Characteristics of Foveating and Defoveating Fast Phases in Latent Nystagmus

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Purpose. Under certain conditions, the fast phases of latent/manifest latent nystagmus (LMLN) can defoveate the target of interest instead of foveating it, as was thought to be their only function. LMLN fast phases in the waveforms from four subjects were studied with the goals of better understanding their characteristics and determining what triggers both foveating and defoveating fast phases.

Methods. Eye movement records were made using both the scleral search coil and infrared methods. Relationships of fast-phase sizes with slow-phase positions and velocities before and after fast phases were analyzed, as were relationships of saccade size with peak velocity and duration.

Results. The data showed that LMLN with defoveating fast phases occurred in the presence of higher slow-phase velocities. Also, larger saccade sizes corresponded to larger presaccadic and postsaccadic slow-phase velocities. The peak velocities and durations of LMLN fast phases were in the same ranges as normal saccades.

Conclusions. Defoveating fast phases with decreasing-velocity slow phases may be the result of the addition of saccadic pulses to linear slow phases. Mechanisms are suggested to explain the switch from foveating to defoveating fast phases in LMLN. (*Invest Ophthalmol Vis Sci.* 1998;39:1751-1759)

L atent/manifest latent nystagmus (LMLN) is characterized by saccadic fast phases in the direction of the fixating eye and slow phases with linear or decreasing-velocity profiles in the opposite direction. This nystagmus is referred to as "latent nystagmus" (LN) under monocular viewing conditions (i.e., one eye covered) and "manifest latent nystagmus" (MLN) under binocular viewing conditions. In a study of a rare individual with LMLN and exceptionally good visual acuity, we found that the fast phases can move the eyes away from the target of interest (defoveating) instead of toward (foveating) it, as was thought to be their only function.[1] We verified the generalizability of our calibration procedure on a second subject with high acuity. The defoveating fast phases appeared to occur with larger amplitude nystagmus and higher slow-phase veloc-

ities. It was suggested that the defoveating fast phase strategy might be used to provide higher visual acuities. For such defoveating fast phases with decreasing-velocity slow phases, the target will drift into the foveal area near the ends of the slow phases when the velocities are lower.[1] Lower velocities can improve visual acuity if they occur while the image is in the foveal area, where the sensitivity of visual acuity to retinal slip velocity is large.

In the present study of four individuals (subjects 1, 2, 3, and 4 [S1, S2, S3, and S4, respectively]) with LMLN and differing acuities, we present a quantitative evaluation of the slow-phase velocity and position, before and after the fast phase, that is expected to provide information about the criteria used to switch from foveating to defoveating fast phases. An understanding of this mechanism will be useful in constructing a control-system model of LMLN. A positive correlation between fast-phase size and eye position before fast phases would suggest that position error is used to calculate fast-phase size. Relationships between fast-phase size and slow-phase velocity may also aid in understanding the underlying mechanism for fast-phase generation. In addition, if fast-phase saccadic amplitude relationships with peak velocity and duration are the same in LMLN as in normal saccades, then fast-phase generation in LMLN can be presumed to eminate from the saccadic pulse generator with similar constraints. Finally, by studying how efference copy is used in LMLN, we will uncover capabilities of this internal monitoring system in the normal.

METHODS

Recording

Horizontal and vertical rotations of both eyes were recorded using the scleral search coil method with 6-foot field coils (CNC Engineering, Seattle, WA). The coil system bandwidth was 0 to 150 Hz, linear range of greater than $\pm 20°$ and sensitivity of $0.1°$ in both planes. The subject's stabilized head remained within the 30-cm cube of the magnetic field where the translation artifact was less than $0.03°/cm$. Data were filtered (bandwidth 0-90 Hz) and digitized at 200 Hz with 16-bit resolution using a data transition board (DT2801/5716A; Data Translation, Marlboro, MA). Scleral-coil (Skalar, Delft, The Netherlands) gain was calibrated using a protractor device capable of rotations in each plane. The mean foveation position of each eye was set to $0°$ to align it to the target position during fixation in primary position (see Analysis section). This is routinely done for most other types of eye movement recording methods, and although it does not guarantee that the $0°$ eye position coincides with a target image on the center of the fovea, it does place $0°$ at the subject's chosen point of fixation; except for rare cases of extrafoveal fixation or certain types of foveal aplasia, it is reasonable to equate $0°$ with the foveal center, especially when the subject has good vision. The precision of this method has been shown to approach the foveation ability of normal subjects (SD of fixation is 6 minutes of arc). In a subject with congenital nystagmus (CN) and 20/25 acuity, the SD of foveation periods was 13 minutes of arc.[2] Despite oscillations like CN and LMLN, individuals with good acuity repeatedly foveate the target with remarkable accuracy. In addition, shortly after our calibration procedures for both infrared and coil methodologies resulted in identifying the defoveation strategy used in LMLN, it was independently veri-

fied in two laboratories by using scanning laser ophthalmoscopes. Horizontal eye movement recordings were also made using infrared (IR) reflection. In the horizontal plane, the system is linear to ±20° and monotonic to ±25° to 30° with a sensitivity of 0.25°. The IR signal from each eye was calibrated with the other eye behind cover to obtain accurate position information and document small tropias and phorias hidden by the nystagmus. Eye positions and velocities (obtained by analog differentiation of the position channels) were displayed on a strip chart recording system (type R612 dynograph; Beckman, Fullerton, CA). The total system bandwidth (position and velocity) was 0 to 100 Hz. Infrared data were digitized at 200 Hz with 12-bit resolution using a DT2801 board (Data Translation).

