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活体共聚焦显微镜观察视网膜激光光凝术对角膜上皮下神经的影响

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[摘　要]　**目的：**应用活体共聚焦显微镜(in vivo confocal microscopy，IVCM)观察视网膜激光光凝术对角膜上皮下神经的影响。**方法：**收集行视网膜激光光凝术的患者36例46眼，分为糖尿病性视网膜病变(diabetic retinopathy，DR)组(14例22眼)与非DR组(22例24眼)，在治疗前及治疗后1周、1个月应用IVCM采集两组角膜基底层下神经纤维图像，使用Image J和Neuron J软件计算其长度及密度。**结果：**DR组术前角膜神经纤维主干密度(corneal nerve fiber density，CNFD)、角膜神经纤维分支密度(corneal nerve branch density，CNBD)和角膜神经纤维长度(corneal nerve fiber length，CNFL)均低于非DR组，角膜神经弯曲度(corneal nerve fiber tortuosity，CNFT)高于非DR组。两组间角膜神经总分支节点密度(corneal total branch node，CTBN)无显著差异。DR组光凝术后CNFD，CNFL测量值持续降低，术前、术后1周、术后1个月3个观察时段两两之间的差异有统计学意义；光凝术后1个月CNFT与术前的差异有统计学意义。非DR组光凝术后CNFD，CNFL持续降低，术前、术后1周、术后1个月3个观察时段两两之间的差异有统计学意义；CNBD持续升高，术后1周、术后1个月测量值与术前的差异有统计学意义；CNFT持续升高，术后1周、术后1个月测量值与术前的差异均有统计学意义。**结论：**IVCM结合附属软件可量化评估角膜上皮下神经，糖尿病状态和视网膜激光光凝均可对角膜上皮下神经造成损伤。

[关键词]　共聚焦显微镜；角膜神经；激光光凝术；糖尿病

Effect of retinal photocoagulation on corneal sub-basal nerve observed by *in vivo* confocal microscopy

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Abstract　**Objective:** To evaluate the effect of retinal photocoagulation on corneal sub-basal nerve using *in vivo* confocal microscopy (IVCM). **Methods:** In this study, 46 eyes of 36 cases were enrolled. All patients were divided into

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two groups, 22 eyes in the diabetic retinopathy (DR) group and 24 eyes in the non-diabetic retinopathy (NDR) group. IVCM images were obtained to observe sub-basal nerve plexus before retinal photocoagulation and 1 week, 1 mouth after the treatment. Image J and Neuron J software were used for analysis. **Results:** In the DR group, before retinal photocoagulation, the corneal nerve fiber density (CNFD), corneal nerve branch density (CNBD) and corneal nerve fiber length (CNFL) were lower than those in the NDR group while the corneal nerve fiber tortuosity (CNFT) was higher than that in the NDR group. There were no significant differences in corneal total branch node (CTBN) between two groups. The CNFD, CNFL were decreased constantly in the DR group. No statistical significance was observed in either CNBD or CTBN at any time point. After the treatment, the CNFT was enhanced; however, significant differences were noted between 1 week and 1 month. In the NDR group, CNFD, CNFL were declined continually to 1 month, whereas CNBD was increased. CTBN was slightly elevated at each time point without statistical significance. After treatment, CNFT was significantly increased, whereas no statistical significance was observed between 1 week and 1 month. **Conclusion:** IVCM combined with assistant software could be used to quantify corneal sub-basal nerve fiber. Retinal photocoagulation as well as diabetes mellitus can injure corneal sub-basal nerve fiber.

Keywords *in vivo* confocal microscopy; corneal sub-basal nerve fiber; photocoagulation; diabetes mellitus

视网膜激光光凝术是视网膜疾病的主要治疗手段之一，常用于糖尿病性视网膜病变(diabetic retinopathy，DR)、视网膜裂孔、视网膜静脉阻塞(retinal vein occlusion，RVO)、中心性浆液性视网膜病变等疾病的治疗[1]。视网膜光凝主要利用激光的热效应，使作用部位组织发生病理变化[2]。然而作为一种破坏性治疗方法，激光光凝易对视网膜结构、功能造成损伤，导致视野缺损[3-4]、继发性黄斑水肿[5]、脉络膜厚度降低[6-8]等并发症。近年来，视网膜激光光凝术导致的眼表损伤逐渐受到重视[9]。活体共聚焦显微镜(in vivo confocal microscopy，IVCM)是一种新型光学显微镜，具有无创、高分辨率等优点，可在体观察角膜上皮细胞基底层下神经纤维[10]。本研究将应用IVCM从形态学角度评估视网膜激光光凝术对角膜上皮下神经的影响。

