Quantitative DCE-MRI: An Efficient Diagnostic Technique for Evaluating Early Micro-environment Permeability Changes in Ankylosing Spondylitis

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Research article

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Abstract

Background: In the management of early inflammatory joint of ankylosing spondylitis (AS), there is a need for reliable noninvasive quantitative methods to closely monitor synovial inflammation to predict early diagnosis.Cognizant to this,studies geared on improving techniques for quantitative evaluation of micro-environment permeability of the joint space are necessary.Such improved techniques may provide tissue perfusion as important biological parameters and can further help in understanding the origin of early changes associated with AS.

Aims:To prospectively evaluate the diagnostic performance and determine longitudinal relationships of early micro-environment active in the joint space of the sacroiliac joint (SIJ) with a rat model by using quantitative dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI).

Methods: Thirty wistar male rats were randomly assigned to the model (n= 15) or control (n = 15) group. All rats underwent DCE-MRI of SIJ region at fixed time points(12, 17 and 22 weeks),between September 2018 and October 2019. Differences in permeability parameters between the two groups at the same time point were compared by using an independent samples *t* test.Spearman correlations of DCE-MRI parameters with different time points in model group were analyzed.All statistical analyses were performed with software.

Results: At 12 weeks,the K^{trans},K_{ep} and V_e values in the model group were slightly lower than those in control group,but all the differences were not statistically significant ($p>0.05$).Compared with control group,the transfer constant (K^{trans})values increased significantly at 17 weeks and 22 weeks in model group,while the rate constant (K_{ep}) and volume of extravascular extracellular space(V_e) significantly increased only at 22weeks($p<0.05$).The K^{trans},K_{ep} and V_e were positively correlated with increasing time points (r=0.94, P□0.01 for K^{trans}; r=0.93, P□0.01 for K_{ep}; and r= 0.89, P□0.01 for V_e).

Conclusions: Quantitative DCE-MRI parameters are valuable for evaluating the early longitudinal relationship of micro-environment permeability changes in the joint space of SIJ.

Background

Ankylosing spondylitis(AS) is a chronic inflammatory disease that affect approximately 0.1-2% of the general population[1]. It affects mostly the young adults and its etiology is still unknown.Cognizant to this,early detection of abnormal changes associated with AS is of paramount importance.Moreover,monitoring the progress of these changes is also important because any delays in accurate diagnosis of AS can result in serious disabilities and economic cost[2].Improving the understanding of early changes of AS can help in identifying patients who can significantly benefit from early clinical interventions.

Diagnosis of AS often depends on the clinical symptoms and imaging abnormities. Sacroiliitis is the most important clinical manifestation of AS[3].However,there is high variability in clinical diagnosis and scoring systems that are mostly subjective. Evaluating active progression of AS by magnetic resonance imaging (MRI) had been widely accepted,which is a sensitive, non-invasive method that can permit the visualization of active and structural lesions,even in the absence of radiographically evident disease[4-9].However,the DCE-MRI performance in AS simply used signal intensity changes over time to assess inflammation changes in the SIJ still remained subjective,limited by the inability to provide objective quantitative parameters,which was suggested as an imaging biomarker that is sensitive to disease progression.

In recent years,quantitative dynamic contrast enhanced magnetic resonance imaging(DCE-MRI),basing on a pharmacokinetic model,have been successfully used to assess changes in different diseases[3,10-12].It can provide sufficient information on microenvironment changes or quantitatively evaluate certain inflammation processes that reflect the intrinsic properties of tissues[13].In the management of early inflammatory AS joint, there is also a need for reliable noninvasive quantitative methods to closely monitor synovial inflammation to predict early diagnosis.As such,the interrelationship between early longitudinal pathologic changes of AS with quantitative MRI parameters should be focused on.

In 2019, the ASAS-MRI work group came up with new updated definitions for joint space enhancement.In these guidelines,increased signal on contrast-enhanced images of the joint space of the cartilaginous portion of the SIJ reflected inflammation at the osteochondral interface,as this would be consistent with the understanding of early histopathological feature of AS[14].Cognizant to this,studies geared on improving techniques for quantitative evaluation of micro-environment permeability of the joint space before edema and inflammation visualized in adjacent bone marrow of SIJ are necessary.Such improved techniques may provide tissue perfusion as important biological parameters and can further help in understanding the origin of early changes associated with AS.

