

# Clinical value of phenylephrine testing in the upper and lower eyelids of patients with aponeurotic and congenital eyelid ptosis

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Received: 2021-03-29

Accepted: 2021-11-02

## Abstract

• **AIM:** To characterize the phenylephrine test in aponeurotic and congenital eyelid ptosis, to determine the appropriate timing of the phenylephrine test, and to assess the responses of the upper and lower eyelids.

• **METHODS:** This was a retrospective analysis of 140 eyes of 87 patients (mean age 52.29±16.45y; 22 males, 65 females) with upper eyelid ptosis. Totally 88.6% had aponeurotic and 11.4% had congenital ptosis. For the evaluation of the responses of the upper and lower eyelids to topical 2.5% phenylephrine, the scleral show height, the marginal reflex distance (MRD) between the inferior margin of the upper eyelid and pupillary light reflex (MRD1), and between the central portion of the lower eyelid and pupillary light reflex (MRD2) were measured at the 2<sup>nd</sup>, 5<sup>th</sup>, and 15<sup>th</sup> minutes. The changes of MRD1 and MRD2 with time ( $\Delta$ MRD1 and  $\Delta$ MRD2) were evaluated.

• **RESULTS:** The mean MRD1, MRD2, and scleral show heights increased within 5min after testing, remaining largely stable between the 5<sup>th</sup>-15<sup>th</sup> minutes. The percentage of eyes with a greater response in MRD1 increased with increased severity of ptosis ( $P<0.05$ ). Eyes with aponeurotic ptosis were more responsive to phenylephrine testing than congenital ptosis. The mild ptosis group had lower scleral show measurements and higher  $\Delta$ MRD2 values. The  $\Delta$ MRD1 and  $\Delta$ MRD2 values were poorly correlated in all measurement times.

• **CONCLUSION:** Performing the phenylephrine test 5min after instilling the reagent is adequate to assess the maximum response of the upper and lower eyelids. The upper and lower eyelid responses in phenylephrine testing are poorly correlated. However, the  $\Delta$ MRD2 is related with baseline scleral show degree that may be a postoperative predictive factor. Further studies are necessary to determine the relationship between the responses of the lower eyelids to phenylephrine testing.

• **KEYWORDS:** eyelid ptosis; phenylephrine testing; scleral show; aponeurotic ptosis; congenital ptosis.

**DOI:10.18240/ijo.2022.09.06**

**Citation:** Gedar Totuk OM, Altinel MG, Kanra AY, Aykan U. Clinical value of phenylephrine testing in the upper and lower eyelids of patients with aponeurotic and congenital eyelid ptosis. *Int J Ophthalmol* 2022;15(9):1444-1452

## INTRODUCTION

Eyelid ptosis, which is an abnormal function of the levator palpebra superioris muscle or Müller's tarsal muscle, is one of the common eyelid disorders seen in oculoplastic surgery. The etiology of ptosis can be congenital, myogenic, neurogenic, and aponeurotic<sup>[1-4]</sup>. Ophthalmic plastic surgeons evaluate levator function (LF) and response to topical phenylephrine for the preoperative evaluation and determination of the appropriate surgical method for ptosis repair, but there is an underestimated situation; upper eyelid ptosis can change the lower eyelid position in both congenital and aponeurotic subgroups of ptosis to maintain the horizontal visual axis without inclination of the head in the primary gaze position<sup>[1-4]</sup>. The possible mechanism of this harmony is a compensatory contraction of the superior rectus/levator complex and simultaneous lower eyelid retractor, thereby displacing the globe upward in the orbit and retracting the lower eyelid with a dynamic lower scleral show<sup>[1-2]</sup>. Few previous studies have highlighted this issue and have shown that lower scleral show improves after ptosis surgery<sup>[1-4]</sup>. The need for a detailed evaluation of the lower eyelid for more

precise and successful ptosis surgery prompted us to design this study.

The levator palpebra superioris, the major upper eyelid elevator muscle, contains striated muscle fibers and acts together with Müller's muscle<sup>[5]</sup>. Müller's muscle and the lower eyelid tarsal muscle are sympathetically stimulated smooth muscles that contract and widen the interpalpebral fissure in the presence of a topical adrenergic such as phenylephrine, a direct alpha-1 adrenergic agonist<sup>[6]</sup>. The response to topical phenylephrine is predictive of the outcome of a Müller's ptosis repair<sup>[7]</sup>. Although interpalpebral fissure height is dependent on the lower eyelid position, changes in the lower eyelid position with phenylephrine are not usually measured before surgery<sup>[8]</sup>. Eyelid position is frequently described using the marginal reflex distance (MRD) alone for the upper eyelids<sup>[9]</sup>.

This study aimed to determine the time in which the maximal response of upper and lower eyelids to phenylephrine testing occurred, the correlation between the upper and lower eyelids, and to compare the test results of different groups of ptosis etiology and severity at different time points.

## SUBJECTS AND METHODS

**Ethical Approval** This study was approved by the Institutional Ethics Committee of Bahcesehir University (Date 4.9.2019, No. 2019-12/05), and conducted in compliance with the latest version of the Declaration of Helsinki. Informed consent was obtained from all of the patients.

