ISCEV extended protocol for the dark-adapted full-field ERG b-wave transfer (intensity-response) function

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Abstract

The International Society for Clinical Electrophysiology of Vision (ISCEV) standard for full-field electroretinography (ERG) describes a minimum procedure but encourages more extensive testing. This ISCEV extended protocol describes an extension of the ISCEV standard, in which methods to record and evaluate the growth of the dark-adapted (DA) ERG b-wave with increasing stimulus strength are described. The protocol includes use of the lowest flash strength required to generate a reliable DA ERG b-wave and a series of flashes of increasing strengths used to define the maximal b-wave amplitude. The ERG transfer ("intensity-response") function can more comprehensively characterize generalized rod system function than the ISCEV-standard ERG protocol, and may be of diagnostic or prognostic value in disorders that cause generalized rod system dysfunction.

Keywords. Clinical standards; Electroretinogram (ERG); Full-field ERG; International Society for Clinical Electrophysiology of Vision (ISCEV); Dark-adapted (DA); Intensity-response (IR); Retinopathy; Naka-Rushton

Introduction

The International Society for Clinical Electrophysiology of Vision (ISCEV) standard for full-field electroretinography (ERG) describes a minimum set of tests but encourages the use of additional ERG protocols for clinical ERG testing.(1) This extended protocol describes the dark-adapted (DA) ERG transfer function, historically referred to as the "intensity-response" (I-R) function, a specialized procedure that is well established and broadly accepted by experts in the field. This protocol was prepared by the authors in accordance with ISCEV procedures (http://www.iscev.org/standards/index.html#guide2procedures).

Scope and Applications

The ERG is a graded response, i.e., its amplitude, timing and waveform change with increasing stimulus strength (Fig 1). This protocol describes the process of recording dark-adapted ERGs using a series of increasing stimulus strengths, and of analyzing the data by their fit to a heuristic model. The derived parameters of the model characterize the maximal rod-mediated retinal response and provide a measure of retinal sensitivity that may aid understanding of pathophysiology in some retinopathies.

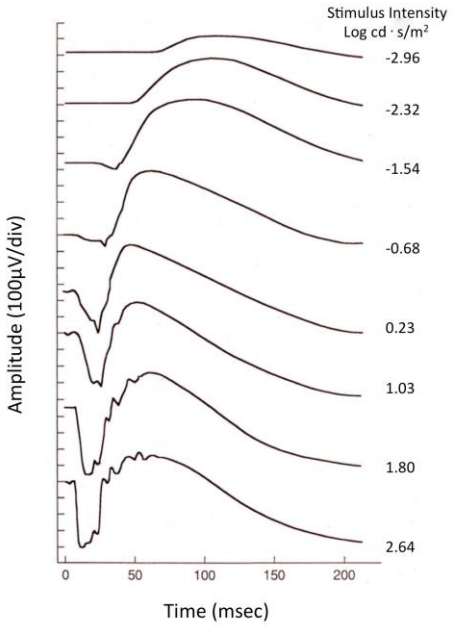

Figure 1. Human ERG waveforms measured over a > 5 log unit range of stimulus strengths. Figure initially appeared in Principles and Practice of Clinical Electrophysiology of Vision. Reprinted with permission of Mosby Year Book, Inc.(3)

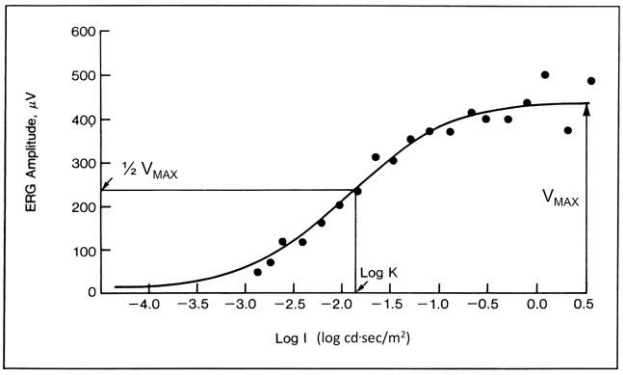

Figure 2. DA ERG b-wave as a function of stimulus strength.

