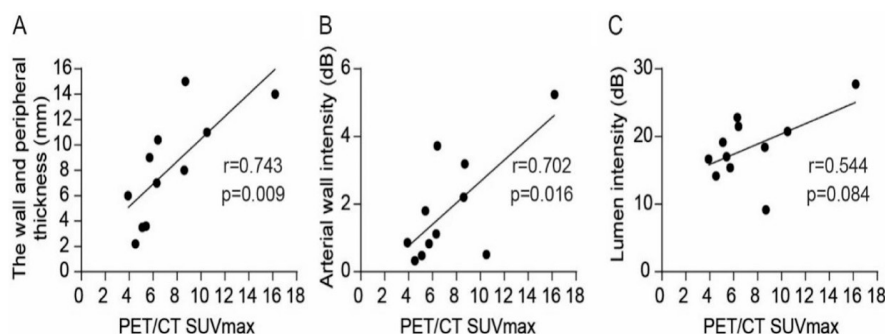


Fig. 2. Correlations between contrast-enhanced ultrasound parameters and PET / CT SUVmax. **A-B:** The contrast-enhanced parameters of the tube wall and peripheral thickness (mm) and the arterial wall strength (dB) are significantly correlated with PET/CT SUVmax values. **C:** There is no statistically significant correlation between lumen intensity (dB) and PET/CT SUVmax values.

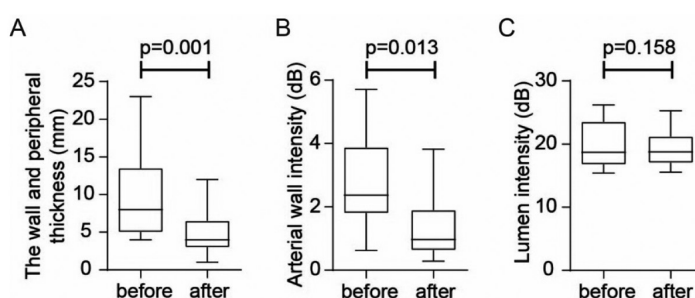


Fig. 3. Comparison of contrast ultrasound parameters before and after treatment. **A-B:** The tube wall and peripheral thickness (mm) as well as arterial wall intensity (dB) significantly decreased after treatment. **C:** There is no statistically significant change in the lumen intensity (dB) after treatment.

shown by PET/MRI are different before and after treatment. Besides assessing RPF disease activity, PET can also help distinguish RPF lesions from retroperitoneal tumours (12). PET is suggested to be a reliable tool for evaluating RPF disease activity. PET/CT or PET/MRI examinations, however, require radioactive agents and are expensive and therefore cannot be used frequently during the follow-up of RPF patients.

The microbubble contrast agent used by CEUS is small enough (3–5 μm) to circulate through the lungs and can be used to assess neovascularisation. Kim *et al.* (13) have found that CEUS is an inexpensive, noninvasive method for evaluating aortic and common iliac arterial disease. Schinkel *et al.* (14) have evaluated the CEUS manifestations of large-vessel vasculitis (LVV), including the degree of vascular wall thickening and stenosis, and found that contrast enhancement shows a positive correlation with the degree of vascu-

larisation within the plaque. Germano *et al.* (15) have used the CEUS method to assess the disease activity of macrovascular vasculitis, and found that the grade of new angiogenesis assessed by CEUS is related to the degree of inflammation shown by PET. RPF is also associated with the presence of inflammatory lesions around the aorta and iliac artery (16). Our study observed positive correlations between CEUS parameters (tube wall and peripheral thickness, arterial wall intensity) and PET/CT SUVmax values before treatment. However, there was no correlation between the SUVmax value and lumen intensity (dB). Comparison of CEUS parameter data before and after treatment showed that CEUS parameters such as lesion thickness and lesion enhancement intensity decreased significantly in RPF patients after treatment. Our results suggest that CEUS parameters are helpful for the diagnosis of retroperitoneal fibrosis, and can directly reflect the changes in lesions,

which helps determining RPF disease activity and therapy efficacy.

Serum acute phase reactants are commonly used to evaluate inflammation and treatment response (17). However, elevated APR levels can occur for a number of reasons, making these parameters insensitive and poorly specific. Several studies have suggested that acute phase reactants such as ESR and CRP can help assess RPF disease activity, though this remains to be investigated (18). Mn *et al.* (19) have found that the mean levels of CRP and ESR in patients with imaging remission are often higher, but the difference did not reach statistical significance; therefore, they have considered that elevated ESR and CRP levels are not valuable predictors of the response of RPF patients to corticosteroid therapy. Our study found that the SUVmax value of 11 patients before treatment had no correlation with ESR and CRP levels. Furthermore, there was no significant correlation between tube wall and peripheral thickness or lumen intensity and ESR or CRP levels. The literature data and our results strongly indicate a low specificity of APR in evaluating RPF activity.

Our study has some limitations. Firstly, the sample size of our study is relatively small, leading to low statistical power. We did not compare the CEUS examination with a golden standard method, pathology, in assessing the disease activity of RPF, which makes the conclusion of our study not so convincing. Additionally, the CEUS examination needs to be performed by an experienced sonographer.

Conclusion

We uncovered that CEUS parameters including lesion thickness and lesion enhancement intensity has the potential to be indicators of RPF disease activity.

Key messages

- Our prospective study revealed a positive correlation between contrast-enhanced ultrasound (CEUS) parameters (tube wall and peripheral thickness, arterial wall intensity) and positron emission tomography/computed tomography (PET/CT) standardised uptake (SUVmax) values in patients with idiopathic retroperitoneal fibrosis (RPF) before treatment.
- CEUS parameters such as lesion thickness and lesion enhancement intensity decreased significantly after treatment.
- CEUS parameters are helpful for the diagnosis of idiopathic RPF, and can directly identify the changes in lesions, which can aid in determining RPF disease activity and medication efficacy.

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