Protocol

During IR recording, the subject was seated at the center of a 5-foot radius arc containing LED targets. The head was stabilized in the primary position, and the subject was instructed to move only the eyes to view each target as it was turned on. During search coil recording, targets were presented on a translucent screen 5 feet from the subject. This research followed the Declaration of Helsinki guidelines and informed consent was obtained.

Analysis

Subject 1 was also instructed to fixate a "star" target that was projected from an ophthalmoscope onto the retina. It was observed that during binocular viewing, a low-amplitude MLN occurred with fast phases that brought the target image onto the fovea. Although calibrated, coil data were adjusted for bias during analysis. In accordance with previously developed methodology,[1] the bias was adjusted so that the fast phases during low-amplitude MLN brought the image of the target onto the fovea. Subjects 2 and 4 had a low-amplitude LMLN (approximately 0.3° to 0.7° during both-eye [BE] viewing), and the bias was adjusted so that the target was near the center of the fovea at the ends of the fast phases. Subject 3 showed a nulling of LN for a short time period as the nonfixating right was brought toward alignment with the fixating left eye. The eye position trace of the fixating eye was bias adjusted so that during this brief null period, the target was imaged near the center of the fovea.

Because the strabismus angle of the nonviewing eye may have an effect on LMLN intensity, data points were chosen where the angle of the nonfixating eye (as defined by the ends of the fast phases) was relatively stable, that is, when the angle of the nonfixating eye was changing less than 0.5°/sec. For the analysis of the saccadic size relationships to presaccadic and postsaccadic position and velocity, the first step of this analysis was to define the beginning and end of the fast phase. The start of the fast phase was defined to be the position on the unfiltered velocity trace just before the velocity changed direction as a result of the saccade. The central-point difference method was used to calculate the velocity. The end of the fast phase was defined to be the position where the slow-phase velocity began to assume a decreasing exponential or linear-velocity profile. Some recordings of S1 contained noise (50–55 Hz). In these, the data points used in the central-point difference were separated by 20 msec (i.e., $4T$, where T, the sampling period,

was 5 msec) to provide smoothing, aiding in choosing the beginning and ending points of the fast phases. To reduce the effects of noise, position records were filtered with a 7-point moving average filter. Presaccadic position points were chosen from these filtered traces at 70 msec and 30 msec before the start of the fast phases. The range of 30 msec to 70 msec corresponds to estimates necessary to make normal corrective saccades using efference copy. The motor command must be executed approximately 30 msec before the saccade occurs and the decision cannot be made more than 70 msec prior or the previous, incorrect saccade might not be completed. Postsaccadic position points were chosen 30 msec after the fast phases, including dynamic overshoots, if present. Presaccadic and postsaccadic velocities were also chosen at 70 msec and 30 msec before, and 30 msec after, the fast phases from the filtered velocity traces in records where noise was not present. In noisy records, presaccadic velocities at 70 msec and 30 msec were obtained graphically. Postsaccadic velocities were not obtained from these records. These slow-phase points (70 msec and 30 msec) were chosen far enough away (14 and 6 sample points, respectively) from the saccades so that broadened saccade data (from the 7-point moving averaging and central-point differentiation) would not interfere. Fast-phase amplitude was defined as the difference between the position 30 msec after the fast phase and 30 msec before the fast phase.

Presaccadic position and velocity were plotted in phase planes. Further details on the use of phase planes may be found elsewhere.[1,3]

For data analysis of the saccadic amplitude relationships to duration and peak velocity, only recordings in which noise was not a problem were analyzed. Saccadic amplitude was defined as the difference between the maximum and minimum position of fast phases. The central-point difference method was used to obtain the velocity trace. The points used for the calculation were separated by $2T$ (10 msec). Saccadic duration was obtained from the velocity trace, where T_i was defined as the time data point just before the velocity changed direction at the beginning of the saccade and T_f as the time data point closest to the time when the velocity at the end of the saccade changes direction.

