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黄斑水肿对糖尿病性视网膜病变黄斑区光学相干断层扫描血管成像测量值的影响

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[摘　要]　**目的：**评估光学相干断层扫描血管成像(optical coherence tomography angiography，OCTA)在糖尿病性黄斑水肿(diabetic macular edema，DME)患眼的黄斑区微血管改变及其与视功能的相关性。**方法：**采用横断面研究，纳入临床检查确诊的无糖尿病性黄斑水肿的糖尿病性视网膜病变(diabetic retinopathy，DR)患者23例24只眼(明确无DME组)及曾经罹患过黄斑水肿但经抗血管内皮生长因子(vascular endothelial growth factor，VEGF)治疗后水肿消退的DR患者14例16只眼(DME经抗VEGF水肿消退组)。受检者均行眼压(intraocular pressure，IOP)、收缩压/舒张压(systolic blood pressure/diastolic blood pressure，SBP/DBP)、黄斑中心凹敏感度(foveal sensitivity，FT)及OCTA技术测量黄斑区3 mm×3 mm范围内中心凹无血管灌注区面积(foveal avascular zone，FAZ)、浅层毛细血管密度(superior vessel density，SVD)、深层毛细血管密度(deep vessel density，DVD)。采用Pearson分析FT与其年龄，眼灌注压(ocular perfusion pressure，OPP)，平均动脉压(mean arterial pressure，MAP)，FAZ，SVD，DVD之间的相关性。**结果：**两组受检眼性别、年龄、眼灌注压对比差异无统计学意义，FT，FAZ，SVD，DVD比较，差异亦无统计学意义(均P>0.05)。相关性检验结果显示：两组受检眼之间FT与SVD，DVD比较，差异无统计学意义(均P>0.05)；明确无DME组中，FT与FAZ之间呈中等程度负相关，差异有统计学意义(r=−0.554，P<0.01)；而DME经抗VEGF水肿消退组中，FT与FAZ比较，差异无统计学意义(P>0.05)。**结论：**与明确无DME组相比，DME经抗VEGF水肿消退组OCTA各参数差异无统计学意义，提示抗VEGF治疗DME具有安全性。此外，黄斑水肿对糖尿病性视网膜病变患者OCTA中FAZ与FT的相关性有影响。

[关键词]　糖尿病性视网膜病变；黄斑水肿；光学相干断层扫描血管成像；抗血管内皮生长因子

Effect of macular edema on the measurement of optical coherence tomography angiography in macula of diabetic retinopathy

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Abstract **Objective:** To quantitatively evaluate the macular microvascular changes in optical coherence tomography (OCTA) in patients with diabetic macular edema (DME) and its relationship with visual function. **Methods:** Twenty-three patients (24 eyes) with diabetic retinopathy (DR) without diabetic macular edema and 14 patients with DR who had macular edema but regained edema after anti-VEGF treatment (the DME subsided group) into the study. All subjects underwent intraocular pressure (IOP), systolic blood pressure/diastolic blood pressure (SBP/DBP), foveal sensitivity (FT), foveal avascular zone (FAZ), superior vessel density(SVD), and deep vessel density (DVD) in a 3 mm × 3 mm OCTA scan of macular. Pearson was used to analyze the correlation between FT and age, ocular perfusion pressure (OPP), mean arterial pressure (MAP), FAZ, SVD, DVD. **Results:** There was no significant difference in sex, age and eye perfusion pressure between the two groups. There were no significant differences between FT, FAZ, SVD and DVD (all P>0.05). Correlation test showed that there were no significant differences in FT, SVD and DVD between the two groups (all P>0.05). In addition, there was a significant difference between FT and FAZ (P<0.01). However, there was no significant difference between FT and FAZ in the DME subsided group (P>0.05). **Conclusion:** There is no significant difference in OCTA parameters between two groups, indicating the safety of anti-vascular endothelial growth factor in treating DME. In addition, macular edema exerts an effect on the relationship between FAZ and FT by OCTA.