Naka and Rushton(4) were the first to model the growth of the ERG b-wave with increasing stimulus strength. Figure 2 is an example of b-wave amplitude data recorded as a function of log flash strength in a normal human observer.

They showed that the hyperbolic function

$$V = V_{max} I^n / I^n + K^n$$

where *V (*μV) is the ERG b-wave amplitude generated in response to flash strength *I* (cd-s/m^2), provided a reasonable fit to b-wave amplitudes throughout most of the stimulus range. The derived parameter V_{max} (μV) is the asymptotic amplitude of the function, *K* (cd-s/m^2) is the flash strength that elicits a response that is ½ V_{max}, and *n* is a dimensionless number representing the slope of the curve and generally considered to equal 1. V_{max} has been interpreted as an index of both the number of rods responding and the gain (μV/quanta) for each b-wave generator. A reduction in V_{max} can occur secondary to loss of photoreceptors, disruption of the dark current, inner retina dysfunction or some other type of response compression. The parameter K has been interpreted as an index of retinal sensitivity that represents the efficiency of quantal capture. An elevation in K would shift the entire IR function to the right, indicating that a stronger stimulus is required to elicit b-waves of comparable amplitude. Reductions in V_{max} and elevations in K may be seen individually, or more frequently, in combination in many retinal diseases. Figure 2 is an example of b-wave amplitude data recorded as a function of log flash strength in a normal human observer.

Intensity-response function parameters V_{max} and K may be used to obtain additional information about the etiology or prognosis in a number of disorders. Naka-Rushton parameters have helped characterize fundamental differences between the mechanisms of rod dysfunction and degeneration in rod-cone dystrophy (retinitis pigmentosa; RP) and cone-rod dystrophy (18). Patients with RP typically show a loss in V_{max} along with an elevation in K, whereas patients with cone-rod dystrophy usually show normal values for these parameters. An important exception to this pattern is KCNV2-retinopathy ("cone dystrophy with supernormal rod ERG"), characterized by generalized cone dysfunction and pathognomonic DA ERG changes and an abnormal ERG I-R function. (45, 51)

Figure 3 shows an illustrative example of a normal I-R function compared with a case of central retinal vein occlusion (CRVO). There is loss in V_{max} in the affected eye of 0.13 log but an elevation in K of 0.92 log. The fellow eye also showed a large elevation in K (0.61 log) with a normal V_{max}, highlighting the possibility of subclinical involvement.

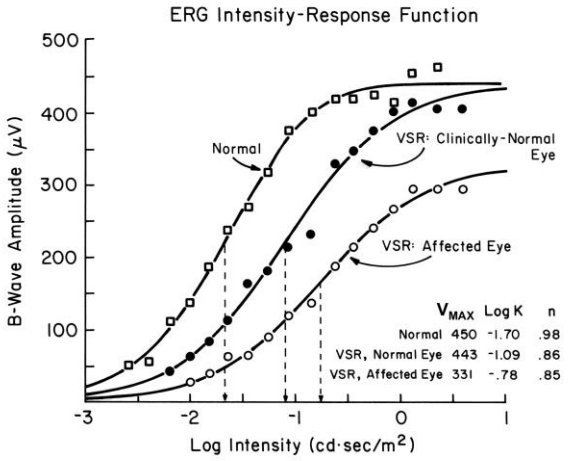

Figure 3. ERG intensity-response functions in the affected and clinically normal eyes of a patient with venous-stasis retinopathy, compared to an age-similar normal subject.