Because of the sampling rate (200 Hz), values of saccadic amplitude, duration, and peak velocity were affected. The error in saccadic size was only approximately 1.5% when cubic splines were fit through the data points; this correction was applied to the data in Figures 2A and 2B. An estimate of the peak velocity error can be made by considering the magnitude of the sinusoidal response function of the central-point difference method, which is the absolute value of $\sin(\omega T)/T$, where T is the time between samples and ω is frequency. The precision of this correction may be slightly affected by the difference between the actual saccade profile and a sinusoidal approximation. Therefore, we report the uncorrected values for the peak velocities (versus saccadic amplitude) in Figure 6A. From the relatively small presaccadic velocities and shapes of the ends of the fast phases, there was a broadening of the duration (8 msec), and this correction was applied to the data in Figure 2b. This estimate was made by constructing fast phases that resemble those in this study and evaluating the effects of sampling at 200 Hz. Data analysis (and filtering, if required), statistical computation of means and SD, and graph-
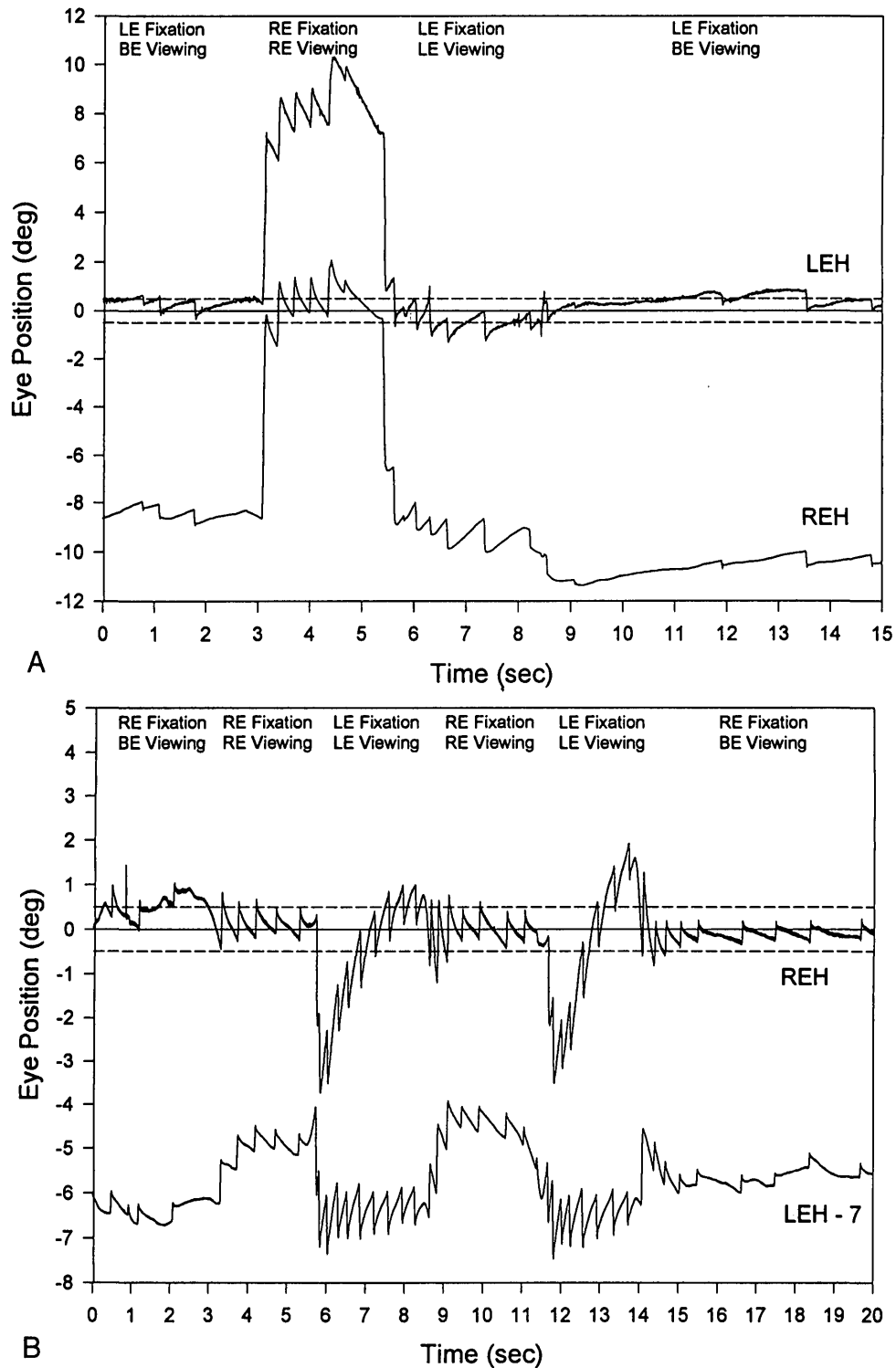
FIGURE 1.   Right- (REH) and left-eye (LEH) horizontal recordings using magnetic scleral search coil. (A) Subject 1; (B) subject 2. *Dashed lines* indicate the ±0.5° foveal extent. (B) LEH was shifted leftward for clarity, as indicated. BE, both eyes; RE, right eye; LE, left eye (e.g., BE Viewing, both eyes open).

ical presentation were performed using either the ASYST (Keithley, Taunton MA) or MATLAB (MathWorks, Natick, MA) software for scientific computing. Additional analysis was performed using MATLAB (MathWorks) and SigmaStat (Jandel, San Rafael, CA). SigmaPlot (Jandel) was used to plot some of the data.

