

Diastolic Double-Product: A New Entity to Consider in Normal-Tension Glaucoma Patients*

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ABSTRACT: **Background:** Vascular insufficiency is considered to play an important role in the pathogenesis of normal-tension glaucoma (NTG). Autoregulation of blood flow in the eye has been shown to be impaired in NTG, resulting in the inability to compensate for changes in intraocular pressure or blood pressure in order to maintain adequate perfusion.

Objectives: To evaluate the occurrence of combined bradycardia-hypotension during 24 hour monitoring of blood pressure and heart rate in patients with NTG.

Methods: Eleven NTG patients participated in the study. All had episodic symptoms of dizziness or lightheadedness, but were confirmed as not having a diagnosis of orthostatic hypotension. Twenty-four hour monitoring was performed with systemic blood pressure and heart rate automatically measured every 20 minutes during daytime and every hour during the night. The cardiac diastolic and systolic double products (dDP and sDP) at each reading were calculated by multiplying the heart rate by the respective blood pressure. dDP < 3600 and sDP < 5400 (corresponding to a heart rate of 60 beats/min and a blood pressure of 60 and 90 mmHg, respectively) were considered abnormally low, and dDP < 2500 and sDP < 4000 (corresponding to a heart rate 50 beats/min and a blood pressure of 50 and 80 mmHg, respectively) were considered severely abnormal.

Results: dDP was abnormally low in all 11 NTG patients on at least one occasion, the majority occurring during the nighttime hours, while abnormally low sDP was present in 8 of the 11 patients. The mean cumulative duration of low dDP readings was 4.2 ± 3.2 hours. Severely low dDP readings were observed in six patients.

Conclusions: Abnormally low dDP was recorded in all NTG patients, lasting more than an hour in the majority of cases. Abnormally decreased dDP may represent a state of cardiovascular autonomic dysregulation, resulting in low ocular perfusion in certain NTG patients.

KEY WORDS: blood pressure, bradycardia, hypotension, normal-tension glaucoma

IMAJ 2012; 14: 240–243

Vascular insufficiency is considered to play an important role in the pathogenesis of normal-tension glaucoma [1-3]. Nocturnal hypotension with corresponding sharp drops in blood pressure (nocturnal dips) has been reported to occur more frequently in patients with NTG [4-6]; however, its effect on ocular blood flow is still undetermined [7].

The capability to autoregulate blood flow ensures tissue perfusion to essential organs, whereas disruption of this normal autoregulatory function may compromise tissues [8,9]. Autoregulation in the eye has been shown to be impaired in NTG, resulting in the inability to compensate for changes in intraocular pressure or blood pressure in order to maintain adequate perfusion [10,11].

The cardiac double product is a well-recognized entity, initially introduced to describe cardiac workload [12]. For that purpose, it is calculated by multiplying the systolic blood pressure (in mmHg) by the heart rate in beats/min. The resultant systolic double product correlates with the cardiac workload. As diastole comprises about two-thirds of the cardiac cycle, tissue perfusion is prone to be more affected by a low diastolic blood flow. The normal physiologic compensatory mechanism to hypotension is an increase in heart rate. As tissue perfusion is related to both BP and HR, the diastolic double product, calculated by multiplying diastolic BP by HR, may serve as a better indicator of tissue perfusion. Low dDP may also indicate abnormal cardiovascular autonomic regulation, which may be abnormal in primary open-angle glaucoma patients [13].

Prior published studies reported data on BP monitoring only, disregarding changes in HR. In this study 24 hour BP and HR monitoring was performed in NTG patients, and the double products were calculated. The purpose of this report is to introduce the concept of “double product” in the context of NTG and to examine it in a defined subgroup of NTG patients over the course of 24 hours.

NTG = normal-tension glaucoma
BP = blood pressure
HR = heart rate
dDP = diastolic double product

*This study was presented in part as an abstract at the 2006 annual ARVO meeting, Florida, USA.

