Hans Journal of Ophthalmology 眼科学, 2019, 8(4), 141-151
Published Online December 2019 in Hans. http://www.hanspub.org/journal/hjo
https://doi.org/10.12677/hjo.2019.84023

Hans汉斯

The Relationship of Blood Pressure with POAG and NTG: A Systematic Review and Meta-Analysis

Ye Lu, Xiaohui Zhang*

Ophthalmology Department, The Second Affiliated Hospital, Medical College, Xi'an Jiaotong University, Xi'an Shaanxi
Email: *yanke1zhang@163.com

Received: Nov. 14th, 2019; accepted: Dec. 2nd, 2019; published: Dec. 9th, 2019

Abstract

Purpose: We aimed to estimate the differences of systolic blood pressure, diastolic blood pressure, and fluctuation amplitudes between groups to find out the relationship of BP with POAG and NTG by systematic review and meta-analysis. Methods: We had searched Cochrane library, Web of Science, PubMed, MEDLINE database, CNKI and clinicaltrials.gov register platform to find relevant controlled trials ranging from May 1990 to April 2019. Five studies, including 315 individuals, were identified by STROBE statements had been analyzed. Results: For the relationship, only the nocturnal diastolic pressure fluctuation of POAG and NTG was statistically significantly fluctuate larger than negative controls (mean difference 2.41, 95% credible interval [CrI] 0.08 to 4.0). No statistical differences were found in systolic blood pressure, diastolic blood pressure, and nocturnal systolic blood pressure fluctuation. Conclusion: The nocturnal diastolic pressure fluctuation is closely related to POAG and NTG, which is highly inferred to be a risk factor to POAG and NTG.

Keywords

Primary Open Angle Glaucoma, Normal Tension Glaucoma, Systolic Blood Pressure, Diastolic Blood Pressure, Meta-Analysis

血压波动与青光眼的联系

——昼夜血压波动是开角型青光眼、正常眼压型青光眼发生的危险因素的系统评价和meta分析

卢　叶，张晓辉*

*通讯作者。

文章引用: 卢叶, 张晓辉. 血压波动与青光眼的联系[J]. 眼科学, 2019, 8(4): 141-151. DOI: 10.12677/hjo.2019.84023

西安交通大学医学院第二附属医院眼科，陕西 西安
Email: *yanke1zhang@163.com

收稿日期：2019年11月14日；录用日期：2019年12月2日；发布日期：2019年12月9日

摘 要

目的：通过meta分析分别研究组间昼夜收缩压、舒张压及其波动幅度的差异，了解系统血压的高低及其昼夜血压波动幅度对开角型青光眼发病的影响。方法：检索Cochrane library，Web of Science，PubMed，MEDLINE，CNKI和美国国立卫生研究院试验注册平台(www.clinicaltrials.gov)等数据库，查找自1990年5月起至2019年4月的关于POAG、NTG和血压波动的相关文献。通过STORBE statement观察性研究评价方法对文献进行评估，涉及315名参与者的5篇文献满足条件纳入分析。结果：开角型青光眼患者和对照组之间昼夜平均收缩压、舒张压差异不具有显著性，昼夜收缩压波动不具有显著性。青光眼患者的舒张压波动幅度(Z = 2.99, p = 0.003 < 0.05)高于对照组，差异有显著性，具有统计学意义。结论：昼夜舒张压波动与原发性开角型青光眼(Primary Open Angle Glaucoma, POAG)和正常眼压性青光眼(Normal Tension Glaucoma, NTG)密切相关，这被高度提示其为POAG和NTG的发病危险因素。

关键词

开角型青光眼，正常眼压型青光眼，动态血压，血压波动，Meta分析

1. 背景

作为以视野丧失和视神经受损为特征的疾病，青光眼是世界主要致盲疾病之一[1] [2]。在房角开放性青光眼中，最常见的类型是原发性开角型青光眼(Primary Open Angle Glaucoma, POAG)和正常眼压性青光眼(Normal Tension Glaucoma, NTG)。尽管青光眼发病机理的假说仍存在争议，但已被明确的青光眼损害风险只有高眼压(Intraocular Pressure, IOP) [3]。POAG 和 NTG 具有相似的疾病进展，二者均表现为进行性的视野丧失和视网膜神经纤维层变薄[4]。区别在于，与 POAG 相比，NTG 的 IOP 几乎不会超过 21 mmHg [3]。这些现象表明，发生房角开放性青光眼损害不仅是高眼压的结果，还有其他尚未明确定义的因素。

年龄，种族，遗传因素，中央角膜变薄，近视和糖尿病[5]，跨层板筛网压[6] [7] [8]，血管功能障碍是青光眼患病和进展的危险因素[9]。甚至有些研究认为，血压和 IOP 的调节可能存在共同或交叉的通路[10]。血压(Blood Pressure, BP) 24 小时内动态变化，可以反映循环系统的血管功能和同动力状态[2] [11]。已有研究证明，血压波动是心脏，肾脏和大脑等多个终末器官损伤的危险因素[12]。此外，青光眼的眼底损害与视盘(Optic Nerve Head, ONH)的眼血流量(Ocular Blood Flow, OBF)紊乱显著相关[13]。其中 ONH 的营养可能取决于眼灌注压(Ocular perfusion pressure, OPP)，后者反映了平均动脉血压和 IOP 之间的差异。对于血压对青光眼眼底损害进展的影响研究逐渐受到重视，一些研究者认为较高的血压水平有促进 POAG 和 NTG 的发展的作用[14]，但另一些研究者却则认为低水平血压才是 POAG 和 NTG 的发病机制[15]。因此，我们旨在通过系统的回顾和 meta 分析来探究 BP 在 POAG 和 NTG 的病理过程中所起的作用。

