

· 临床研究 ·

## 慢性肾脏病与脑小血管病患者磁共振弥散张量成像的相关性研究

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**【摘要】目的** 探讨慢性肾脏病(CKD)与脑小血管病(SVD)患者磁共振弥散张量成像(DTI)的关系。**方法** 选取2012年10月至2014年5月南京医科大学附属南京医院神经内科诊治的54例SVD患者, 根据肾小球滤过率(GFR)将患者分为CKD组(17例)和非CKD组(37例)。行常规磁共振成像(MRI)和DTI检查, 观察感兴趣区部分各向异性(FA)及表观扩散系数(ADC)的变化, 分析FA、ADC值与GFR的相关性。**结果** 与非CKD组比较, CKD组双侧半卵圆中心、丘脑和右侧额叶FA值明显降低( $P < 0.05$ ); CKD组双侧半卵圆中心、右侧额叶ADC值明显升高( $P < 0.05$ )。Pearson相关分析示, 双侧半卵圆中心及左侧丘脑FA值与GFR呈正相关( $r = 0.591, P = 0.000; r = 0.544, P = 0.000; r = 0.282, P = 0.039$ ); 双侧半卵圆中心ADC值与GFR呈负相关( $r = -0.490, P = 0.000; r = -0.405, P = 0.002$ )。**结论** DTI能更敏感地发现SVD患者脑微观结构的变化, DTI与GFR有密切的关系, 能为评价CKD并发SVD提供研究工具。

**【关键词】** 肾脏病, 慢性; 脑小血管疾病; 肾小球滤过率; 弥散张量成像

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## Correlation of chronic kidney disease with diffusion tensor imaging in patients with cerebral small vessel disease

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**【Abstract】Objective** To investigate the correlation of chronic kidney disease (CKD) with diffusion tensor imaging (DTI) in the patients with cerebral small vessel disease (SVD). **Methods** A total of 54 patients with confirmed SVD according to expert consensus admitted in the Nanjing Hospital from October 2012 to May 2014 were enrolled in this study. They were divided into 2 groups based on the glomerular filtration rate (GFR): CKD group [GFR < 60(ml/min · 1.73)m<sup>2</sup>,  $n = 17$ ] and non-CKD group ( $n = 37$ ). All of them received conventional magnetic resonance imaging (MRI) and DTI. The fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values were measured in the regions of interest. The correlation of FA and ADC with GFR was analyzed. **Results** Compared to the non-CKD group, the CKD group had significantly lower FA values in the bilateral centrum semiovale, thalamus and right frontal lobes ( $P < 0.05$ ), and obviously higher ADC values of the bilateral centrum semiovale and the right frontal lobes ( $P < 0.05$ ). Pearson correlation analysis showed that the FA values of bilateral centrum semiovale and left thalamus were positively correlated with GFR ( $r = 0.591, P = 0.000; r = 0.544, P = 0.000; r = 0.282, P = 0.039$ ), and the ADC values of bilateral centrum semiovale were negatively correlated with GFR ( $r = -0.490, P = 0.000; r = -0.405, P = 0.002$ ). **Conclusion** DTI can more sensitively detect the cerebral microstructural changes in SVD patients, and is closely associated with GFR. So it can be used to evaluate CKD complicated with SVD.

**【Key words】** kidney disease, chronic; cerebral small vessel diseases; glomerular filtration rate; diffusion tensor imaging

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脑小血管病(cerebral small vessel disease, SVD)是导致老年血管性认知障碍、痴呆以及步态和平衡障碍、情绪低落、尿失禁等的主要原因之一<sup>[1]</sup>。早期发现和处理血管危险因素特别是SVD具有重要意义。慢

性肾脏病(chronic kidney disease, CKD)已被证实是SVD的一个独立的危险因素<sup>[2]</sup>。近年来, 关于CKD与SVD的研究多集中在常规磁共振成像(magnetic resonance imaging, MRI)可见的脑白质病变区, 而脑

