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Relationship between Marrow Perfusion and Bone Mineral Density: a Pharmacokinetic Study of DCE-MRI*

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***Abstract*—A reduced bone perfusion has been found for osteoporotic subjects in previous studies. However, the physiological changes underlying the varied perfusion function is not well known yet. Tofts model is one of the most frequently used pharmacokinetic models in analyzing perfusion process. This study modified the Tofts model by replacing the arterial input function (AIF) by a new algorithm. The modified model was then employed to analyze vertebral bone marrow perfusion in subjects with different bone mineral density (BMD). Eighty-two male subjects were involved in this study and classified into three groups (normal, osteopenia, and osteoporosis) according to T-score. BMD was measured by dual-energy X-ray absorptiometry (DXA). The quantitative parameters derived from the pharmacokinetic model, K^{trans} (extravasation transfer efficiency for blood perfusion) and v_e (extravascular extracellular space for blood perfusion), showed a significant reduction in subjects with lower BMD, respectively. The results suggested that with the bone mineral content lost, the vascular wall properties as well as the bone marrow content may also vary. The resultant perfusion change may also influence the bone nutrition supply in reverse.**

I. Introduction

Osteoporosis is a common bone disease in elderly. In recent decades, clinical, epidemiological and histological studies have indicated a link between vascular disease and osteoporosis [1-4]. The vascular variation in tissue can be reflected by perfusion function, which has been measured by dynamic contrast-enhanced MRI (DCE-MRI) in previous studies [5,6]. Bone perfusion is a physiological process, refering to a diverse process dependent on factors such as tissue blood flow, capillary capacitance and permeability, interstitial diffusion, interstitial space volume, and venous return [7,8]. Our previous studies have shown how semi-quantitative perfusion parameters (enhancement maximum, E_{max}, and enhancement slope, E_{slope}) are consistently reduced in osteopenic and osteoporotic bone compared to normal bone mineral density (BMD) subjects [5,6,9]. Another work using a modified Brix model to analyze bone perfusion indicated that the blood perfusion volume reduced in osteoporotic bone compared to subjects with normal BMD [10]. However, both methods had limitation in evaluation the underlying physiological property for bone perfusion. Semi-quantitative method only can indicate the trend in perfusion change while the assumption of Brix model cannot reflect the bone perfusion change under a varied arterial input function (AIF). There were studies reported the importance of AIF selection for the pharmacokinetic analysis of DCE-MRI [11,12]. Therefore, the AIF should be included in the bone marrow perfusion investigation.

The objective of this study is to characterize bone perfusion properties in a quantitative way by adopting personalized AIF. Tofts model, which is classical model for DCE-MRI analysis, was modified through replacing the fixed AIF by a personalized AIF function. Quantitative parameters, K^{trans} (extravasation transfer efficiency for blood perfusion) and v_e (extravascular extracellular space for blood perfusion), were extracted and compared among groups defined as normal, osteopenia, and osteoporosis.

II. Methodology

A. Subjects

In order to avoid gender influence, only male subjects were selected. This study involved a reassessment of DCE-MRI raw data obtained in one previous study [5]. Subjects were excluded if they had (a) clinical or imaging evidence of renal osteodystrophy or other metabolic bone disease other than osteoporosis or a known malignancy, (b) a history of lumbar spinal surgery or irradiation, or (c) MR imaging evidence of large intravertebral disk herniation, hemangioma, or moderate to severe vertebral fracture of L3. Eighty-two subjects (age 72.4±3.6 yrs) in total were involved in this retrospective study. The study was approved by the Ethics committee, Chinese University of Hong Kong with all participating subjects providing written consent.

B. Data acquisition

Area bone mineral density (BMD) of L3 level was measured by the dual-energy X-ray absorptiometry (DXA).