Intensity-response functions also have been used to evaluate the timeline of retinal development and aging (33,47,56,62), and toxicity and efficacy in pharmaceutical studies (35,39,48,49,50). They have been recorded in many degenerative retinal disorders (10,14,16-20,26,34,55,58), as well as in congenital stationary night blindness (CSNB), in which they revealed differences between the complete and incomplete forms (64). The IR function may also be of use in other disorders such as

age-related macular degeneration (AMD; 12), altitude retinopathy (44), central retinal artery and vein occlusions (8,9,21,27,31,32) and diabetic retinopathy (7,59,63).

Patients who have an elevation in log K will also have a delay in b-wave timing, because peak times change with stimulus strength, and thus, retinal sensitivity to that stimulus level. ERG peak time measurements can be used to estimate retinal sensitivity loss, and have been used to predict proliferative retinopathy in CRVO (8, 31, 32) and diabetic retinopathy.(7)

Patient Population

Patients of all ages able to tolerate ganzfeld stimulation, referred for investigation of rod-mediated retinal function. Using this paradigm, patients with cone-mediated abnormalities will usually show minimal changes in the derived parameters produced by the curve fit to the data. (14)

Technical Issues

This protocol has the same requirements as those outlined under the Basic Technology section of the ISCEV ERG protocol [1]. Additional considerations are outlined below.

a) Range of flash strengths. To adequately characterize the I-R function, flash stimuli must span a range that includes the lowest flash strength required to generate a reliable DA ERG b-wave and that required to generate a maximal b-wave amplitude. This normally occurs over a range of 3.5 to 4 log units of flash strengths.

b) Inter-stimulus interval. The inter-stimulus interval should be sufficiently long to maintain the same level of dark adaptation throughout the procedure. The ISCEV ERG standard specifies an inter-stimulus interval of 2 seconds for DA 0.01 and 10 seconds for DA 3.0, but there are no specific recommendations for stimuli between these 2 stimulus strengths. It is recognized that the IR function will asymptote at stimuli lower than DA 3.0 for most individuals.

c) Amplifier gain. Amplifier gain will need to be higher for the dim stimuli, and should be increased until responses can be seen well enough to judge reliability.

d) Signal averaging. Averaging is not usually required for generating waveforms for IR analysis as long as responses are replicable. Small waveforms or responses of long peak time may be prone to noise or intrusion of blink and eye movement artifacts.

e) Fitting the function. Near the asymptote of the IR function, a second hyperbolic function can be seen in normal subjects (see fig. 4). By showing that this is observed in rod monochromats, Peachey et al. (22) suggested that the second limb did not result from an interaction between rod and cone systems but is more likely to represent destructive interference between the processes responsible for the a- and b-waves, since b-wave amplitudes are measured from the trough of the a-wave to the peak of the b-wave.

f) Nomenclature of the function. In seminal studies and older publications the ERG "intensity-response" function is used to describe the ERG stimulus-response series or ERG transfer function. It is acknowledged that flashes should be described in terms of strength rather than intensity but the widely used term "intensity-response" (I-R) function is retained in reference to historical data and older publications.

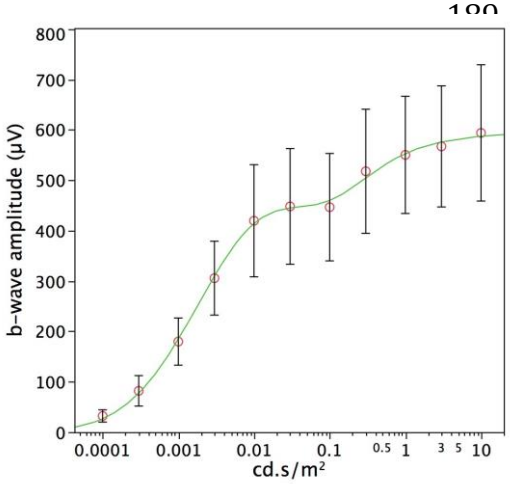

Figure 4. An IR function recorded from normal subjects (n=85): Circles are averages, error bars the 95% confidence limits and the green line a mathematical model that comprises the 2nd limb, seen above flash strengths of approximately 0.1cd.s./m².