1 对象与方法

1.1 对象

纳入2017年4至11月同济大学附属第十人民医院眼科接受视网膜激光光凝治疗的患者。病史，检查视力、眼压、裂隙灯检查、眼底。根据诊断将患者分为DR组和非DR组：DR组需经内科确诊糖尿病，眼底荧光血管造影检查诊断为DR且需接受激光光凝治疗[11]；非DR组要求眼部诊断明确且无糖尿病病史。排除标准：1)瞳孔过小而无法进行激光光凝术；2)已继发玻璃体大量积血、大面积视网膜脱离；3)合并全身免疫性疾病；4)佩戴角膜接触镜；5)具有眼科手术及眼外伤史；6)有角膜炎等眼表疾病；7)因小睑裂等异常无法配合检查及治疗。DR组纳入患者14例22眼，非DR组纳入RVO患者6例6眼、视网膜裂孔患者16例18眼，两组患者性别和年龄差异无统计学意义。本研究经同济大学附属第十人民医院伦理委员会审核批准，患者均签署知情同意书。

1.2 方法

采用海德堡激光共聚焦断层扫描系统3代的Rostock角膜模块对角膜上皮神经丛进行观察，该系统放大倍率为800，分辨率1 μm，激光波长670 nm，观察视野为0.16 mm^2。受检者坐于操纵台前，受检眼以0.4%盐酸奥布卡因进行表面麻醉。调整操纵台高度使下颌与前额分别固定在下颌托与前额托上，开睑器开睑，令患者注视前方，预设置两者接触的焦平面深度为0。前移物镜至与其角膜轻微接触，微调物镜位置，观察受检者角膜中央区域，转动焦平面调节环以获得不同深度的图像，在单眼的角膜中央区域内任意选择3点行立体扫描，从中挑选出

中央基底层下上皮神经最丰富且最清晰的图像进行分析，所有操作均由同一位经验丰富的医师完成。

各项指标测量结束后用复方托吡卡胺滴眼液扩瞳，10 min/次，共3次。对个别瞳孔难以扩开的患者予以加点1~2次直至瞳孔充分扩开。采用0.4%盐酸奥布卡因滴眼液行表面麻醉，放置Volk全视网膜激光透镜。视网膜激光光凝术采用Zeiss VISULAS 532 nm激光机。激光参数：激光时间0.2 s，间隔时间0.2~0.3 s，光斑反应II~III级，两个光斑间隔1个光斑直径，光斑止于距离视盘周围1~1.5 PD处。所有患者视网膜光凝由同一位经验丰富的医师完成。

1.3 图像处理

将采集的图像(图1)以Image J图像分析软件打开，参考张栋等[12]的方法，应用Neuron J插件定量观察：1)角膜神经纤维主干密度(corneal nerve fiber density，CNFD)：每平方毫米图像中神经纤维主干数量(条/mm^2)；2)角膜神经纤维分支密度(corneal nerve branch density，CNBD)：每平方毫米图像中神经纤维主干的分支数量(条/mm^2)；3)角膜神经纤维长度(corneal nerve fiber length，CNFL)：每平方毫米图像中神经纤维总长度(mm/mm^2)；4)角膜神经总分支节点密度(corneal total branch node，CTBN)：每平方毫米图像中神经纤维分支交点数量(个/mm^2)；5)角膜神经弯曲度(corneal nerve fiber tortuosity，CNFT)：图像中神经纤维弯曲程度，分为0~4级，等级越高弯曲度越大。

1.4 术后随访

术后予术眼普拉洛芬滴眼液局部使用。分别于1周、1个月进行随访，以上述方法获取术后IVCM图像。对分多次完成视网膜光凝治疗患者以最后一次治疗完成开始计算随访时间。

1.5 统计学处理

使用SPSS 24.0统计软件进行分析，数据以均数±标准差($\bar{x}\pm s$)表示。两组患者基础测量值比较采用独立样本t检验，视网膜激光光凝术治疗前后各测量值比较采用配对样本t检验，$P<0.05$为差异有统计学意义。