白质病变周围看似正常的脑白质微结构是否受到影响,目前研究较少。本研究以54例SVD患者为研究对象,对其进行磁共振弥散张量成像(diffusion tensor imaging, DTI)研究,探讨CKD与DTI之间的关系。

## 1 对象与方法

### 1.1 研究对象

选取2012年10月至2014年5月南京医科大学附属南京医院神经内科诊治的SVD患者54例,均符合SVD专家共识的诊断标准<sup>[3]</sup>。其中男性46例,女性8例;年龄44~90(66.44±12.25)岁;均为右利手,且签署知情同意书。均经影像学证实,MRI显示有腔隙性脑梗死或脑白质病变,无皮质下及分水岭梗死,皮质下无直径>15mm的病灶,脑白质病变Fazekas分级<2级;颈部血管超声显示无明显颈动脉狭窄;血管MRI显示无颅内大动脉狭窄或闭塞。排除标准:(1)颅脑损伤、颅内肿瘤、多发性硬化、帕金森病、痴呆、癫痫等累及中枢神经系统的疾病;(2)嗜酒、吸毒或其他精神性药物滥用者(如抗精神病药、苯二氮 类药等);(3)合并严重内科急症,如心肺肝肾功能衰竭、感染、免疫性疾病等;(4)MRI禁忌证或已知的幽闭恐怖症。

### 1.2 方法

1.2.1 肾小球滤过率(glomerular filtration rate, GFR)的测定 患者在入院第2日清晨,空腹采外周静脉血4ml,用于肾功能、血脂等生化指标的测定,由奥林巴斯AU5421全自动生化分析仪完成。血总胆固醇≥5.18mmol/L为高胆固醇血症,三酰甘油≥1.70mmol/L为高三酰甘油血症(hypertriglyceridemia, HTG),血清超敏C反应蛋白(high-sensitivity C-reactive protein, hs-CRP),正常参考值<3mg/L。GFR由血肌酐水平通过Cockcroft-Gault公式估算,GFR<60(ml/min·1.73m<sup>2</sup>)定义为CKD<sup>[4]</sup>,根据CKD诊断标准分组,CKD组17例,非CKD组37例。

1.2.2 头颅MRI检查 采用Philips, Achieva Tx 3.0T MRI系统,在入院24h内进行头颅MRI检查,扫描序列及参数包括,T1WI[重复时间(repetition time, TR)/回波时间(echo time, TE)2000/20ms],T2WI(TR/TE 3000/80ms),液体衰减反转恢复序列[(FLAIR)TR/TE/TI 11000/125/2800ms],DWI(TR/TE 2245/90ms,FOV 210×210×118,矩阵140×109像素,bmax1000s/mm<sup>2</sup>)。DTI扫描采用单次激发SE EPI序列(TR/TE 6636/90,NEX 2;FOV 224×224×120,矩阵112×112,像素大小为2mm×

2mm×2mm,层厚2mm,层间距0.2mm,60层连续扫描)。15个方向上施加弥散梯度和一个没有弥散加权的采集,其中b=800s/mm<sup>2</sup>。

1.2.3 图像后处理 数据处理应用Philips专用后处理软件EWS2.6.3.3对DTI原始采集图像进行后处理,应用弥散对齐软件包对DTI原始图像进行对齐,进行涡流校正以及头动校正,提高图像质量,显示部分各向异性(fractional anisotropy, FA)图,表观扩散系数(apparent diffusion coefficient, ADC)图。在FA图及ADC图上基于感兴趣法分别测得两侧额叶、半卵圆中心、尾状核、豆状核、丘脑等感兴趣区(region of interest, ROI,约8mm<sup>2</sup>)的FA值及ADC值。所有测量值均由两位与本研究无关的独立研究者完成,一共测量3次,取其平均值。