**Study Design and Patients** This was a retrospective analysis of 140 eyes of 87 patients with upper eyelid ptosis who were referred to our clinic between September 2018 and May 2019. Our study included eyes with aponeurotic and congenital upper eyelid ptosis with good LF (>8 mm). The exclusion criteria were eyelid pathologies such as lower eyelid laxity, a history of previous eyelid surgery or trauma (traumatic ptosis), tumors causing mechanical ptosis or any other known eyelid disease; neurotoxin application 5mo before the phenylephrine testing; systemic or neurologic diseases that might affect eyelid position (such as Parkinson's disease, Horner syndrome, stroke, cranial nerve palsy, thyroid eye disease, myasthenia gravis).

Baseline ophthalmologic examinations for ptosis included: measurements of Snellen visual acuity, MRD1 defined as the distance from the light reflex to the upper lid margin and MRD2 as the distance to the lower lid margin, LF, scleral show height, and slit-lamp anterior and posterior segment examinations. Eyes with aponeurotic ptosis were divided into four subgroups: age-related, post-operative, contact lens (CL)-induced, and idiopathic etiology.

**Study Procedures and the Measurements** Patients' demographics, side of ptotic eye, etiology of ptosis, and concomitant systemic and ocular diseases were recorded. MRD1, MRD2, and scleral show height were measured at

baseline, and the 2<sup>nd</sup>, 5<sup>th</sup>, and 15<sup>th</sup> minutes of the phenylephrine testing, and recorded by the same author (Gedar Totuk OM). All measurements are given in units of 0.5 mm.

For the assessment of LF, the patient's frontalis muscle was stabilized with a finger placed above the brow while the patient looked from far downgaze to far upgaze. The distance from the upper palpebral margin position in the down-gaze and the upper palpebral margin position in upgaze is the LF. This measurement was performed before the test only. LF was evaluated as excellent (13-15 mm), good (8-12 mm), fair (5-7 mm), and poor (4 mm)<sup>[10]</sup>.

MRD1 is the distance between the inferior margin of the upper eyelid and the pupillary light reflex in the primary position of gaze. The normal range of MRD1 is 4-4.5 mm. It is measured using a millimeter ruler held adjacent to the patient's lateral canthus while the patient is in the sitting position, looking at a light source (a penlight) placed 50 cm away from the margin of the upper eyelid. A finger is placed over the patient's brow to ensure frontalis relaxation<sup>[11]</sup>. Ptosis was defined as mild if the MRD1 was >1.5 mm, moderate if it was 0.5-1.5 mm, and severe if it was <0.5 mm. MRD1 has a negative value if the upper lid margin obstructs the corneal reflex. This value is based on the elevation of the ptotic eyelid until the light reflex appears<sup>[10]</sup>.

MRD2 is the distance between the central portion of the lower eyelid and the pupillary light reflex in the primary position of gaze.

The scleral show is an anatomic condition in which the scleral area is abundantly visible. Its height is the distance between the central portion of the lower eyelid and the central portion of the inferior corneal limbus. Baseline scleral show height is classified as 0, 0.5-1, and >1 mm.

In the phenylephrine testing, one drop of phenylephrine 2.5% solution (Mydrin 2.5%, Alcon Laboratories Inc., Fort Worth, TX, USA) was instilled in the inferior cul-de-sac of the ptotic eye. The examiner's finger depressed the lower lid while instilling the phenylephrine drop.

The response of the Müller's muscle to phenylephrine is characterized by the change in MRD1 ( $\Delta$ MRD1).  $\Delta$ MRD1 is equal to the post-phenylephrine MRD1 value minus the baseline MRD1 value for each time point.  $\Delta$ MRD1 was categorized as follows: 0, 0.5-1, 1.5-2, and >2 mm.

The response of the lower eyelid tarsal muscle to phenylephrine is quantified using the change in MRD2 ( $\Delta$ MRD2) and the scleral show height.  $\Delta$ MRD2 is post-phenylephrine MRD2 value minus the baseline MRD2 value for each time point.  $\Delta$ MRD2 equals the change of the scleral show height.  $\Delta$ MRD2 was categorized as follows: 0, 0.5-1 or >1 mm.

**Statistical Analysis** Statistical analysis was performed using the IBM SPSS Statistics 22 package (IBM SPSS, Turkey). The

Shapiro-Wilk test was used to examine the normality of data distribution. The study data are summarized using descriptive statistics including the mean±standard deviation (SD), median for continuous variables, and numbers and percentages for categorical variables. Data were analyzed using the Kruskal-Wallis test, followed by Dunn's post hoc test to compare pairs. The Mann-Whitney *U* test was used to compare quantitative variables between two groups. The Wilcoxon signed-rank test was used for comparing quantitative variables in the groups. Analysis of qualitative variables was performed using the Chi-square test and the Fisher-Freeman-Halton test. Spearman's rho test was used for correlation analysis between parameters. Probability values of less than 0.05 were considered significant.

## RESULTS

**Baseline Clinical Characteristics of the Study Patients** The mean age of the patients was 52.29±16.45 (range, 16-80)y. Twenty-two (25.3%) of the patients were male and 65 (74.7%) were female. The eyelid ptosis was unilateral in 34 (39.1%) patients and bilateral in 53 (60.9%) patients. The ptosis duration (years) was recorded as 7.19±11.47 (range 0.08-45)y. According to the etiology, 124 eyes (88.6%) had aponeurotic and 16 eyes (11.4%) had congenital ptosis. The most common aponeurotic ptosis subgroup was senile ptosis (72%). The severity of ptosis was mild or moderate in 114 eyes (81.4%; Table 1).