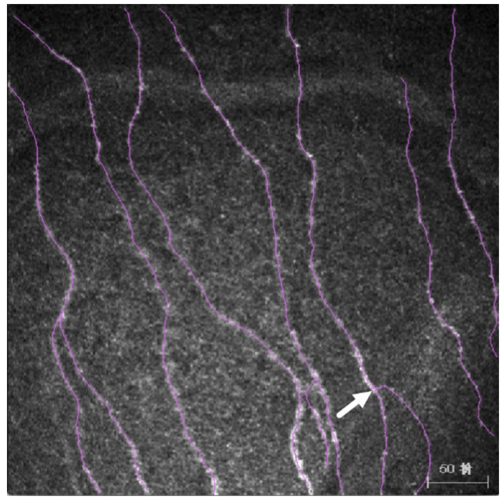

图1 应用Image J和Neuron J软件分析健康人角膜IVCM图像

Figure 1 IVCM imaging analysis of the cornea in healthy controls by Image J and Neuron J software

紫线表示Neuron J自动识别的神经纤维走行，箭头示神经节点。

Purple curves represent the corneal nerve fiber identified with Neuron J software, and the arrow points out one of corneal branch nodes.

2 结果

DR组术前CNFD，CNBD和CNFL均低于非DR组，CNFT高于非DR组，差异均有统计学意义(均$P<0.05$)；两组间术前CTBN的差异无统计学意义($P>0.05$，图2)。

DR组光凝术后CNFD，CNFL测量值持续降低，术前、术后1周、术后1个月3个观察时段两两之间的差异有统计学意义($P<0.05$)；CNBD，CTBN光凝前后无明显变化，3个时段两两之间的差异无统计学意义($P>0.05$)；光凝术后CNFT较术前持续升高，但仅术后1个月与术前的差异有统计学意义($P<0.05$)。

非DR组光凝术后CNFD，CNFL持续降低，术前、术后1周、术后1个月3个观察时段两两之间的差异有统计学意义($P<0.05$)；CNBD持续升高，术后1周、术后1个月测量值与术前的差异有统计学意义($P<0.05$)；光凝术后CTBN呈增长趋势，但3个时段两两之间的差异无统计学意义($P>0.05$)；CNFT持续升高，术后1周、术后1个月测量值与术前的差异均有统计学意义($P<0.05$)。