The occurrence of a 2nd limb may confound standard application of the Naka-Rushton function, because the data variation does not follow a single hyperbolic function. If a single Naka-Rushton equation is forced to fit all of the data, the result will be a spuriously high V_{max} and an elevated log K. The latter is illustrated in fig 5, which shows fits of the Naka-Rushton function to data obtained from one subject. When all of the data are fit together (dashed line), estimates of V_{max} increased from 233μV to 438 μV, and the corresponding log K estimates increased from -1.89 to -1.03, when compared to the parameters obtained from fitting just the 1st limb (solid line).

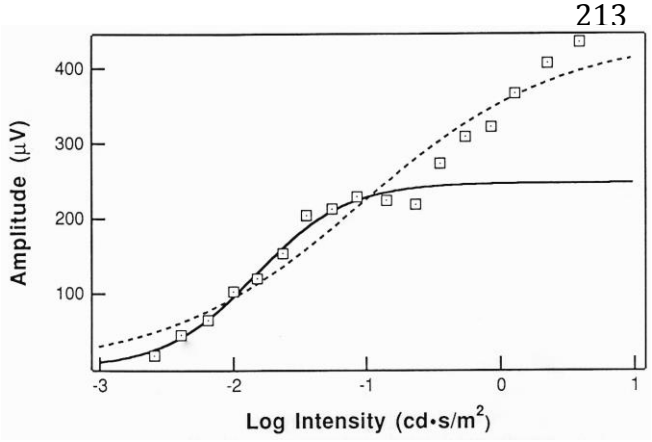

Figure 5. B-wave intensity-response data, fit by single Naka-Rushton equations to all of the data (dashed line) and to just the first limb (solid line). Figure reprinted with permission of Documenta Ophthalmologica.(5)

A heuristic method for identifying and excluding the 2nd limb has been described(5). The optimal stimulus increment size for recognizing the 2nd limb was 0.4 log unit up to about the point the b-wave begins to grow rapidly, and 0.2 log unit steps afterward. The smaller increment is necessary to recognize the occurrence of a 2nd limb when it exists. The 2nd limb can also be excluded manually, i.e. those data points that do not form a part of the single hyperbolic function can be omitted prior to Naka-Rushton fit.

Calibration

All stimuli should be individually calibrated and rechecked over time. Nominal flash strengths or nominal increments in flash strengths should not be used. Standard ERG stimuli have a very short duration (10 μs for xenon bulbs), so a calibration device that can time-average flashes is required. Low strength flashes from a xenon source generally vary more than flashes from LEDs and may require assessment of multiple flashes to measure mean flash strength. LED sources can produce more reliable flash stimuli because their output is determined by the current applied to them. Most conventional ERG equipment that is manufactured currently use LEDs, which produce more stable flash strengths.

Protocol Specifications

This protocol follows the same procedures for patient preparation and recording that are outlined under the Clinical Protocol section of the ISCEV ERG protocol(1). Other specifications are listed below.

a) Flash strengths. Flash stimuli should span a range of approximately 3.5 to 4.0 log units. In the absence of dysfunction the typical range would be approximately -3.5 to 0.5 log cd•s/m^2, starting with the lowest flash strength that will generate a reliable ERG b-wave (>10 μV) up to a flash strength that generates a maximal b-wave response. Initially, stimuli should be recorded in increasing steps of about 0.4 log units, until the b-wave amplitude begins to grow rapidly (near log K). Thereafter, we recommend that step sizes be reduced to 0.2 – 0.3 log units, if the data are to be fit by a single saturating function. Thus, at a minimum, about a dozen points should be recorded in a normally-sighted subject.

b) Inter-stimulus interval. To avoid light adaptation this protocol specifies a time between flashes of 2 seconds up to 0.01 cd·s/m^2; at least 3 seconds for stimuli up to 0.1 cd·s/m^2; 5 seconds for stimuli up to 3 cd·s/m^2, and 10 seconds for higher flash strengths.

c) Amplifier gain. There is no specific requirement for amplifier gain except that it needs to be high enough to evaluate the waveform and may need to be increased for responses to dim stimuli.

d) Signal averaging. If averaging is needed or desired, a small number of 3 to 10 sweeps are usually sufficient. Care must be taken to exclude spurious signals, such as eye movement and blink artefacts, from averaged responses.