Thirty-three (37.9%) of 87 patients had an accompanying systemic disease, the most common was hypertension (16%), followed by thyroid diseases (11.4%). Sixty-one (43.6%) of 140 eyes had previous ophthalmic disease or surgery. The most common previous ophthalmic surgery was phacoemulsification+intraocular lens implantation (12.8%). The most common accompanying ophthalmic disease or condition was dry eye syndrome (5%), and CL use (6.4%).

**Phenylephrine Testing Measurements** The mean MRD1, MRD2, and scleral show heights before phenylephrine testing (baseline) were 1.39±1.20, 4.29±0.62, and 0.29±0.62 mm, respectively. These values increased within 5min after testing but remained largely stable between the 5<sup>th</sup>-15<sup>th</sup> minutes (Figure 1). The ΔMRD1 and ΔMRD2 were 0.62±0.60 and 0.07±0.18 at the 2<sup>nd</sup> minute of the test, and 1.48±1.03 and 0.59±0.63 at the 5<sup>th</sup> minute, respectively. The values of the ΔMRD1 and ΔMRD2 at the 15<sup>th</sup> minute remained the same as the 5<sup>th</sup> minute. The ΔMRD1 and ΔMRD2 values showed a significant but weak correlation at all measurement times (Table 2).

At baseline, the scleral show height was 0 and 0.5-1 mm in 67.1% and 27.1% of eyes, respectively (Figure 2). The percentage of eyes with scleral show height of 0.5-1 mm or >1 mm was significantly higher in patients aged over 60y compared with those aged under 60y (39.4% vs 27%, *P*=0.044). The

**Table 1 Baseline ptosis data of study patients**

Items	<i>n</i> (%)
Side of ptosis	
Unilateral	34 (39.1)
Bilateral	53 (60.9)
Etiology of ptosis ( <i>n</i> =140)	
Aponeurotic	124 (88.6)
Idiopathic	16 (12.9)
Senile	90 (72.6)
CL induced	9 (7.3)
Post-operative	9 (7.3)
Congenital	16 (11.4)
Severity of ptosis	
Mild	67 (47.9)
Moderate	47 (33.6)
Severe	26 (18.6)
LF	
Good	53 (37.9)
Excellent	87 (62.1)

CL: Contact lens; LF: Levator function.

**Table 2 Spearman rho correlation coefficients between ΔMRD1 and ΔMRD2 at different time points**

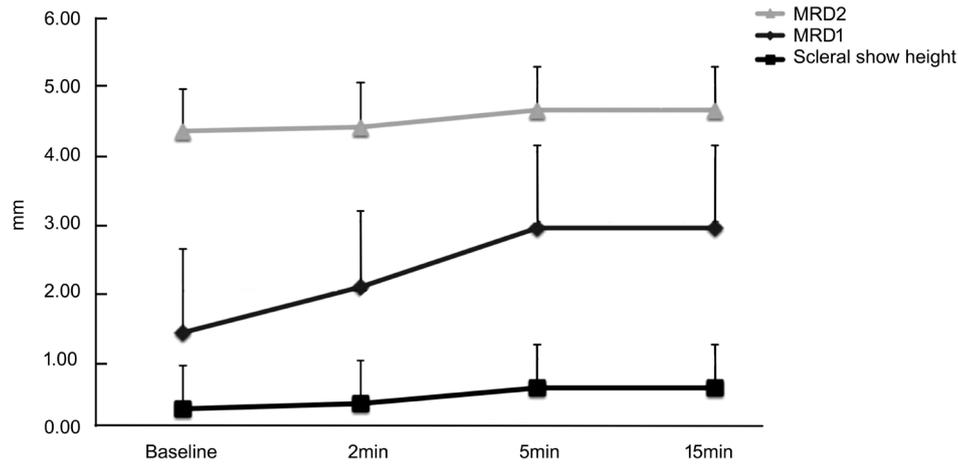
Items	ΔMRD1 (mm)-ΔMRD2 (mm)
2 <sup>nd</sup> minute	
<i>r</i>	0.257
<i>P</i>	0.002 <sup>a</sup>
5 <sup>th</sup> minute	
<i>r</i>	0.246
<i>P</i>	0.003 <sup>a</sup>
15 <sup>th</sup> minute	
<i>r</i>	0.246
<i>P</i>	0.003 <sup>a</sup>

ΔMRD1: Change of margin reflex distance 1; ΔMRD2: Change of margin reflex distance 2. <sup>a</sup>*P*<0.05.