2. 方法

2.1. 搜索方案

对于此 meta 分析，我们搜索了 Cochrane Library、Web of Science、PubMed、MEDLINE 数据库以及 clinial.gov 临床实验注册网，以找 1990 年 5 月至 2019 年 4 月的到相关对照试验。有关搜索策略的详细信息，请参阅附录一。该研究无注册信息。

纳入标准和排除标准

1) 纳入标准

(1) 根据典型的青光眼眼底变化被、视野缺损和开放性前房角而IOP始终高于21 mmHg诊断为POAG，IOP 始终低于 21 mmHg 患者诊断为而 NTG；

(2) 对照试验；

(3) 独立的昼夜血压数据；

(4) 独立的收缩压和舒张压数据；

(5) 对测量动态血压的方式有详细说明。

2) 排除标准

(1) 资料不完整；

(2) 不同种类的参数无法合并分析；

(3) 二次研究。

2.2. 数据提取和质量评估

两名研究者(LY，ZXH)独立选择研究，并根据“STROBE 声明－观察研究报告中应包括的项目清单”[16]评估了研究质量，其中有 22 项，每满足一项记为 1 分，15 分及以上纳入研究。

2.3. 数据收集与分析

两名研究者(LY，ZXH)从纳入的试验中提取了相关信息。识别的数据通过 RevMan 软件(版本 5.2；Cochrane Collaboration，英国牛津)进行了分析。所有数据均为连续数据，采用倒差法进行分析。BP 波动的均值和标准差结果计算方法如下[17]。

$$\Delta\text{mean} = \text{mean}_{\text{daytime}} - \text{mean}_{\text{nighttime}}$$

$$\text{SD}_{\text{mean}} = \sqrt{\text{SD}_{\text{daytime}}^2 + \text{SD}_{\text{nighttime}}^2 - 2\rho * \text{SD}_{\text{daytime}} * \text{SD}_{\text{nighttime}}}$$

2.4. 统计分析

我们采用了随机效应分析合并数据，包括效应量(Mean Deviation, MD)及其置信区间(Confidence Interval, CI)。所有数据均报告为平均值(mean) ± 标准差(SD)。森林图用来表示结果，其中线条代表不同研究的估计值，方框以图形表示每个研究的权重。

3. 结果

3.1. 文献搜集

我们检索获得了 510 篇已发表的候选文献(见图 1)。通过浏览标题和摘要排除了 461 项研究。此外，全文阅读后排除了 44 项研究，其中 20 项因缺失昼夜血压的独立数据，9 项研究目的及设立结果不同不能合并，15 项研究数据结果采用了不同的数据分析方法。符合所有标准的 5 项研究[18] [19] [20] [21] [22]

被纳入本研究。

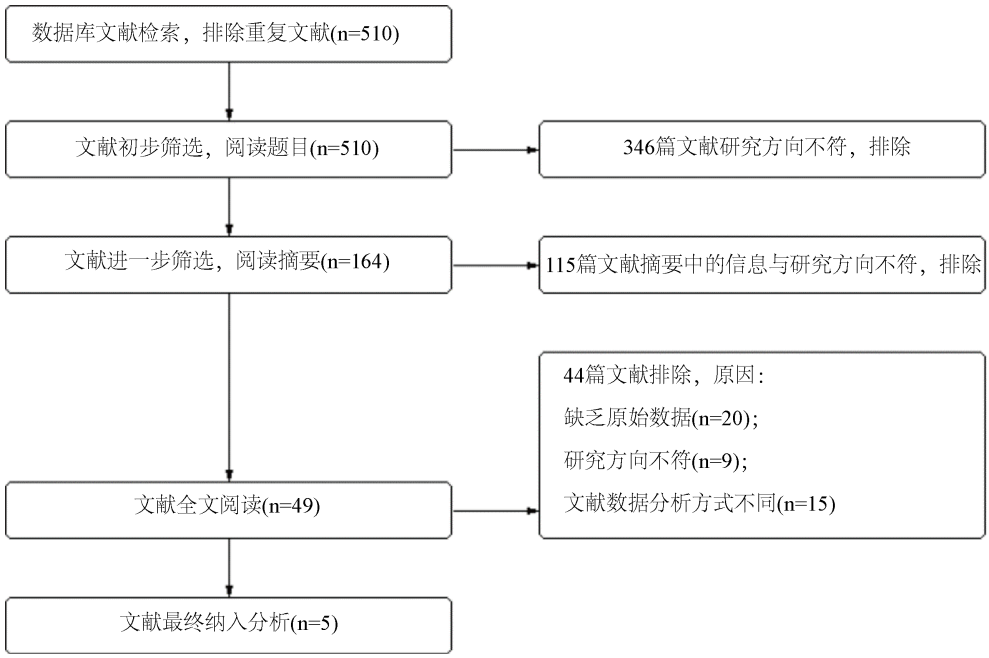

Figure 1. Flow diagram of the bibliographic selection
图 1. 文献筛选流程图

3.2. 纳入研究的特征

共收集从 1996 年到 2013 年的 5 项研究，共包括 315 名受试者(见表 1)。所有研究均为横断面研究。POAG、NTG 和对照组之间在性别比和年龄上没有显着差异。如果研究间异质性较大则应用随机效应模型将合并研究结果。动态血压监测装置的版本来自原始文献。表 2 和表 3 列出了从纳入研究中收集和计算的各项数据。

