

# Objective Quantification of Spontaneous Retinal Venous Pulsations Using a Novel Tablet-Based Ophthalmoscope

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**Purpose:** Dynamic assessment of retinal vascular characteristics can aid in identifying glaucoma-specific biomarkers. More specifically, a loss of spontaneous retinal venous pulsations (SVPs) has been reported in glaucoma, but a lack of readily available tools has limited the ability to explore the full potential of SVP analysis in glaucoma assessment. Advancements in smart technology have paved the way for the development of portable, noninvasive, and inexpensive imaging modalities. By combining off-the-shelf optical elements and smart devices, the current study aims to determine whether SVPs can be detected and quantified using a novel tablet-based ophthalmoscope in glaucoma and glaucoma suspects.

**Methods:** Thirty patients, including 21 with confirmed glaucoma (9 men; average age  $75 \pm 8$  years) and 9 glaucoma suspects (5 men; average age  $64 \pm 9$  years), were studied. All patients had intraocular pressure measurements, Humphrey visual field assessment, optical coherence tomography, and a 10-second videography of the retinal circulation. The retinal vasculature recordings ( $46^\circ$  field of view at 30 frames per second) were analyzed to extract SVP amplitudes.

**Results:** SVPs were detected and quantified in 100% of patients with glaucoma and those with suspected glaucoma using the novel device. The average SVP amplitudes in glaucoma and glaucoma suspects were  $42.6\% \pm 10.7\%$  and  $34\% \pm 6.7\%$ , respectively.

**Conclusions:** Our results suggest that a novel tablet-based ophthalmoscope can aid in documenting and objectively quantifying SVPs in all patients.

**Translational Relevance:** Outcomes of this study provide an innovative, portable, noninvasive, and inexpensive solution for objective assessment of SVPs, which may have clinical relevance in glaucoma screening.

## Introduction

Spontaneous retinal venous pulsations (SVPs) are changes in caliber of the retinal veins at the optic nerve head, usually at the hemi-veins of the central retinal vein as they join to form the central vein or where it exits at the lamina cribrosa.<sup>1</sup> The mechanism by which SVPs occur is complex. Intraocular pressure (IOP), retinal venous pressure (RVP), and cerebrospinal fluid pressure (CSFp) are all thought to play a role in their generation. These factors create a pressure gradi-

ent between the intraocular and retrobulbar spaces, which is said to be a main driver in the generation of SVPs.<sup>2,3</sup> Reduced or absent SVPs have been reported as a risk factor for glaucoma and its progression,<sup>4-6</sup> with absent SVPs reported in up to approximately 50% of patients with glaucoma.<sup>5</sup> These findings may be due to elevated RVP, reduced ocular blood flow<sup>7,8</sup> and/or lower mean CSFp compared with nonglaucomatous patients, which can decrease the amplitude of SVPs.<sup>9</sup> Other identified factors known to reduce SVPs are the combination of elevated CSFp and reduced IOP, which can decrease the intravascular pressure gradient.<sup>5,10-13</sup>

The first record of SVPs were from Coccius in 1853, using the newly invented direct ophthalmoscope.<sup>14</sup> By the 1920s, SVPs were measured using ophthalmodynamometry, which involved applying digital pressure to the eye, resulting in an increase in IOP and enabling the visualization of SVPs. The minimum force required to induce SVPs, referred to as ophthalmodynamometric force, was used to quantify SVP.<sup>15</sup> Both these methods are subjective and dependent on observation and therefore are disposed to bias and inconsistency. Other factors that may contribute to unreliability in these methods include interobserver variation, the presence of microsaccades and/or fixation nystagmus, and variations in the ophthalmoscope lens power used. Hence, recent studies have focused on developing objective measures of SVP that are able to quantify the presence and degree of SVPs rather than the subjective binary classification of present or absent. These methods have included quantitative techniques of vessel diameter measurement,<sup>13</sup> lateral displacement of the blood vessels,<sup>16</sup> and hemoglobin concentration.<sup>17</sup>

The Dynamic Vessel Analyzer (DVA) is an optical-based device used to measure SVP pulsatility along vessel markers based on processing algorithms, producing a continuous SVP trace. A recent study compared subjective and objective methods of SVP detection using indirect ophthalmoscopy (75D lens) and DVA methods, respectively.<sup>4</sup> The authors reported subjective SVP detection in only 64.1% of patients with glaucoma when indirect ophthalmoscopy assessment was conducted. In comparison, SVPs were objectively detected in all patients using the DVA, including those with advanced glaucoma who have previously been reported as having absent SVPs.<sup>4</sup> This demonstrates the increased accuracy in SVP detection through objective means.