RESULTS

Eye movement recordings are shown for S1 and S2 in Figures 1A and 1B. The subjects exhibited defoveating fast phases occurring with larger slow-phase velocities in addition to foveating fast phases. In Figure 1A, there was a transition from
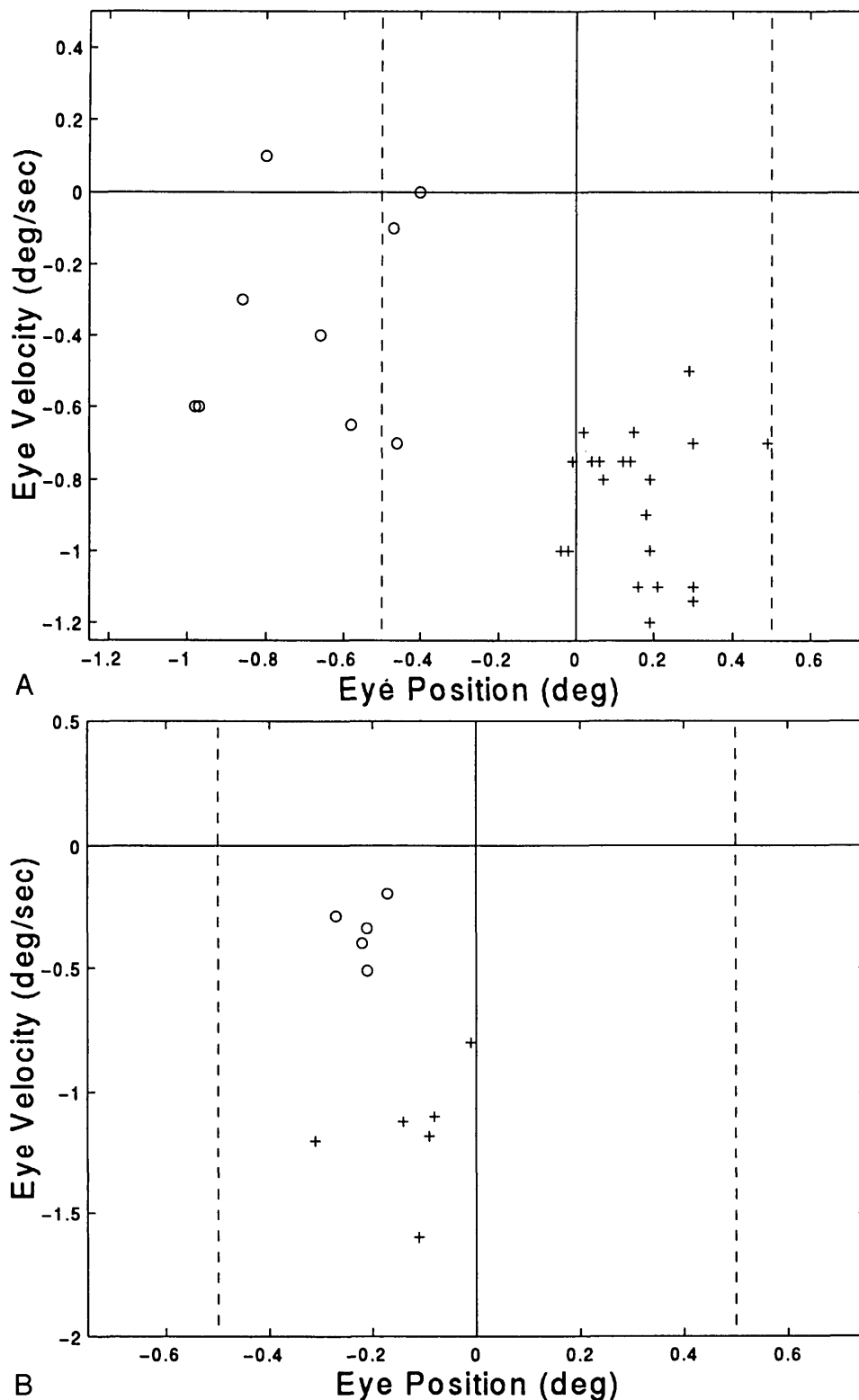
Figure 2.   Phase-plane data 70 msec before fast phases. (A) Subject 1; left-eye fixation. (B) Subject 2; right-eye fixation. (○) foveating; (+) defoveating fast phases. *Dashed lines* indicate the limits of the foveation window (±0.5° by ±4°/sec).

foveating leftward fast phases (left eye [LE] fixation/BE viewing) to defoveating rightward and leftward fast phases (right eye [RE] and LE fixation/RE and LE viewing, respectively) and

finally a return to foveating leftward fast phases (LE fixation/BE viewing). Figure 1B shows fast-phase transitions for S2 that are similar to those in Figure 1A.
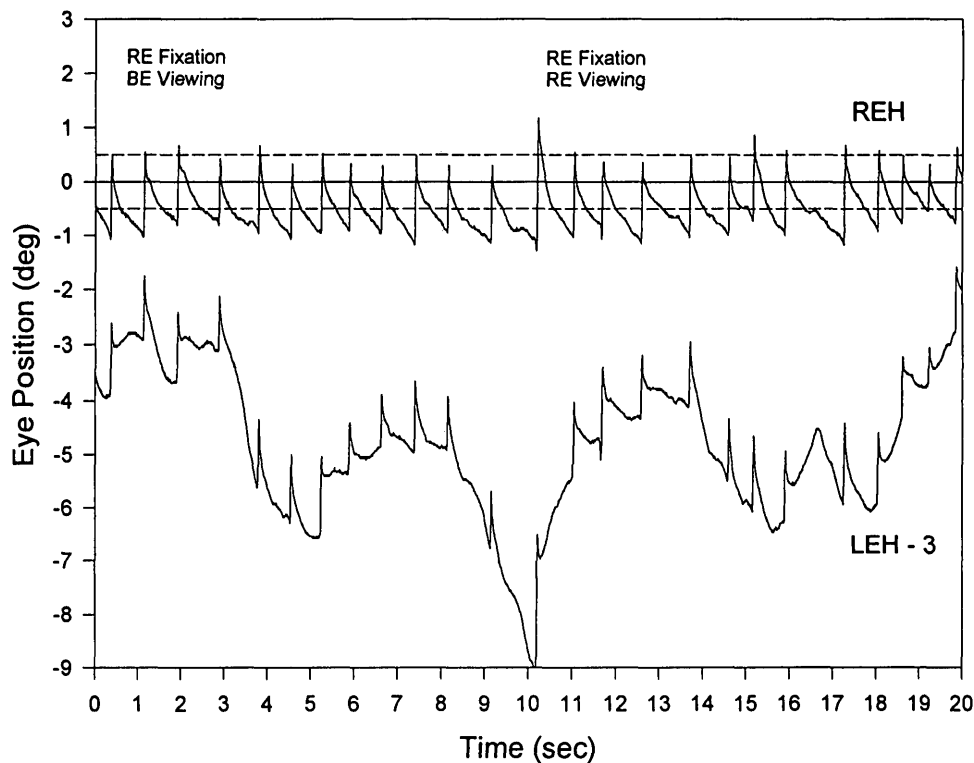
FIGURE 3.   Right- (REH) and left-eye (LEH) horizontal recordings of subject 2 using infrared reflection. *Dashed lines* indicate the ±0.5° foveal extent. LEH was shifted leftward for clarity, as indicated. BE, both eyes; RE, right eye; LE, left eye (e.g., BE Viewing, both eyes open).