The purpose of this study was to utilize quantitative DCE-MRI to dig deeper into investigating the longitudinal relationship of early micro-environment permeability in the joint space of SIJ before onset of active bone marrow changes in an AS rat model.

Methods

2.1 Animals

Our study began in September 2018 and ended in October 2019.All experiments were approved by the Institutional Animal Care and Use Committee and were performed in accordance with the National Institutes of Health guidelines for the use of laboratory animals.Thirty six-week-old male wistar rats(Weight,160-200g;Department of Experimental Animal breeding Co., Ltd) were used in the study. Each cage housed five rats at 20°C to 25°C, with a 12 h light-dark cycle and standard laboratory rat diet and water were available ad libitum.

2.2Rat AS model

The experiment was performed when all rats had been acclimatized in a Specific Pathogen Free(SPF) environment for one week.Thirty male wistar rats were randomly divided into 2 groups, including the model group(n=15) and control (n =15) group.The AS models were established by reference to the past successful experience[9],as following:in the model group,1 mg proteoglycan protein was dissolved in 1 ml sterile normal saline with 1 ml Freund's complete adjuvant(FCA) and was immediately administered intraperitoneally with 0.2 ml for each rat,,then followed with mixed solvent consisted of the same volume of proteoglycan protein and Freund's incomplete adjuvant (FIA) after 2 weeks and 4 weeks respectively.The control group were injected the same amount of saline instead of proteoglycan by the same way and time point.Each rat was weighted before the MRI scan. At 12 ,17 , 22 weeks after the last induction,five rats at each time point of each group were randomly selected for MRI examination and then sent for pathology acquisition.

2.3 MR Examination

MRI examination was performed on a 3.0 Tesla (T) magnet (GE Discovery 750; GE Healthcare) with a matched eight-channel animal coil (Wankang Medical Technology Co., Ltd, China) of the bilateral SIJ at 12 ,17 , 22 weeks after the last induction.MRI sequences were obtained using the following protocols:Axial T2-weighted with fat-saturated [repetition time/echo time (TR/TE):3000/96 ms;matrix size:192×192;slice thickness:0.8mm;field of view (FOV):6.0×6.0;number of excitations (NEX):4];Coronal fs T1 FSE(TR/TE:500/13.5ms; matrix size:192×192;slice thickness:0.8 mm;FOV:6.0×6.0;NEX:4);DCE-MRI:fat saturated contrast enhanced T1 images with liver acquisition with volume acceleration(LAVA) sequence(TR/TE: 5.7/2.0ms; matrix size: 128×128;slice thickness:2.0mm;FOV:12×12; NEX:2).Once the baseline scan was finished,1ml gadopentetate dimeglumine contrast agent (BeiLu Pharmaceutical Co.,Ltd,Beijing,China; dose:0.5 mmol/kg)was rapidly injected manually,followed by 2ml saline flush into the tail vein through a intravenous catheter.The fat-saturated contrast enhanced T1-weighted images with LAVA sequence was obtained with 960 images of 80 phases for approximately 5 minutes of scanning.

2.4 Image Analysis

The quantitative DCE-MRI analysis was processed on the Advantage Workstation(ADW4.7version,GE,US).All MRI examinations were independently processed by two radiologists (with 15 years and 8 years of experience in reading musculoskeletal system MR images with the doubleblind method).Regions of interest (ROI) were manually positioned in the upper,middle and lower third of the joint space with the maximum transverse level of SIJ on magnified DCE-MRI images and then the ROIs were copied and pasted onto the K^{trans} maps, K_{ep} maps, and V_e maps(Fig1).Total of 3 ROIs (2-4mm^2) for each side and then the bilateral average values were calculated for analysis,as shown in Figure 1.

