

脉络膜在角膜塑形镜控制近视中的作用研究进展

刘 玥

山东大学第二临床学院, 山东 济南

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摘 要

近视作为一种全球性的高发性疾病, 其发病机制和防控手段备受关注。角膜塑形镜(orthokeratology, OK镜)被证明可以有效抑制近视眼的眼轴增长, 作为近视控制的重要手段正在被广泛应用, 但OK镜控制眼轴增长的具体机制目前尚不清楚。研究发现, 近视发生发展过程中存在脉络膜的改变, 主要是脉络膜厚度(choroidal thickness, ChT)降低和脉络膜血流灌注(choroidal blood perfusion, ChBP)减少。同时有研究表明, 在使用OK镜抑制眼轴增长的过程中, 存在ChT增厚和ChBP增多等改变。近期研究发现, 早期的脉络膜改变与远期的近视转变有相关性。同时, OK镜配戴早期1月时的脉络膜改变可以预测远期1年后的近视控制效果。综合分析, 在OK镜控制近视的过程中, 脉络膜的改变起到一定的积极作用。通过药物和技术手段控制脉络膜的厚度和血流灌注可以作为近视防控的新思路和新导向。

关键词

角膜塑形镜, 脉络膜, 近视, 机制

Research Progress in the Role of the Choroid in the Control of Myopia with Orthokeratology

Yue Liu

The Second Clinical College, Shandong University, Jinan Shandong

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Abstract

Myopia, a prevalent global disease, has been paid considerable attention in the pathogenesis and

preventive strategies. Orthokeratology has been demonstrated to effectively inhibit axial elongation in myopic eyes, serving as a possible method for myopia control. However, the specific mechanism by which orthokeratology controls axial elongation remains unclear. Studies have observed choroidal changes during the progression of myopia, characterized primarily by the decrease in choroidal thickness (ChT) and choroidal blood perfusion (ChBP). Simultaneously, research indicates that control of axial elongation with orthokeratology is associated with increased ChT and enhanced ChBP. Recent studies have found that early choroidal changes are correlated with long-term myopia progression. Moreover, choroidal changes observed one month after the initiation of orthokeratology can predict myopia control outcomes one year later. Taken together, these findings suggest that choroidal changes play an important role in modulating myopia progression with orthokeratology. Regulating choroidal thickness and blood perfusion through pharmaceutical and technological means may provide new insights and strategies for myopia prevention and control.

Keywords

Orthokeratology, Choroid, Myopia, Mechanism

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1. 引言

近视是一种常见的屈光不正，指当眼睛调节放松时，来自远处物体的平行光线进入眼内，通过屈光间质聚焦在视网膜前方。近视的全球患病率在 2010 年时已达到 28.3%，到 2050 年预计将增至 49.8%，同时高度近视的发生率也将达到 9.8% [1]。近视不仅会引视力及视觉质量下降，还可能导致黄斑变性、视网膜劈裂、视网膜脱离等多种并发症。预计到 2050 年，全球人口的 0.19% (约 1850 万人)可能会因近视性黄斑变性致盲[2]。因此，了解近视发生发展的危险因素，加强近视防控迫在眉睫。

近视的发生发展与脉络膜密切相关。近视进展过程中存在脉络膜厚度(choroidal thickness, ChT)降低和脉络膜血流灌注(choroidal blood perfusion, ChBP)减少的改变[3]。在高度近视眼中，ChT 和 ChBP 的改变可能先于视功能损伤的发生[4]。因此，早期监测近视患者脉络膜组织形态和血流灌注改变，对了解近视进展、预防病理性眼底改变至关重要。近些年，随着光学相干断层扫描血管成像(optical coherence tomography angiography, OCTA)技术的迅速发展，活体脉络膜的血管影像得以被快速、无创、逐层三维显示[5]。OCTA 技术能提供具有良好可信度的脉络膜结构和血流的量化指标，有助于理解脉络膜在近视调控中的作用。

2. 脉络膜在近视发展中的作用

脉络膜介于视网膜与巩膜之间，是高度血管化的组织，其血管按管径大小共分为三层，由外到内分别为：脉络膜大血管层、中血管层以及毛细血管层。脉络膜血管汇集了眼球内约 73% 的血液，主要通过毛细血管层向外层视网膜及中心凹无血管区提供营养支持。除了丰富的血管外，脉络膜还含有多种非血管驻留细胞，由胶原纤维和结缔组织支撑构成完整的脉络膜系统[6]。

越来越多的研究表明，在近视发病机制中存在着“信号级联理论”，即视觉信号从视网膜传递到视网膜色素上皮，经过脉络膜，最后参与巩膜重塑和眼球生长[7]。在屈光发育过程中，长期异常视觉刺激会破坏正视化的进程，引起巩膜后极部过度增长，导致近视的发生和发展[8]。近年来，诸多研究揭示了脉络膜参与调控近视的发生、发展。脉络膜结构和脉管系统的变化是近视的标志性特征之一。随着近视