Figures 2A and 2B show phase planes of gaze position and velocity 70 msec before the fast phases. We chose 70 msec to allow computation time to generate the proper motor command and to coincide with our analysis of braking saccade generation.[4] Figure 2A shows data from leftward fast phases of S1 and Figure 2B from rightward fast phases of S2. For consistency and ease of comparison, the data are all represented as rightward fast phases (data from leftward fast phases were multiplied by −1). The area enclosed by the dashed lines is a region of retinal error position and retinal slip velocity where higher visual acuity occurs and is referred to as the "foveation window." Presaccadic eye positions were always in the same quadrant for foveating fast phases but could vary for defoveating fast phases. Both S1 and S2 were recorded on two different occasions and, when constructing the above phase planes, data from the same session were used for each subject. The phase planes show that presaccadic eye velocities tended to be greater for defoveating fast phases. Differences in the median velocities for foveating and defoveating presaccadic fast phase velocity were significant ($P < 0.001$ using the Mann-Whitney Rank Sum Test). The presaccadic velocities were −0.40°/sec and −0.80°/sec, respectively, for the foveating and defoveating cases for S1 during left-eye fixation and −0.34°/sec and −1.17°/sec, respectively, for S2 during right-eye fixation. Data from S1 for rightward fast phases show similar results except for one 15-second record during RE fixation/RE viewing. In this recording there was a transition from defoveating to foveating fast phases, during which the slow-phase velocities did not decrease. Thus, during RE viewing with a slow-phase velocity

near 1.5°/sec, this subject had both foveating and defoveating fast phases.

Figures 1A and 1B showed that occlusion of one eye led to higher slow-phase velocities. However, this was not always the case. For example, an IR eye movement recording of S2 (Fig. 3), taken 15 months after the scleral search coil recording, showed no difference in slow-phase velocity during RE fixation/BE or RE viewing. In addition, the subject's rightward fast phases were foveating under both conditions. The mean slow-phase velocity (when the angle of the non-fixating eye was changing less than 0.5°/sec) was also higher (1.3°/sec) during BE viewing in the later recording compared with slow-phase velocity during BE viewing from the earlier session (0.35°/sec).

Figure 4 shows the relationship between saccadic size and presaccadic (Fig. 4A) or postsaccadic (Fig. 4B) position for foveating fast phases of S2. The other subjects showed similar patterns in the foveating mode (i.e., good correlation of size with presaccadic position and very low correlation of size with postsaccadic position). Figures 4C and 4D show saccade size versus position data for defoveating fast phases of S1. In this case, the saccade size versus presaccadic position correlation was lower than for the foveating mode. The saccade size versus postsaccadic position correlation, however, was higher than in the foveating mode.

Figure 5A is a plot of saccade size versus the presaccadic velocity for all four subjects. A correlation of 0.57 was obtained for a linear fit of the data (−0.150A + 0.496). Figure 5B is a plot of saccade size versus postsaccadic velocity. A correlation of
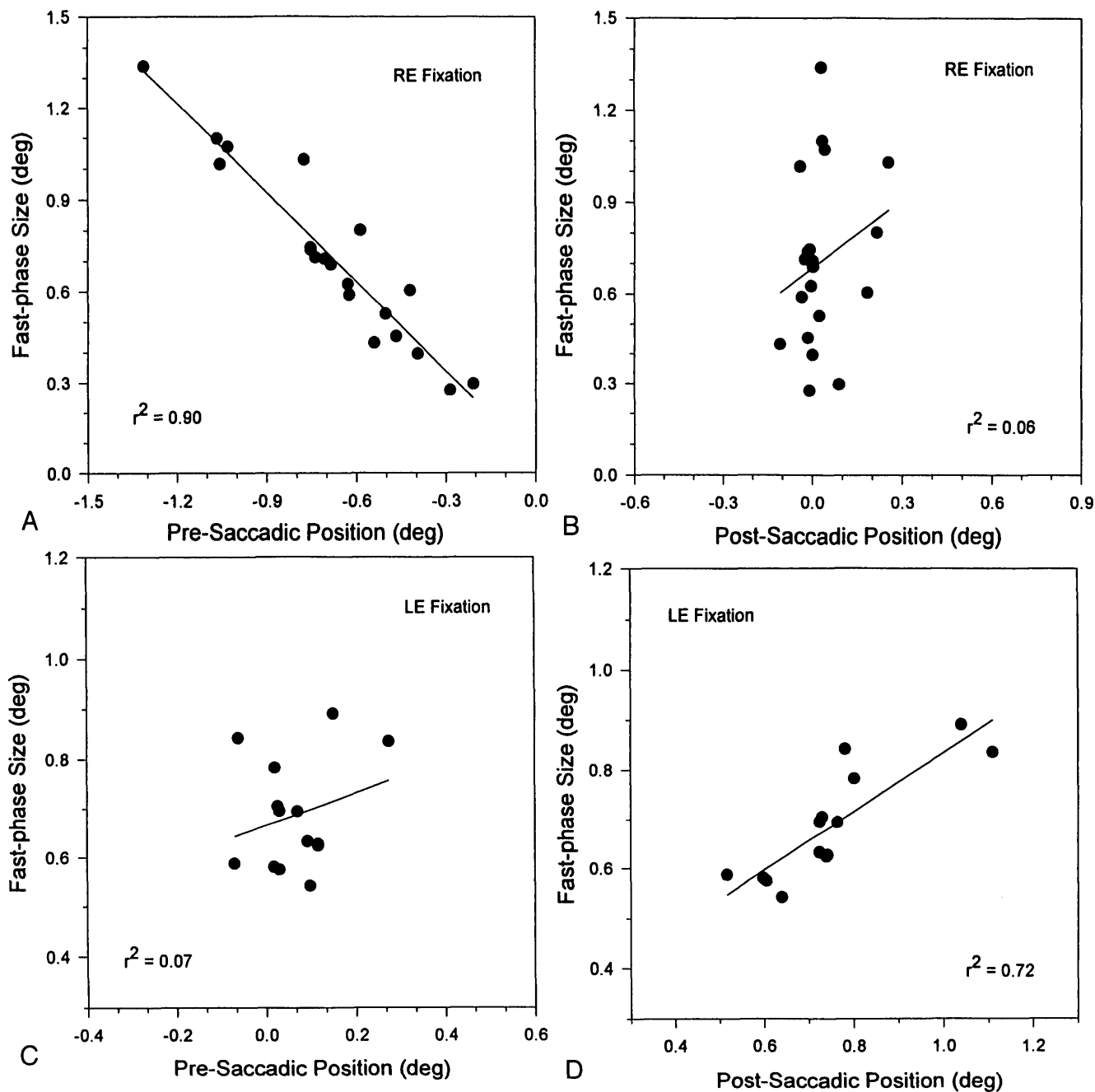
Figure 4.   Presaccadic and postsaccadic position versus fast-phase size relationships. (A, B) Subject 2; (C, D) subject 1. RE, right eye; LE, left eye.