MR imaging was performed at 1.5T (Intera NT, Philips,

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Best, Netherlands). Axial T1-weighted (TR/TE, 450/11 ms; 4 mm thick) MR image of the mid-L3 vertebrae was obtained. Dynamic contrast enhancement MRI (DCE-MRI) data were acquired through the mid-L3 vertebral body region. Dynamic MR imaging was performed using a short T1-weighted gradient-echo sequence (2.7/0/95; prepulse inversion time, 400 ms; flip angle, 15°). A total of 160 dynamic images were obtained with a temporal resolution of 543 ms, resulting in a total interrogation time of 87 seconds. A bolus of gadoteric acid (Dotarem, Guer-Guerbet, Aulnay, France) at a concentration of 0.15 mmol per kilogram body weight was injected via a power injector (Spectris; Medrad, Indianola, Pa) at a rate of 2.5 mL/s through a 20-gauge antecubitial vein intravenous catheter (Angiocath; Infusion Therapy Systems, Sandy, Utah). Injection was followed by a 20-mL saline flush. Dynamic MR imaging started at the same time as contrast medium injection started ("time zero" or T_0).

C. Data processing

Region of interest (ROI) was drawn manually on the T1-weighted MRI image, which was co-registered to the DCE images, to obtain the characteristic signal. The ROI was drawn encompassing the cancellous bone of vertebral body (as shown in Fig.1). Signal intensity within the ROI was averaged to generate a time-signal intensity curve for each ROI, which was saved for off-line analysis.

Tofts model was employed and modified. Originally the pharmacokinetic process was defined by Tofts et al by using differential equation for a two compartment model [7].

$$\frac{dC_t}{dt} = K^{trans} C_p - K^{trans} C_t / v_e \qquad (1)$$

where v_e is the extravascular extracellular space (EES); C_t and C_p are the concentration of the contrast agent in the EES and plasma space respectively, K^{trans} (min^{-1}) is the extravasation transfer constant.

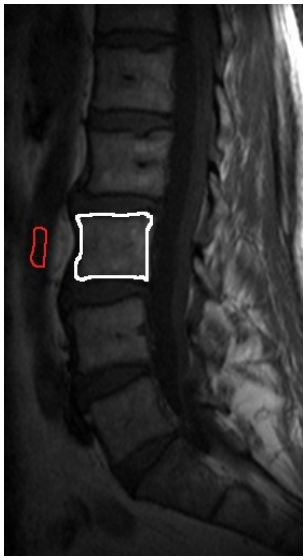

Fig. 1 ROI drawn in T1-weighted MR image in sagittal plane. The left red ROI was for abdominal arterial and the ROI on the right was for the bone marrow respectively.

In Eq.1, $C_p(t)$, which is also called AIF, can be regarded as the contrast agent source to be perfused into the tissue. In original Tofts model, the AIF was assumed by a fixed bi-exponential equation, which was derived from experiment. However, the AIF could be different for subjects even under the same experiment conditions. In this study, we employed an algorithm [11] to model AIF for each subject and integrate this formulism into Tofts model to derive pharmacokinetic parameters. The AIF was modeled as

$$C_p(t) = A \cdot t \cdot \exp(-t \cdot B) + C[1 - \exp(-t \cdot D)] \cdot \exp(-t \cdot E) \qquad (2)$$

where A, B, C, D, and E are density and time constants respectively. This AIF is reasonable and similar in form to that of Simpson et al. [13].

For each data set, AIF was first characterized by fitting the AIF signal with Eq.2 from the starting point (shown in Fig.2.a). The derived model parameters of AIF were then substituted into Eq.1. The pharmacokinetic parameters, K_{trans} and v_e were obtained by fitting the bone marrow characteristic signal from the starting point to the end by the Eq.1 using the least square method (shown in Fig.2.b).

In total, 164 ROIs of 82 subjects were analyzed. The subjects were classified into three groups according to the T-score derived from the BMD with the criteria of WHO.