进展, 脉络膜血管结构可能会发生改变, 比如脉络膜变薄、血管管腔直径减小, 血管密度降低, 血流灌注减少等[9][10]。在近视发生发展过程中, 对于 ChT 和 ChBP 的改变是否互为因果, 尚缺乏明确的解答。

2.1. 近视发展过程中 ChT 的改变

在 20 世纪 90 年代, 雏鸡最早被报道 ChT 会因离焦现象而发生短暂变化。给雏鸡施加正镜片后, ChT 会迅速增加以响应近视离焦, 而对于远视离焦, ChT 则减少[11]。之后的研究在豚鼠、狨猴、猕猴等动物中也观察到这种近视发展过程中 ChT 的变化。在自发性近视、形觉剥夺性近视和负镜片诱导性近视 3 种类型的豚鼠近视模型中, 均观察到脉络膜变薄的现象[12]。这说明 ChT 的调节不只对离焦信号做出响应。

近些年, 临床上也开展了大量近视相关的脉络膜研究。研究发现, 近视相关的脉络膜变薄与近视程度呈正相关[13]。随着近视儿童的屈光度和眼轴长度的增加, ChT 不断变薄, 并且其显著变薄主要见于近视进展较快的儿童[14]。以上现象展现了近视进展过程中 ChT 的调节。

脉络膜似乎主动参与了近视的发生发展过程, 并且增厚和变薄反应可能存在多种机制。Wallman 等发现, 在去除形觉剥夺或在近视离焦干预的雏鸡眼中, ChT 显著增加, 并且脉络膜中蛋白多糖的数量显著高于近视眼[15]。这表明脉络膜中的渗透活性分子的数量可以调节 ChT。其次, 脉络膜血管通透性的变化也会影响 ChT。炎症或缺氧等病理条件会使血管通透性增加, 导致液体渗透进入脉络膜, 引起脉络膜短暂增厚, 而长期的病理状态, 例如在病理性高度近视中, 脉络膜血管通透性变化可能导致脉络膜的营养支持减少, 引起脉络膜组织的萎缩和变薄[16]。此外, 视网膜色素上皮可能通过调节视网膜和脉络膜之间的离子交换、液体运输来调节 ChT [17]。还有观点认为, 非血管平滑肌的收缩或舒张可以通过改变血管直径进而调节 ChT, 即 ChT 变化与 ChBP 的调节有联动相关性[18]。

2.2. 近视发展过程中 ChBP 的改变

ChBP 改变与近视密切相关。动物研究发现, 与非近视组相比, 自发性近视、形觉剥夺性近视、负镜片诱导性近视这 3 种豚鼠近视模型的 ChT 和 ChBP 都减少, 并且 ChT 和 ChBP 的改变呈正相关[12]。形觉剥夺性近视雏鸡的 ChBP 减少、脉络膜毛细血管网密度减少, 而去除剥夺因素后, ChBP 增加[9]。

临床研究发现, 随着近视进展, 脉络膜的中血管层、大血管层出现明显的变薄、萎缩[19]。大血管层和中血管层的损失是近视眼脉络膜变薄的主要原因。除此之外, 近视眼中脉络膜毛细血管灌注降低、血管密度降低也会导致脉络膜血容量下降[20]。上述改变在病理性近视患者眼中更加明显[21]。有研究发现, 与非近视儿童相比, 高度近视儿童的血清中参与内源性血管收缩的内皮素-1 (ET-1) 表达水平显著上调。过度表达的 ET-1 可能通过促进脉络膜血管收缩, 导致 ChBP 降低, 加速近视进展。

在近视眼中, 脉络膜变薄和血液灌注减少往往同时表现出来, 且均在近视刺激解除后呈恢复趋势。解除雏鸡模型的形觉剥夺刺激后, ChBP 与中央凹下脉络膜厚度(subfoveal choroidal thickness, SFCT)均增加, 并且 ChBP 的变化先于 SFCT [22]。这提示, ChBP 的增加可能触发或者驱动 SFCT 的增加。为了进一步探索二者之间的关系, 有研究在截断豚鼠的颞侧睫状动脉后观察脉络膜的改变。该研究发现, 在灌注不足的颞侧象限, ChT 显著减少, 在血供完好的鼻侧象限, ChBP 和 ChT 均无明显变化[12]。此外, 血管扩张药物(西地那非)的全身给药引起 SFCT 增加[23]。这些发现表明, ChBP 的改变可能是 SFCT 变化的主要驱动因素。