The use of dynamic imaging (i.e., real-time retinal videography) has previously been used to determine SVP amplitude successfully.<sup>13,18,19</sup> This study introduces a novel approach to real-time videography and SVP analysis using a tablet (iOS operating system) with an add-on 20D binocular indirect ophthalmoscope lens. Previous methods of SVP analysis have been performed using costly, nonportable devices. This tablet-based ophthalmoscope is both portable and not costly and records the retinal blood circulation while maintaining a relatively high frame rate of 30 frames per second. While devices such as the Heidelberg-Spectralis optical coherence tomographer (OCT) have better image quality, they are limited by lower frame rate, mobility, and ease of use. The modern DVA technology developed specifically for videography and assessment of retinal vasculature is also nonportable and limited by contrast requirements.<sup>20</sup> Our novel approach to videography and SVP analysis addresses these issues.

## Method

### Data Collection

Thirty participants (average age  $71.8 \pm 9.7$  years; 14 men) were recruited for this study, including 21 with confirmed glaucoma and 9 with suspected glaucoma. Patients were selected from an ophthalmology clinic and not included if they had diabetes and/or if the patients had current or previous vascular or retinal pathology. All had a standard ophthalmic examination, including medical history, visual acuity corrected with glasses if worn, IOP measurement using Goldmann tonometry, and Humphrey Visual Field (HVF) assessment (HFA II-i series, operating system 5.1, Dublin, CA) using the SITA-Standard strategy and stimulus size III (white).

Optic nerve imaging was carried out on OCT, using either the Spectralis OCT (Heidelberg Eye Explore version 1.10.20, Dossenheim, Germany, using the retinal nerve fiber layer [RNFL] algorithm) for 25 patients, including 8 glaucoma suspects, or the Cirrus HD-OCT (version 5.2.1.12 Optic Disc Cube  $200 \times 200$ , Carl Zeiss Meditec, Dublin, CA) for 5 patients, one of whom was a glaucoma suspect. All patients at the same visit had an additional dilated (1% tropicamide [Mydracyl] Alcon, Macquarie Park, Sydney, NSW) 10-second videography of venous circulation at the optic nerve head using the tablet-based 20D ophthalmoscope,

Glaucoma was diagnosed in the presence of definite glaucomatous optic neuropathy and/or visual field defects with mean deviation (MD) ranging from  $-9.52$  to  $-1.57$  dB and progressive change in either assessment. A comprehensive assessment was undertaken by an experienced glaucoma specialist (AA), combining conventional indirect ophthalmoscopy, OCT RNFL analysis (Heidelberg Spectralis), and Hoddap-Anderson criteria for HVF progression.<sup>21</sup>

Glaucoma suspects were defined as having elevated IOP or a suspicious-appearing optic disc with no progressive changes in either and a normal visual field with MD range of  $-1.88$  to  $0.59$  dB, assessed on examination by AA.

### Retinal Videography

Retinal videography was performed using the ProMovie video camera application on an iOS operating device (iPad Mini4; Apple, Inc., Cupertino, CA, USA). Imaging settings such as exposure and focus were adjusted manually as required for each patient to ensure maximum contrast of the optic nerve head and retinal vessels. Videos were taken centered on the optic disc and digital zoom was maintained at  $2.2\times$  across all



**Figure 1.** Magnified frames from an SVP video (left eye) from a 68-year-old woman captured using a 20D tablet-based ophthalmoscope. *Left* image is a magnified original frame. The *right* image is the *green* channel of the same frame with Contrast Limited Adaptive Histogram Equalization (CLAHE) application.

participants to ensure consistency. Participants were instructed to refrain from blinking while a 10-second photographic video was recorded. Although the tablet-based ophthalmoscope is designed for handheld use, for the purpose of video stability, a slit-lamp mount was used. Images of the device setup are included in [Appendix 1](#).