Table 1. Characteristics of trials included in the meta-analysis
表 1. 纳入文献的基本特征

作者	年份	研究对象	样本量	性别比(男/女)	动态血压测量仪器
Mroczkowska, S.	2013	POAG	39	21/18	Cardiotens-01; Meditech Ltd
Ramli, N	2013	NTG	127	61/66	NIblood pressure VS800
Plange, N	2006	NTG	79	34/45	SpacelabsMedical, Redmond, WA, USA
Riccadonna, M	2003	POAG	30	10/20	TM-2421, A&D, LTD, Japan
Meyer, J. H	1996	NTG	40	27/13	90207-32 monitor, Spacelabs

POAG 原发性开角型青光眼；NTG 正常眼压性青光眼。

3.3. 统计分析

对于纳入的结果分析，只有 POAG 和 NTG 患者的昼夜舒张压(Diastolic Blood Pressure, DBP)波动显著高于阴性对照组(平均差异 2.41，95%置信区间[CI] 0.08 至 4.0) (见图 2)。POAG 和 NTG 患者昼夜收缩压(systolic blood pressure, SBP)波动与对照组相比(MD 2.37，95%CI −0.99 至 5.74)没有显着差异(见图 3)。此外，组间独立的日间及夜间 SBP 和 DBP 的结果不显著(见图 4~7)。

敏感性分析显示，分别排除了研究中包含的任一研究，异质性始终存在，但先前的分析结果没有改变，两组之间昼夜 DBP 波动仍然存在显着差异(见附录二)。

Table 2. Data of diurnal and nocturnal systolic blood pressure fluctuation
表 2. 昼夜收缩压波动数据

作者	发表年限	分组	日间	夜间	波动幅度	样本量
Mroczkowska, S.	2013	病例组	133.2 ± 18.86	115 ± 17.34	15.47 ± 4.31	19
		对照组	125.3 ± 11.87	107.7 ± 7.4	17.6 ± 4.94	20
Ramli, N.	2013	病例组	135.78 ± 16.57	124.36 ± 18.98	11.44 ± 4.63	72
		对照组	136.1 ± 25.4	131.84 ± 15.58	4.26 ± 10.66	55
Plange, N.	2006	病例组	131.8 ± 12.3	116 ± 11.2	15.8 ± 2.85	51
		对照组	128.2 ± 15.3	111.2 ± 11.7	17 ± 4.68	28
Riccadonna, M.	2003	病例组	126.6 ± 9.1	104.7 ± 9.4	21.9 ± 2.09	13
		对照组	123.4 ± 9.6	106.6 ± 7.2	16.8 ± 3.04	17
Meyer, J. H.	1996	病例组	129 ± 13.41	118 ± 14.75	11 ± 3.41	20
		对照组	131 ± 12.07	123 ± 11.62	8 ± 4.56	20

表内血压数据均报告为平均值(mean) ± 标准差(SD)。

Table 3. Data of diurnal and nocturnal diastolic blood pressure fluctuation
表 3. 昼夜舒张压波动数据

作者	发表年限	分组	日间	夜间	波动幅度	样本量
Mroczkowska, S.	2013	病例组	77.93 ± 12.49	62.09 ± 11.31	15.84 ± 4.34	19
		对照组	73.69 ± 9.9	61.3 ± 6.1	12.29 ± 4.17	20
Ramli, N.	2013	病例组	78.5 ± 9.6	73.3 ± 8.64	13.4 ± 2.09	72
		对照组	79.2 ± 7.6	76.24 ± 8.31	2.96 ± 1.91	55
Plange, N.	2006	病例组	82.4 ± 8.3	69 ± 8.6	15.99 ± 8.4	51
		对照组	79.8 ± 9.3	63.9 ± 7.4	13.1 ± 1.31	28
Riccadonna,M.	2003	病例组	78 ± 5.9	64.9 ± 5.9	21.9 ± 2.09	13
		对照组	76.3 ± 4.4	65.4 ± 6.4	10.9 ± 2.32	17
Meyer, J. H.	1996	病例组	79 ± 9.39	66 ± 10.28	13 ± 2.37	20
		对照组	76 ± 9.8	68 ± 8	8 ± 2.68	20

表内血压数据均报告为平均值(mean) ± 标准差(SD)。

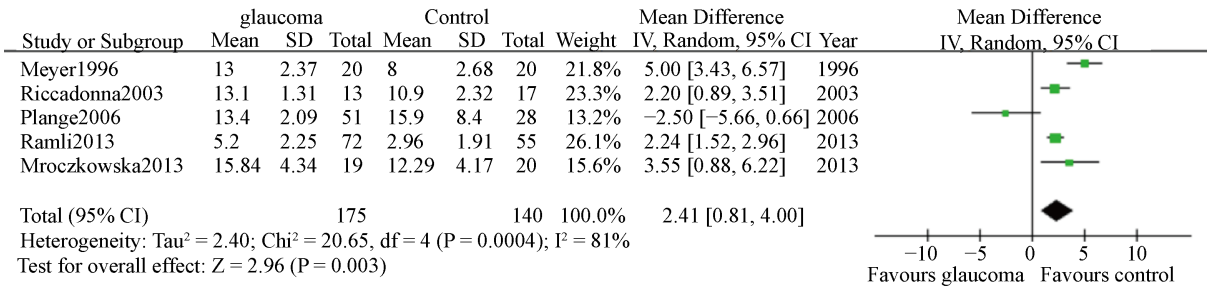

Figure 2. Nocturnal DBP fluctuation of POAG and NTG patients was significantly higher than that of the control subjects via Z = 2.96, *P* = 0.003
图 2. 病例组及对照组昼夜舒张波动存在统计学差异(Z = 2.96, *P* = 0.003)