Keywords diabetic retinopathy; macular edema; optical coherence tomography angiography; anti-vascular endothelial growth factor

玻璃体腔注射抗血管内皮生长因子(vascular endothelial growth factor，VEGF)药物治疗糖尿病性黄斑水肿(diabetic macular edema，DME)可改善患者视力，减轻黄斑区水肿。光学相干断层扫描血管成像(optical coherence tomography angiography，OCTA)可观察黄斑区视网膜结构，量化糖尿病性黄斑缺血的程度。已有研究[1]应用OCTA来量化糖尿病性视网膜病变(diabetic retinopathy，DR)患者在罹患DME的情况下黄斑中心凹无血管灌注区面积(foveal avascular zone，FAZ)及黄斑区血管密度的变化及其与视力的相关性。但罹患DME经抗VEGF治疗消退的DR患者与无DME的DR患者黄斑区缺血程度及与视力的相关性是否发生变化，目前并不明确。为进一步研究DME对DR患者黄斑缺血的影响，本研究对比观察OCTA对明确无DME、曾经罹患DME但经抗VEGF治疗水肿消退的两组患眼的FAZ、浅层毛细血管密度(superior vessel density，SVD)、深层毛细血管密度(deep vessel density，DVD)的测量差异，并选择中心凹视觉敏感度阈值(foveal threshold，FT)作为视功能评估指标，结合OCTA各参数，初步分析两组患眼黄斑缺血程度与视功能的相关性，现报告如下。

1 对象与方法

1.1 对象

将2017年3~7月上海市第十人民医院眼科检查确诊的37例(40只患眼)无黄斑水肿DR患者(明确无DME组)及年龄、性别相匹配的曾经罹患过黄斑水肿但经抗VEGF治疗后水肿消退的DR患者(DME经抗VEGF水肿消退组)纳入研究。其中明确无DME组23例24只眼中，男11例(11只眼)，女12例(13只眼)，年龄39~71(59.21±9.26)岁；DME经抗VEGF水肿消退组14例16只眼中，男10例(10只眼)，女4例(6只眼)，年龄40~71(53.44±8.43)岁。无DME组纳入标准：1)患者均符合糖尿病性视网膜病变DR的诊断标准，且不存在DME；2)除糖尿病外，无其他全身疾病；3)无手术史及眼部外伤史；4)除DR改变外无其他眼部疾病。DME经抗VEGF水肿消退组纳入标准：1)患者均符合糖尿病性视网膜病变DR的诊断标准，且曾罹患DME但经抗VEGF治疗后水肿消退；2)除糖尿病外，无其他全身疾病；3)无手术史及眼部外伤史；4)除DR改变外无其他眼部疾病。排除标准：1)存在DME的DR患者；2)合并其他眼底疾病，如视网膜静脉阻塞、息肉状脉络膜血管样病变、老年性黄

斑变性等；3)最佳矫正视力(best corrected visual acuity，BCVA)<0.1及固视力差无法配合检查者；4)因不能理解配合仪器测量或屈光间质混浊造成图像信号强度评分(signal strength index，SSI)低于50分者；5)有严重影响眼部健康的全身系统性疾病，如高血压、甲亢等。本研究经同济大学附属第十人民医院医学伦理委员会审核批准，患者及其家属均知情同意。

1.2 方法

受检者均行裂隙灯显微镜、间接检眼镜、非接触眼压计、血压计、OCTA检查及FT测量。FT测量采用Humphrey II型视野分析仪(德国Zeiss公司)，测量3次，取其平均值作为FT值。

受检者在接受上述常规眼科检查后均行OCTA(美国Optovue公司)检查，采用AngioVue Retina模式扫描完成，黄斑区扫描范围选用3 mm×3 mm，嘱患者注视机器内蓝色视标至少保持3 s，依次完成横向和纵向扫描后获得视网膜脉络膜分层血流图像，每个区域扫描2次，保留清晰度最高的图片，选用视网膜中央无血管区、视网膜浅层和视网膜深层血流图像进行分析(图1，图2)。所有受检者的OCTA检查均由同一名熟练的眼科技师完成。

平均动脉压(mean arterial pressure，MAP)=[收缩压(systolic blood pressure，SBP)+2×舒张压(diastolic blood pressure，DBP)]/3，眼灌注压(ocular perfusion pressure，OPP)=2×MAP/3−眼压(intraocular pressure，IOP)。

1.3 统计学处理

应用SPSS 22.0统计软件进行分析。服从正态分布的数据以均数±标准差($\bar{x}\pm s$)表示。组间计量资料比较采用独立样本t检验，相关性分析采用Pearson相关性分析法。P<0.05为差异有统计学意义。