An additional five healthy individuals were recruited to determine the reproducibility and intraindividual variability of the device. Each individual had retinal videography performed three times, each at 10-minute intervals.

## Data Analysis

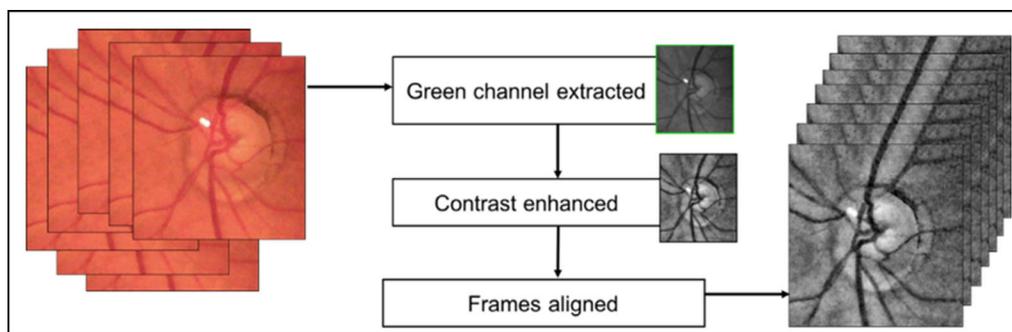
The digital video recordings were saved and exported as individual frames to an image-analysis program, ImageJ (previously National Institutes of Health [NIH] Image).<sup>22</sup> To enhance visibility of the vessels, the color channels of each frame were split, extracting the green channel to reveal the highest contrast of retinal vasculature.<sup>23</sup> A contrast equalization plugin (CLAHE; ImageJ) was then applied to each frame enhance image contrast for greater accuracy in the detection of vessel borders, as seen in [Figure 1](#).

The frames were then aligned to eliminate ocular movements such as those arising from fixation nystagmus or decompensation. For this, the optic disc in the first frame of the video was manually selected and used as a reference for the entire video. Normalized correlation coefficient was then used as the matching method—this function detects the landmark or the most similar image pattern in every slice (in this

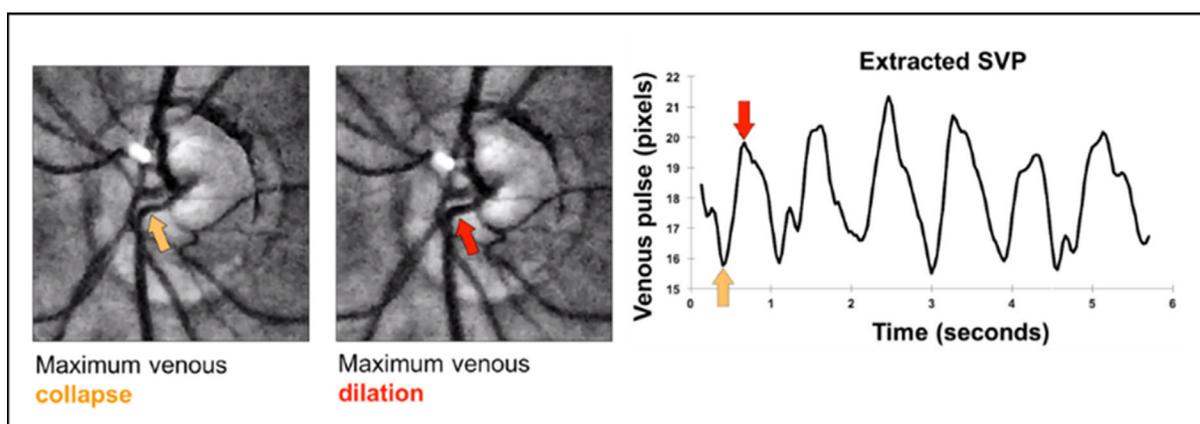
case, the optic nerve). Each slice is adjusted to align the landmark pattern to keep it in the same position throughout the stack. More specifically, the algorithm compares each frame against the reference region of interest (the optic disc) by sliding (i.e., moving) the patch one pixel at a time (left to right, up to down) ([Fig. 2](#)). The algorithm was implemented in the ImageJ software using the “template matching” plugin.