Response Evaluation

The DA ERG b-wave amplitudes should be measured as described in the ISCEV ERG standard (1). The b-wave amplitudes at different flash intensities should then be input into one of the many commercially or privately available computer programs that provide a fit to the data using a Naka-Rushton-type function. Many of these programs use the Michaelis-Menten equation for enzyme kinetics. The Michaelis-Menten equation is the same as the Naka-Rushton equation except that it assumes a slope (n) of 1. The program used, in addition to fitting a curve to the data, should also provide estimates of the maximum amplitude (V_{max}) and the semi-saturation constant (K). The plot of b-wave amplitude vs. flash strength should be visually examined to determine if there is a second limb, and the computer fit to the data should be adjusted either by omitting the points on the limb and refitting the data, or by using a heuristic method that fits both limbs and eliminates the second (5).

Reporting

In some cases a qualitative description of the I-R function may be sufficient to corroborate or suggest a diagnosis e.g. abnormal I-R in KCNV2-retinopathy. Parameters V_{max} and log K should be reported, as well as normal ranges for fully dilated eyes. It is recognized that for some applications, a qualitative description of the I-R function may be sufficient to corroborate or suggest a diagnosis. Eyes with smaller pupils will have an increasingly dimmer retinal illuminance (measured in trolands), which will affect the value for log K. For this reason, pupil size should always be measured. Compensation for light attenuation from small pupils is possible using table 1, and any correction to log K should be clearly acknowledged.

If the pupil diameter is:	Then the pupil log area is:	And this number should be added to the value of log K:
8 mm	1.70	0
7 mm	1.59	-0.11
6 mm	1.45	-0.25
5 mm	1.29	-0.41
4 mm	1.10	-0.60

Table 1. The effect of pupil size on estimates of log K.

10. Justification for the Protocol Details

A literature review was performed using the Medline search engine, for human studies that used the words ERG and intensity response or Naka-Rushton or Michaelis-Menten or luminance response. Studies dealing with the photopic hill, photopic negative responses (PhNRs), wavelets and multifocal ERGs were excluded. Table 2 shows the results of this search.

Of 57 studies evaluated (Table 2), 60% used a flash strength range of 3.5 to 4.5 log units (range = 2.5 – 7.5). Forty-seven percent used a flash step size of either 0.2 or 0.25 log, but there was a spread of data, shown in figure 6. The larger step sizes could easily misidentify a 2nd limb unless lower luminances were used. Most studies used the Naka-Rushton function to analyze the data.

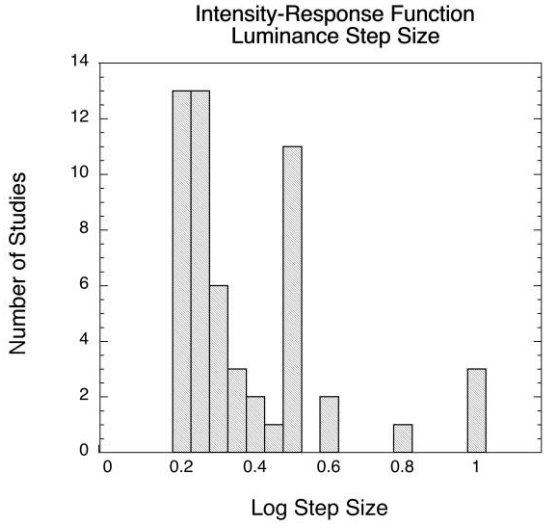

Figure 6. Luminance step sizes used for collection of ERG "intensity-response" data.

