

Characterising Quantitative Spontaneous Retinal Venous Pulsations in Glaucoma

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the degree of

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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.

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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 videography 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

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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 | Radial 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 |