The vessels were selected for measurement by an orthoptist (SS) at the central retinal vein (CRV) where possible. When the CRV was not visible (anatomical variations), the closest point to the CRV at the optic disk was selected for measurement. A manual selection was made along the transverse axis of the vessel, perpendicular to the vessel orientation. All vessel calibers were measured at the vessel of interest, using a method described by Fischer et al.<sup>24</sup> and implemented in Image J. In brief, the inner vessel diameter is estimated based on the red blood cell column using a full width at half-maximum algorithm. The diameter of the selected vessel is measured five times in each frame of the video. A moving average window of three is then applied to obtain vessel diameter at the selected location on each frame of the video. These measurements were then exported to an Excel (Microsoft, Redmond, WA, USA) spreadsheet for analysis. To remove baseline wandering, a moving average algorithm was also applied.

The frame-by-frame change in diameter was plotted against time, producing a quantified SVP trace ([Fig. 3](#)). SVP amplitude was then determined using a two-step calculation, utilizing the percentage change in vessel caliber to eliminate the effects of vessel size variation between individuals, ensuring that any changes



**Figure 2.** Schematic of image enhancement process using ImageJ.



**Figure 3.** Left images: Two magnified, cropped, and enhanced frames from the same eye at seven frames apart (approximately 0.25 seconds). The yellow arrow points to the vessel location at maximum venous collapse and the red arrow points to the vessel location at maximum venous dilation. Right image: Corresponding SVP trace with yellow and red arrows indicating resultant SVP troughs and peaks.

observed in vessel pulsatility are driven by pathophysiologic changes rather than interindividual vessel diameter variation. First, the change in average venous diameter ( $\Delta$  venous diameter) of each participant was calculated as  $\frac{\text{peak}-\text{trough}}{\text{mean vessel caliber}}$ . This information was then used to calculate the average percentile pulse, calculated as  $\frac{\Delta \text{ venous diameter} \times 100}{\text{mean vessel caliber}}$ , to reveal the SVP amplitude of each individual.

GraphPad Prism (GraphPad Software, La Jolla, CA, USA) was used for data analysis and visualization. Linear regression was applied to visualize the strength of correlations alongside use of Pearson correlation tests to quantify the correlation strength and statistical significance (significant at the  $P < 0.05$  level; two-tailed). Descriptive statistics were also conducted to reveal the basic distribution of the data.

## Ethics

This study was performed in accordance with the guidelines of the tenets of the Declaration of Helsinki and approved by the University of Technology Sydney's Human Research Ethics Committee.

Written consent was obtained from each patient following an explanation of the nature of the study.

## Results

The average age of participants was  $72 \pm 10$  years, with patients with glaucoma having a significantly higher average age ( $75 \pm 8$  years) compared with glaucoma suspects ( $64 \pm 9$  years). A summary of patient demographics and mean values for IOP, global average RNFL, and HVF is presented in Table 1.

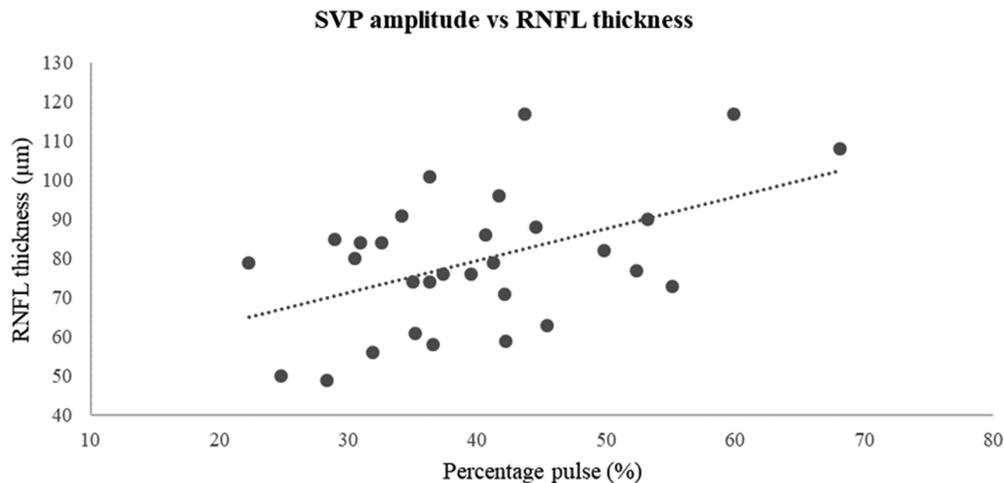
### SVPs were Identified in 100% of Patients when Assessed Objectively

