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行政院國家科學委員會專題研究計畫成果報告

椎體血液灌流：動態顯影 MRI 與 MRA 之評估

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Abstract

OBJECTIVE: The lumbar intervertebral disc is the avascular tissue in adult. The major nutrition supplies rely on diffusion from vertebral bodies. The aim of this study is to evaluate blood perfusion of the lumbar vertebrae with dynamic gadolinium-enhanced MR imaging (DCE-MRI) and their relationship to adjacent disc degeneration.

MATERIALS AND METHODS: 25 patients (50 vertebras) were enrolled and DCE-MRI with FSPGR sequence was performed in each patient. The peak signal enhancement in each vertebra was calculated from the time signal after curve fitting of the pharmacokinetic model. Two grouping methods were used in this study. Method A was defined as the two vertebral discs adjacent to the vertebral body evaluated with DCE-MRI, forming two groups: A1, the normal group (vertebra between two normal discs), and A2 degeneration group (vertebra between two degenerative discs), were separately assessed from 50 vertebrae. Student t test was used to compare the peak enhancement of the two groups. Method B was assessed with clustered by patients, forming three patient groups: B1, the normal group (two vertebrae with each between two normal discs), degeneration group I (one vertebra between two normal discs and one between two degenerative discs), and degeneration group II (two vertebras with each between two degenerative discs), were separately assessed from 25 patients. Comparison of normalized peak enhancement (the peak signal enhancement ratio of two vertebrae) among the three groups was performed using ANOVA and Student t-test.

RESULTS: In method A, the peak enhancement values of degeneration group (0.2450 ±0.0038) vs. normal group (0.2703 ±0.0025) did not reach statistic significant (P=0.11). In Method B, subjects in the degeneration group I had significantly lower normalized peak enhancement (0.8455±0.0036) compared with subjects in the normal group (0.9880±0.0022) and degeneration group II (0.9730±0.0066).

CONCLUSION: The normalized method can reduce variety of perfusion and enhance the divergence that we focused on. We, therefore, demonstrate the vertebral marrow perfusion has close relationship to disc degeneration.

Introduction

Dynamic contrast-enhanced MR imaging (DCE-MRI) has been used widely in assessing blood perfusion of bone marrow. The lumbar intervertebral disc is the avascular tissue in the adult. Its nutrition occurs by diffusion from surrounding blood vessels [1]. Impaired flow in lumbar arteries is markedly associated with decreased diffusion in lumbar discs and may play an important role as a promoter of disc degeneration as assessed by MR angiographic study. The study implied that disc degeneration is highly related to blood perfusion [2]. Atherosclerotic changes in the lumbar area also has high relation to disc degeneration [3], and low-back pain [4, 5]. Therefore, insufficient nutrition has been proposed to be the primary cause of the degenerative process of a disc. However, there is no prior study to verify the relationship between vertebral marrow perfusion and degeneration disc using DCE-MRI. As we all knew that multiple factors contribute vertebral perfusion. These factors include age, sex, bone marrow density, fat marrow content, exercise and career. We can eliminate or reduce the bias in perfusion study by using normalization method. The aim of this study is to verify blood perfusion of the lumbar vertebrae with DCE-MRI relating to adjacent intervertebral disc degeneration.

Materials and Methods

Selection of patients This study recruited 50 consecutive patients who had DCE-MRI for lumbar examination. Of these 50, patients who had diabetes mellitus, major systemic disease, underlying malignancy, or prior lumbar spinal surgery were excluded. Finally, a total of 25 patients who had low-back pain and degenerative disc diseases were recruited.

MRI protocol All patients were performed on a 1.5-T MR scanner (LX, Horizon,

General Electric, Milwaukee, Wis.) with a spine array coil. DCE-MRI was employed to measure the perfusion of the lumbar vertebral body. Sagittal PD-weighted and T2-weighted images of the lumbar spine were obtained using dual echo of fast spin-echo MR (TR/TE1/TE2, 4000/20/105, ETL, 9, FOV) sequences. Sagittal T1-weighted spin echo MR images (TR/TE, 600/20) were acquired. Three axial images of the vertebral bodies (L1, L2, and L3) were selected for measurement. The DCE-MRI with use of fast RF-spoiled gradient-recalled (FSPGR) sequence (TR/TE=10/1.4 ms; flip angle=30°; FOV=30x15-cm; matrix size=256x160; slice thickness=10mm) were acquired. The interval time between each measurement was 3.1 sec and total acquired time was 8 minutes. A total of 480 images were obtained. Gd-DTPA was used with a total dose of 0.1 mmole/kg via auto-injector at a rate of 2 ml/sec, and the injection was followed by a 10ml saline flush at the same rate.