Three quantitative DCE-MRI indexes,K^{trans},K_{ep},and V_e were calculated automatically by arterial input function according to the following eqs. [10]:

$K^{trans} = V_e \times K_{ep}$;

$C_t = V_e \times C_e$;

$= K^{trans} C_p - K^{trans} C_t / V_e$;

where C_t,C_e,and C_p are the concentrations of the contrast agent in the tissue, extravascular-extracellular space,and plasma, respectively.

2.5 Histologic assessment

All rats of each time point were intraperitoneally injected with 1% pentobarbital (Sigma company) to euthanize them.The SIJ were then cut across the midline and removed. They were fixed in 10% formalin for one or two days and the acid-decalcified with 10% methanoic acid for one week.They were then embedded in paraffin and dehydrated in graded ethanol.The tissues were then cut into sections and stained with hematoxylin for 8 minutes and the with eosin for 2 minutes.The pathological changes of the SIJ were observed under a microscope (MODEL BX53F, OLYMPUS, Tokyo,Japan) by an experienced pathologist without knowledge of the final group allocation status.

2.6 Statistical Analysis

The IBM SPSS 23.0 software(Armonk,NY) and Med Calc 15.8 (Mariakerke,Belgium) were used for statistical analyses.Quantitative parameters are expressed as the means±standard deviation.Data were tested for normality analysis using the Kolmogorov–Smirnov test and then with the Levene test for variance homogeneity analysis.Differences in permeability parameters between the two groups at the same time point were compared by using an independent samples *t* test.In order to evaluate interobserver variability, the coefficient of variation (CV) was calculated for the two sets of measurements.Interobserver agreement was evaluated using interclass coefficient correlation(ICC) and Bland-Altman analysis.Spearman correlations of DCE-MRI parameters with different time points in model group were analyzed.*P* values of less than 0.05 were considered as statistically significant.

Results

3.1 Interobserver Reproducibility

Table 1 revealed that measurements of the DCE-MRI parameters (K^{trans}、K_{ep} and V_e)were reliable,possessing excellent interobserver reproducibility with interclass coefficient correlation ranging from 0.82 to 0.90.The coefficient of variation (CV) ranged from 1.9 to 11.6%.Bland-Altman plots showed good agreement between interobserver DCE-MRI parameter measurements(Figure 2) .

Table 1:Interobserver reproducibility in the assessment of DCE-MRI parameters

Parameter	Interclass coefficient correlation (95% CI)	Coefficient of variation (%)
K^{trans}	0.90(0.81-0.94)	11.6
K_{ep}	0.90(0.82-0.95)	9.9
V_e	0.82(0.66-0.91)	1.9

Data are presented as means (95%CI) or n(%). Interobserver agreement was evaluated by using interclass coefficient correlation(ICC)analysis and interobserver variability was calculated by using the coefficient of variation (CV).

3.2 DCE-MRI Parameters

All imaging examinations were performed successfully at each different time point in both the model group and control group.There were no positive findings of adjacent bone marrow signal intensity changes in fs axial T2WI and coronal fs T1WI images by visual observation in all the rats of model and control groups.On the DCE-MRI pictures,different degrees of increased signal of the joint space of the cartilaginous portion of the SIJ can be seen.

The control group had no significant differences in DCE-MRI parameters over time.With the increase of weeks,all the DCE-MRI parameters gradually increased at different degrees of model group(Table2).At 12 weeks,the K^{trans},K_{ep} and V_e values in the model group were slightly lower than those in control group,but all the differences were not statistically significant ($p>0.05$).Compared with control group, the K^{trans} was markedly and significantly increased at 17 weeks and 22 weeks in model group,while K_{ep} and V_e were significantly increased only at 22weeks($p<0.05$)(Table 2)(Figure 3). To evaluate the DCE-MRI parameters as monitoring progression markers of early micro-environment permeability changes in the joint space of SIJ,we correlated them with different time points on behalf of different stages of inflammation in model group by reference of pathological findings.We found a statistically significant positive correlation between the K^{trans} , K_{ep} and V_e with increasing time points (r=0.94, P□0.01 for K^{trans}; r=0.93, P□0.01 for K_{ep}; and r= 0.89, P□0.01 for V_e).