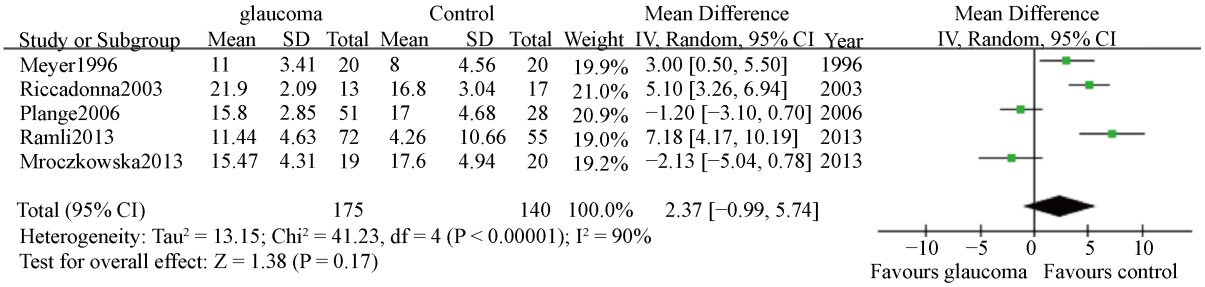

Figure 3. No statistically significant differences of the nocturnal SBP fluctuation of Forest plot comparison existed between 2 groups via Z-test, $P = 0.17$

图 3. 病例组及对照组昼夜收缩压波动无显著差异(Z = 1.38, $P = 0.17$)

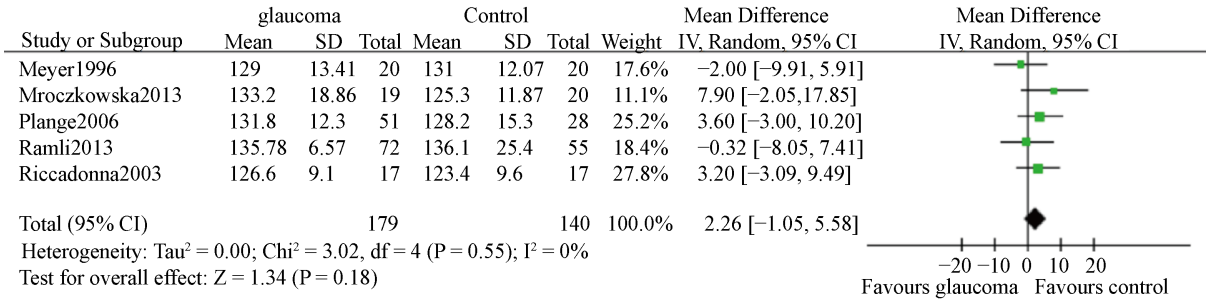

Figure 4. No statistically significant differences of the systolic blood pressure during daytime of Forest plot comparison existed between 2 groups via Z-test, $P = 0.18$.

图 4. 病例组及对照组日间收缩压无显著差异(Z = 1.34, $P = 0.18$)

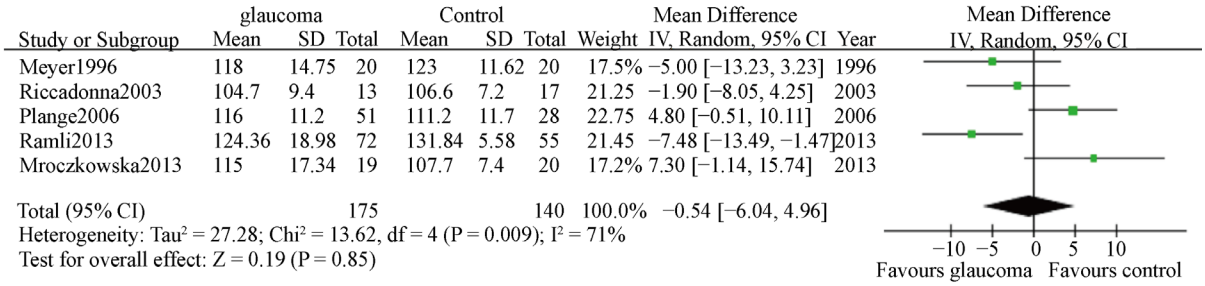

Figure 5. No statistically significant differences of the systolic blood pressure during nighttime of Forest plot comparison existed between 2 groups via Z-test, $P = 0.95$

图 5. 病例组及对照组夜间收缩压无显著差异(Z = 0.19, $P = 0.95$)

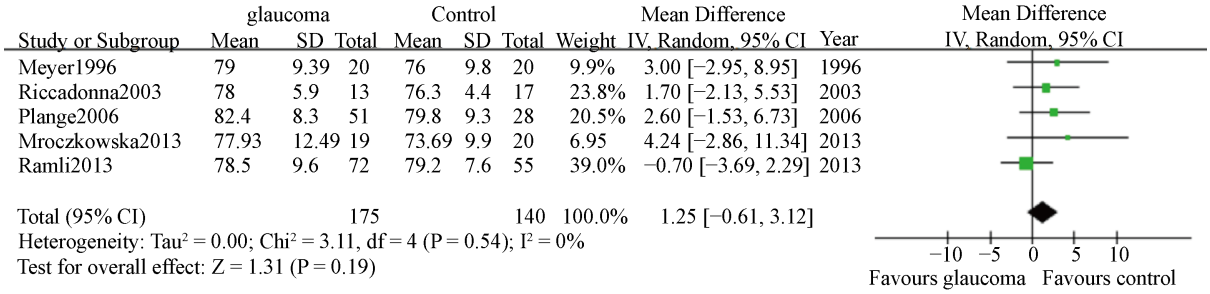

Figure 6. No statistically significant differences of the diastolic blood pressure during daytime of Forest plot comparison existed between 2 groups via Z-test, $P = 0.19$

图 6. 病例组及对照组日间舒张压无显著差异(Z = 1.31, P=0.19)