Image analysis The MR imaging findings of intervertebral discs (L1-2 to L4-5) on T1WI and T2WI were analyzed independently by two radiologists on a workstation (Advantage Windows; GE Medical Systems), and a consensus was reached. The signal intensities of intervertebral discs were compared with cerebrospinal fluid. The intervertebral discs were classified as: grade 0 (normal disc), disc with high signal intensity or subtle intranuclear cleft; grade 1 (mild degeneration), disc with decreased signal intensity but maintain normal height; and grade 2 (severe degeneration), disc with markedly decreased signal intensity and loss of height.

Data analysis The data of DCE-MRI images was transferred to a personal computer, and was processed by software developed in-house using Matlab (The MathWorks, Inc., Natick, MA, U.S.A.). The data of DCE-MRI was analyzed using a pharmacokinetic two-compartment model [6], which is assumed that the relative signal change has a linear proportional to Gd-DTPA concentration. The signal-time-curve can be described by a mathematical formula with relation of signal in tissue with Gd-DTPA bolus injection:

$$\frac{S(t)-S_0}{S_0}=\frac{A}{(k_{21}-k_{el})}(\exp(-k_{el}t)-\exp(-k_{21}t))$$

where S (t) indicates the time signal after administration of Gd-DTPA, S_0 represents the precontrast signal, the amplitude of uptake A, exchange rate k_{21}, and washout rate k_{el}. Signal time values were measured in operator-defined regions of interest (ROIs) over the whole vertebral body. The fitted signal-time curve of ROI, which signal averaged by all pixels, was calculated using this equation by nonlinear least square error curve fitting. In this study, the peak enhancement value $(\frac{S_{max}-S_0}{S_0})$ of fitted signal-time curve was computed for evaluating vertebral perfusion.

Statistical analysis In method A, the peak enhancement was evaluated for degeneration vs. normal group using Student t testing (two tails). The $P < 0.05$ was considered to indicate a statistically significant difference. In method B, comparison of normalized peak enhancement among the three groups was made using ANOVA and Student t-test (two tails). The results were considered statistically significant when $P < 0.01$.

Results

The data of DCE-MRI images was analyzed by manual ROI of whole vertebra (Fig. 1A) . The fitted signal-time curve was calculated using the Brix's model by nonlinear least square error curve fitting (Fig. 1B). The peak enhancement value of fitted signal-time curve was computed in each vertebra. According our criteria of the discs examined in this study, 25 patients (total 50 discs) were included to be a database in this study. In method A, there were

23 vertebrae in degeneration group and 27 vertebrae in normal group. Figure 2 shows the distribution of peak enhancement value in degeneration and normal group. The peak enhancement values are close between degeneration group (0.2450 ±0.0038) and normal group (0.2703 ±0.0025), but did not reach significant (P=0.11).

In method B, 7 subjects were classified into the degeneration group I, 8 subjects were the degeneration group II, and 10 subjects were normal group. The mean age of the subjects was 62 years (range, 24–77 years) in the degeneration group I, 77 years (range, 70–85 years) in the degeneration group II, and 40 years (range, 25–58 years) in the normal group. Because all the vertebrae between two normal discs were L1 and all the vertebrae between two degenerative discs were L3 in the degeneration group I, that may make the normalized peak enhancement values were not only the ratio of degeneration to normal, but also L3 to L1. For comparing under same condition, the normalized peak enhancement values were also calculated from L3 divided by L1 in other two groups. The normalized peak enhancement values of the three groups are plotted in Figure 3. When normalized peak enhancement was analyzed, subjects in the degeneration group I had the lowest normalized peak enhancement (0.8455±0.0036) compared with subjects in the normal group (0.9880±0.0022) and subjects in the degeneration group II (0.9730±0.0066) (Fig 3). The observed difference in normalized peak enhancement between degeneration group I and normal group reached statistic significant (P<0 .01), as was the observed difference between degeneration group I and II was significant (P<0 .01). The normalized peak enhancement observed between normal and degeneration group II was not significant (P=0.32).