330 Table 2. Literature used for analysis.
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Citation	Luminance Range	Luminance Step Size	Method of Fitting	Patient Population
(9)	6 log (-2.58 to 3.58 log cd·s/m^2)	0.5 log	none	Central Retinal Artery Occlusion
(10)	3 log	15 steps (0.2 log)	Naka-Rushton	RP
(11)	5 log	11 steps (0.5 log)	logistic function	27 patients after renal transplant
(12)	3.7 log (-2.9 to 0.6 log cd·s/m^2)	15 steps (0.25 log)	Naka-Rushton	AMD
(13)	3.25 log		Naka-Rushton	
(14)	4.0 log (-2 to 2 log scot td-s)	16 steps (0.25 log)	Naka-Rushton	RP
(15)	3.5 log	6 steps (0.6 log)	Naka-Rushton	Isotretinoin toxicity
(16)	7.5 log	0.5 log or 1.0 log	none	Supernormal rod ERG
(17)	4.1 log (using rod isolation)	0.2 log per step	Naka-Rushton	RP
(18)	4.1 log (using rod isolation)	0.2 log per step	Naka-Rushton	RP, Cone Dystrophy
(19)	4.1 log (using rod isolation)	0.2 log per step	Naka-Rushton	RP
(20)	3.5 log (-2.61 to 0.87 log cd·s/m^2)	18 steps (0.2 log)	Naka-Rushton	X-linked RP
(21)	4 log	8 steps (0.5 log)	Naka-Rushton	CRVO
(22)	4 log	17 steps (0.25 log)	Naka-Rushton	Normal and Achromatopsia
(23)	3.8 log (-2.97 to 0.82 log cd·s/m^2)	18 steps (0.2 log)	Naka-Rushton	Albinism
(24)	4 log	13 steps (0.3 log)	Naka-Rushton	Cone-Rod Degeneration
(25)	3.8 log (-2.97 to 0.82 log cd·s/m^2)	18 steps (0.2 log)	Naka-Rushton	Sickle Cell Retinopathy
				Elevated Cyclic Guanosine Monophosphate-Type
(26)	3.5 log (-1.5 to 2 log scot td-s)	13 steps (0.25 log)	Naka-Rushton	Human Retinal Degeneration
(27)	3.6 log	8 steps (0.6 log)	Naka-Rushton	Central Retinal Vein Occlusion
(28)	4.5 log (-3.6 to 0.9 log cd·s/m^2)	10 steps (0.45 log)	Naka-Rushton	Normal
(29)	5 log (-1 to 4.0 log scot td-s)	19 steps (0.26 log)	Naka-Rushton	
(30)	3.6 log	13 steps (0.27 log)	Naka-Rushton of 1st limb	Normal
(31)	4 log	0.2 log per step	Naka-Rushton	Central Retinal Vein Occlusion
(32)	Threshold to 0.29 log cd·s/m^2	0.2 log	Naka-Rushton	Central Retinal Vein Occlusion
(33)	2.5 log (-2.0 to 0.5 log scot td-s)	0.28 log	Naka-Rushton	Normal over the lifespan
(34)	3.25 log (-1.19 to 2.04 log scot td-s)	unspecified	Naka-Rushton	RP and Normal
(35)	3.50 log (-4.5 to -1 log cd·s/m^2)	0.2 log per step	Naka-Rushton	Sildenafil toxicity
(36)	3.25 log (-4.25 to -1 log cd·s/m^2)	14 steps (0.25 log)	Naka-Rushton	Normal
(37)	5.0 log (to 25.2 cd·s/m^2)	0.3 (Boston site); 1 log (Cambridge site)	Naka-Rushton	Normal Children and Adults