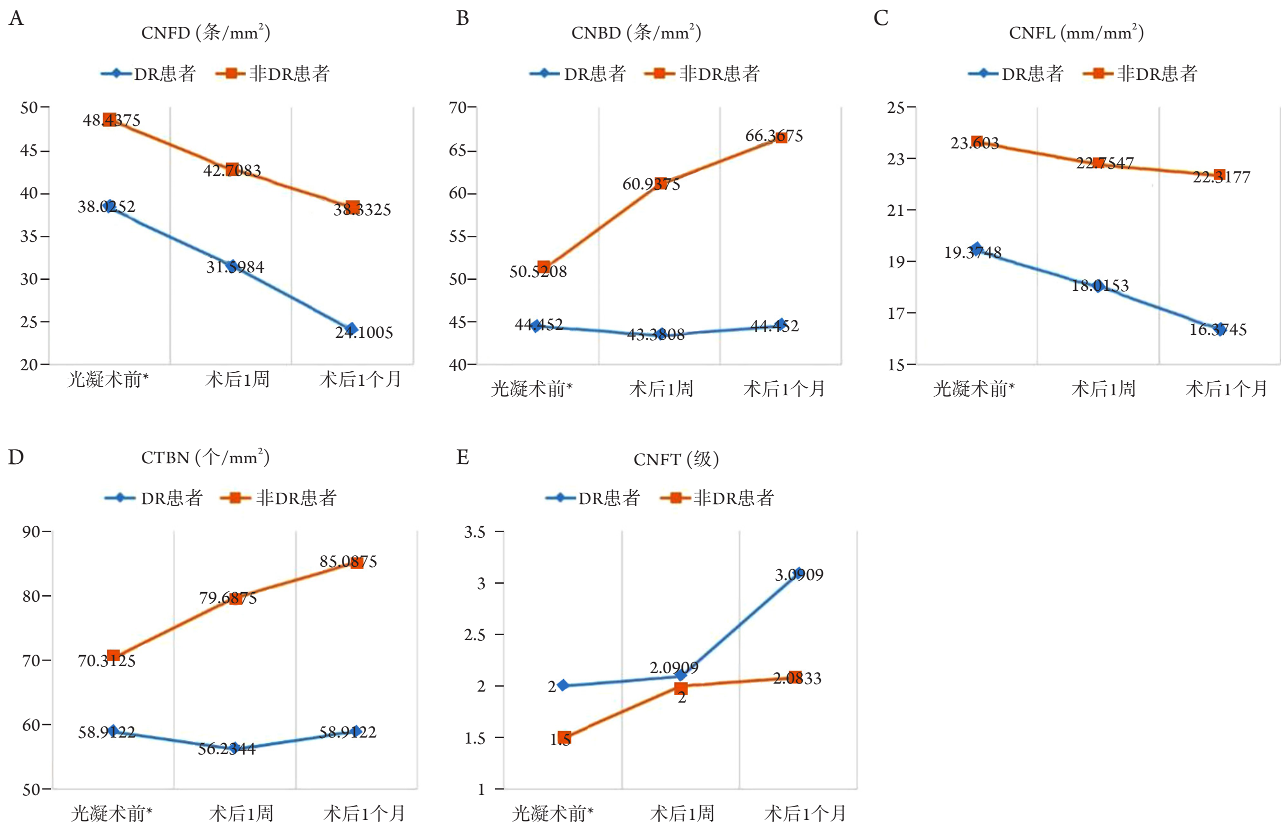

图2 两组视网膜激光光凝术后1个月角膜上皮下神经的变化

Figure 2 Changes of corneal sub-basal nerve within 1 month after retinal photocoagulation between two groups

(A)两组患者术前、术后1周、术后1个月两两之间角膜神经主干密度(条/mm²)的差异均有统计学意义；(B)非DR组术后1周、术后1个月分别与术前的角膜神经分支密度(条/mm²)的差异有统计学意义，DR患者3个时间点两两之间的差异无统计学意义；(C)两组患者术前、术后1周、术后1个月两两之间角膜神经纤维长度(mm/mm²)的差异均有统计学意义；(D)两组患者术前、术后1周、术后1个月两两之间角膜神经节点密度(个/mm²)的差异均无统计学意义；(E)非DR组术后1周、术后1个月分别与术前的角膜神经弯曲度分级的差异有统计学意义，DR患者术前、术后1周分别与术后1个月的差异有统计学意义。DR组与非DR组光凝术前基础测量值相比，*P<0.05。

(A) There were significant differences of CNFD between each pair of baseline, 1 week after and 1 month after retinal photocoagulation in two groups; (B) There were significant differences of CNBD between 1 week after retinal photocoagulation to baseline and 1 month after retinal photocoagulation to baseline in the NDR group, but no significant difference before and after retinal photocoagulation of CNBD in the DR group; (C) There were significant differences of CNFL between each pair of baseline, 1 week and 1 month after retinal photocoagulation in two groups; (D) There was no significant difference of CTBN between any pair of baseline, 1 week and 1 month after retinal photocoagulation in the two groups; (E) There were significant differences of CNFT between 1 week after retinal photocoagulation to baseline and 1 month after retinal photocoagulation to baseline in the NDR group, and between 1 week after retinal photocoagulation to 1 month after retinal photocoagulation and baseline to 1 month after retinal photocoagulation in the DR group. Compared with baselines of the DR group and the DR group before retinal photocoagulation, *P<0.05.

3 讨论

正常人的角膜无色透明，有大量神经纤维分布，丰富的神经支配不仅保证角膜的感觉功能，还具有营养和代谢作用。角膜感觉神经由三叉神经眼支的终末支睫状神经发出，从角膜缘角膜基质的2/3处进入，形成基质神经丛，该神经丛发出分支，垂直穿过前弹力层进入上皮，形成上皮内神经丛；并由角膜边缘向角膜中央走行，在角膜4个象限的分布无明显差异[13-14]。Stern等[15]提出