PATIENTS AND METHODS

A defined population of NTG patients with episodic symptoms suggestive of insufficient vascular autoregulation enrolled in the study. Symptoms were episodic dizziness or lightheadedness upon postural change, but blood pressure readings in supine and upright positions failed to diagnose orthostatic hypotension. None of the patients suffered from hypertension, ischemic heart disease, sleep apnea or diabetes mellitus, and only one smoked regularly.

The diagnosis of NTG was based on clinical evaluation and visual field examination. Visual field examination was performed with the 24-2 SITA-fast or SITA-standard program on the Humphrey field analyzer (HFA, Carl Zeiss Meditec Inc., Dublin, CA, USA). IOP prior to treatment was < 22 mmHg, and all patients had enlarged cups and corresponding visual field defects, representative of the NTG diagnosis. Patients were not using any oral medications on a regular basis. The majority of patients were using beta-blocker eye drops. Treatment with this medication was withheld for one month prior to and during the BP monitoring period. These patients were followed on a weekly basis, and other topical medications were added as necessary to control the IOP at the previously established level.

Ambulatory 24 hour monitoring of BP and HR (Oscar 2, SunTech Medical, Morrisville, NC, USA) was performed in each enrolled case. All patients continued their normal daily activities during the monitoring period. Systemic BP and HR were automatically measured every 20 minutes during daytime (6 a.m. to 11 p.m.) and every hour during night-time. The diastolic and systolic double product (dDP and sDP) at each reading was calculated by multiplying the HR by the respective BP. dDP < 3600 (corresponding to a BP of 60 mmHg and a HR of 60 beats/min, which are the lower limits of normal in the resting state for these parameters) and sDP < 5400 (corresponding to a BP of 90 mmHg and a HR of 60 beats/min, which are the lower limits of normal for these parameters) were considered abnormally low. dDP < 2500 and sDP < 4000 (corresponding to a HR of 50 beats/min and a BP of 50 and 80 mmHg, respectively, which are 10 beats/min and 10 mmHg or more below the lower limits of normal range) were considered severely abnormal.

The study was approved by the Ethics Committee, and all study procedures conformed to the tenets of the Declaration of Helsinki.

RESULTS

Table 1 shows the characteristics of the study population. All 11 patients were female, and their age range was 37–67 years.

IOP = intraocular pressure
sDP = systolic double product

Table 1. Baseline characteristics of the study population (n=11)

Age at presentation, mean (SD)	52.5 (9.5)
Females	11/11
Episodic dizziness/lightheadedness*	11/11
Raynaud's-like phenomenon**	9/11
Migraine	5/11
Smoking	1/11
Sleep apnea	0/11
Visual fields – abnormal findings	11/11
Family history of glaucoma	4/11
Body mass index, mean (SD)***	23.2 (3.1)

* Episodic dizziness or lightheadedness following postural change, but no orthostatic hypotension upon blood pressure readings in supine and upright positions

** Transient white or bluish discoloration of fingers or fingertips upon exposure to cold temperatures

*** Normal values 18.5–25

Table 2. Number (%) of patients with abnormally low systolic and diastolic double products (sDP and dDP) in the study population (n=11)

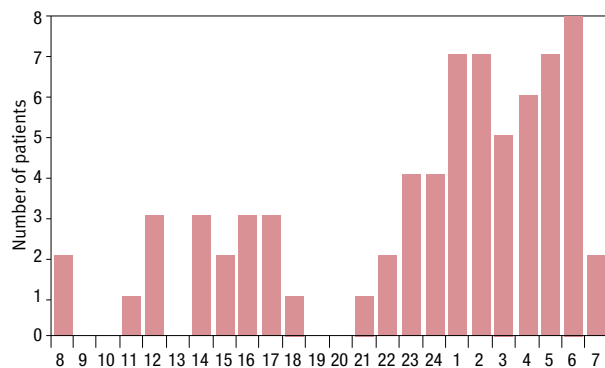
	Low sDP (< 5400)	Low dDP (< 3600)	Severely low sDP (< 4000)	Severely low dDP (< 2500)
Abnormal readings	8 (73%)	11 (100%)	5 (45%)	6 (54%)
Abnormal readings lasting > 1 hour per episode	3 (27%)	8 (73%)	0	2 (18%)