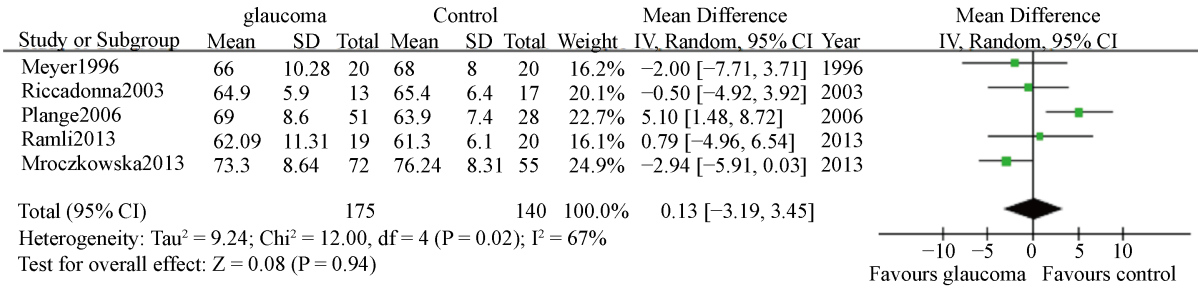

Figure 7. No statistically significant differences of the diastolic blood pressure during nighttime of Forest plot comparison existed between 2 groups via Z-test, $P = 0.94$

图 7. 病例组及对照组夜间舒张压无显著差异($Z = 0.08$, $P = 0.94$)

4. 讨论

青光眼的通常被认为是多种因素导致的视神经病变，而其中血管相关因素是可疑风险之一[23]。24小时动态血压监测可以直接观察青光眼与血压波动之间的关系。血管功能是决定 DBP 水平的决定因素之一。这项 meta 分析的结果证明较大的昼夜舒张压波动是 POAG 和 NTG 发生的高风险因素。

在健康和高血压个体中已广泛观察到夜间血压降低程度约为日间血压水平的 10%~20%。然而，越来越多的研究表明，过大的昼夜血压波动(超过 20%的水平)是造成终末器官损害的危险因素[24] [25]。近来实验证据表明血压波动对于而同属于终末器官 ONH 的损伤可能与 NTG 的发病机制有关[26]。青光眼患者视盘血管可能更容易受到血压过度波动的影响，从而导致视盘出血(Optic Disc Hemorrhages, ODH)。视盘血管血流减少引起微循环障碍和青光眼性视盘损害[26] [27]。Tokunaga 的报道指出，在 NTG 和 POAG 中，夜间血液的非生理性减少(包括过大和最小的 BP 波动)与青光眼的进展有关[15]。Lee 等人的研究提到，与夜间血压无下移和低下移的 NTG 患者相比，血压过度下移(夜间血压的降低水平大约是日间平均血压水平的 20%左右)的视野缺损的进展显著加快[28]。越来越多的证据表明，青光眼患者合并存在血管功能障碍，这是引起昼夜 DBP 过度波动的原因[29]。青光眼患者的眼底浅表血管复合物和视网膜血管丛密度均低于常人，因此更容易受到较大的血压波动的影响[30]。Mitchell 等人的研究个结果提示开角型青光眼(OAG)的眼底视网膜小动脉直径明显比正常人小，而正常眼压和高眼压青光眼之间的小动脉直径无显着差异[30]。另一项超过 14 个月的随访研究提出表明 POAG 眼的黄斑血管密度损失明显快于健康人[31]。

OPP 是计算出的 BP 与 IOP 之差，可以用于衡量眼血流量大小[29]。生理状态下，即使 OPP 发生了变化，但通过眼部自动调节(局部机制)可以使眼血流量保持在恒定水平[32]。既往研究表明，青光眼患者对于急性 OPP 改变自身调节调节出现异常，导致眼部血流异常，继而引起视神经缺血[33] [34]。据报道，NTG 和 POAG 患者的视盘出血(ODH)发生率比正常人高[34] [35]。一些研究暗示在随访期间 ODH 的检测可能与某些 NTG 患者的夜间血压异常波动有关，ODH 可能与 NTG 患者的视觉缺陷有关[36]。由于 ONH 的实际血流不能直接测量，在临床研究中一直使用 OPP 对其进行测量[2]。可以假设，由于 BP 与 OPP 之间的密切关系，BP 波动幅度的增加可能引起了 OPP 变异性或波动性的增加，这对 ONH 的血流量有一定影响[37]。随访期间检测 ODH 发生率是前瞻性研究中观察视野缺损进展(Visual Defect Progression, VDP)的有效预测指标[38]。

此外，最近的一项研究表明，NTG 患者在 5 年进展期，其 BP 和 OPP 的舒张参数均显著降低，这使研究者认为夜间 DOPP 降低是 NTG 患者青光眼视野进展的独立预测因素[27]。Topouzis 等已经证明，由抗高血压治疗引起的 DBP 大幅波动也与无青光眼患者的视杯扩大和视盘边缘减少有关[39]。这种相互作用表明，控制高血压病史引起的血压波动可能会促进青光眼神经病的进展，这使临床相关治疗陷入了窘

境[40]。因此，需要进行更多的前瞻性研究来探究明确血压波动幅度和时间与 ODH、VDP 之间相互作用的关系。我们可以更多地关注不同程度的血压下降与青光眼神经病变之间的关系，以及血压波动是否与 VDP 有关，以及动态血压监测设备在青光眼的早期发现和早期治疗中的临床应用。

我们的研究中也存在一些局限性。首先，问题来自文献本身，大多数相关研究是横断面研究，其可靠性不如队列研究和随机对照试验。其次，检索出研究中参数和数据分析方法千差万别，以至于我们难以提取适当的数据。第三，目前的文献缺乏对于 ODH 如何影响视野丧失进展的特定机制的研究。此外，我们的研究仅发现舒张压波动对 POAG 和 NTG 有积极作用，而 SBP 波动的作用尚不清楚，这需要更多的实验来证明。