Table 2:DCE-MRI parameters in the model and control groups at each time point

Time Point	Model Group	Control Group	*P*
K^{trans}			
Week 12	0.98±0.01	1.06±0.08	0.056
Week 17	1.23±0.08	1.09±0.01	0.023*
Week 22	2.18±0.31	1.03±0.05	<0.001*
K_{ep}			
Week 12	1.05±0.04	1.10±0.03	0.055
Week 17	1.25±0.07	1.17±0.02	0.053
Week 22	2.21±0.28	1.11±0.06	<0.001*
V_e			
Week 12	0.88±0.01	0.91±0.03	0.068
Week 17	0.96±0.02	0.93±0.02	0.057
Week 22	0.98±0.01	0.92±0.02	0.003*

Data are presented as means (SD).*P* values for differences between different groups of same time point were determined by independent samples *t* test.*Statistically significant differences ($p < 0.05$).

3.3 Findings at Histopathology

At week 12,positive histologic evidence of inflammation was entirely absent in synovium,cartilage,subchondral bone and bone marrow of bilateral SIJ in 5 model rats.At week 17,inflammatory cellular infiltrate within synovium were present in 4 model rats of bilateral SIJ and one model rats of unilateral SIJ initially.At week 22,definite pannus forming of synovium could be seen in 5 model rats of bilateral SIJ with 2 rats had hemorrhage and damage on the surface of cartilage.There are no positive histologic evidence of inflammation of all rats in each time point of control group.

Discussion

In our study,the potential of quantitative DCE-MRI analysis to elucidate the longitudinal relationship of early inflammation micro-environment permeability in the joint space of SIJ before onset of active structural changes and bone destruction was well demonstrated.

AS is a chronic progressive rheumatic disorder that affects the SIJ. It is a challenge to recognize the disease early and thus proper diagnosis is often made long after manifestation of symptoms[15].Inflammation is an important indicator of the activity of AS. It plays a key role in early

identification and the earlier detection of synovitis is important to prevent the development of structural changes.MRI has become particularly crucial in early disease detection without the risk of radiation exposure and follow-up SpA sacroiliitis[16-18].Understanding the pathophysiologic relationship between early inflammation micro-environment changes in the SIJ and the role of MRI in accurate monitoring of disease progression can significantly improve the understanding of disease evolution.Our study was aimed at improving early diagnosis of AS using functional MRI sequences by reference of pathological changes.

K^{trans}, K_{ep} and V_e parameters reflect perfusion and permeability,the reverse transportation of gadolinium chelate back to the vascular space as well as extravascular extracellular space volume.In the present study,there were no significant differences between the model group and control group based on DCE-MRI parameters assessing in the joint space of SIJ at 12 weeks after induction.These results were consistent with the pathological results which showed no significant positive inflammatory changes at 12 weeks. At 17 weeks, the K^{trans}, K_{ep} and V_e values in the model group were higher than those of the control group.However, only the differences of K^{trans} between the two groups were statistically significant.The previous investigations have noted that in early stages of axial SpA, pannus formation helps in understanding the associated pathological changes[19].It is characterized by formation of high vascular granulation tissue by the inflamed synovium and/or subchondral bone marrow.Inflammation may subsequently trigger the formation of angiogenesis by increasing the density of the micro-vessels that provide a channel for expression of mediation and invasion of inflammatory cells and this in turn exacerbates local damage to the cartilage[20/21].Based on pathological results,local infiltration of inflammatory cells of the subsynoviocytic and areolar connective tissue in the early stage may led to the increase of vascular permeability. A related view is that François R J *et al*.[22]have reported that a small number of lymphocytes and plasma cells with a large number of macrophages infiltrated the subsynoviocytic and areolar connective tissue in a systematic histological study of early SIJ.