泪腺功能单位的概念，即泪膜、角结膜上皮、泪腺、眼睑及其相互联系的神经支配共同形成一个功能单位，在解剖上相连续，并存在共同的反馈机制。在角膜神经损伤的病理状态下，如准分子激光术后[16]、眼钝挫伤[17]、长期佩戴角膜接触镜[18]、长期局部药物应用[19]、病毒性角膜炎等[20]，泪膜反馈环路受到破坏，泪膜稳定性下降，泪液分泌量减少；同时，角膜知觉敏感度下降，触觉阈值升高引起瞬目减少，进一步增加泪液蒸发，最终导致干眼。

Bouheraoua等[21]研究报道：视网膜脱离患者接受360°视网膜激光光凝治疗后，角膜上皮下神经纤维密度、角膜上皮厚度及角膜敏感度显著下降。崔浩等[22]发现：RVO患者行视网膜激光光凝治疗6个月后，角膜上皮下神经纤维密度降低，走形弯曲，角膜知觉减退。邢怡桥等[23]发现：DR患者激光治疗术后进行泪液分泌量和泪膜破裂时间均有下降。本研究应用基于IVCM的多种形态学指标观察视网膜激光光凝对角膜上皮下神经的短期效应，结果表明：无论是否为DR患者，接受激光治疗均会使角膜神经纤维遭受不同程度的损伤，具体表现为角膜中央上皮下神经密度、主干数目降低及弯曲度增加，这与文献[24-26]报道的干眼相关角膜神经纤维改变相符合。

在完成激光光凝术后1个月的随访期内，两组CNFD和CNFL均持续下降。相反，两组基础CTBN无显著差异，激光后1周及1个月的CTBN相比基础值的差异也均无统计学意义，提示CTBN对评价糖尿病或激光损伤并不敏感。从基础状态比较中可知CNFT已受糖尿病影响发生改变，这或可解释非DR组光凝术后1周的CNFT相比术前的下降有统计学意义，而DR组却没有：CNFT基于主观判断测得，按照Oliveira-Sato的分级标准[27]，0级CNFT定义为神经纤维走行接近直线，1级为稍微可见弯曲，本研究中非DR组基础CNFT大多处于这两个等级；相比基础状态本已处于具有轻-中等弯曲的2级CNFT的DR患者，同等程度弯曲改变在CNFT较平直的非DR组中可能更易被识别出。而光凝术后1个月与1周时CNFT的比较，非DR组无统计学意义，DR组却有差异，可能与激光损伤效应累计有关。值得注意的是，在激光光凝术后1个月的随访期内，非DR组CNBD随时间延长而显著增加，而DR组无明显变化。Zhang等[28]通过对干燥综合征患者角膜神经形态的对比研究，提出：CNBD增加是由于干眼激活的的负反馈调控机制诱导神经出芽状再生，因此CNBD可作为反映神经生长、修复活跃程度的指标。DR患者则可能由于神经营养因子家族表达减少、相关作用通路受抑制等原因[29]，光凝术后CNBD的代偿性增加较为有限。

激光光凝治疗造成角膜神经损伤的机制目前尚不明确。既往研究[30-33]认为其原因主要有3点：1)激光辐射损伤光凝斑下的睫状神经，反映为其末梢分支-角膜神经的形态改变或密度降低；2)激光能量通过角膜神经进入眼内时带来的直接热损伤；3)激光治疗过程中角膜接触镜所致缺氧和机械损伤。此外，由于DR患者接受视网膜激光光凝治疗方案相对其他疾病具有特殊性，本研究将此类患者单独列为一组进行观察。He等[34]研究报道：5年以上病程糖尿病患者的角膜上皮下神经相比正常人存在结构异常。De Cilla等[35]发现：经激光光凝治疗的DR患者的角膜上皮下神经纤维密度较未经治疗的DR患者减少，而未经治疗DR患者相应指标又较正常对照人群偏低。结合上述研究与本研究结果推测，糖尿病状态是造成角膜上皮下神经损伤的危险因素，并可能存在独立于激光光凝之外的机制，二者造成的损伤一定程度上或可叠加。

综上所述，本研究应用IVCM观察DR和非DR组在接受视网膜激光光凝术后1个月内角膜上皮下神经的改变，发现非DR组的基础状态优于DR患者，两类患者光凝术后角膜神经主干密度和长度均持续下降，但非DR组应对神经损伤的修复能力可能较好。临床上视网膜激光光凝治疗相关干眼应引起重视，如何优化治疗策略、减轻激光对角膜神经纤维的损伤，仍待进一步研究。

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