### 1.3 统计学处理

采用SPSS19.0统计软件,两组FA值、ADC值的比较采用独立样本t检验,相关性采用Pearson相关分析。以P<0.05为差异有统计学意义。

## 2 结果

### 2.1 两组患者基本资料比较

与非CKD组比较,CKD组GFR明显降低(P<0.001)。两组年龄、性别、糖尿病史、高血压病史、高胆固醇血症、HTG、hs-CRP比较,差异均无统计学意义(P>0.05;表1)。

表1 两组患者基本资料比较  
Table 1 Comparison of general characteristics between non-CKD group and CKD group

| Item                                                  | Non-CKD group<br>(n = 37) | CKD group<br>(n = 17) |
|-------------------------------------------------------|---------------------------|-----------------------|
| Age(years, $\bar{x} \pm s$ )                          | 65.70 ± 13.18             | 68.06 ± 10.10         |
| Male/female(n/n)                                      | 31/6                      | 15/2                  |
| Diabetes[n(%)]                                        | 9 (24.3)                  | 5 (29.4)              |
| Hypertension[n(%)]                                    | 15 (40.5)                 | 8 (47.1)              |
| Hypercholesterolemia[n(%)]                            | 6 (16.2)                  | 3 (17.6)              |
| HTG[n(%)]                                             | 7 (18.9)                  | 4 (23.5)              |
| hs-CRP(mg/L, $\bar{x} \pm s$ )                        | 1.82 ± 3.48               | 2.06 ± 3.82           |
| GFR[ml/(min · 1.73m <sup>2</sup> ), $\bar{x} \pm s$ ] | 69.26 ± 7.43              | 50.65 ± 7.37***       |

CKD: chronic kidney disease; HTG: hypertriglyceridemia; hs-CRP: high-sensitivity C-reactive protein; GFR: glomerular filtration rate. Compared with non-CKD group, \*\*\*P<0.001

### 2.2 两组患者各脑区FA值比较

与非CKD组比较,CKD组双侧半卵圆中心、丘脑和右侧额叶FA值明显降低(P<0.05);而两组双侧尾状核、豆状核和左侧额叶FA值比较,差异均无统计学意义(P>0.05;图1,表2)。

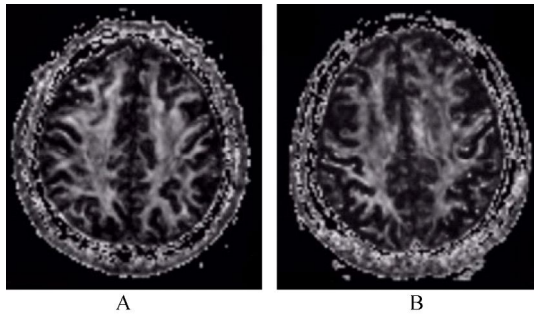


图1 半卵圆中心FA图

Figure 1 FA of centrum semiovale

FA: fractional anisotropy; CKD: chronic kidney disease. A: non-CKD group; B: CKD group

表2 两组各脑区FA值比较

Table 2 Comparison of the FA values in the brain regions between non-CKD group and CKD group ( $\bar{x} \pm s$ )

| Region                  | Non-CKD group<br>(n = 37) | CKD group<br>(n = 17) |
|-------------------------|---------------------------|-----------------------|
| Left centrum semiovale  | 0.458 ± 0.067             | 0.387 ± 0.065**       |
| Right centrum semiovale | 0.478 ± 0.049             | 0.387 ± 0.076**       |
| Left caudate nucleus    | 0.201 ± 0.048             | 0.200 ± 0.046         |
| Right caudate nucleus   | 0.207 ± 0.056             | 0.195 ± 0.059         |
| Left lentiform nucleus  | 0.233 ± 0.057             | 0.214 ± 0.059         |
| Right lentiform nucleus | 0.226 ± 0.061             | 0.233 ± 0.063         |
| Left thalamus           | 0.295 ± 0.055             | 0.258 ± 0.054*        |
| Right thalamus          | 0.289 ± 0.047             | 0.251 ± 0.053*        |
| Left frontal lobe       | 0.419 ± 0.083             | 0.375 ± 0.090         |
| Right frontal lobe      | 0.435 ± 0.092             | 0.368 ± 0.096*        |