At 22 weeks, K^{trans}, K_{ep} and V_e significantly increased in the model group than control group.These changes indicated increased permeability and extravascular extracellular space volume of the capsulitis and synovitis in SIJ. This was attributed to infiltration of the inflammatory cells and pannus formation in the synovial area with increased microcirculation and greater capillary permeability. This result was consistent with that of Zhang *et al.*[3] who found that K^{trans}, K_{ep} and V_e of AS patients in the active group were significantly higher than those of AS patients in the inactive group patients using quantitative DCE-MRI.These results revealed that quantitative DCE-MRI parameters could differentiate between active and inactive AS.Higher K^{trans} and K_{ep} values are associated with increased microcirculation and greater capillary permeability of inflammatory tissues in the active sacroiliitis.Another previous study[23]has shown DCE-MRI parameters of the K^{trans},k_{ep}, and V_e could be used to detect synovial inflammation in patients with early arthritis and correlated with synovial expression of the endothelial cell (EC) marker von Willebrand factor (vWF) ,which could facilitate the evaluation of joints inaccessible to next proper clinical examination.Our result was similar to the above report that quantitative DCE-MRI can provide

performance for detecting early inflammation micro-environment permeability in SIJ of AS. In addition, there was a statistically significant positive correlation between the K^{trans} , K_{ep} ,V_e with increasing weeks and changes in the K^{trans} occurred earlier than K_{ep} and V_e.Based on our results,the K^{trans} was more sensitive than the other parameters and it may has a potentially efficacy to predict early inflammatory activity more timely.

We evaluated the interobserver variability for quantitative DCE-MRI parameter measurements. Our results indicated good agreements between the two radiologists for the measurements of quantitative DCE-MRI parameters.Because the accuracy of the result is highly depend on ROI delineating, in order to minimize the selection bias,we placed the ROIs in the upper,middle and lower third of the joint space with the maximum transverse level of SIJ on contrast-enhanced images by the reference of increased signal of the joint space,according to the new update of definitions and validation by the ASAS-MRI work group[14].However, standardization of strategies for ROI determination should be done in other subsequent in depth studies.

The present study was supported by grants from the Shandong Provincial Natural Science Foundation(grant no. ZR2017MH105)and Academic promotion programme of Shandong First Medical University (grant no.2019QL017).

Limitations

Nevertheless,this study was limited by several factors.Firstly,changes in DCE-MRI parameters were not assessed after the 22nd week.The sample size used was relatively small and thus further prospective analyses of a larger number of samples is needed to validate our results.Secondly,in our previous work[9],we have successfully investigated the diagnostic performance of semi-quantitative DCE-MRI in detecting the early activity of sacroiliitis in AS and this present study is the extension of earlier work.However,the correlation of semi-quantitative and quantitative DCE-MRI parameters were not evaluated.In the future,the performance comparison of different contrast-enhanced models should be investigated.Moreover,the higher magnification MR images were not compared with the corresponding pathological images in the present study and it was our ongoing study in depth.

Conclusion

In conclusion,quantitative DCE-MRI parameters are valuable for evaluating the early micro-environment permeability changes in the joint space of SIJ.In particular, K^{trans} is a sensitive and timely index for demonstrating early inflammatory activity in AS,which provided an new method for clinician to take effective measures with suspected synovitis in patients at risk of developing AS.

Abbreviations

DCE-MRI:Dynamic contrast-enhanced magnetic resonance imaging;

SIJ:Sacroiliac joint

AS:Ankylosing spondylitis;

LAVA:Liver acquisition with volume acceleration;

ICC:Inter-class correlation coefficient;

CV:Coefficient of variation;

SpA:Spondyloarthropathies.

Declarations

Ethics Approval and Consent to Participate

The study was approved by the Institutional Animal Care and Use Committee and was performed in accordance with the National Institutes of Health guidelines for the use of laboratory animals.

Consent to publish

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' Contributions

H Y:Conceptualization,Writing- Original draft preparation.

J Q:Conceptualization,Writing- Reviewing and Editing.

L J:Formal analysis,Supervision,Software.

J L:Data curation,Methodology.

XZZ:Formal analysis, Data curation,Methodology.

QQY:Visualization,Software.

JZZ:Resources,Project administration.