综上，根据我们的综述和 meta 分析，舒张压波动被证实与 POAG 和 NTG 显着相关，这表明舒张压波动是其中的高风险因素。因此，动态血压监测应广泛应用于眼科实践中的监测，尤其是对于那些怀疑有 POAG 和 NTG 的受试者。一旦舒张压血压波动异常增加，还可以对视网膜神经纤维层进行光学相干断层扫描、视野和 IOP 检查、以明确诊断 POAG 和 NTG。

5. 结论

本文采用 meta 分析的方式检索了 1990 年 5 月至 2019 年 4 月的到相关对照试验，对符合目的的文献筛选整理合并后获得了血压与青光眼疾病发生之间联系的统计结果，其中昼夜舒张压波动与 POAG 和 NTG 的发展密切相关，这高度提示昼夜舒张压波动为 POAG 和 NTG 的发病危险因素。此前的相关研究均针对青光眼患者个体，研究间存在一定差异致使二者关系仍存在争议，本文将符合要求的文献进行合并，为研究血压和青光眼之间的相关性提供统计学数据。

参考文献

[1] Chen, C.L., Bojikian, K.D., Wen, J.C., Zhang, Q.Q., Xin, C., Mudumbai, R.C., Johnstone, M.A., Chen, P.P. and Wang, R.K. (2017) Peripapillary Retinal Nerve Fiber Layer Vascular Microcirculation in Eyes with Glaucoma and Single-Hemifield Visual Field Loss. *JAMA Ophthalmology*, **135**, 461-468. https://doi.org/10.1001/jamaophthalmol.2017.0261

[2] Tham, Y.-C., Lim, S.-H., Gupta, P., Aung, T., Wong, T.Y. and Cheng, C.-Y. (2018) Inter-Relationship between Ocular Perfusion Pressure, Blood Pressure, Intraocular Pressure Profiles and Primary Open-Angle Glaucoma: The Singapore Epidemiology of Eye Diseases Study. *The British Journal of Ophthalmology*, **102**, 1402-1406. https://doi.org/10.1136/bjophthalmol-2017-311359

[3] Samsudin, A., Isaacs, N., Tai, M.-L.S., Ramli, N., Mimiwati, Z. and Choo, M.M. (2016) Ocular Perfusion Pressure and Ophthalmic Artery Flow in Patients with Normal Tension Glaucoma. *BMC Ophthalmology*, **16**, 39. https://doi.org/10.1186/s12886-016-0215-3

[4] Nitta, K., Wajima, R., Tachibana, G., Inoue, S., Ohigashi, T., Otsuka, N., Kurashima, H., Santo, K., Hashimoto, M., Shibahara, H., *et al*. (2017) Prediction of Visual Field Progression in Patients with Primary Open-Angle Glaucoma, Mainly Including Normal Tension Glaucoma. *Scientific Reports*, **7**, 15048. https://doi.org/10.1038/s41598-017-15267-y

[5] Hayreh, S.S., Zimmerman, M.B., Podhajsky, P. and Alward, W.L. (1994) Nocturnal Arterial Hypotension and Its Role in Optic Nerve Head and Ocular Ischemic Disorders. *American Journal of Ophthalmology*, **117**, 603-624. https://doi.org/10.1016/S0002-9394(14)70067-4

[6] Ren, R., Zhang, X., Wang, N., Li, B., Tian, G. and Jonas, J.B. (2011) Cerebrospinal Fluid Pressure in Ocular Hypertension. *Acta Ophthalmologica*, **89**, e142-e148. https://doi.org/10.1111/j.1755-3768.2010.02015.x

[7] Kim, J.-A., Kim, T.-W., Lee, E.J., Girard, M.J.A. and Mari, J.M. (2018) Microvascular Changes in Peripapillary and Optic Nerve Head Tissues After Trabeculectomy in Primary Open-Angle Glaucoma. *Investigative ophthalmology & Visual Science*, **59**, 4614-4621. https://doi.org/10.1167/iovs.18-25038

[8] Loiselle, A.R., de Kleine, E., van Dijk, P. and Jansonius, N.M. (2018) Noninvasive Intracranial Pressure Assessment Using Otoacoustic Emissions: An Application in Glaucoma. *PLoS ONE*, **13**, e0204939. https://doi.org/10.1371/journal.pone.0204939

[9] Kashiwagi, K., Hosaka, O. and Tsukahara, S. (1997) Comparison of Nocturnal Dip of Blood Pressure and Other Blood Circulatory Parameters in Normal Tension Glaucoma and Normal Subjects. *Investigative Ophthalmology & Visual Science*, **38**, 1268.

[10] Skrzypecki, J., Grabska-Liberek, I., Przybek, J. and Ufnal, M. (2018) A Common Humoral Background of Intraocular and Arterial Blood Pressure Dysregulation. *Current Medical Research and Opinion*, **34**, 521-529. https://doi.org/10.1080/03007995.2017.1415203

[11] Rothwell, P.M. (2010) Limitations of the Usual Blood-Pressure Hypothesis and Importance of Variability, Instability, and Episodic Hypertension. *The Lancet* (*London*, *England*), **375**, 938-948. https://doi.org/10.1016/S0140-6736(10)60309-1

[12] Mancia, G. and Grassi, G. (2000) Mechanisms and Clinical Implications of Blood Pressure Variability. *Journal of Cardiovascular Pharmacology*, **35**, S15-S19. https://doi.org/10.1097/00005344-200000004-00003