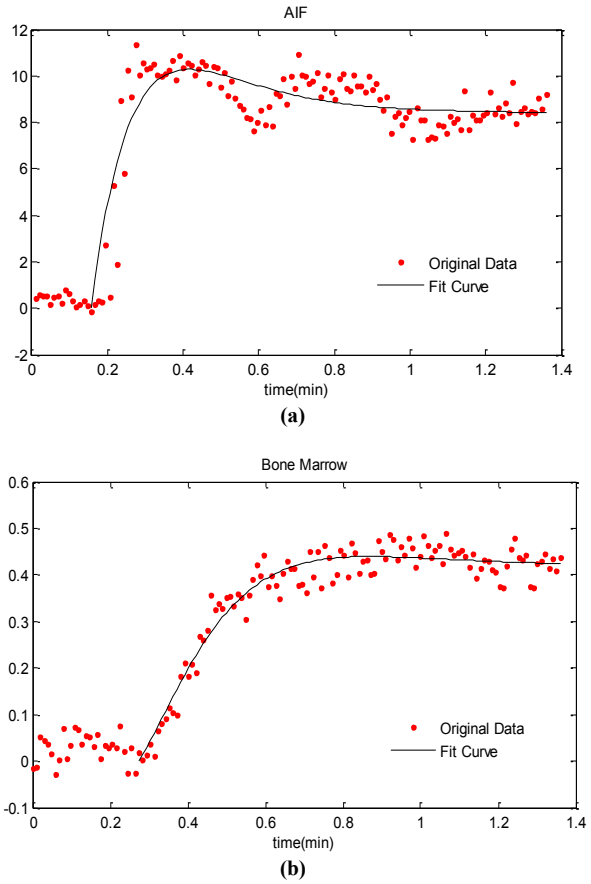

Fig. 2 Data processing on DCE data. (a) Curve fitting by AIF model to derive characteristic parameters, (b) Curve fitting by pharmacokinetic model. The solid and smooth lines are the fitting results.

Analysis of variance method (ANOVA) was employed to evaluate differences in pharmacokinetic parameters among groups with different BMD. Statistical analysis was performed using statistical software (SPSS 16.0). A p value of less than 0.05 was considered statistically significant.

III. RESULTS

For perfusion quantification, parameters K_{trans} and v_e were derived to indicate the perfusion extravasation transfer constant and the EES respectively. ANOVA analysis results are summarized in Table 1. Age shows no significant difference among the three groups. The two investigated pharmacokinetic parameters showed a significant decrease in groups with lower BMD compared to normal group.

TABLE 1 ANOVA ANALYSIS RESULTS

Param	Group(N)	Mean	SD	P-value
K^{trans} (min^{-1})	Normal (n=15)	0.189	0.097	0.005
	Osteopenia (n=25)	0.169	0.165	
	Osteoporosis (n=42)	0.091	0.084	
V_e	Normal (n=15)	0.029	0.015	0.001
	Osteopenia (n=25)	0.025	0.015	
	Osteoporosis (n=42)	0.015	0.012	
Age (yrs)	Normal (n=15)	73.69	3.79	0.667
	Osteopenia (n=25)	72.24	2.83	
	Osteoporosis (n=42)	72.07	3.88	

IV. DISCUSSIONS

DCE-MRI is a useful and widely used method of assessing tissue perfusion and has been used to study bone perfusion in recent years in a variety of physiological and disease conditions. DCE-MRI can provide a direct measurement of tissue perfusion in a living system, which can reflect the blood supply in a microenvironment. Bone is composed of trabecular and cortical bone. All of the trabecular bone and the inner two-thirds of the cortical bone receive its blood supply from the marrow cavity. Our previous DCE-MRI studies have shown how perfusion parameters are reduced in osteoporotic bone [6,9,10]. This study further evaluated the bone perfusion in osteoporotic bone by a modified Tofts model, which reflected the contrast agent transfer efficiency and the EES which is for the contrast agent to perfuse.

After a bolus injection, tissue concentration of gadolinium is determined by local blood flow, capillary capacitance, vessel permeability, interstitial space and interstitial diffusion. The reduction in K^{trans} implied a degenerated blood vessel function, which could be a decreased vessel wall permeability. Such reduction could also diminish the nutrition exchange between the bone tissue and the vessel.