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Figures

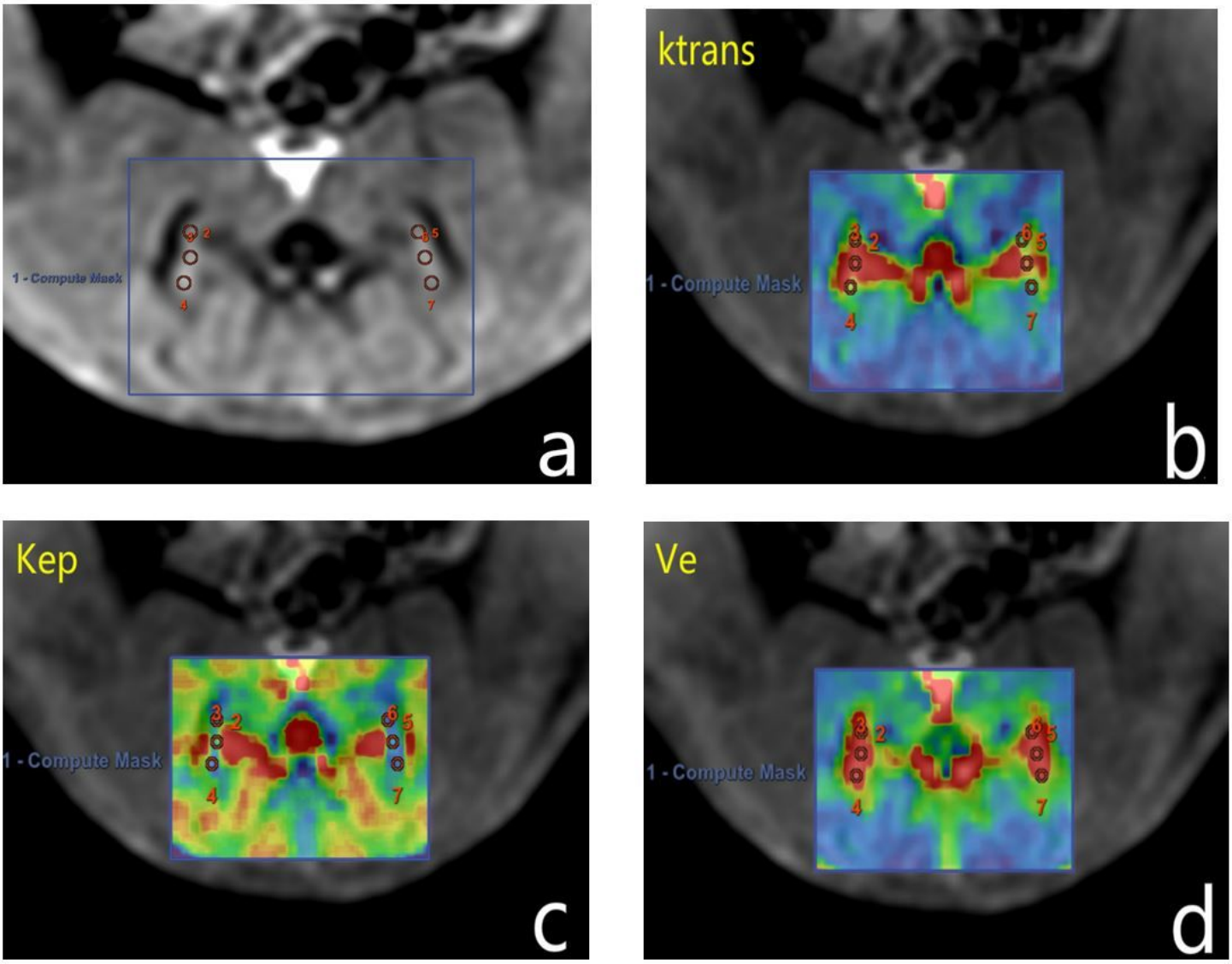

Figure 1

Representative images of ROIs outlined. Image(a) shows that ROIs have been manually drawn on magnified DCE-MRI image of model group rat at week 22,and that the colour parametric maps of Ktrans (b), Kep (c) and Ve(d) are automatically generated.