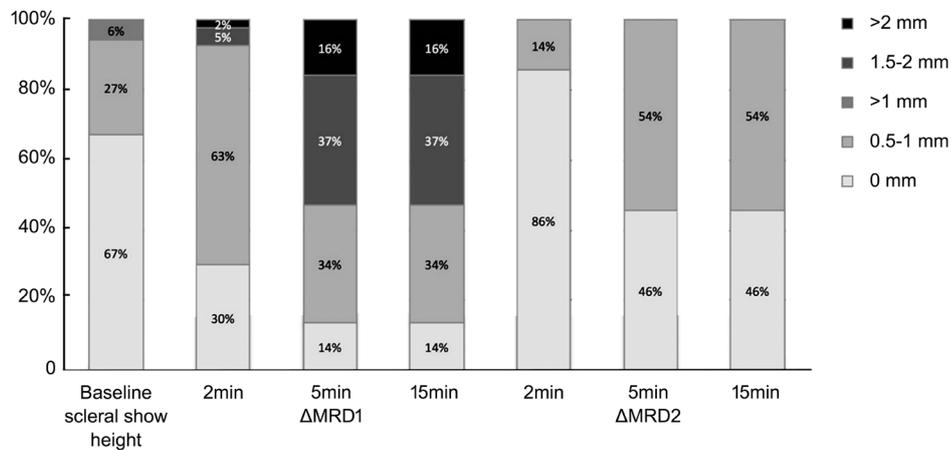
ΔMRD1 was 0.5-1 mm in 62.9% of eyes in the 2<sup>nd</sup> minute of phenylephrine testing, and >1.5 mm in 52.8% of eyes at the 5<sup>th</sup> and 15<sup>th</sup> minute (Figure 2). Similarly, the percentage of eyes with a ΔMRD2 of 0.5-1 mm increased from 14.3% in the 2<sup>nd</sup> minute to 54.3% at both the 5<sup>th</sup> and 15<sup>th</sup> minutes (Figure 2).

### Effect of the Etiology and Severity of Ptosis on Phenylephrine Test Findings

The evaluation of the mean values of MRD1, ΔMRD1, MRD2, ΔMRD2, and scleral show height, with respect to the etiology of ptosis, showed that regardless of the etiology, an increase was observed in all parameters at all measurement times after phenylephrine testing (*P*<0.05; Table 3). The ΔMRD1 was highest in eyes with CL-induced ptosis and lowest in eyes with congenital ptosis at the 5<sup>th</sup> and 15<sup>th</sup> minutes (*P*<0.005; Table 3). On the other hand, scleral



**Figure 1** The mean MRD1, MRD2, and scleral show height values at the 2<sup>nd</sup>, 5<sup>th</sup>, and 15<sup>th</sup> minutes of phenylephrine testing. Vertical deviations represent standard deviation.



**Figure 2** Percentage of eyes with ptosis classified according to baseline scleral show height and response in  $\Delta$ MRD1 and  $\Delta$ MRD2 to phenylephrine testing at the 2<sup>nd</sup>, 5<sup>th</sup>, and 15<sup>th</sup> minutes.

show height was highest in eyes with idiopathic ptosis, and lowest in those with senile ptosis at the 5<sup>th</sup> and 15<sup>th</sup> minutes ( $P=0.015$ ; Table 3).

Considering the percentage of eyes in the classifications of MRD1,  $\Delta$ MRD1, MRD2, and  $\Delta$ MRD2, a higher percentage of eyes with senile or CL-induced ptosis showed  $>1.5$  mm  $\Delta$ MRD1; other etiology groups showed less change in MRD1 at the 5<sup>th</sup> and 15<sup>th</sup> minutes ( $P=0.005$ ; Table 4). When the  $\Delta$ MRD2 was taken into consideration, it was observed that the percentage of eyes with the greatest change (0.5-1 mm) was highest in the eyes with idiopathic ptosis, and CL-induced ptosis at the 5<sup>th</sup> and 15<sup>th</sup> minutes (87.5% vs 66.7%, respectively;  $P=0.038$ , Table 4).

The percentage of older patients (aged over 60y) was highest in eyes with senile ptosis and post-operative ptosis ( $P<0.001$ ; Table 4). Severe ptosis was also more common in eyes with senile ptosis and post-operative ptosis than in the other etiology groups ( $P=0.015$ ; Table 4). The baseline scleral show height increased with increasing severity of ptosis ( $P=0.047$ ;

Table 4). The percentage of eyes with higher  $\Delta$ MRD1 also increased with increasing severity of ptosis at the 2<sup>nd</sup>, 5<sup>th</sup>, and 15<sup>th</sup> minutes of the phenylephrine test ( $P=0.003$ ,  $P<0.001$ , and  $P<0.001$ , respectively; Table 4).

## DISCUSSION

The use of topical phenylephrine in ptotic eyes was popularised by Putterman and Fett<sup>[12]</sup>, and has been used to predict the surgical outcomes of ptosis correction. In this study, we aimed to evaluate the changes in the upper and lower eyelid positions with phenylephrine testing, and to determine the appropriate timing of phenylephrine tests according to the responses at the 2<sup>nd</sup>, 5<sup>th</sup>, and 15<sup>th</sup> minutes. We also assessed the effect of the etiology and severity of ptosis on eyelid positions after phenylephrine testing. Studies vary in the time after phenylephrine instillation at which MDR1 measurements are acquired to evaluate the patient's reaction to the drug<sup>[13]</sup>. Most oculoplastic surgeons use the phenylephrine test in preoperative planning, waiting at least 5min before measuring MRD1<sup>[14]</sup>. In our study, the measurements of the 5<sup>th</sup> and 15<sup>th</sup>