[13] Han, X., Yang, T., Zhang, J., Yu, S., Guo, X., Yan, W., Hu, Y. and He, M. (2018) Longitudinal Changes in Intraocular Pressure and Association with Systemic Factors and Refractive Error: Lingtou Eye Cohort Study. *BMJ Open*, **8**, e019416. https://doi.org/10.1136/bmjopen-2017-019416

[14] Lee, N.Y., Jung, Y., Han, K. and Park, C.K. (2017) Fluctuation in Systolic Blood Pressure Is a Major Systemic Risk Factor for Development of Primary Open-Angle Glaucoma. *Scientific Reports*, **7**, 43734. https://doi.org/10.1038/srep43734

[15] Tokunaga, T., Kashiwagi, K., Tsumura, T., Taguchi, K. and Tsukahara, S. (2004) Association between Nocturnal Blood Pressure Reduction and Progression of Visual Field Defect in Patients with Primary Open-Angle Glaucoma or Normal-Tension Glaucoma. *Japanese Journal of Ophthalmology*, **48**, 380-385. https://doi.org/10.1007/s10384-003-0071-6

[16] von Elm, E., Altman, D.G., Egger, M., Pocock, S.J., Gotzsche, P.C. and Vandenbroucke, J.P. (2008) STROBE Initiate. The Strengthening the Reporting of Observation Studies in Epidemiology (STORBE) Statement; Guidelines for Reporting Observation Studies. *Journal of Clinical Epidemiology*, **61**, 344-348. https://doi.org/10.1016/j.jclinepi.2007.11.008

[17] Higgins, J.P.T. and Green, S. (2005) Cochrane Handbook for Systematic Reviews of Interventions 4.2.5. http://www.cochrane.org/resources/handbook/hbook.htm

[18] Ramli, N., Nurull, B.S., Hairi, N.N. and Mimiwati, Z. (2013) Low Nocturnal Ocular Perfusion Pressure as a Risk Factor for Normal Tension Glaucoma. *Preventive Medicine*, **57**, S47-S49. https://doi.org/10.1016/j.ypmed.2013.01.007

[19] Mroczkowska, S., Benavente-Perez, A., Negi, A., Sung, V., Patel, S.R. and Gherghel, D. (2013) Primary Open-Angle Glaucoma vs Normal-Tension Glaucoma: The Vascular Perspective. *JAMA Ophthalmology*, **131**, 36-43. https://doi.org/10.1001/2013.jamaophthalmol.1

[20] Plange, N., Kaup, M., Daneljan, L., Predel, H.G., Remky, A. and Arend, O. (2006) 24-H Blood Pressure Monitoring in Normal Tension Glaucoma: Night-Time Blood Pressure Variability. *Journal of Human Hypertension*, **20**, 137-142. https://doi.org/10.1038/sj.jhh.1001959

[21] Riccadonna, M., Covi, G., Pancera, P., Presciuttini, B., Babighian, S., Perfetti, S., Bonomi, L. and Lechi, A. (2003) Autonomic System Activity and 24-Hour Blood Pressure Variations in Subjects with Normal- and High-Tension Glaucoma. *Journal of Glaucoma*, **12**, 156-163. https://doi.org/10.1097/00061198-200304000-00011

[22] Meyer, J.H., Brandi-Dohrn, J. and Funk, J. (1996) Twenty Four Hour Blood Pressure Monitoring in Normal Tension Glaucoma. *British Journal of Ophthalmology*, **80**, 864-867. https://doi.org/10.1136/bjo.80.10.864

[23] Bechtoille, A. and Bressondumont, H. (1994) Diurnal and Nocturnal Blood-Pressure Drops in Patients with Focal Ischemic Glaucoma. *Graefes Archive for Clinical and Experimental Ophthalmology*, **232**, 675-679. https://doi.org/10.1007/BF00171383

[24] Kwon, J., Lee, J., Choi, J., Jeong, D. and Kook, M.S. (2017) Association between Nocturnal Blood Pressure Dips and Optic Disc Hemorrhage in Patients with Normal-Tension Glaucoma. *American Journal of Ophthalmology*, **176**, 87-101. https://doi.org/10.1016/j.ajo.2017.01.002

[25] Jin, S.W., Seo, H.R., Rho, S.S. and Rho, S.H. (2017) The Effects of Nocturnal Dip and Blood Pressure Variability on Paracentral Scotoma in Early Open-Angle Glaucoma. *Seminars in Ophthalmology*, **32**, 504-510. https://doi.org/10.3109/08820538.2015.1123733

[26] Binggeli, T, Schoetzau, A. and Konieczka, K. (2019) In Glaucoma Patients, Low Blood Pressure is Accompanied by Vascular Dysregulation. *EPMA Journal*, **9**, 387-391. https://doi.org/10.1007/s13167-018-0155-5

[27] Raman, P., Suliman, N.B., Zahari, M., Kook, M. and Ramli, N. (2018) Low Nocturnal Diastolic Ocular Perfusion Pressure as a Risk Factor for NTG Progression: A 5-Year Prospective Study. *Eye*, **32**, 1183-1189. https://doi.org/10.1038/s41433-018-0057-8

[28] Lee, J., Choi, J., Jeong, D., Kim, S. and Kook, M.S. (2015) Relationship between Daytime Variability of Blood Pres-

sure or Ocular Perfusion Pressure and Glaucomatous Visual Field Progression Reply. *American Journal of Ophthalmology*, **160**, 845-846. https://doi.org/10.1016/j.ajo.2015.06.021

[29] Bata, A.M., Fondi, K., Witkowska, K.J., Werkmeister, R.M., Hommer, A., Vass, C., Resch, H., Schmidl, D., Popa-Cherecheanu, A., Chua, J., *et al*. (2019) Optic Nerve Head Blood Flow Regulation during Changes in Arterial Blood Pressure in Patients with Primary Open-Angle Glaucoma. *Acta Ophthalmologica*, **97**, e36-e41. https://doi.org/10.1111/aos.13850