(38)	3.7 log (-0.7 to 3.0 log scot td-s) using rod isolation	unspecified	Naka-Rushton	Cone Dystrophy
(39)	3.50 log (-4.5 to -1 log cd·s/m^2)	0.2 log per step	Naka-Rushton	Sildenafil toxicity
(40)	4.0 log (-5.01 to -.96 log cd·s/m^2) blue light	11 steps (0.36 log)	Naka-Rushton	Normal - circadian rhythm
(41)	4.0 log (-3.95 to 0.05 log cd·s/m^2)	0.3 log; # of steps depending on start of 2nd limb	Naka-Rushton	Depression
(42)	3.25 log (-4.25 to -1.0 log cd·s/m^2) green light	14 steps (0.23 log)	Naka-Rushton	Normal-dilated vs undilated
(43)	3.25 log (-4.25 to -1.0 log cd·s/m^2) green light	14 steps (0.23 log)	none	Normal
(44)	4.5 log (-4.5 to 0.03 log cd·s/m^2)	11 steps (0.40 log)	Naka-Rushton	toxicity
(45)	4.06 log (-3.0 - 1.06 log cd·s/m^2)	8 steps (0.5 log)	none	KCNV2 Retinopathy
(46)	3.25 log (-4.25 to -1.0 log cd·s/m^2)	14 steps (0.23 log)	sigmoid curve	Normal, Patients with seasonal affective disorder
(47)	4.9 log (-3.27 to 2.16 log scot td-s) using rod isolation	0.4 log	Naka-Rushton	Preterm infants with and without ROP
(48)	3.5 log (-3.27 to 0.26 log cd·s/m^2)	8 steps (0.5 log)	Naka-Rushton	toxicity (bevacizumab)
(49)	4 log (-3.62 to 0.38 log cd·s/m^2)	4 steps (1.0 log)	Naka-Rushton	Patients (unknown diagnosis) receiving bevacizumab
(50)	4.9 log (-1.95 to 2.95 log scot td-s)	0.3 log	Naka-Rushton	Normal
(51)	5 log (-4 to 1 log cd·s/m^2)	10 steps (0.5 log)	Naka-Rushton	KCNV2 Retinopathy
(52)	5 log (-4 to 1 log cd·s/m^2)	10 steps (0.5 log)	Naka-Rushton	Normal
(53)	4.2 log (-0.7 to 3.5 log scot td-s)	7 steps (0.5 log)	H2 clearance curves	Normal
(54)	5.5 log (-4.5 to 1.0 log cd·s/m^2)	0.5/0.25 log	Naka-Rushton	Glaucoma/Normal (35/17)
(55)	3.5 log (-1.5 to 2 log scot td-s)	13 steps (0.27 log)	Naka-Rushton	RP Heterozygotes/Normal (11/19)
(56)	4 log (-3 to 1 log cd·s/m^2)	0.25 (adult) 0.5 (infant)	Naka-Rushton	Infant ROP/Adult Normal (19/3)
(57)	3.9 log (-3.95 to -0.05 log cd·s/m^2)	0.3 log	Naka-Rushton	Normal (10)
(58)	not specified	not specified	Naka-Rushton	RP/CRD/Normal (11/17/50)
(59)	3.1 log (-3.1 to 0 log cd·s/m^2)	variable (0.35 to 0.82 log)	Naka-Rushton	Diabetics/Normal (65/10)
(5)	threshold to 0.6 log cd·s/m^2	0.2 log	Naka-Rushton	CRVO/Normal (94/124)
(60)	3.8 log (-3.0 to 0.8 log cd·s/m^2)	18 steps (0.2 log)	Naka-Rushton	Normal (30)
(61)	3.0 log (-2.9 to 0.1 log cd·s/m^2)	0.3-0.4 log	Naka-Rushton	Normal (45: 61 eyes)
(62)	not specified	7 steps	Naka-Rushton	Normal (269)
(63)	4.0 log (-3.8 to 0.2 log cd·s/m^2)	0.2 log	1. Naka-Rushton 2. NR to first limb 3. Log model (-3.8 to -2.2	Diabetics/Normal (152/40)

			log cd-s/ m^2)	
(64)	5 log	0.3 log	Naka-Rushton	CSNB

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