Table 3 The mean MRDI values at 2<sup>nd</sup>, 5<sup>th</sup>, and 15<sup>th</sup> min phenylephrine test with respect to etiology of ptosis

Items	Idiopathic		Senile		Contact lens-induced		Post-operative		Congenital		<sup>1</sup> P (between etiology subgroups)
	Mean±SD (median)	<sup>2</sup> P (vs baseline)	Mean±SD (median)	<sup>2</sup> P (vs baseline)	Mean±SD (median)	<sup>2</sup> P (vs baseline)	Mean±SD (median)	<sup>2</sup> P (vs baseline)	Mean±SD (median)	<sup>2</sup> P (vs baseline)	
<b>MRDI (mm)</b>											
Baseline	2.41±0.88 (3)		1.11±1.22 (1)		2.06±0.73 (2)		1.22±0.97 (1)		1.66±0.96 (2)		<0.001 <sup>c</sup>
2 <sup>nd</sup> min	3.13±0.87 (3.3)	0.002 <sup>b</sup>	1.8±1.02 (2)	<0.001 <sup>c</sup>	2.83±0.87 (3)	0.008 <sup>b</sup>	1.67±1.22 (1.5)	0.023 <sup>a</sup>	2.06±0.95 (2.3)	0.006 <sup>b</sup>	<0.001 <sup>c</sup>
5 <sup>th</sup> min	3.78±0.91 (4)	0.001 <sup>b</sup>	2.77±1.12 (3)	<0.001 <sup>c</sup>	3.89±0.6 (4)	0.005 <sup>b</sup>	2.33±1.62 (2.5)	0.026 <sup>a</sup>	2.5±1.2 (2.5)	0.002 <sup>b</sup>	<0.001 <sup>c</sup>
15 <sup>th</sup> min	3.78±0.91 (4)	0.001 <sup>b</sup>	2.77±1.12 (3)	<0.001 <sup>c</sup>	3.89±0.6 (4)	0.005 <sup>b</sup>	2.33±1.62 (2.5)	0.026 <sup>a</sup>	2.5±1.2 (2.5)	0.002 <sup>b</sup>	<0.001 <sup>c</sup>
<b>ΔMRDI (mm)</b>											
2 <sup>nd</sup> min	0.47±0.46 (0.5)		0.69±0.66 (0.5)		0.78±0.44 (1)		0.44±0.39 (0.5)		0.41±0.42 (0.5)		0.175
5 <sup>th</sup> min	1.13±0.59 (1)		1.66±1.13 (1.5)		1.83±0.35 (2)		1.11±0.93 (1.5)		0.84±0.75 (0.8)		0.005 <sup>b</sup>
15 <sup>th</sup> min	1.13±0.59 (1)		1.66±1.13 (1.5)		1.83±0.35 (2)		1.11±0.93 (1.5)		0.84±0.75 (0.8)		0.005 <sup>b</sup>
<b>MRD2 (mm)</b>											
Baseline	4.34±0.4 (4.3)		4.24±0.63 (4)		4.17±0.5 (4)		4.67±0.97 (4.5)		4.34±0.54 (4)		0.140
2 <sup>nd</sup> min	4.56±0.51 (4.5)	0.008 <sup>b</sup>	4.31±0.64 (4)	0.001 <sup>b</sup>	4.17±0.5 (4)	0.999	4.67±0.97 (4.5)	0.999	4.38±0.53 (4.3)	0.564	0.108
5 <sup>th</sup> min	4.94±0.6 (5)	0.001 <sup>b</sup>	4.49±0.62 (4.5)	<0.001 <sup>c</sup>	4.56±0.39 (4.5)	0.020 <sup>a</sup>	4.89±0.82 (4.5)	0.046 <sup>a</sup>	4.66±0.57 (4.5)	0.004 <sup>b</sup>	0.015 <sup>a</sup>
15 <sup>th</sup> min	4.94±0.6 (5)	0.001 <sup>b</sup>	4.49±0.62 (4.5)	<0.001 <sup>c</sup>	4.56±0.39 (4.5)	0.020 <sup>a</sup>	4.89±0.82 (4.5)	0.046 <sup>a</sup>	4.66±0.57 (4.5)	0.004 <sup>b</sup>	0.015 <sup>a</sup>
<b>ΔMRD2 (mm)</b>											
2 <sup>nd</sup> min	0.22±0.26 (0)		0.07±0.17 (0)		0±0 (0)		0±0 (0)		0.03±0.13 (0)		0.004 <sup>b</sup>
5 <sup>th</sup> min	0.59±0.33 (0.5)		0.25±0.27 (0)		0.39±0.33 (0.5)		0.22±0.26 (0)		0.31±0.31 (0.5)		0.004 <sup>b</sup>
15 <sup>th</sup> min	0.59±0.33 (0.5)		0.25±0.27 (0)		0.39±0.33 (0.5)		0.22±0.26 (0)		0.31±0.31 (0.5)		0.004 <sup>b</sup>
<b>Scleral show height (mm)</b>											
Baseline	0.34±0.4 (0.3)		0.24±0.63 (0)		0.17±0.5 (0)		0.67±0.97 (0.5)		0.34±0.54 (0)		0.140
2 <sup>nd</sup> min	0.56±0.51 (0.5)	0.008 <sup>b</sup>	0.31±0.64 (0)	0.001 <sup>b</sup>	0.17±0.5 (0)	0.999	0.67±0.97 (0.5)	0.999	0.41±0.52 (0.5)	0.157	0.093
5 <sup>th</sup> min	0.94±0.6 (1)	0.001 <sup>b</sup>	0.49±0.62 (0.5)	<0.001 <sup>c</sup>	0.56±0.39 (0.5)	0.020 <sup>a</sup>	0.89±0.82 (0.5)	0.046 <sup>a</sup>	0.66±0.57 (0.5)	0.004 <sup>b</sup>	0.015 <sup>a</sup>
15 <sup>th</sup> min	0.94±0.6 (1)	0.001 <sup>b</sup>	0.49±0.62 (0.5)	<0.001 <sup>c</sup>	0.56±0.39 (0.5)	0.020 <sup>a</sup>	0.89±0.82 (0.5)	0.046 <sup>a</sup>	0.66±0.57 (0.5)	0.004 <sup>b</sup>	0.015 <sup>a</sup>