2 结果

独立样本t检验结果显示：两组受检眼FT，FAZ，SVD，DVD相比，差异无统计学意义(均P>0.05，表1)。

相关性检验结果显示：两组受检眼之间FT与SVD，DVD相比，差异无统计学意义(均P>0.05)；此外，明确无DME组中，FT与FAZ之间呈中等程度负相关，差异有统计学意义(r=−0.554，P<0.01)；而DME经抗VEGF水肿消退组中，FT与FAZ比较，差异无统计学意义(P>0.05；表2，图3)。

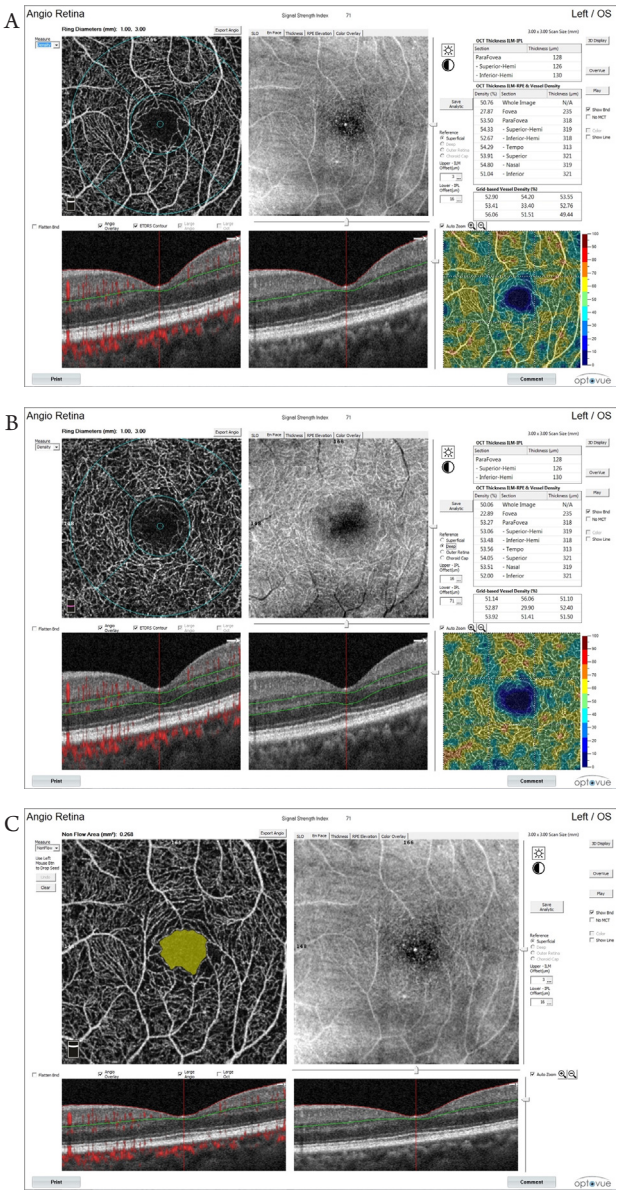

图1 明确无DME组OCTA生成的黄斑区图像

Figure 1 Image of macular area generated in the absence of OCTA of the DME group

(A)浅层毛细血管；(B)深层毛细血管；(C)黄斑中心凹无血管灌注区。

(A) Superficial capillaries; (B) Deep capillaries; (C) Macular foveal avascular perfusion region.