In this defined population, all cases had episodic dizziness or lightheadedness upon postural change, but no orthostatic hypotension upon blood pressure readings in supine and upright positions. Nine patients had additional evidence of abnormal vascular reactivity with Raynaud's-like phenomenon (transient white-bluish discoloration of fingers upon exposure to cold temperatures) or migraine. The median IOP (22 eyes) was 16 mmHg (range 11–20). At baseline, median systolic BP was 110 mmHg (range 96–127) and median diastolic BP 67 mmHg (range 62–72).

All 11 patients had at least one abnormally low dDP during the 24 hour monitoring period [Table 2]. Severely low dDP was recorded in 6 patients (54%), all of them having a history of clinical manifestations suggestive of abnormal vascular reactivity, as described above. Abnormally low dDP occurred predominantly at night (11 p.m. to 6 a.m.), although 5 patients had low dDP also in the morning (7–8 a.m.) or afternoon (12–6 p.m.) [Figure 1]. The median dDP in this group of patients was borderline or low throughout most of the night [Figure 2]. sDP and dDP as low as 3196 and 1692 were recorded, respectively, corresponding to a BP reading of 68/36 mmHg and HR of 47 beats/min.

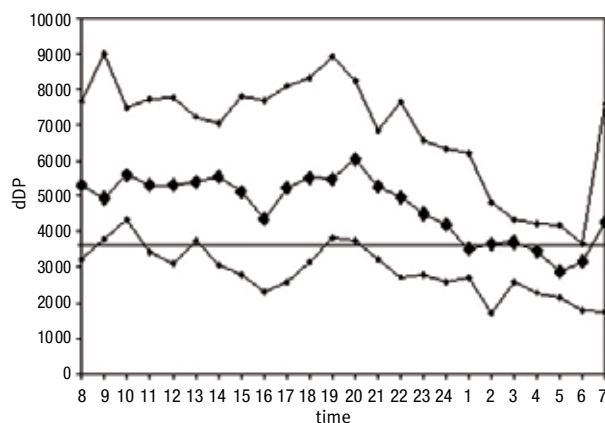
There were 5.1 ± 2.7 episodes of low dDP per patient throughout the 24 hour recording. In 73% of the patients, these episodes of low dDP lasted at least one hour. In this group of

Figure 1. Number of normal-tension glaucoma patients with abnormally low diastolic double product throughout the 24-hour blood pressure and heart rate monitoring



dDP = diastolic double product (diastolic blood pressure in mmHg x heart rate in beats/min), time = hour of the day of monitoring, starting at 8 am

Figure 2. Median and range of diastolic double product in 11 normal-tension glaucoma patients throughout the 24-hour blood pressure and heart rate monitoring.



dDP = diastolic double product (diastolic blood pressure in mmHg x heart rate in beats/min), time = hour of the day of monitoring, starting at 8 am. Bold line = median dDP, thin lines = range of dDP (highest and lowest dDP), horizontal line = lower range of normal dDP

11 patients, the mean cumulative duration of low dDP was 4.2 ± 3.2 hours.

DISCUSSION

NTG is a multifactorial optic neuropathy, but insufficient vascular autoregulation is considered to be present in at least some patients. Low BP, excessive BP dips and low ocular perfusion pressure have been reported to be linked to NTG pathology [4,5-7,14]. Population-based epidemiological studies have shown that low diastolic BP and low diastolic ocular perfusion pressure (the difference between diastolic BP and the IOP) are major risk factors for the genesis and

progression of POAG [8,15-19]. Vascular insufficiency is considered even more deleterious in patients with NTG [4,5]. The increased prevalence of nocturnal arterial hypotension in NTG patients has been well established by Hayreh and colleagues [4] in a large series that included 114 patients with anterior ischemic optic neuropathy, 131 with NTG and 30 with POAG. Further, patients with visual field deterioration also had lower night-time diastolic BP [4]. It is important to note that low diastolic BP has been associated with optic disk damage even in non-glaucoma subjects [20]. Previous studies that recognized the deleterious effect of low nocturnal BP reported mean BP values; however, mean values alone may not reflect periods of severe ocular hypoperfusion, contributing to the pathogenesis of glaucoma.