2.3. 脉络膜在近视发展过程中的调控作用

在近视发生发展过程中, 脉络膜改变、巩膜缺氧和近视的发生发展密切相关。脉络膜循环的动静脉氧差仅为 3%。高氧分压对于满足视网膜和巩膜的氧气需求至关重要[24]。当脉络膜 ChBP 明显减少时,

视网膜和巩膜都将暴露在相对缺氧的环境中。巩膜缺氧是近视发展过程中导致巩膜重塑的关键因素。巩膜缺氧会诱导巩膜细胞表型的变化(即成纤维细胞转分化为肌成纤维细胞),导致 I 型胶原蛋白合成减少[25]。作为巩膜细胞外基质的主要成分[26], I 型胶原蛋白的减少会使巩膜变薄,失去弹性和韧性[27],最终导致眼轴过度伸长。

通过干预脉络膜血流灌注,可以影响巩膜缺氧和近视的发生发展。在豚鼠的球周注射血管扩张药物(哌唑嗪)可以增加 ChBP,有效抑制形觉剥夺性近视眼的眼轴伸长,缓解巩膜缺氧[28]。反之,注射噻吡罗会促进近视的发展,使近视眼中 ChT 和 ChBP 的减少量增加,并加重巩膜缺氧水平。对干预眼分离断豚鼠颞侧睫状动脉或球周注射去氧肾上腺素会减少 ChBP,引起近视漂移,并且这两种干预措施也会导致巩膜缺氧[29]。

脉络膜改变在近视控制中发挥着重要作用。早期动物实验发现,给雏鸡施加+10D 镜片 1 小时后,干预眼的眼轴伸长量在后续 2 天内明显小于未干预的对侧眼[11]。临床研究发现,近视眼 ChT 的增加与近视进展几率的降低相关。一项为期 2 年的前瞻性随访研究显示,短期的脉络膜改变可以作为儿童未来近视进展情况的预测指标[30]。将 ChT 3 个月的变化量添加到近视预测模型中,预测性能得到显著改善(受试者工作特征曲线下面积从 0.650 增加到约 0.800)。改善 ChBP 与减缓近视进展的相关性在 ω -3 多不饱和脂肪酸(ω -3 PUFA)的应用中得到进一步研究。 ω -3 PUFA 可以抑制形觉剥夺性近视豚鼠的 ChBP 减少,减轻巩膜缺氧,减缓近视进展。补充 ω -3 PUFA 还可以缓解由近距离工作引起的 ChBP 下降[31]。这些发现表明,改善脉络膜的血管系统有望成为近视控制的新思路。

3. OK 镜配戴过程中的脉络膜改变

作为近视干预的重要手段,OK 镜在全球范围内得到广泛应用。在过去的数十年间,OK 镜抑制近视进展的有效性得到大部分临床研究的验证。一项为期 5 年的研究表明,与单光框架眼镜相比,OK 镜可以使近视儿童的眼轴伸长率在 3 年内显著降低,这种效果在 OK 塑形镜控制近视的第一年(0.38 ± 0.20 mm vs 0.19 ± 0.09 mm, $p = 0.0002$)最为明显[32]。

3.1. OK 配戴过程中 ChT 的改变

近些年,OK 镜干预近视过程中的脉络膜改变受到关注。临床研究发现,用于近视干预的 OK 镜可使 ChT 增厚,而配戴框架镜的近视眼中会有不同程度的 ChT 减少。脉络膜增厚的改变最早可在戴镜第一周末观察到[33]。在长期(2 年)随访过程中,OK 镜配戴组的眼轴伸长率更低,并且 ChT 的增厚改变($0 \sim +20$ μ m)明显大于同期单光框架眼镜配戴组($-40 \sim 0$ μ m)[34]。目前,配戴 OK 镜引起 ChT 增厚改变的持续时长尚不明确[33][35]。配戴 OK 镜是否可以引起 ChT 增加,患者选择、镜片验配参数的调整、配戴时长等因素对脉络膜增厚效应的影响还有待进一步多样本量的研究。

3.2. OK 镜干预近视过程中脉络膜血流的改变

配戴 OK 镜可以改善近视儿童脉络膜的血流灌注。研究发现,OK 镜在控制眼轴伸长的同时可使脉络膜毛细血管灌注面积增大,改善脉络膜的血流灌注[36]。在戴镜早期(1 周时),ChT、脉络膜血管指数(choroidal vascularity index, CVI)均显著增加,并在 3 个月内维持稳定状态[35]。在 OK 镜配戴期间,眼轴伸长率的减慢伴随着脉络膜血管管腔和基质成分含量的增加[37]。在 OK 镜控制近视进展的过程中,脉络膜血流的改善发挥了一定的积极作用。