However, all the normalized peak enhancement values were smaller than 1 in degeneration group I. For strict comparison, the normalized peak enhancement values were calculated from the vertebrae with smaller peak enhancement to the larger one in degeneration group II and normal group. Figure 4 shows the results. The results were same with figure 3, the significant difference was between degenerative disc group I and normal group (P<0 .01) and between degeneration group I and II (P<0 .01), it was no significant difference between normal and degeneration group II (P=0.09).

Discussion

There are two distinct routes that supply nutrients to the disc via the endplate and the anulus periphery and that most of the discs relies on nutrients supplied by the endplate route [7]. There is strong evidence that a fall in nutrient supply is associated with disc degeneration[1]. MR imaging studies indicated that penetration into discs was slow, with peak intensities in the nucleus reached after 6 hours and the signal persisting the central disc for at least 24 hours[8, 9]. The association between disc degeneration and disturbances to nutrient supply are strong.

Due to slowly permeability of contrast media from vertebral to disc, it is not useful to directly measure the enhancement at disc by MR image in clinical examination, but it is practical to measure the enhancement at vertebra.

As we aforementioned, the disc degeneration has high relation to blood supply and the major blood supply of disc is diffusion from vertebral body. Could we measure the vertebral perfusion to verify, to some degree, the mechanism of the disc degeneration? In this study, Figure 2 shows the disc degeneration is not related to the effect vertebral perfusion. There are multifactors which may influence the perfusion in vertebral marrow, including age, sex, tumor, fracture, bone marrow density, fat marrow content, exercise and career [10].Therefore, in this study, as shown on Figure 3 and 4, we eliminated those influenced factors by

normalization method by making ratio between two vertebrae. Results of the normalized ratio indicated the two types of vertebra perfusion which degenerative to normal disc in degeneration group I, same type of vertebral perfusion that normal to normal disc in normal group, and same type of vertebral perfusion that degenerative to degenerative disc in degeneration group II. Our results showed that the vertebra perfusion with degenerative disc could be reduced more 10% comparing the normal one (normalized peak enhancement: 0.8455±0.0036 in the degeneration group I), and the vertebral perfusion with same disc condition was similar (normalized peak enhancement: 0.9880±0.0022 in the normal group, and 0.9730±0.0066 in the degeneration group II). The results showed the normalized peak enhancement in group I was significantly lower than the other two groups (Fig. 3), although the same data showed it was no significant difference (Fig. 2). Our results obviously demonstrated the vertebra perfusion could be reduced as disc degenerated and the variation was successfully depressed using the normalization method.

Although the results showed the normalized peak enhancement is significant difference between group I and other two group, we may concern the difference come from those values larger than 1 (Fig 3). For strict comparison, the normalized peak enhancement values were calculated from the vertebra with smaller peak enhancement to the larger one in degeneration group II and normal group that force all ratios were smaller than 1 . Our results showed the variation of vertebra perfusion with same disc condition was smaller than 10% comparing each one (normalized peak enhancement: 0.9621±0.0007 in the normal group, and 0.9332±0.0014 in the degeneration group II). The results still showed the normalized peak enhancement in group I was significantly lower than the other two groups (Fig. 3).

The normalized method can reduce variety of perfusion and enhance the divergence that we focused on. We, therefore, demonstrated that the vertebral marrow perfusion had close relationship to disc degeneration.