The other parameter, v_e, which indicated the interstitial space, was also decreased in osteoporotic bone. With the bone mineral content lost, there must be changes in bone marrow content to result in a smaller interstitial space. In our previous study, such change is most probably the marrow fat content increase. The diminished interstitial space would inverse influence the blood supply to bone tissue.

As a conclusion, our results confirmed previous findings and provided further details in bone marrow perfusion characteristics and BMD loss. Further investigation is still needed to provide more evidence on the perfusion physiologies with the BMD loss.

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REFERENCES

[1] S.Y. Wong, T. Kwok, J. Woo, et al. Bone mineral density and the risk of peripheral arterial disease in men and women: results from Mr. and Ms Os, Hong Kong. *Osteoporos Int.*, vol. 16, pp. 1933-1938, 2005.

[2] Y. Z. Bagger, L. B. Tanko, P. Alexandersen, H. B. Hansen, G. Qin, C. Christiansen. The long-term predictive value of bone mineral density measurements for fracture risk is independent of the site of measurement and the age at diagnosis: results from the Prospective Epidemiological Risk Factors study. *Osteoporos Int.*, vol. 17, pp.471-477, 2006.

[3] M. Laroche, L. Moulinier, P. Leger, D. Lefebvre, B. Mazieres, H. Boccalon. Bone mineral decrease in the leg with unilateral chronic occlusive arterial disease. *Clin Exp Rheumatol*., vol. 21, pp. 103-106, 2003.

[4] R. A. Mangiafico, E. Russo, S. Riccobene, et al. Increased prevalence of peripheral arterial disease in osteoporotic postmenopausal women. *J Bone Miner Metab.*, vol. 24, pp. 125-131, 2006.

[5] J. F. Griffith, D. K. Yeung, G. E. Antonio, et al. Vertebral bone mineral density, marrow perfusion, and fat content in healthy men and men with osteoporosis: dynamic contrast-enhanced MR imaging and MR spectroscopy. *Radiology*., vol. 236, pp. 945-951, 2005.

[6] J. F. Griffith, D. K. Yeung, G. E. Antonio, et al. Vertebral marrow fat content and diffusion and perfusion indexes in women with varying bone density: MR evaluation. *Radiology*., vol. 241, pp. 831-838, 2006.

[7] P. S. Tofts. Modeling tracer kinetics in dynamic Gd-DTPA MR imaging. *J Magn Reson Imaging*., vol. 7, pp. 91-101, 1997.

[8] R. Luypaert, S. Boujraf, S. Sourbron, M. Osteaux. Diffusion and perfusion MRI: basic physics. *Eur J Radiol*., vol. 38, pp. 19-27, 2001.

[9] J. F. Griffith, D. K. Yeung, P. H. Tsang, et al. Compromised bone marrow perfusion in osteoporosis. *J Bone Miner Res*., vol.23, pp. 1068-1075, 2008

[10] H. T. Ma, J. F. Griffith, D. K. Yeung, P. C. Leung, Modified Brix Model Analysis of Bone Perfusion in Subjects of Varying Bone Mineral Density, *J Magn Reson Imaging.*, vol. 31, no. 5, pp. 1169-1175, May 2010.

[11] T. E. Yankeelov, J. J. Luci, M. Lepage, R. Li, L. Debusk, et al. Quantitative pharmacokinetic analysis of DCE-MRI data without an arterial input function: a reference region model, *Magnetic Resonance Imaging.*, vol. 23, pp. 519-529, 2005.

[12] I. A. Mendichovszky, M. Cutajar, I. Gordon, Reproducibility of the aortic input function (AIF) derived from dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) of the kidneys in a volunteer study, *European Journal of Radiology*., vol. 71, pp. 576-581, 2009.

[13] N. E. Simpson, Z. He, J. L. Evelhoch, Deuterium NMR tissue perfusion measurements using the tracer uptake approach: I. Optimization of methods, Magn Reson Med., vol. 42, pp. 42-52, 1999