UTS UNIVERSITY OF TECHNOLOGY SYDNEY

Characterising Quantitative Spontaneous Retinal Venous Pulsations in Glaucoma

by Sahar Shariflou

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Doctor of Philosophy: Orthoptics

Under the supervision of Dr Mojtaba Golzan, Professor Kathryn Rose and Dr Ashish Agar.

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Certificate of Original Authorship

I, Sahar Shariflou declare that this thesis, is submitted in fulfilment of the requirements for the award of Doctor of Philosophy, in the Graduate School of Health at the University of Technology Sydney. This thesis is wholly my own work unless otherwise referenced or acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis. This document has not been submitted for qualifications at any other academic institution.

This research is supported by the Australian Government Research Training Program.

Signature: Production Note: Signature removed prior to publication. Date: 4th April 2022

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Thesis abstract

Spontaneous retinal venous pulsations (SVPs) are a dynamic vascular marker for glaucoma, which is a leading cause of irreversible blindness across the globe. Since the discovery of SVPs, their presence has been variably reported in patients with glaucoma, some even reporting absent SVPs. Recent objective quantification of SVPs has led to an increase in their detection. There is a need to explore the possibility of SVPs being used as a potential marker for glaucoma screening in clinical practice. Current devices that are used to assess SVPs pose limitations that deem current SVP detection unfeasible for screening outside metropolitan and in remote areas and for use in mobile clinics that service underprivileged and remote communities where there is likely to be many cases of undetected glaucoma.

This thesis aims to assess the effectiveness of a novel tablet-based ophthalmoscope to detect and quantify SVPs in glaucoma with the aid of computer analysis. This device was used to perform fundus videoscopy in 170 participants recruited from three ophthalmic clinics in Sydney. All participants had a confirmed diagnosis of glaucoma or glaucoma suspect. SVP amplitudes were extracted from raw videos using a custom-written algorithm. Standard structural (RNFL thickness) and functional (VF loss) clinical markers for glaucoma, as well as intraocular pressure (IOP) and retinal ganglion cell (RGC) estimates were also recorded and documented. SVP distribution, and its association with the established clinical structural and functional measures were assessed.

Using tablet-based ophthalmoscopy, SVPs were detected and quantified in all participants, regardless of glaucoma status. The largest SVP amplitudes were detected in normal tension glaucoma (NTG; 32.5%), followed by primary open-angle glaucoma (POAG; 28.7%) and glaucoma suspects (26.3%). A significant association was found between SVP amplitudes and clinical markers in NTG and POAG with the highest correlations being between SVP amplitude - RNFL thickness (p=0.1) and SVP amplitude - RGC count (p<0.001) in NTG and POAG respectively. When evaluating which clinical marker can distinguish between confirmed glaucoma and glaucoma suspects, SVP analysis was found to be comparable to standard clinical markers. More specifically, SVPs can separate POAG from glaucoma

suspects as effectively as RNFL thickness. SVPs can also separate POAG from NTG as effectively as IOP measurements.

The novel device used in this thesis overcomes many of the disadvantages of current commercial techniques, particularly portability and ease of use. The novel device and technique can be used to detect and quantify SVPs in all participants with glaucoma, regardless of glaucoma severity. The findings of this thesis indicate that SVPs are associated with clinical markers that are known to occur during the early glaucomatous changes. The potential benefits that this may offer in the early detection of glaucoma, consequent management and evaluation of progression are substantial. When combined with RGC count, SVP amplitude analysis may provide benefits to traditional glaucoma assessments where often structural and functional glaucomatous loss are only clinically detected once substantial RGC loss has already occurred. Further studies are required to determine if longitudinal SVP changes are associated with progressive glaucoma and whether SVPs can be used as a marker for monitoring disease progression.

Publications, Presentations and Awards

Journal publications:

Gheisari, S., Shariflou, S., Phu, J., Kennedy, P.J., Agar, A., Kalloniatis, M. and Golzan, S.M., 2021. A combined convolutional and recurrent neural network for enhanced glaucoma detection. Scientific reports, 11(1), pp.1-11. (Appendix 5)

Shariflou, S., Agar, A., Rose, K., Bowd, C. and Golzan, S.M., 2020. Objective quantification of spontaneous retinal venous pulsations using a novel tablet-based ophthalmoscope. Translational Vision Science & Technology, 9(4), pp.19-19. (Appendix 6)

National and international presentations:

Shariflou, S., Agar, A., Rose, K. and Golzan, S.M., 2019. Assessment of spontaneous retinal venous pulsations in glaucoma patients on medical treatment over two years. 8th World Glaucoma Congress, Melbourne, Australia.

Shariflou, S., Agar, A., Rose, K. and Golzan, S.M., 2019. The accuracy of spontaneous venous pulsation assessment in discriminating glaucoma from glaucoma suspects. ARVO, The Association for Research in Vision and Ophthalmology Conference, Vancouver, Canada.