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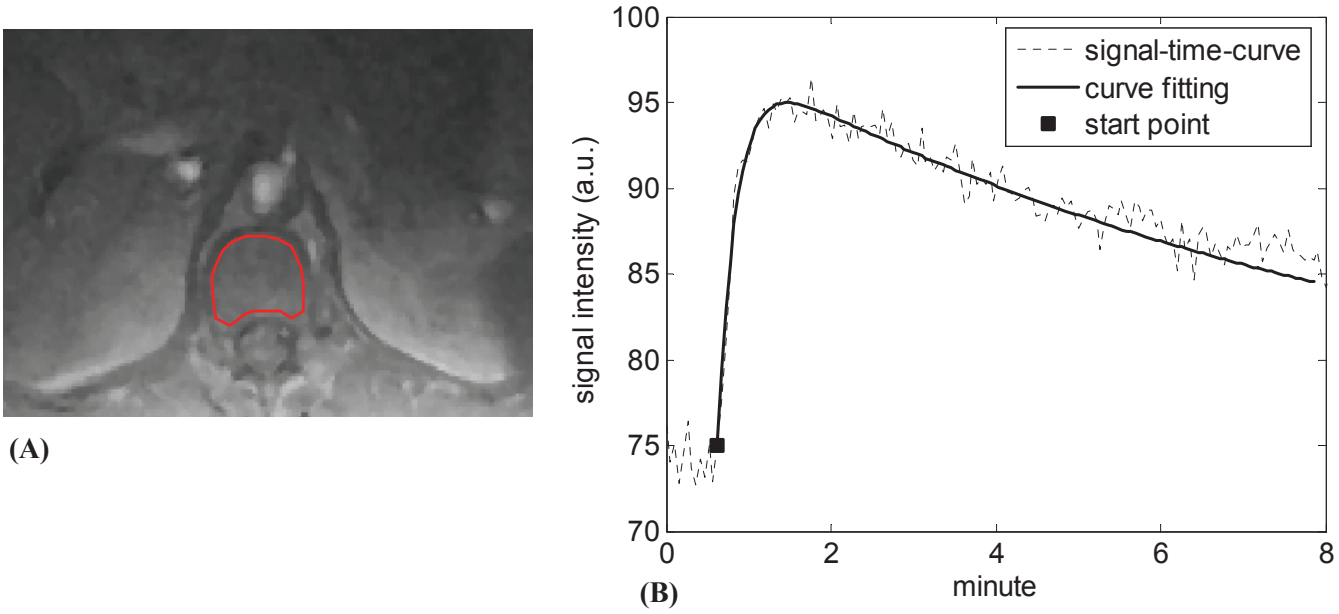

Figure 1 **(A)** Signal time values were measured in operator-defined regions of interest (ROIs) over the whole vertebral body. **(B)** The fitted signal-time curve of ROI, which signal averaged by all pixels, was calculated using this equation by nonlinear least square error curve fitting. The peak enhancement value ($\frac{S_{max} - S_0}{S_0}$) of fitted signal-time curve was computed for evaluating vertebra perfusion.

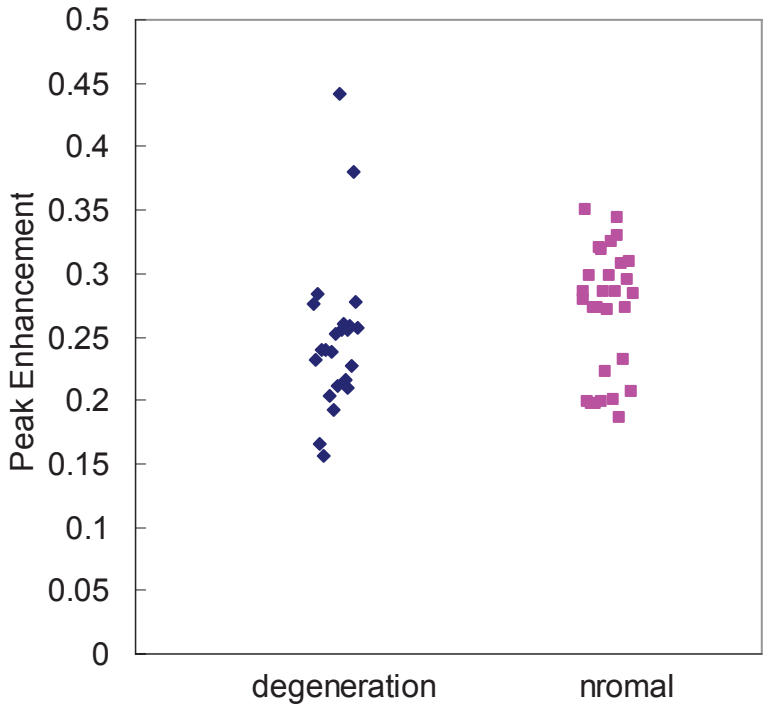

Figure 2. Scatterplot shows the distribution of the peak enhancement values. The spread are overlap between degeneration group (0.2450 ±0.0038) and normal group (0.2703 ±0.0025). There is no significant difference between two groups (P=0.11).