Raw videos of retinal circulation were first observed before computer analysis. SVPs were visible to the naked eye in 67% of glaucoma suspects and 62% of patients with confirmed glaucoma. However, computer analysis revealed the presence of SVPs in 100% of participants in both groups, with a mean SVP

**Table 1.** Patient Demographics and Mean Values

Characteristic	Glaucoma	Glaucoma Suspects	<i>P</i> value
Sex, male, No.	9	5	
Age	75.2 ± 8.3	64.0 ± 8.6	<0.001
IOP (mm Hg)	13.9 ± 3.2	16.2 ± 4.2	0.1
RNFL (μm)	80.9 ± 18.1	76.2 ± 16.4	0.5
HVF MD (dB)	-3.5 ± 3.0	-1.9 ± 1.8	0.1

Values are presented as mean ± SD unless otherwise indicated.

**Figure 4.** Correlation between SVP amplitude and RNFL thickness ( $P = 0.006$ ,  $r = 0.49$ ).

amplitude of  $40\% \pm 10\%$  across patients with glaucoma and glaucoma suspects. Mean SVP amplitudes were significantly lower ( $P = 0.03$ ) in suspects ( $34\% \pm 6.7\%$ ) compared with those with a confirmed diagnosis of glaucoma ( $43\% \pm 10.7\%$ ).

all measurements. The standard deviation of SVP variability for each individual varied from 0.2% to 3.7% with an overall average standard deviation of 2.6% for each participant that was not significantly significant (one-way analysis of variance;  $P = 0.68$ ).

### SVPs are Correlated with RNFL Thickness

Data were pooled from both patients with glaucoma and glaucoma suspects, and linear regression was used to study the association between SVP amplitudes, RNFL thickness, and HVF MD. We found a positive and significant correlation between SVP amplitudes and RNFL thickness ( $P = 0.006$ ,  $r = 0.49$ ) (Fig. 4). A similar positive association between HVF MD and SVP amplitude across all participants were observed, but this was not statistically significant ( $P = 0.58$ ,  $r = 0.10$ ).

### SVP Measures are Reproducible Using the Tablet-Based Ophthalmoscope

The average age of healthy participants recruited for the feasibility study was  $27 \pm 5$  years. The average overall SVP percentile pulse was  $12\% \pm 3\%$  across

## Discussion

In this study, we explored the use of a novel tablet-based ophthalmoscope to objectively detect and quantify SVPs. We also investigated the relationship between SVP amplitudes and other established structural and functional assessment parameters for glaucoma (RNFL thickness and HVF MD). Our results showed that using a tablet-based digital ophthalmoscope, we were able to visualize and quantify SVPs in all participants. Furthermore, consistent with our previous findings,<sup>4</sup> we observed a positive correlation between SVP amplitudes and RNFL thickness. Further studies of SVP assessment are required to determine the sensitivity and specificity of SVPs in glaucoma diagnosis and also to explore the addition of SVP assessment as a parameter for glaucoma risk evaluation.