Shariflou, S., Agar, A., Rose, K. and Golzan, S.M., 2018. Spontaneous venous pulsations assessed using a novel tablet-based ophthalmoscope are associated with retinal ganglion cell counts in glaucoma and glaucoma suspects. The Royal Australian and New Zealand College of Ophthalmologists (RANZCO); 50th Annual Scientific Congress, Adelaide, Australia.

Shariflou, S., Agar, A., Rose, K. and Golzan, S.M., 2018. Dynamic retinal vascular assessment: An innovative approach for early glaucoma screening. Orthoptic Association of Australia; 75th Annual Scientific Conference, Adelaide, Australia

Shariflou, S., Agar, A., Rose, K. and Golzan, S.M., 2018. Amplitudes of spontaneous venous pulsations are associated with retinal ganglion cell count estimates in glaucoma. ARVO, The Association for Research in Vision and Ophthalmology Conference, Honolulu, Hawaii.

Shariflou, S., Agar, A., Rose, K. and Golzan, S.M., 2017. Quantifying spontaneous retinal venous pulsations using a novel tablet-based ophthalmoscope. RANZCO Cossom Scientific Meeting, Sydney, Australia.

Shariflou, S., Agar, A., Rose, K. and Golzan, S.M., 2017. Quantifying spontaneous retinal venous pulsations using a novel tablet-based ophthalmoscope. Orthoptic Association of Australia; 74rd Annual Scientific Conference, Perth, Australia.

Awards:

This thesis was supported by the National Health & Medical Research Council Postgraduate Scholarship.

Ophthalmic Research Institute of Australia (ORIA) Star awarded at the RANZCO 50th Annual Scientific Congress, Adelaide, Australia (2018).

ARVO hot topics highlight at The Association for Research in Vision and Ophthalmology Conference, Honolulu, Hawaii (2018).

Best research presentation awarded at the RANZCO Cossom Scientific Meeting, Sydney, Australia (2017).

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Glossary of Abbreviations

Abbreviation	Full term
%	Percentage
%Δ	Percentage change
µm	Micrometre
ACA	Anterior ciliary artery
ACG	Angle-closure glaucoma
AI	Artificial intelligence
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ART	Automatic real-time
AUD	Australian dollar
AUROC	Area under the receiver operating characteristic curve
CA	California
CD	Cup to disc
CFEH	Centre for Eye Health
CLAHE	Contrast Equalization plugin
CNS	Central nervous system
CRA	Central retinal artery
CRAE	Central retinal artery equivalent
CRV	Central retinal vein
CRVE	Central retinal vein equivalent
CSFp	Cerebrospinal fluid pressure
D	Dioptres

DARC	Detection of Apoptosing Retinal Cells
dB	Decibels
DCPx	Deep capillary plexus
DVA	Dynamic Vessel Analyzer
FAZ	Foveal avascular zone
FNR	False negative rate
FPR	False positive rates
fps	Frames per second
GHT	Glaucoma hemifield test
GMPE	Glaucoma Module Premium Edition
HFA	Humphery Visual Field Analyser
HR	High resolution
HS	High speed
HTG	High-tension glaucoma
ICA	Internal carotid artery
ICP	Intracranial pressure
ICPx	Intermediate capillary plexus
IOP	Intraocular pressure
iOS	iPhone operating system
IR	Infrared reflectance
LDF	Laser Doppler Flowmetry
LGN	Lateral geniculate nucleus
LPCA	Long posterior ciliary artery
LSF	Laser Speckle Flowgraphy
MD	Mean deviation

MES	Marsden Eye Specialists
MGC	M ganglion cell
mmHg	Millimetre of mercury
mPPG	Modified photoplethysmography
NIH	National Institutes of Health
NTG	Normal tension glaucoma
OAG	Open-angle glaucoma
OCT	Optical coherence tomography
OCT-A	Optical coherence tomography-angiogram
OD	Optic disc
P1G cell	P1 midget ganglion cell
PACG	Primary angle-closure glaucoma
PCA	Posterior ciliary artery
PDP	Pattern deviation plot
POAG	Primary open-angle glaucoma
PPG	Photoplethysmography
PSD	Pattern standard deviation
r	Correlation coefficient
RGC	Retinal ganglion cell
RNFL	Retinal nerve fibre layer
RPCP	Radical peripapillary capillary plexus
RVBA	Retinal vascular bifurcation angle
RVP	Retinal venous pressure
SAP	Standard automated perimetry
SPCA	Short posterior ciliary artery

SVP	Spontaneous retinal venous pulsation
TD	Total deviation
UNSW	University of New South Wales
USA	United States of America
UTS	University of Technology Sydney
V-CDR	Vertical cup to disc ratio
VF	Visual field
VFA	Visual field analysis
VFI	Visual field index