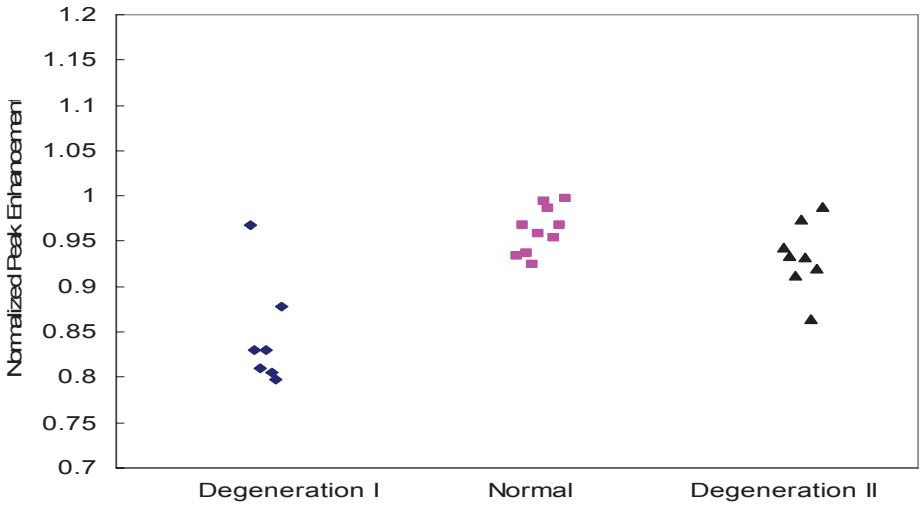

Figure 3 Scatterplot shows the distribution of the normalized peak enhancement values. The normalized peak enhancement is a ratio of two peak enhancement at same subject. In the degeneration group I, the ratio is the peak enhancement of vertebra between two degenerative discs to the vertebra between two normal discs. Coincidentally, all the vertebras with two degenerative discs were L3 and the normal ones were L1 in the degeneration group I. For comparing under same condition, the normalized peak enhancement values were also calculated from L3 divide by L1 (L3/L1) in other two groups. The mean and SD is 0.8455±0.0036 in the degeneration group I, 0.9880±0.0022 the normal group, and 0.9730±0.0066in the degeneration group II. It is significant difference between normal and group I ($P < 0.01$), and between group I and group II ($P < 0.01$). There is no significant difference between normal and degeneration group II ($P=0.32$).

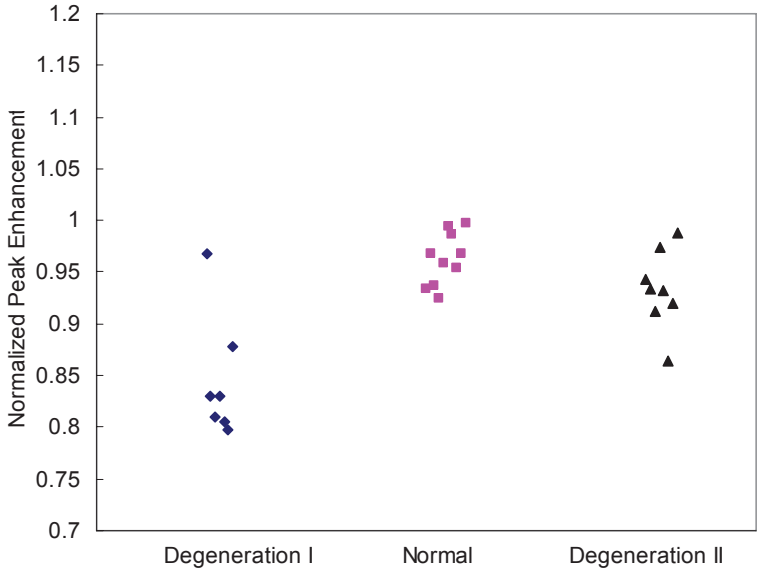

Figure 4 Scatterplot shows the distribution of the normalized peak enhancement values. According the definition of normalized peak enhancement, the results in degeneration group I is not only L3/L1 but also smaller than 1. For strict comparison, the normalized peak enhancement values were calculated from the vertebra with smaller peak enhancement to the larger one in degeneration group II and normal group. The mean and SD is 0.8455±0.0036 in the degeneration group I, 0.9621±0.0007 in the normal group, and 0.9332±0.0014 in the degeneration group II. It is significant difference between normal and degeneration group I ($P < 0.01$), and between degeneration group I and II ($P < 0.01$). There is no significant difference between normal and degeneration group II ($P=0.09$).