<sup>1</sup>Kruskal-Wallis test; <sup>2</sup>Wilcoxon Signed-rank test. <sup>a</sup>P<0.05, <sup>b</sup>P<0.01, <sup>c</sup>P<0.001. Min: Minute; MRD: Margin reflex distance; ΔMRD: Change of margin reflex distance; SD: Standard deviation.

**Table 4 Number of eyes classified by age, levator function, and phenylephrine test measurements with respect to etiology and severity** *n* (%)

Items	Etiology of ptosis					<i>P</i>	Severity of ptosis			<i>P</i>
	Unknown etiology	Senile	Contact lens-induced	Post-operative	Congenital		Mild	Moderate	Severe	
Age, y						<0.001 <sup>a</sup>				0.003 <sup>a</sup>
<40	6 (37.5)	0	8 (88.9)	0	13 (81.3)		21 (31.3)	5 (10.6)	1 (3.8)	
40-60	10 (62.5)	31 (34.4)	1 (11.1)	2 (22.2)	3 (18.8)		23 (34.3)	17 (36.2)	7 (26.9)	
>60	0	59 (65.6)	0	7 (77.8)	0		23 (34.3)	25 (53.2)	18 (69.2)	
Levator function						0.013 <sup>a</sup>				
Good	2 (12.5)	35 (38.9)	1 (11.1)	6 (66.7)	9 (56.3)		-	-	-	
Excellent	14 (87.5)	55 (61.1)	8 (88.9)	3 (33.3)	7 (43.8)		-	-	-	
Ptosis severity						0.015 <sup>a</sup>				
Mild	14 (87.5)	34 (37.8)	7 (77.8)	3 (33.3)	9 (56.3)		-	-	-	
Moderate	1 (6.3)	35 (38.9)	2 (22.2)	4 (44.4)	5 (31.3)		-	-	-	
Severe	1 (6.3)	21 (23.3)	0	2 (22.2)	2 (12.5)		-	-	-	
Baseline scleral show height						0.402 <sup>a</sup>				0.047 <sup>a</sup>
0	9 (56.3)	65 (72.2)	7 (77.8)	4 (44.4)	9 (56.3)		51 (76.1)	30 (63.8)	13 (50)	
0.5-1 mm	7 (43.8)	19 (21.1)	2 (22.2)	4 (44.4)	6 (37.5)		15 (22.4)	14 (29.8)	9 (34.6)	
>1 mm	0	6 (6.7)	0	1 (11.1)	1 (6.3)		1 (1.5)	3 (6.4)	4 (15.4)	
2 <sup>nd</sup> min ΔMRD1						0.946 <sup>a</sup>				0.003 <sup>a</sup>
0	6 (37.5)	25 (27.8)	2 (22.2)	3 (33.3)	6 (37.5)		23 (34.3)	11 (23.4)	8 (30.8)	
0.5-1 mm	9 (56.3)	56 (62.2)	7 (77.8)	6 (66.7)	10 (62.5)		43 (64.2)	33 (70.2)	12 (46.2)	
1.5-2 mm	1 (6.3)	6 (6.7)	0	0	0		1 (1.5)	3 (6.4)	3 (11.5)	
>2 mm	0	3 (3.3)	0	0	0		0	0	3 (11.5)	
5 <sup>th</sup> min ΔMRD1						0.005 <sup>a</sup>				<0.001 <sup>a</sup>
0	2 (12.5)	10 (11.1)	0 (0)	3 (33.3)	4 (25)		6 (9)	8 (17)	5 (19.2)	
0.5-1 mm	9 (56.3)	28 (31.1)	1 (11.1)	1 (11.1)	8 (50)		35 (52.2)	8 (17)	4 (15.4)	
1.5-2 mm	5 (31.3)	32 (35.6)	8 (88.9)	4 (44.4)	3 (18.8)		26 (38.8)	19 (40.4)	7 (26.9)	
>2 mm	0	20 (22.2)	0	1 (11.1)	1 (6.3)		0	12 (25.5)	10 (38.5)	
15 <sup>th</sup> min ΔMRD1						0.005 <sup>a</sup>				<0.001 <sup>a</sup>
0	2 (12.5)	10 (11.1)	0	3 (33.3)	4 (25)		6 (9)	8 (17)	5 (19.2)	
0.5-1 mm	9 (56.3)	28 (31.1)	1 (11.1)	1 (11.1)	8 (50)		35 (52.2)	8 (17)	4 (15.4)	
1.5-2 mm	5 (31.3)	32 (35.6)	8 (88.9)	4 (44.4)	3 (18.8)		26 (38.8)	19 (40.4)	7 (26.9)	
>2 mm	0	20 (22.2)	0	1 (11.1)	1 (6.3)		0	12 (25.5)	10 (38.5)	
2 <sup>nd</sup> min ΔMRD2						0.014 <sup>b</sup>				0.421 <sup>a</sup>
0	9 (56.3)	78 (86.7)	9 (100)	9 (100)	15 (93.8)		55 (82.1)	41 (87.2)	24 (92.3)	
0.5-1 mm	7 (43.8)	12 (13.3)	0	0	1 (6.3)		12 (17.9)	6 (12.8)	2 (7.7)	
5 <sup>th</sup> min ΔMRD2						0.038 <sup>b</sup>				0.055 <sup>a</sup>
0	2 (12.5)	47 (52.2)	3 (33.3)	5 (55.6)	7 (43.8)		24 (35.8)	24 (51.1)	16 (61.5)	
0.5-1 mm	14 (87.5)	43 (47.8)	6 (66.7)	4 (44.4)	9 (56.3)		43 (64.2)	23 (48.9)	10 (38.5)	
15 <sup>th</sup> min ΔMRD2						0.038 <sup>b</sup>				0.055 <sup>a</sup>
0	2 (12.5)	47 (52.2)	3 (33.3)	5 (55.6)	7 (43.8)		24 (35.8)	24 (51.1)	16 (61.5)	
0.5-1 mm	14 (87.5)	43 (47.8)	6 (66.7)	4 (44.4)	9 (56.3)		43 (64.2)	23 (48.9)	10 (38.5)	