[30] Chang, M., Yoo, C., Kim, S.W. and Kim, Y.Y. (2011) Retinal Vessel Diameter, Retinal Nerve Fiber Layer Thickness, and Intraocular Pressure in Korean Patients with Normal-Tension Glaucoma. *American Journal of Ophthalmology*, **151**, 100-105. https://doi.org/10.1016/j.ajo.2010.07.025

[31] Shoji, T., Zangwill, L.M., Akagi, T., Saunders, L.J., Yarmohammadi, A., Manalastas, P.I.C., Penteado, R.C. and Weinreb, R.N. (2017) Progressive Macula Vessel Density Loss in Primary Open-Angle Glaucoma: A Longitudinal Study. *American Journal of Ophthalmology*, **182**, 107-117. https://doi.org/10.1016/j.ajo.2017.07.011

[32] Hafez, A.S., Bizzarro, R.L.G., Rivard, M. and Lesk, M.R. (2003) Changes in Optic Nerve Head Blood Flow after Therapeutic Intraocular Pressure Reduction in Glaucoma Patients and Ocular Hypertensives. *Ophthalmology*, **110**, 201-210.

[33] Kocaturk, T., Akgullu, C., Evlicoglu, G.E., Omurlu, I.K., Cakmak, H., Eryilmaz, U. and Dayanir, V. (2017) Diurnal Blood Pressure Parameters in Normal Tension Glaucoma, Primary Open Angle Glaucoma, and Healthy Subjects. *Anatolian Journal of Cardiology*, **18**, 62-67.

[34] Sodhi, P.K. and Vidula Garg, E. (2017) Association Between Nocturnal Blood Pressure Dips and Optic Disc Hemorrhage in Patients With Normal-Tension Glaucoma. *American Journal of Ophthalmology*, **181**, 176-177. https://doi.org/10.1016/j.ajo.2017.06.028

[35] Okuno, T., Sugiyama, T., Kojima, S., Nakajima, M. and Ikeda, T. (2004) Diurnal Variation in Microcirculation of Ocular Fundus and Visual Field Change in Normal-Tension Glaucoma. *Eye*, **18**, 697-702. https://doi.org/10.1038/sj.eye.6700749

[36] Springelkamp, H., Wolfs, R.C., Ramdas, W.D., Hofman, A., Vingerling, J.R., Klaver, C.C. and Jansonius, N.M. (2017) Incidence of Glaucomatous Visual Field Loss after Two Decades of Follow-up: The Rotterdam Study. *European Journal of Epidemiology*, **32**, 691-699. https://doi.org/10.1007/s10654-017-0270-y

[37] Choi, J., Lee, J.R., Lee, Y., Lee, K.S., Na, J.H., Han, S. and Kook, M.S. (2013) Relationship between 24-Hour Mean Ocular Perfusion Pressure Fluctuation and Rate of Paracentral Visual Field Progression in Normal-Tension Glaucoma. Invest Ophth Vis Sci, **54**, 6150-6157. https://doi.org/10.1167/iovs.13-12093

[38] Kwon, J., Lee, J., Choi, J., Jeong, D. and Kook, M.S. (2017) Association between Nocturnal Blood Pressure Dips and Optic Disc Hemorrhage in Patients With Normal-Tension Glaucoma Reply. *American Journal of Ophthalmology*, **181**, 177-178. https://doi.org/10.1016/j.ajo.2017.06.027

[39] Topouzis, F., Coleman, A.L., Harris, A., Jonescu-Cuypers, C., Yu, F., Mavroudis, L., Anastasopoulos, E., Pappas, T., Koskosas, A. and Wilson, M.R. (2006) Association of Blood Pressure Status with the Optic Disk Structure in Non-Glaucoma Subjects: The Thessaloniki Eye Study. *American Journal of Ophthalmology*, **142**, 60-67. https://doi.org/10.1016/j.ajo.2006.02.055

[40] Levine, R.M., Yang, A., Brahma, V. and Martone, J.F. (2017) Management of Blood Pressure in Patients with Glaucoma. *Current Cardiology Reports*, **19**, 109. https://doi.org/10.1007/s11886-017-0927-x

附录

一、Search Strategies

1 controlled clinical trial.pt. (93121)

2 placebo.ab. (198677)

3 trial.ab. (467720)

4 groups.ab. (1925262)

5 1 or 2 or 3 or 4 (2415198)

6 exp animals/ not humans.sh. (4591520)

7 5 not 6 (2022298)

8 exp glaucoma/ (50335)

9 exp normal tension glaucoma/ (607)

10 exp primary open angle glaucoma/ (13385)

11 (NTG or POAD).tw. (3027)

12 or/8-11 (52518)

13 exp blood pressure/ (282446)

14 12 and 13 (510)

二、敏感性检测

1) 剔除 Meyer, J. H. 1996

SMD 2.801 (95% CI 0.357，5.245) I^2 = 97.7%, Z = 2.25, *P* = 0.025

2) 剔除 Riccadonna, M 2003

SMD 2.095 (95% CI 0.053，4.136) I^2 = 97.6%, Z = 2.01, *P* = 0.044

3) 剔除 Plange, N. 2006

SMD 3.198 (95% CI 0.972，5.424) I^2 = 96.6%, Z = 2.82, *P* = 0.005

4) 剔除 Ramli, N. 2013

SMD 1.872 (95% CI 0.545，3.199) I^2 = 92.4%, Z = 2.77, *P* = 0.006

5) 剔除 Mroczkowska, S. 2013

SMD 3.094 (95% CI 0.615，5.574) I^2 = 97.7%, Z = 2.45, *P* = 0.014