0.59 was obtained for a linear fit $(-0.161A + 0.019)$. Both show increased fast-phase sizes with increased presaccadic and postsaccadic slow-phase velocities.

Figures 6A and 6B, respectively, show saccadic peak velocity and duration versus saccadic amplitude during fast phases of LMLN. In Figure 6A, the solid curve $(58A^{0.89\circ}/sec)$ is a best-fit to our data in the form of cA^b. It is similar to the dotted $(65A^{0.97\circ}/sec)$ and dashed $(76A^{0.77\circ}/sec)$ curves.[5,6] In Figure 6B, the dotted $(21A^{0.4}$ msec) and dashed $(26A^{0.15}$ msec) curves are also derived from the literature.[5,7] Again, our data are similar.

DISCUSSION

Subjects with LMLN have a nystagmus, which occurs during fixation with one eye, characterized by fast phases in the direction of the fixating eye. The oppositely directed slow phases have linear or decreasing-velocity profiles. The cause of the slow phase has been hypothesized to be an incorrect egocentric direction signal,[8] an unbalanced signal from the motion detection pathways,[9] or an optokinetic defect.[10] In this study, we did not attempt to study the cause of LMLN, but rather the characteristics of its fast phases.
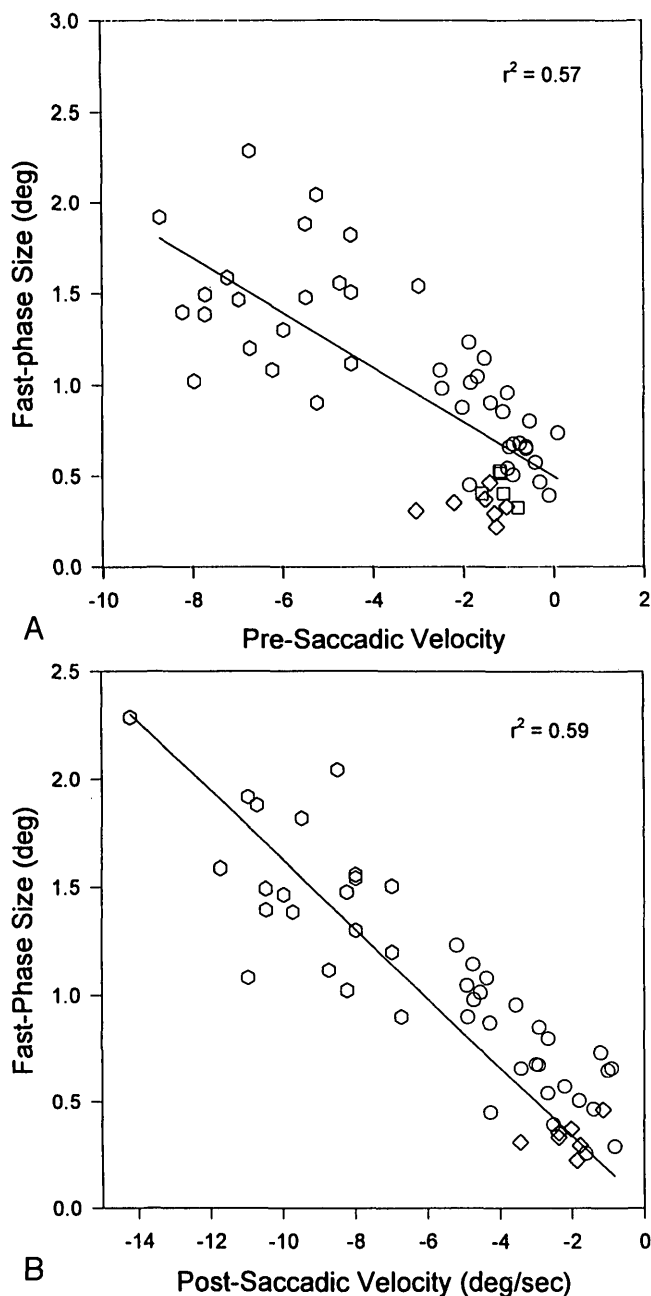
FIGURE 5. Presaccadic and postsaccadic velocity versus fast-phase size relationships. (O) Subject 1; (□) subject 2; (Ⓞ) subject 3; (◇) subject 4.