FA: fractional anisotropy; CKD: chronic kidney disease. Compared with non-CKD group, \* $P < 0.05$ , \*\* $P < 0.01$

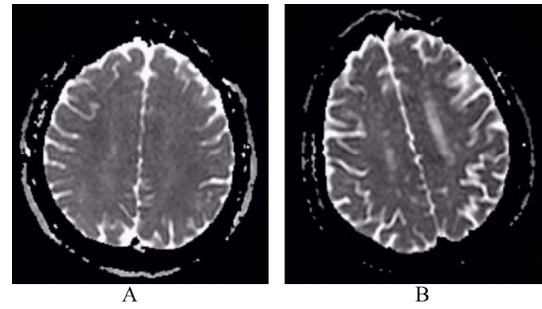


图2 半卵圆中心ADC图

Figure 2 ADC of centrum semiovale

ADC: apparent diffusion coefficient; CKD: chronic kidney disease. A: non-CKD group; B: CKD group

表3 两组各脑区ADC值比较

Table 3 Comparison of the ADC values in the brain regions between non-CKD group and CKD group ( $10^{-3} \text{mm}^2/\text{s}$ ,  $\bar{x} \pm s$ )

| Region                  | Non-CKD group<br>(n = 37) | CKD group<br>(n = 17) |
|-------------------------|---------------------------|-----------------------|
| Left centrum semiovale  | 0.734 ± 0.088             | 0.895 ± 0.266*        |
| Right centrum semiovale | 0.733 ± 0.094             | 0.877 ± 0.270*        |
| Left caudate nucleus    | 0.715 ± 0.094             | 0.769 ± 0.172         |
| Right caudate nucleus   | 0.729 ± 0.080             | 0.784 ± 0.142         |
| Left lentiform nucleus  | 0.706 ± 0.126             | 0.753 ± 0.172         |
| Right lentiform nucleus | 0.740 ± 0.138             | 0.801 ± 0.187         |
| Left thalamus           | 0.767 ± 0.113             | 0.794 ± 0.115         |
| Right thalamus          | 0.765 ± 0.083             | 0.794 ± 0.139         |
| Left frontal lobe       | 0.778 ± 0.076             | 0.777 ± 0.124         |
| Right frontal lobe      | 0.767 ± 0.074             | 0.822 ± 0.102*        |

ADC: apparent diffusion coefficient; CKD: chronic kidney disease. Compared with non-CKD group, \* $P < 0.05$

### 2.3 两组患者各脑区ADC值比较

与非CKD组比较, CKD组双侧半卵圆中心、右侧额叶ADC值明显升高( $P < 0.05$ ); 而两组双侧尾状核、豆状核、丘脑和左侧额叶ADC值比较, 差异均无统计学意义( $P > 0.05$ ; 图2, 表3)。

### 2.4 Pearson相关分析

双侧半卵圆中心及左侧丘脑FA值与GFR呈正相关( $r = 0.591$ ,  $P = 0.000$ ;  $r = 0.544$ ,  $P = 0.000$ ;  $r = 0.282$ ,  $P = 0.039$ ); 双侧半卵圆中心ADC值与GFR呈负相关( $r = -0.490$ ,  $P = 0.000$ ;  $r = -0.405$ ,  $P = 0.002$ )。

## 3 讨论

SVD是指脑小血管的各种病变所导致的临床、认知、影像学及病理表现的综合征<sup>[5]</sup>。影像学表现分为脑白质病变、腔隙性脑梗死和脑微出血<sup>[6]</sup>。病变累及颅内小血管(包括小动脉、微动脉、前毛细血管和小静脉)<sup>[7]</sup>。CKD是脑白质病变、静息性脑梗死与脑微出血的独立危险因素, 肾损害可预测SVD的存在和严重性<sup>[8]</sup>。小血管病是系统疾病, 小血管病在某一器官