<sup>a</sup>Chi-square test, <sup>b</sup>Fisher-Freeman-Halton test. Min: Minute; MRD: Margin reflex distance.

minutes MRD1, MRD2, scleral show height,  $\Delta$ MRD1, and  $\Delta$ MRD2 were better than the measurements of the 2<sup>nd</sup> minute. In accordance with previous reports, in our study, the values did not change after the 5<sup>th</sup> minute and remained stable up to the 15<sup>th</sup> minute. The results of this study indicated that maximal responses with phenylephrine occurred in 5min after administration in all groups. Therefore, patients do not have to wait for long after drop placement in a busy clinic setting.

In our study, we used one drop of 2.5% phenylephrine instead of 10%. In a report, eyelids receiving 10% phenylephrine were an average of 0.2 mm higher than the same eyelids tested with 2.5% phenylephrine<sup>[15]</sup>. Given that this is a small and clinically insignificant magnitude of difference, and there is a higher risk of adverse systemic adverse effects of high-dose phenylephrine such as subarachnoid hemorrhage, ventricular arrhythmia, and severe hypertension, 2.5% phenylephrine should be chosen instead of 10%<sup>[10]</sup>. In our study, the most common concomitant systemic disease was hypertension (16%), one patient had coronary artery disease, and another had cerebrovascular disease. Using 10% phenylephrine could be a potential risk for these patients, thus 2.5% phenylephrine was preferred. We detected no adverse effects during or after the test.

We observed a non-response ( $\Delta$ MRD1: 0) or low response ( $\Delta$ MRD1: 0.5-1 mm) to phenylephrine testing was seen more in the congenital ptosis groups. In previous phenylephrine test studies, this group was generally excluded and not studied, accordingly, it was not possible to make direct comparisons. The exact mechanism of ptosis in congenital ptosis is different from aponeurotic ptosis, so the differences in the responses may be due to the insufficient myogenic structure in congenital ptosis<sup>[16-19]</sup>. Heisel *et al*<sup>[20]</sup> reported that orbital septa in patients with congenital ptosis demonstrate consistent histologic disorganization and fibrosis.

Eighty-eight percent of eyelids with CL-related ptosis had a high  $\Delta$ MRD1 response to phenylephrine in the 5<sup>th</sup> and 15<sup>th</sup> minutes of the test. Lee<sup>[21]</sup> reported that all eyelids with CL-related ptosis had a high response to phenylephrine. In our study, in the senile ptosis group, 22.2% of the eyelids responded  $>2$  mm, and 52.8% responded  $>1.5$  mm in the 5<sup>th</sup> and 15<sup>th</sup> minutes. These findings in phenylephrine response may help surgeons decide which eyelids should undergo Müller's muscle resection surgery.

Eyelids with mild ptosis are known to benefit most from Müller's muscle resection surgery because this technique can raise the lid by up to 2 mm<sup>[22-25]</sup>. In our study, non-response ( $\Delta$ MRD1: 0) was seen slightly more in the moderate and severe ptosis groups than in the mild ptosis group. However, in the mild ptosis group, the rate of eyelids that had a  $\Delta$ MRD1 response of  $\geq 1.5$  mm, was 38.8% at the 5<sup>th</sup> and 15<sup>th</sup> minutes, 9% did not respond, and the responses were insufficient in 52.2%.