Our data show that in the presence of low-velocity slow phases, the fast phases bring the target image near the center of the foveal area by using position error in the programming of the foveating fast-phase size (Figs. 4A, 4B). Thus, a simple description of LMLN fast-phase generation, at least in the foveating mode, would include a mechanism in which the eye drifts away from the desired target to a position error threshold (tolerance), at which point a saccadic fast phase is generated. Because LMLN subjects can show the same waveforms in the dark,[11] it appears that a motor copy of eye position is compared with an internal threshold in the programming of the fast-phase size. Our data also show (Figs. 6A, 6B) that the fast

phases in LMLN have have amplitude versus duration and amplitude versus peak velocity characteristics similar to normal saccades, suggesting that the generation of the two does not differ significantly.

The switch to defoveating fast phases may have an explanation at the ocular-motor level. A number of reports[12,13] indicate that the normal saccadic system uses position and velocity information to program saccades. If a retinal velocity error correction is added to position error, then the error threshold for triggering a fast phase may be reached sooner as retinal error velocity increases. The fast phase would then be triggered with less position error, leading to a defoveating fast phase. Another possibility, because larger defoveating fast phases occurred during higher slow-phase velocities (Figs. 2A, 2B, 5A), is that larger retinal slip velocity is used to program larger fast phases, with the resulting defoveating fast phases allowing the target to drift into the fovea near the end of the slow phases. One mechanism that would explain the shape of the decreasing-velocity slow phases occurring with defoveating fast phases is the addition of saccadic pulses to the linear-slow-phase LMLN. Figure 5b supports this hypothesis, as larger initial slow-phase velocities would be expected with the larger saccadic-pulse eye movements.

Although defoveating fast phases occurred with higher slow-phase velocities, a higher slow-phase velocity did not necessarily guarantee that the fast phases would be defoveating. In S2, Figure 1B shows that foveating fast phases occurred during BE viewing in the presence of higher slow-phase velocities (when the strabismus angle of the nonfixating eye was changing by more than 0.5°/sec during the transition from monocular to binocular viewing). During RE viewing in the same record, defoveating fast phases occurred with higher slow-phase velocities. In addition, when S2 was recorded in a later session (Fig. 3), there was no transition from foveating to defoveating when going from BE to RE viewing. Also, the mean slow-phase velocity during OU viewing was higher in the second session (1.5°/sec versus 0.35°/sec). These data were recorded in different rooms: the first using magnetic search coil and the second, IR reflection. In contrast, both data sets from S1 were taken in the same room, and the subject showed defoveating fast phases during monocular viewing in both sessions. This raises the possibility that the lighting conditions or visual background are factors. During the magnetic search coil recordings, the red laser dot was viewed either against an illuminated white background or rectangular square grid, whereas during IR recording, the subject fixated a red LED on a black background. It has been previously reported[9] that when background lighting intensity was increased (from dark to dimly lit), the slow-phase velocity decreased (by 22%). This difference would agree with a difference in the slow-phase velocities of S2 and may be a factor in a velocity set-point about which the transition from foveating to defoveating fast phases occurs.

In summary, defoveating fast phases with decreasing-velocity slow phases appear to consist of saccadic pulses added to linear slow phases. An additional fixation mechanism may further decrease the slow-phase terminal velocity to improve acuity. Defoveating fast phases occurred during higher slow-phase velocities. The velocity set-point, about which the transition to defoveating fast phases occurs, may depend on viewing conditions.
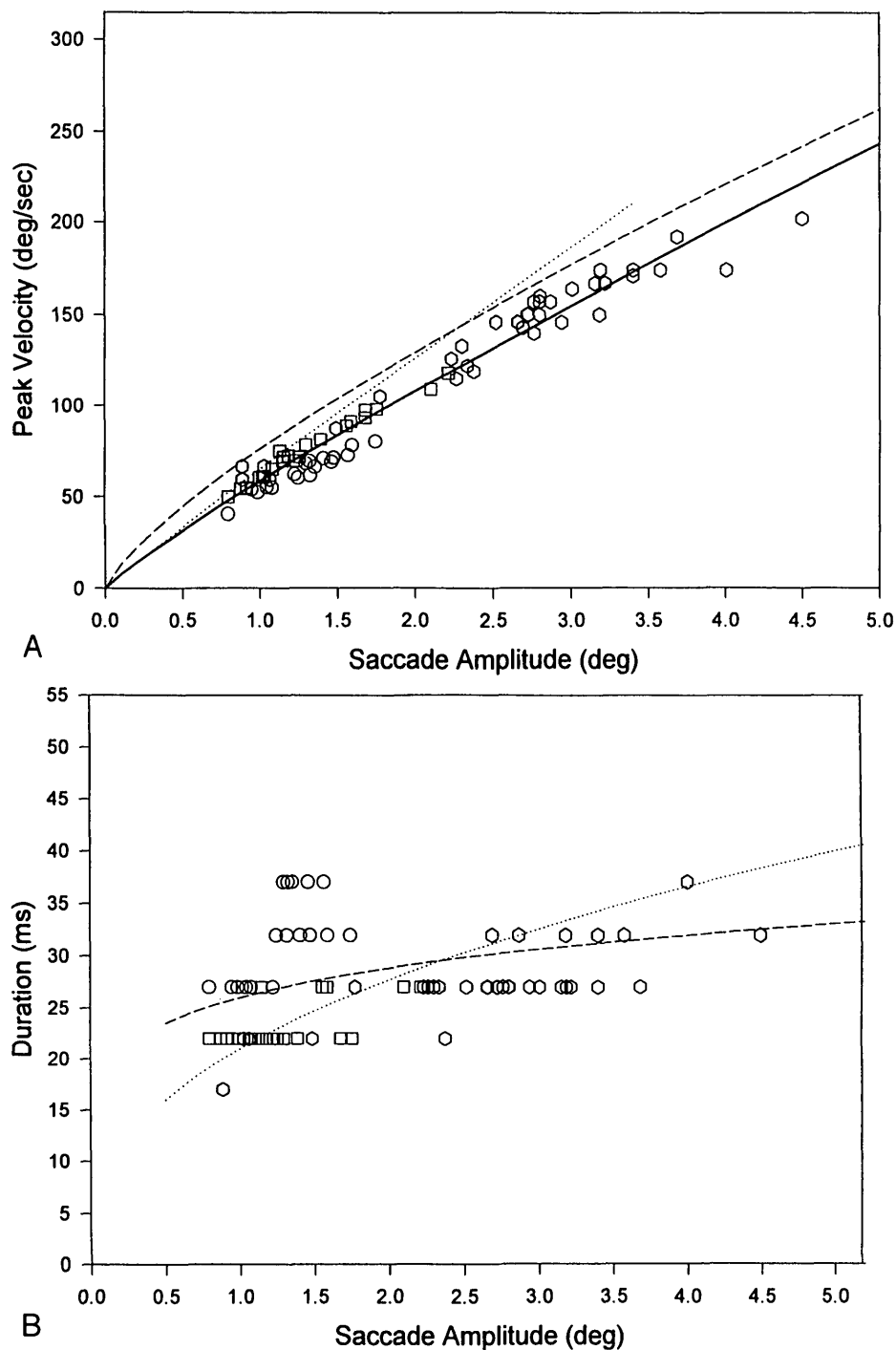
Figure 6. Saccadic peak velocity versus amplitude (A) and duration versus amplitude (B) relationships. (○) Subject 1; (□) subject 2; (◔) subject 3; (◇) subject 4. See text for discussion of the fitted curves.