**Table 2.** Comparison of SVP Detection Devices

Characteristic	Ophthalmoscope			Heidelberg-Spectralis OCT	Dynamic Vessel Analyzer (DVA)
	Tablet Based	Direct (Traditional)	Indirect		
Portability	✓	✓	✓	×	×
Lens strength (D)	20	5	Varied	20	
Approximate cost of device (AUD)	1700	≥600	≥2500	~120,000	Add-on to Heidelberg-Spectralis OCT
Ease of Use	Technical Training Required	Medical Training Required		Technical Training Required	
Dilation required	✓	✓	✓	×	✓
Frame rate (fps)	30	n/a	n/a	15	25
Resolution	77 μm/pixel	n/a	n/a	10 μm/pixel	
Field of view (degrees)	46	5	Varied	25–35 <sup>25</sup>	

n/a, not applicable.

Previous studies of blood vessel width measurement using devices such as the DVA have demonstrated difficulty in taking measurements at the optic nerve head due to image contrast limitations, particularly the reflectivity reported at the optic nerve or lamina cribrosa.<sup>13</sup> Furthermore, the DVA is limited by the need for steady fixation.<sup>20</sup> The ProMovie application used in this study overcomes these limitations by allowing live adjustment of image exposure to overcome image contrast and reflectivity issues, allowing reliable measurements of both the optic nerve head and retina. Our custom-written algorithms also address the issue of unsteady fixation. Other advantages of the tablet-based ophthalmoscope used in this study compared with other devices used in previous studies are summarized in Table 2. Although this novel device does not have a gold standard to compare against, our feasibility results show that the numbers obtained for SVPs are highly reproducible.

Consistent with previous studies that have compared subjective and objective means of SVP detection,<sup>4</sup> this study demonstrates greater detection of SVPs through objective means. SVP amplitudes are often difficult to identify with the naked eye, with reduced amplitudes being below the limits of resolution by the naked eye. This may explain the results of studies that have used subjective means of SVP detection and have detected fewer SVPs in their patients with glaucoma compared with healthy individuals.<sup>5,26</sup>

Contradictory to previous findings and other reports, we found greater SVP amplitudes in patients with glaucoma than in glaucoma suspects. While this is a surprising finding, a previous study conducted by Ren et al.<sup>2</sup> found abnormally low CSFp in patients with glaucoma with normal baseline IOP. This exaggeration of the translaminal pressure gradient causes an exaggeration of SVPs. While baseline IOP (i.e., IOP pretreatment) was not reported in this study, Ren et al.<sup>2</sup> provide a possible explanation of the current results. A study investigating SVP in patients with glaucoma with normal baseline IOP and those with elevated baseline IOP before and after medical treatment is required to further unravel the findings of this study. Second, the number of glaucoma suspects was considerably lower than those with a glaucoma diagnosis ( $n = 9$  vs. 21), and hence the results we have observed may not necessarily be completely representative. Third, it has been reported that SVPs are more frequently observed in older age groups.<sup>27</sup> This may also be a contributing factor, given that the average age of patients with a glaucoma diagnosis was higher than glaucoma suspects. Finally, given the positive correlation between SVP amplitudes and RNFL thickness, reduced SVPs are expected with thinner RNFLs. Hence, the difference may simply be due to lower mean RNFL thickness in glaucoma suspects.

It is well known that glaucoma is associated with RNFL thinning, but contrary to previous reports,<sup>4–6</sup>

we found thinner RNFL in glaucoma suspects than in patients with glaucoma. Previous investigations of retinal blood flow and RNFL thickness have revealed increased ocular blood flow in regions of RNFL thinning in the early stages of glaucoma,<sup>28</sup> with a progressive decline in ocular blood flow observed with increasing glaucoma severity.<sup>7,8,28</sup> A study investigating the effect of glaucoma on SVP amplitude found reduced SVP amplitudes in retinal sectors with greater RNFL loss. The authors also report significantly smaller SVP amplitudes and RNFL thickness in patients with glaucoma compared with normal controls ( $P < 0.0001$ ). The study also investigated individual quadrant analysis of the RNFL (i.e., superior, inferior, nasal, and temporal regions of the RNFL surrounding the optic nerve) and determined positive correlations between SVP amplitude and RNFL thickness.<sup>4</sup>