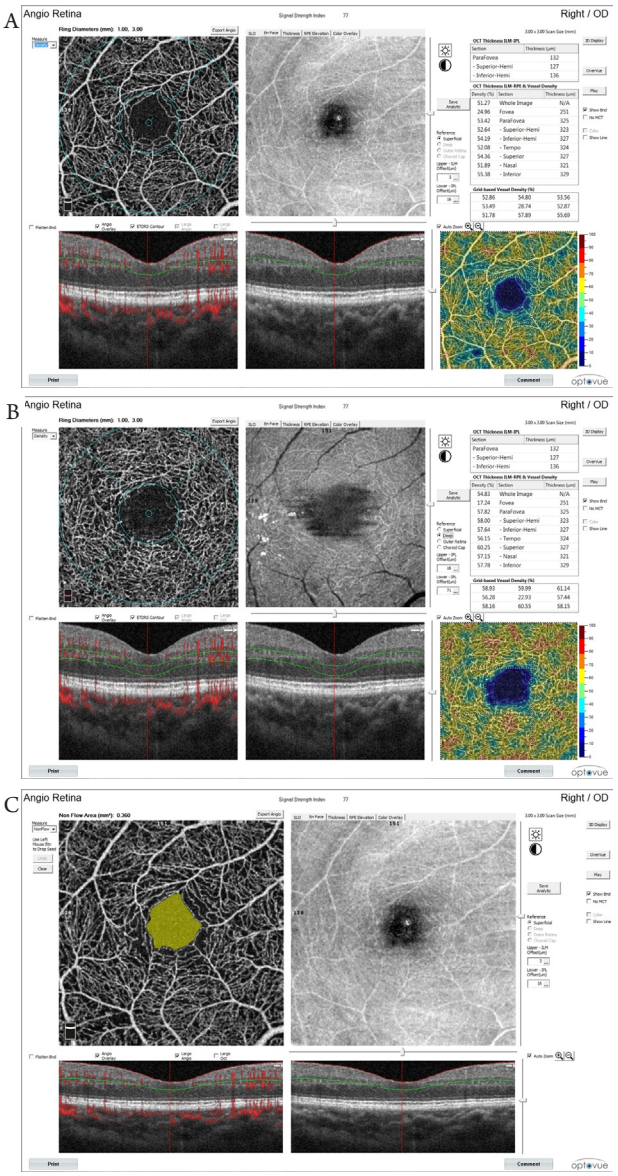

图2 DME经抗VEGF水肿消退组OCTA生成的黄斑区图像

Figure 2 Image of macular area generated by OCTA in the DME with anti-VEGF edema regression group

(A)浅层毛细血管；(B)深层毛细血管；(C)黄斑中心凹无血管灌注区。

(A) Superficial capillaries; (B) Deep capillaries; (C) Macular foveal avascular perfusion area.

表1 两组各指标测量值比较

Table 1 Comparison of measurements between two groups

组别	FT/dB	FAZ/mm^2	SVD/%	DVD/%
明确无DME组	30.54 ± 3.50	0.43 ± 0.10	46.25 ± 5.21	49.97 ± 5.09
DME经抗VEGF水肿消退组	30.19 ± 2.97	0.38 ± 0.14	45.10 ± 4.85	47.47 ± 4.71
t	0.332	1.147	0.707	1.570
P	0.741	0.259	0.484	0.125

表2 两组OCTA各指标与FT的相关性

Table 2 Correlativity of OCTA indicators and FT between two groups

组别	FAZ		SVD		DVD	
	r	*P*	*r*	*P*	*r*	*P*
明确无DME组	−0.554	0.005	−0.373	0.072	0.340	0.104
DME经抗VEGF水肿消退组	−0.253	0.345	−0.161	0.552	0.170	0.529

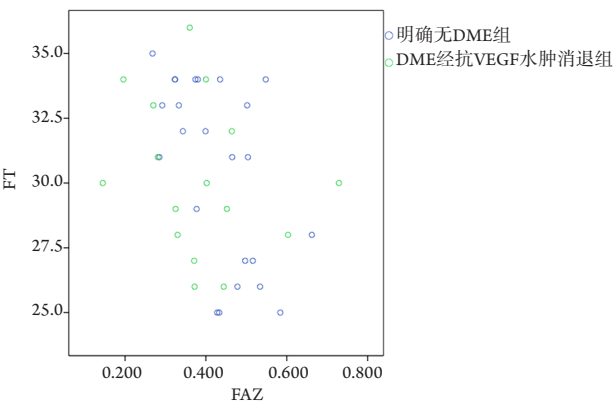

图3 两组FT与FAZ的相关性分析

Figure 3 Correlation analysis OF FT and FAZ between two groups

3 讨论

DME是糖尿病引起的黄斑中心凹一个视盘直径范围内的细胞外液积聚所致的视网膜增厚或硬性渗出沉积，可发生在DR的各个时期，是引起糖尿病患者中心视力下降的重要原因[2-4]。DME的发病机制尚未明确，目前主要认为高血糖导致血管内皮细胞或视网膜内皮细胞功能丢失，血视网膜屏障功能障碍，从而继发DME，其中氧化应激损伤、VEGF及炎症因子发挥重要作用[5-8]。既往针对DME的检查主要依靠荧光素眼底血管造影(fluorescein fundus angiography，FFA)[9]。然而新近