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Aqueous Humor Flow in Sleeping Humans Is Unaffected by Norepinephrine Infusion

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PURPOSE. Intravenous administration of the catecholamine epinephrine is known to have a stimulatory effect on aqueous humor flow in sleeping human subjects, an effect that is augmented by plasma corticosteroids. This study was performed to determine whether the closely related catecholamine norepinephrine has a similar effect on aqueous humor flow.

METHODS. Twenty normal subjects were studied. Aqueous flow was measured by fluorophotometry. At night during sleep, norepinephrine or placebo was infused intravenously (IV) between midnight and 6 AM. The rate of aqueous flow during the norepinephrine infusion was compared with the rate of flow during placebo infusion, with each subject serving as his/her own control. The urinary excretions of epinephrine and norepinephrine were measured at the end of each infusion period.

RESULTS. The norepinephrine infusion caused an 8% increase in systolic blood pressure ($P < 0.001$), a 15% increase in diastolic blood pressure ($P < 0.001$), and a 9% decrease in heart rate ($P = 0.003$) compared with the placebo. The rate of aqueous humor flow during sleep from 12 AM to 6 AM was unchanged by norepinephrine. The rate was 1.27 ± 0.31 μl/min (mean $\pm$ SD) during IV infusion of placebo and 1.30 ± 0.27 μl/min during infusion of norepinephrine ($P = 0.63$).

CONCLUSIONS. An infusion of norepinephrine during sleep that causes measurable changes in cardiovascular parameters has no measurable effects on the rate of aqueous humor flow. The lack of a measurable effect of a norepinephrine infusion contrasts to the stimulatory effect of an epinephrine infusion. (*Invest Ophthalmol Vis Sci.* 1998; 39:1759–1762)

There are numerous reasons to hypothesize that circulating norepinephrine is a stimulator of aqueous humor formation. It has been shown that the closely related catecholamine epinephrine stimulates the flow of aqueous humor when received intravenously (IV) to sleeping human subjects.[1]

Norepinephrine has been tested in some studies. In one study, topical norepinephrine increased aqueous flow in humans, but this effect did not reach statistical significance.[2] Studies in monkey eyes in which norepinephrine was perfused through the anterior chamber showed a slightly higher rate of aqueous flow, but this effect did not reach statistical significance.[3] Studies of catecholamine concentrations in rabbit aqueous humor showed a much higher concentration of norepinephrine than epinephrine.[4]

If norepinephrine were an endogenous stimulator of aqueous humor formation, its action could account for the observations in several published studies. For example, patients without adrenal glands who lack plasma epinephrine maintain a rhythm of aqueous humor flow,[5] suggesting that some other cyclic hormone such as norepinephrine is active. As another example, during sleep deprivation at night when plasma epinephrine is extremely low, but when plasma norepinephrine is higher, aqueous humor flow is higher than it is during sleep when both catecholamines are low.[6] Thus, the flow of aqueous humor correlates better with the combined plasma concentrations of epinephrine and norepinephrine than with the concentration of either catecholamine alone.[6]

The concentration of norepinephrine in plasma is six times the concentration of epinephrine. Its binding affinity is 30% that of epinephrine in experiments with pindolol competition assays in membrane preparations from the human iris-ciliary body.[7] Norepinephrine has one eighth the potency of epinephrine as an activator of adenylate cyclase in human ciliary processes.[8] Thus, theoretically, there is a sufficient concentration of norepinephrine in the plasma during active hours to suggest that it might be able to stimulate receptors in the ciliary body.

The hypothesis that plasma norepinephrine is a stimulator of aqueous humor flow was tested in this study by comparing