3.3. 改变 OK 镜验配参数对脉络膜的影响

在验配 OK 镜时,压缩系数这一参数用以抵消被压平的中央角膜在摘镜后的陡峭化。0.75D 的常规压

缩系数(conventional compression factor, CCF)可能不足以抵消白天的屈光回退,因此,在屈光矫正需求增大时可选择增加压缩系数(increased compression factor, ICF)为 1.75 D 的 OK 镜[38]。镜片的压缩系数增加使得角膜曲率的改变增加。有研究认为,角膜曲率改变越大,眼轴伸长率越低[39] [40]。与 CCF 镜片相比,ICF 镜片产生的角膜曲率改变更大,可能会获得更好的近视控制效果。但由于当前各项研究对角膜区域的划分存在差异,戴镜后角膜曲率变化与眼轴伸长率之间的关联仍有争议[41]。

角膜曲率的改变量会影响周边视网膜离焦量。角膜曲率改变越大,相对应的 ChT 变化可能越大。在配戴 OK 镜早期(1 月),ICF 组的眼轴长度降低(平均值变化: -0.031 mm),但 CCF 组保持不变(平均值变化: 0.003 mm) [42]。除外戴镜导致的角膜中央厚度变薄,剩余的眼轴差异可能来源于不同离焦量引起的不同脉络膜增厚程度。对中度近视儿童为期 2 年的随访显示,ICF 组的眼轴伸长率低于 CCF 组($0.23 \pm 0.08\text{ mm}$ vs $0.30 \pm 0.11\text{ mm}$, $p = 0.015$)且 SFCT 高于 CCF 组($279.04 \pm 35.72\text{ }\mu\text{m}$ vs $254.08 \pm 29.60\text{ }\mu\text{m}$, $p = 0.008$),但在低度近视儿童组中未观察到类似改变[43]。这提示,改变压缩系数会改变角膜曲率变化量,影响近视离焦量、影响 SFCT 改变。相比低度近视患者,中高度近视患者获得更好的近视控制效果的原因之一可能是更大的 SFCT 改变量。

3.4. OK 镜引起脉络膜变化的机制

OK 镜引起脉络膜变化的机制尚不明确。有学者认为,配戴 OK 镜会使周边视网膜处于近视离焦状态,针对这种离焦状态,视网膜可能以“透镜补偿”响应,即眼底组织向前移动,引起脉络膜变厚[44]。也有学者认为,配戴 OK 镜能提高患者裸眼视力,减少异常视觉信号对视觉中枢的刺激。视网膜接收到非异常视觉信号后作用于脉络膜,增加 ChT 及血液灌注[45]。另有观点是,OK 镜的反向几何设计使泪液积聚,对角膜产生负压吸引的效果[46]。这种由戴镜引起的眼部作用力的动态改变可能会影响脉络膜的调节,引起脉络膜增厚与血流灌注增加。OK 镜对脉络膜的具体作用机制还需大量研究探索。

4. OK 镜配戴早期的脉络膜改变可预测远期近视控制效果

眼轴伸长率是临床评估近视防控效果的主要指标,通常需要一年的观察时间。在配戴 OK 镜超过 1 年的近视儿童中,有约 27%的儿童每年的近视进展超过 1.00 D,眼轴长度增加超过 0.40 mm [47]。因此,早期预测近视干预效果,有助于及时调整近视控制策略、减少病理性近视的产生。

对配戴 OK 镜控制近视的儿童而言,脉络膜血管系统的改变与眼轴伸长有关。戴镜 1 月后 ChT 的增加量与戴镜 1 年并停戴 1 月后眼轴长度的增加量呈负相关(标准 β , -0.581) [48]。近视预测模型显示,基线 CVI、戴镜 1 月时 SFCT 的增加量、戴镜 1 月时脉络膜管腔面积的增加量可以作为戴镜 1 年时近视控制效果的预测指标[49],当纳入基线 CVI、1 个月时 SFCT 增加量、年龄和性别作为眼轴伸长快慢的预测指标时,预测模型的受试者工作特征曲线下面积从基础模型的 0.650 达到 0.872 (95% CI: 0.771~0.973)。这显示,增加脉络膜血管系统指标可以显著提高近视进展的预测精度。在该研究中,按戴镜 1 年时的眼轴伸长率是否高于中位水平 0.16 mm,将配戴 OK 镜的近视儿童分为慢进展组和快进展组,在戴镜 1 月时,慢进展组 SFCT 增加和脉络膜管腔面积变大的变化量明显大于快进展组。由此可见,早期 ChT 增加量与后续近视的进展快慢、进展程度相关。脉络膜早期改变有望成为预测 OK 镜干预近视的远期效果的生物标志物。

5. 小结

在近视防控愈发重要的当下,脉络膜被认为是监测和调整近视防控效果的重要靶点。脉络膜早期改变可以预测 OK 镜干预近视的远期效果。精准完善便捷的早期预测指标可以帮助评估不同干预方法的获益程度,及时调整近视干预措施,从而提高最终的近视防控效果。

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