出现的OCTA能够更清晰地显示视网膜深浅层血管及黄斑中心凹无血管区，且OCTA具有无创、方便、快捷、可重复等优点，现已被广泛地应用于眼底疾病的检查[10-11]。已有研究[12-14]证实：DME患者玻璃体腔内VEGF浓度明显高于正常对照人群，VEGF可通过与相应的受体结合从而发挥其生物活性。因此目前临床应用的抗VEGF药物通过阻断VEGF与其受体的结合可有效抑制DME的发生。有研究[15-16]采用OCTA量化DME患者与健康对照组视网膜微循环系统的变化，最终关于DME患眼黄斑区无血管灌注区大小、深浅层血管密度的结果不尽相同。但在无DME或DME经过抗VEGF治疗消退的DR患者黄斑区微循环是否发生变化及与视功能的相关性究竟如何，目前仍缺乏针对性的研究证实。因此，本研究逆向探讨DME经抗VEGF治疗消退患者，以进一步验证曾发生黄斑水肿对黄斑区微循环及视功能的影响，结果显示：两组受检眼FT，FAZ，SVD，DVD比较，差异均无统计学意义，说明黄斑水肿经抗VEGF治疗消退后，并没有进展性黄斑缺血及视功能损害的证据，初步证实玻璃体腔抗VEGF治疗DME可改善黄斑水肿，安全性佳好，这与以往研究[17-19]结果一致。但由于本研究样本量小，随访时间短，其长期疗效及安全性尚需要大样本、多中心的研究加以证实。

FT是通过采用Humphrey II型视野分析仪获得的黄斑中心凹视觉敏感度阈值，显示值越高则灵敏度越高。Flaxel等[20]研究报道：FT与BCVA间具有高度相关性，不仅可作为量化评估视功能的可靠指标，还可作为BCVA的预测因子。近年来，已有研究[21-23]发现黄斑增厚性疾病、视网膜色素变性和青光眼患者的FT与BCVA同样保持良好的一致性。相较FT而言，BCVA是基于红绿测试平衡点的主观结果，更依赖于验光师的经验和受试者的配合程度，FT更能准确地提供黄斑区视功能改变程度，因此本研究选取FT而非BCVA作为反映黄斑区视功能的指标。但同时光敏感度阈值测量属于心理物理学方法，受被测试者情绪、心理状态、认知力及配合程度等影响。本研究结果显示：两组受检眼之间FT与SVD，DVD比较，差异均无统计学意义；而在明确无DME组中，FT与FAZ密切负相关，DME经抗VEGF水肿消退组中，FT与FAZ不相关，导致这一结果的原因可能有：1)研究[15]发现OCTA自动分层可能存在偏差，尤其是当存在DME时可引起视网膜分层错误，且较多研究[24-27]表明：随DR病程进展，FAZ的异常改变及其对视力的影响更为重要，推测两组患者视网膜深浅层血管密度测量值均与视功能不相关。2)既往研究[1,28-29]发现DR患者FAZ增大程度与视力丧失之间呈负相关，这与本研究结果一致。DME经抗VEGF水肿消退组中FT与FAZ两者不相关，其原因可能为：1)导致DR患者视力下降的主要原因是黄斑水肿和光感受器状态特别是椭圆体带的破坏，部分DME患者因光感受器损害严重，即使经抗VEGF治疗水肿消退，视力及视功能也不提高[30-33]。2)既往研究[34-35]证实缺血性DME经VEGF治疗后有可能会加重黄斑缺血，视功能无提高。3)另有部分DME加重DR患者视力的损害，抗VEGF治疗又可改善其视力[34]。

综上所述，本研究总结了黄斑水肿对OCTA黄斑区测量值影响及与视功能相关性，但由于样本量小，同时未将DME的类型和持续时间、血糖控制情况、抗VEGF次数和全身情况等可能对视网膜形态及功能有影响的因素考虑在内，因此有关黄斑水肿对OCTA黄斑区测量值的具体影响及与视功能的相关性仍待进一步研究，有关黄斑中心凹敏感度量化视功能的可靠性及可重复性也需继续探讨。

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