In our study cohort, only three participants with confirmed glaucoma had moderate glaucoma, and the majority had early stage glaucoma<sup>21</sup> and may have less damage to the RNFL than is normally observed in larger cohorts of patients with a diagnosis of glaucoma. Larger sample sizes with even distribution between the groups are needed to reflect the true RNFL distribution expected. The discrepancy could also be due to different OCTs used—Leite et al.<sup>29</sup> demonstrated thinner measurements on the Cirrus OCT compared with the Spectralis OCT ( $P < 0.001$ ). Faghihi et al.<sup>30</sup> also found similar results but demonstrated a significant relationship between intermeasurement differences. A separate analysis was conducted using only the measures obtained from the Spectralis OCT, which was found to exacerbate the difference in RNFL thickness between the groups (mean RNFL thickness was 2.2  $\mu\text{m}$  greater and 3.8  $\mu\text{m}$  thinner in the glaucoma and glaucoma suspects groups, respectively). A similar analysis was not performed on just the Cirrus OCT results as our participant numbers are too small for statistical comparison, with just one participant in the glaucoma suspect group. This participant, however, had a thicker average RNFL than the average RNFL thickness in the participants with glaucoma (91.00  $\mu\text{m}$  and 73.60  $\pm$  10.69  $\mu\text{m}$ , respectively).

Assessment of visual fields is routine in clinical glaucoma practice. It is the major indicator of functional impact of glaucoma in one's quality of life,<sup>31,32</sup> and results are key in influencing management options.<sup>33</sup> Previous studies have demonstrated that worse visual field MD is associated with lower frequency of SVPs in glaucoma.<sup>34</sup> While the correlation we observed between SVP and HVF MD in our small sample of participants was not significant, future studies using larger sample sizes may

reveal stronger correlations that align with previous studies.<sup>34</sup>

Our results demonstrate that the use of a portable and easy-to-use device in detecting and quantifying SVPs is possible and very promising. Further research is necessary to determine the comparability of SVP analysis using this novel technique and established SVP analysis tools and methods, such as the DVA. If these projected studies demonstrate good comparability between devices, it can be proposed that using a tablet-based ophthalmoscope is a more feasible approach to SVP analysis. Furthermore, it will be useful to establish normal age-related changes in SVP amplitude. Studies have looked at the effect of aging on the presence of SVP, but there have been no studies establishing the normal distribution of SVP amplitude with age.<sup>27</sup>

In conclusion, this study has provided proof of principle that using a 20D binocular indirect ophthalmoscope lens in conjunction with a smart digital hardware may be a feasible means of detecting SVPs and can be used for SVP analysis. There is significant potential for future use of the device given its relatively inexpensive, easy-to-use, and portable nature. Future studies with larger sample sizes may resolve the apparently contradictory findings regarding glaucoma suspects.

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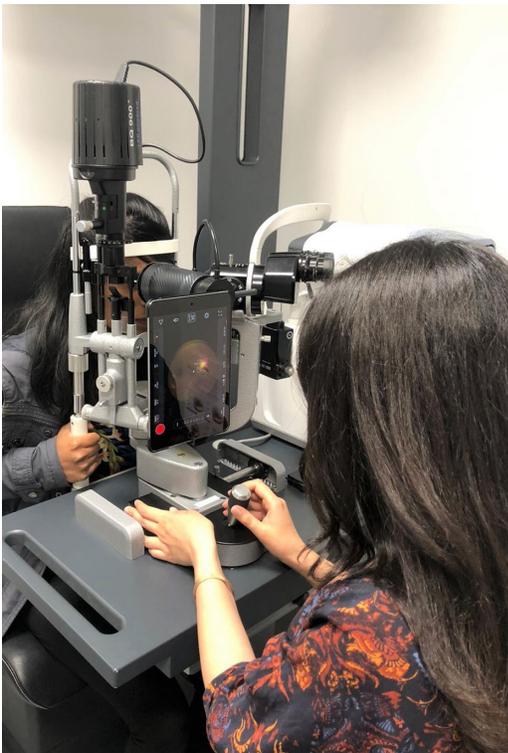
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## Appendix 1

Images 1 and 2.



**Image A2.** Patient and tablet-based ophthalmoscope position during SVP assessment.



**Image A1.** SVP assessment using a tablet-based ophthalmoscope mounted on a slit lamp.