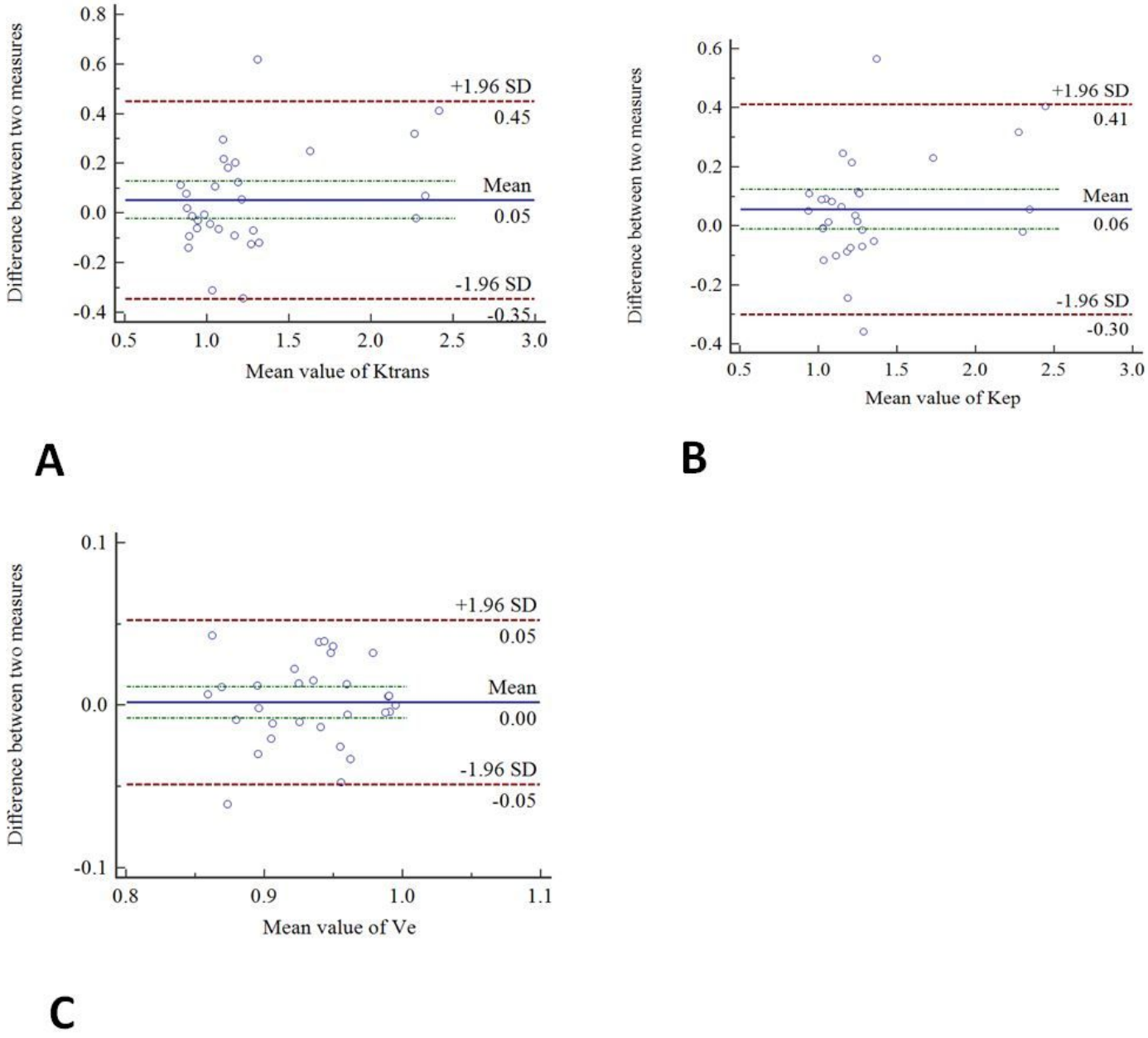

Figure 2

Bland-Altman plots show interobserver reliability for measurement of DCE- MRI parameters(A-C). SD=standard deviation.