发病的同时也可对其他器官带来损害。脑和肾均属于低阻抗终末器官, 其小血管系统的解剖结构和血管调控机制相似, 它们在整个心动周期均暴露于高流量血液冲击下, 肾的小血管病理变化在脑小血管可能同样存在<sup>[9]</sup>。Ito等<sup>[10]</sup>提出了“应变血管假说”, 他们认为该假说可以作为脑-心-肾之间的关联机制。另外, 一氧化氮(nitric oxide, NO)水平下降或许是CKD与SVD关联中的一个关键因素。NO被认为与微血管的功能障碍或损伤有关。Baylis<sup>[11]</sup>通过文献综述得出结论: NO缺乏较常见于肾脏疾病患者, NO通过对微循环和血脑屏障进行调节从而延缓SVD的进展。

GFR作为CKD临床指标, 不但与肾小球小血管疾病密切相关, 也与SVD密切相关, 潘晓帆等<sup>[12]</sup>的研究发现, GFR可能优于心血管危险因素成为小血管疾病的预测指标。Oksala等<sup>[13]</sup>的研究显示, 急性脑梗死患者的SVD与肾功能水平密切相关。伴有SVD和肾功能损害[GFR下降,  $\text{GFR} < 60 \text{ml} (\text{min} \cdot 1.73 \text{m}^2)$ ]的脑卒中患者远期存活率低, 而该研究中涉及的SVD包括脑白质病变、腔隙性脑梗死等。Takahashi等<sup>[14]</sup>对2106例无卒中史的受试者进行研究表明, 无症状脑梗死、皮质下深部白质高信号和脑室旁白质高信号的发病率与

GFR的下降显著相关,轻度的肾功能障碍可能独立于高血压而与SVD的增加相关。

DTI是在MRI弥散加权成像基础上发展起来的功能MRI成像技术,首次实现了对脑白质纤维连接的定量分析,能无创性地评估组织结构的完整性与连通性<sup>[15]</sup>。DTI用所测得的多种参数值进行成像,最常用的是FA值,是指弥散张量中的水分子各向异性部分所占整个弥散张量的比例。FA值越高表明组织的各向异性越强,组织排列得越紧密,FA值的大小与髓鞘、微管、微丝的完整性、神经纤维排列的紧密程度及走行方向密切相关。ADC值反映水分子在组织内的弥散运动能力,ADC值越大,说明组织内所含自由水分子越多,扩散能力越强。将两个参数结合起来可以更准确地了解脑白质的形态改变。

本研究利用DTI,选择性地避开腔隙性梗死和白质病变区,选取T1WI、T2WI看似“正常”的白质区域和部分灰质核团作为ROI进行检查。结果发现,CKD组双侧半卵圆中心、丘脑和右侧额叶FA值显著低于非CKD组,差异有统计学意义;双侧半卵圆中心和右侧额叶ADC值显著高于非CKD组,差异有统计学意义。提示合并CKD的SVD患者常规MRI看似正常的部分区域,在应用DTI技术时可发现神经结构已发生微观变化。de Groot等<sup>[16]</sup>的前瞻性研究显示,利用DTI测定689例老年人常规MRI所见正常脑白质区域微细结构改变,随访3.5年后发现,FA降低、ADC升高的白质区域更易发展为脑白质病变。本研究还发现,CKD组双侧半卵圆中心及左侧丘脑FA值与GFR呈正相关;双侧半卵圆中心ADC值与GFR呈负相关。提示GFR下降预示着脑微观结构的改变,CKD与SVD密切相关。