Lee<sup>[21]</sup> reported that the response rate of eyes to phenylephrine was 88% in mild ptosis. In our study, the rates of mild responder eyelids were less than those reported previously. On the contrary, eyelids with severe ptosis responded better, 38.5% responded extremely well ( $\Delta$ MRD1 $>2$  mm), and 65.4% responded well ( $\Delta$ MRD1 $\geq 1.5$  mm) to phenylephrine testing. Sometimes in severe ptosis, baseline MRD1 values can be very low, therefore even an excellent response may be insufficient for treating ptosis completely. Nevertheless, based on these findings, phenylephrine testing has clinical value for eyes with severe ptosis in the decision for Müller's muscle conjunctival resection (MMCR). In the literature, there were other studies that found results consistent with our study. Nacaroglu *et al*<sup>[26]</sup> compared the outcome of MMCR for mild/moderate versus severe involutional aponeurotic ptosis, and they found that higher surgical success rates were obtained in cases with mild-moderate ptosis and clinically acceptable success rates were obtained in cases with severe ptosis. Sweeney *et al*<sup>[27]</sup> compared outcomes between MMCR ptosis repair and external levator resection (ELR) in patients with severe involutional blepharoptosis, and found that MMCR ptosis repair is an effective approach in treating patients with severe ptosis, and it may offer superior outcomes to ELR. Patel *et al*<sup>[28]</sup> demonstrated that MMCR with or without tarsectomy does provide another alternative to the surgeon for the management of severe involutional blepharoptosis.

Most studies only reported changes in MRD1 values; however, MRD2 measurements are usually disregarded<sup>[15,21-23]</sup>. We reported both lower and upper eyelid responses with measurements of MRD1, MRD2, and scleral show height, and their changes with time. The baseline scleral show degrees were correlated with ptosis severity. The MRD2 measurements indicated that the responses were better at the 5<sup>th</sup> and 15<sup>th</sup> minutes than at the 2<sup>nd</sup> minute, and the results of the 5<sup>th</sup> and 15<sup>th</sup> minutes were the same. For the 2<sup>nd</sup>, 5<sup>th</sup>, and 15<sup>th</sup> minutes  $\Delta$ MRD2 classifications, there was no significant difference between the ptosis severity groups ( $P>0.05$ ). However, the lower eyelid response of the mild ptosis group was better than that of the moderate and severe ptosis groups, and the responses of the moderate group were better than the severe ptosis group at the 2<sup>nd</sup>, 5<sup>th</sup>, and 15<sup>th</sup> minutes. Also, the idiopathic etiology group's lower eyelid responses were faster and better than the other groups. It should be noted that the eyelids in the idiopathic etiology group mostly had mild ptosis, which may account for the good MRD2 response in this group. The  $\Delta$ MRD2 was related with baseline scleral show degree. The mild ptosis group had lower scleral show measurements and higher  $\Delta$ MRD2 values. The  $\Delta$ MRD1 and  $\Delta$ MRD2 values were poorly correlated in all measurement times. In accordance with our results, Kaskouli *et al*<sup>[29]</sup> reported that more severe

myogenic ptosis was significantly associated with more severe preoperative scleral show. Preoperative MRD2 was the only factor predicting postoperative improvement of scleral show in myogenic ptosis<sup>[29]</sup>.

The main limitation of the present study is its retrospective design. The other limitation was that the eyelid measurements were obtained through a simple technique used in daily clinical examinations. Although this technique was shown to produce repeatable results in MRD measurements with deviations of less than 0.5 mm, the accuracy of the measurements could be further improved by using sophisticated techniques such as head position stabilization and digital imaging.

In conclusion, we found that the results of the phenylephrine testing at the 5<sup>th</sup> and 15<sup>th</sup> minutes were both the same, and higher than the 2<sup>nd</sup> minute. Accordingly, it is sufficient to perform the test for 5min. It is possible to obtain more than 2 mm response in eyes with severe ptosis, which may guide the decision to perform Müller's muscle resection. The upper and lower eyelid responses in phenylephrine testing were poorly correlated. However, the  $\Delta$ MRD2 was related with baseline scleral show degree. It has been proposed in previous studies that the evaluation of preoperative scleral show may also be a postoperative predictive factor<sup>[1,3,29]</sup>. Although ptosis and its surgery have been evaluated for many years, studies on the lower and upper lid relationship and its effects on surgical results have been subjects of interest in recent years yet there are very few studies in the literature. In this sense, we think that our study draws attention to this issue, which should be evaluated in greater detail in further studies.

#### ACKNOWLEDGEMENTS

**Authors' contributions:** The conception and design of the study: Gedar Totuk OM, Altinel MG, Kanra AY, Aykan U; Study procedures and the measurements: Gedar Totuk OM; Analysis and interpretation of data: Gedar Totuk OM, Altinel MG, Kanra AY, Aykan U; Drafting the article or revising it critically for important intellectual content: Gedar Totuk OM, Altinel MG, Kanra AY, Aykan U; Final approval of the version to be submitted: Gedar Totuk OM, Altinel MG, Kanra AY, Aykan U.

**Conflicts of Interest:** Gedar Totuk OM, None; Altinel MG, None; Kanra AY, None; Aykan U, None.

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