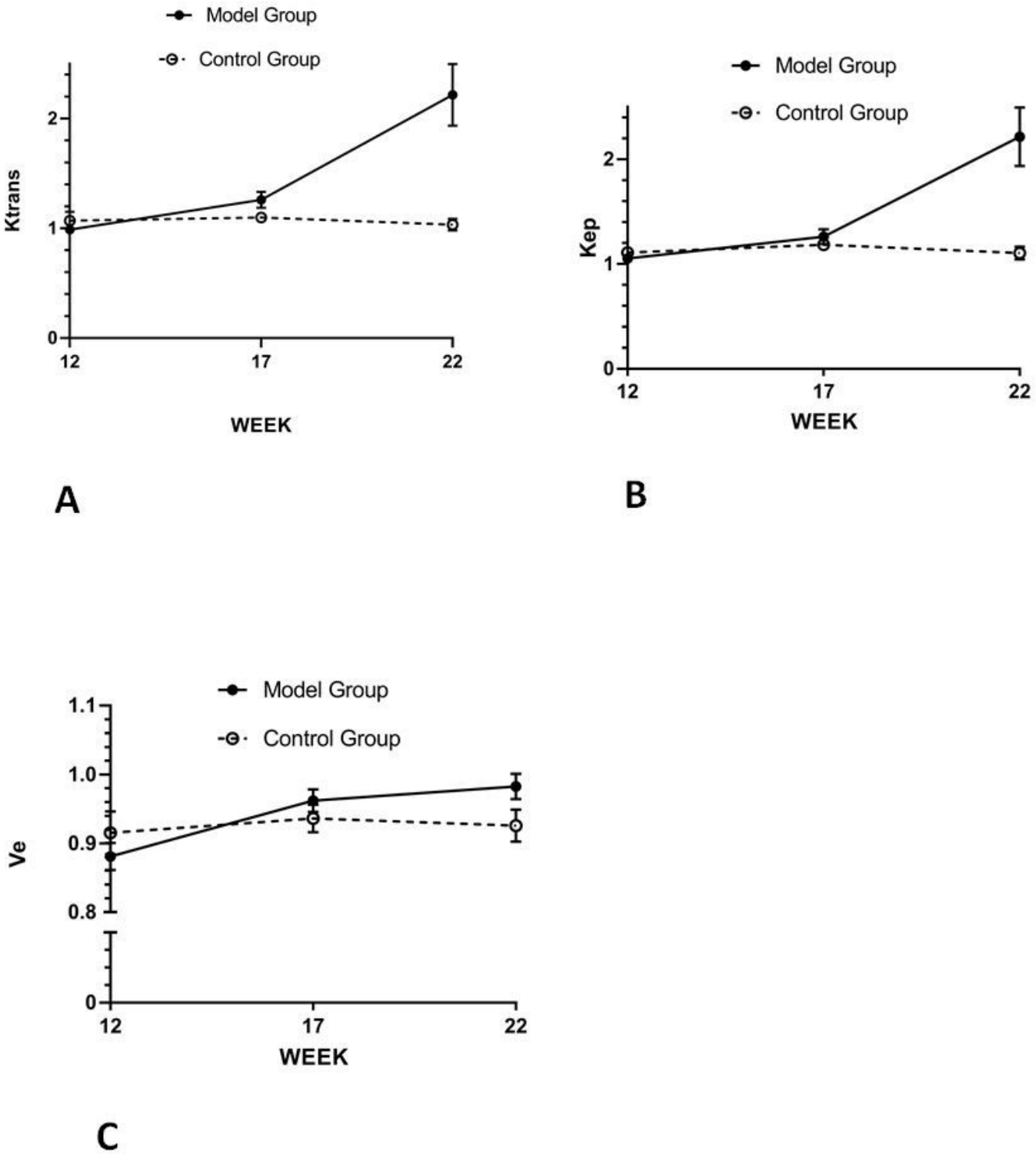

Figure 3

Graphs show longitudinal DCE-MRI parameters in the model and control groups of wistar rats. At 12 weeks,all the differences of Ktrans,Kep and Ve values were not statistically significant between the model and control groups.Compared with control group,the Ktrans (A)was significantly increased at 17 weeks and 22 weeks in model group,while Kep (B)and Ve (C) were significantly increased only at 22 weeks.

Supplementary Files

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- ARRIVE.pdf