Drawing on these reports, we present a novel concept for evaluating BP-related risk assessment in NTG, a calculation of the dDP. It is our hope that this calculation will provide greater insight than stand-alone mean BP or perfusion pressure values for NTG patients. In this pilot investigation, all 11 NTG patients displayed evidence of low dDP, especially apparent during the night-time hours. In 72% of the patients, the abnormally low dDP lasted at least one hour. In all cases, episodes of low diastolic BP were not associated with compensatory tachycardia. During most episodes of low diastolic BP, HR was less than 60 beats/min, suggesting abnormal cardiovascular autonomic regulation.

Bradycardia increases the relative period of diastole in the cardiac cycle, thus further decreasing the mean perfusion pressure. Therefore, low dDP may be associated with increased patient vulnerability to develop glaucomatous damage. This new parameter may help clarify the multitude of previous parameters that have suggested a vascular autoregulatory component in NTG. Galambos et al. [21] demonstrated an insufficient compensatory response to postural changes in patients with NTG and POAG compared to healthy controls. Gherghel and team [13] also described abnormal cardiovascular autonomic function in POAG patients [13]. Calculating dDP in POAG patients may help differentiate between POAG with and without vascular abnormalities, similar to NTG patients.

In our 11 NTG patients we studied the occurrence and duration of abnormally low dDP as it highlighted the severity of hypoperfusion. Assuming that even short periods of severe hypoperfusion may be compounding, intermittent hypoperfusion periods should therefore not be overlooked. The introduction and utilization of the concept of dDP is supported by the data of this pilot study. Calculating dDP is potentially advantageous over measuring diastolic BP alone, as it may more specifically report the presence of impaired cardiovascular autonomic regulation.

POAG = primary open-angle glaucoma

Bonomi et al. [8] suggested that the risk of developing glaucomatous damage increased when diastolic ocular perfusion pressure was less than 55 mmHg. IOP was not measured in our group of NTG patients during the night; however, even if one assumes a good response to topical IOP-reducing agents leading to a reduction of IOP to a level of 10 mmHg, a diastolic ocular perfusion pressure less than 55 mmHg was calculated to be present during 4.6 ± 2.4 hours of the night in our patients.

This study has several inherent limitations: it was planned as a pilot study, with the aim of introducing the term “double-product,” combining data of both HR and BP, in the context of NTG. Therefore, the sample size was small, and no follow-up was available for evaluation of possible visual field progression in association with dDP. This study described a predefined population of NTG patients with episodic symptoms suggestive of insufficient vascular autoregulation such as episodic dizziness or lightheadedness upon postural change and Raynaud’s-like phenomenon. It is unclear whether observations in these patients would be valid for all unselected NTG patients. Only a large-scale longitudinal population study, involving NTG, POAG and matched controls, in which visual field progression is monitored in association with dDP will overcome those limitations and prove the specificity and extent of this study’s findings. At present, it appears that topical beta-blockers should be used with caution in treating patients with NTG.

Acknowledgements

This study was supported in part by an unrestricted grant from Research to Prevent Blindness, New York, NY, USA.

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References

1. Costa VP, Harris A, Stefansson E, et al. The effects of antiglaucoma and systemic medications on ocular blood flow. *Prog Ret Eye Res* 2003; 22: 769-805.
2. Flammer J, Orgul S, Costa VP, et al. The impact of ocular blood flow in glaucoma. *Prog Retin Eye Res* 2002; 21: 359-93.
3. Harris A, Rechtman, E, Siesky B, Junescu-Cuyppers C, McCranor L, Garzozzi HJ. The role of optic nerve blood flow in the pathogenesis of glaucoma.

Ophthalmol Clin North Am 2005; 18: 345-53.