综上所述,DTI可在异常信号出现之前极其敏感地检测到SVD患者脑组织微观结构的变化,且DTI参数值与GFR有密切的关系,为评价CKD并发SVD提供研究工具。

#### 【参考文献】

- [1] Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges[J]. *Lancet Neurol*, 2010, 9(7): 689-701.
- [2] Mogi M, Horiuchi M. Clinical interaction between brain and kidney in small vessel disease[J]. *Cardiol Res Pract*, 2011, 2011: 306189.
- [3] The Diagnosis and Treatment of Cerebral Small Vessel Disease Expert Consensus Group. Expert consensus of diagnosis and treatment of cerebral small vessel disease[J]. *Chin J Intern Med*, 2013, 52(10): 893-896. [脑小血管病诊治专家共识组. 脑小血管病的诊治专家共识[J]. *中华内科杂志*, 2013, 52(10): 893-896.]
- [4] Miwa K, Tanaka M, Okazaki S, *et al*. Chronic kidney disease is associated with dementia independent of cerebral small-vessel disease[J]. *Neurology*, 2014, 82(12): 1051-1057.
- [5] Wardlaw JM, Smith C, Dichgans M. Mechanisms of sporadic cerebral small vessel disease: insights from neuroimaging[J]. *Lancet Neurol*, 2013, 12(5): 483-497.
- [6] Benjamin P, Lawrence AJ, Lambert C, *et al*. Strategic lacunes and their relationship to cognitive impairment in cerebral small vessel disease[J]. *Neuroimage Clin*, 2014, 4: 828-837.
- [7] Hilal S, Ong YT, Cheung CY, *et al*. Microvascular network alterations in retina of subjects with cerebral small vessel disease[J]. *Neurosci Lett*, 2014, 577: 95-100.
- [8] Toyoda K. Cerebral small vessel disease and chronic kidney disease[J]. *J Stroke*, 2015, 17(1): 31-37.
- [9] Liu ZB, Zhao YC. Chronic kidney disease and cerebral small vessel disease[J]. *Clin Misdiagn Misther*, 2013, 26(2): 104-107. [刘振宝, 赵迎春. 慢性肾脏病与脑小血管病[J]. *临床误诊误治*, 2013, 26(2): 104-107.]
- [10] Ito S, Nagasawa T, Abe M, *et al*. Strain vessel hypothesis: a viewpoint for linkage of albuminuria and cerebro-cardiovascular risk[J]. *Hypertens Res*, 2009, 32(2): 115-121.
- [11] Baylis C. Nitric oxide deficiency in chronic kidney disease[J]. *Am J Physiol Renal Physiol*, 2008, 294(1): F1-F9.
- [12] Pan XF, Zhou QD, Hua J, *et al*. Correlative study of renal function and CT quantitative indicators of cerebral small vessel disease[J]. *Chin J Pract Nerv Dis*, 2010, 13(17): 1-3. [潘晓帆, 周其达, 华健, 等. 肾功能与脑小血管疾病CT定量指标的相关性研究[J]. *中国实用神经病杂志*, 2010, 13(17): 1-3.]
- [13] Oksala NK, Salonen T, Strandberg T, *et al*. Cerebral small vessel disease and kidney function predict long-term survival in patients with acute stroke[J]. *Stroke*, 2010, 41(9): 1914-1920.
- [14] Takahashi W, Tsukamoto Y, Takizawa S, *et al*. Relationship between chronic kidney disease and white matter hyperintensities on magnetic resonance imaging[J]. *J Stroke Cerebrovasc Dis*, 2012, 21(1): 18-23.
- [15] Lee SK, Kim DI, Kim J, *et al*. Diffusion-tensor MR imaging and fiber tractography: a new method of describing aberrant fiber connections in developmental CNS anomalies[J]. *Radiographics*, 2005, 25(1): 53-65.
- [16] de Groot M, Verhaaren BF, de Boer R, *et al*. Changes in normal-appearing white matter precede development of white matter lesions[J]. *Stroke*, 2013, 44(4): 1037-1042.

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