4. Hayreh SS, Zimmerman MB, Podhajsky P, Alward WL. Nocturnal arterial hypotension and its role in optic nerve head and ocular ischemic disorders. *Am J Ophthalmol* 1994; 117: 603-24.
5. Hayreh SS, Podhajsky P, Zimmerman MB. Role of nocturnal arterial hypotension in optic nerve head ischemic disorders. *Ophthalmologica* 1999; 213: 76-96.
6. Meyer JH, Brandi-Dohorn J, Funk J. Twenty four hour blood pressure monitoring in normal tension glaucoma. *Br J Ophthalmol* 1996; 80: 864-7.
7. Harris A, Evans D, Martin B, et al. Nocturnal blood pressure reduction: effect on retrobulbar hemodynamics in glaucoma. *Graefe Arch Clin Exp Ophthalmol* 2002; 240: 372-8.
8. Bonomi L, Marchini G, Marraffa M, Bernardi P, Morbio R, Varotto A. Vascular risk factors for primary open angle glaucoma: the Egna-Neumarkt Study. *Ophthalmology* 2000; 107: 1287-93.
9. Pillunat LE, Anderson DR, Knighton RW, Joos KM, Feuer JW. Autoregulation of human optic nerve head circulation in response to increased intraocular pressure. *Exp Eye Res* 1997; 64: 737-44.
10. Harris A, Ciulla TA, Chung HS, Martin B. Regulation of retinal and optic nerve blood flow. *Arch Ophthalmol* 1998; 116: 1491-5.
11. Kashiwagi K, Hosaka O, Kashiwagi F, et al. Systemic circulatory parameters: comparison between patients with normal tension glaucoma and normal subjects using ambulatory monitoring. *Jpn J Ophthalmol* 2001; 45: 388-96.
12. Hermida RC, Fernandez JR, Ayala DE, Mojon A, Alonso I, Smolensky M. Circadian rhythm of double (rate-pressure) product in healthy normotensive young subjects. *Chronobiol Int* 2001; 18: 475-89.
13. Gherghel D, Hosking SL, Armstrong R, Cunliffe IA. Autonomic dysfunction in unselected and untreated primary open angle glaucoma patients: a pilot study. *Ophthalmic Physiol Opt* 2007; 27: 336-41.
14. Choi J, Jeong J, Cho H, Kook MS. Effect of nocturnal blood pressure reduction on circadian fluctuation of mean ocular perfusion pressure: a risk factor for normal tension glaucoma. *Invest Ophthalmol Vis Sci* 2006; 47: 831-6.
15. Leske MC, Connell AM, Wu SY, Hyman LG, Schachat AP. Risk factors for open angle glaucoma: the Barbados Eye Study. *Arch Ophthalmol* 1995; 113: 918-24.
16. Leske MC, Nemesure B, He Q, et al. Patterns of open angle glaucoma in the Barbados Family Study. *Ophthalmology* 2001; 108: 1015-22.
17. Leske MC, Wu SY, Nemesure B, Hennis A. Barbados Eye Studies Group. Incident open angle glaucoma and blood pressure. *Arch Ophthalmol* 2002; 120: 954-9.
18. Quigley HA, West SK, Rodriguez J, Munoz B, Klein R, Snyder R. The prevalence of glaucoma in a population-based study of Hispanic subjects: Proyecto VER. *Arch Ophthalmol* 2001; 119: 1819-26.
19. Tielsch JM, Katz J, Sommer A, Quigley HA, Javitt JC. Hypertension, perfusion pressure and primary open angle glaucoma: a population-based assessment. *Arch Ophthalmol* 1995; 113: 216-21.
20. Topouzis F, Coleman AL, Harris A, et al. Association of blood pressure status with the optic disk structure in non-glaucoma subjects: the Thessaloniki eye study. *Am J Ophthalmol* 2006; 142: 60-7.
21. Galambos P, Vafiadis J, Vilchez SE, et al. Compromised autoregulatory control of ocular hemodynamics in glaucoma patients after postural change. *Ophthalmology* 2006; 113: 1832-6.