Retinal microvascular function: A tractable biomarker of cardiovascular risk?

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Disclosures: The authors are employed by the University of Glasgow, which holds consultancy and research agreements with companies that have commercial interests in the diagnosis and management of angina, including Abbott Vascular, AstraZeneca, Boehringer Ingelheim, GSK, Heartflow, Menarini Pharmaceuticals, Neovasc, Siemens Healthcare and Valo Health. The authors received no support from any of these organisations for the submitted work.

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Word count: 821

Endothelial dysfunction and microvascular disease are multisystem disorders which underpin early atherosclerosis and plaque progression, and are associated with increased cardiovascular risk[1]. Measurement of endothelial function and early detection of endothelial/microvascular dysfunction identifies specific patient subgroups, facilitates risk stratification of patients, and monitoring of disease progression and response to treatment[2].

Multiple methods currently exist to assess endothelial function. These include invasive techniques such as invasive coronary function testing and venous plethysmography, as well as non-invasive techniques such as flow-mediated vasodilation of brachial artery and finger plethysmography. Each method has advantages and disadvantages and the ESC have recommended the continued development of newer techniques and recognised the need for large clinical studies in order to develop reference ranges and assess clinical utility[2].

One novel method is dynamic retinal vessel analysis (DVA). This non-invasive method assesses retinal endothelial function by measuring retinal vessel diameter changes in response to high-frequency flicker light. In healthy patients, high-frequency flicker light stimulates dilatation of retinal arterioles and venules due to a combination of nitric oxide release and neurovascular coupling[3,4]. Flicker-induced dilatation of retinal vessels is impaired in patients with diabetes[5], obesity[6], hypertension[7], and increasing age.

In additional to DVA, static retinal vessel analysis (SVA) can also be performed. This allows for the measurement of the arterio-venous ration (AVR), which has previously been shown to be associated with increased cardiovascular risk[8].

Patients with end-stage renal disease (ESRD) have excessively elevated levels of morbidity and mortality, and cardiovascular disease is the leading cause of mortality in patients with ESRD[9]. Endothelial dysfunction is known to play an important role in the early progression of cardiovascular and renal disease. Microvascular complications of renal disease can often be detected at an earlier stage than macrovascular complications, therefore, measuring endothelial/microvascular function in patients with ESRD presents a potential biomarker for measuring cardiovascular risk and stratifying therapy according to phenotype.

In this study the authors investigated the predictive value of dynamic flicker-induced retinal vessel dilatation and static retinal vessel diameters on all-cause mortality in haemodialysis patients over a 73-month follow-up period.

SVA assessments were performed in 275 patients. Static measurement of retinal arteriolar and venular diameters showed no significant association with all-cause mortality, cardiovascular mortality or infection related mortality. Thus, SVA failed to predict mortality in ESRD patients.

DVA assessments were performed in 214 patients. There were 76 deaths in this group, with the most common cause being cardiovascular death (35 cases, 46%), followed by infection-related death (22 cases, 29%). They found that retinal venular dilatation (vMax) in response to high-frequency flicker light was a strong predictor of all-cause (HR 0.69 [0.54; 0.88]) and infection-related mortality (HR 0.53 [0.33; 0.83]). In addition, patients within the lowest vMax tertile had lower 5-year survival rates compared to the highest tertile (50.6% vs. 82.1%) and also had a higher incidence of infection-related deaths (21.7% vs 4.0%).

Interestingly, when corrected for age and vascular co-morbidities, retinal arteriolar dilatation (aMax) was not predictive of mortality.

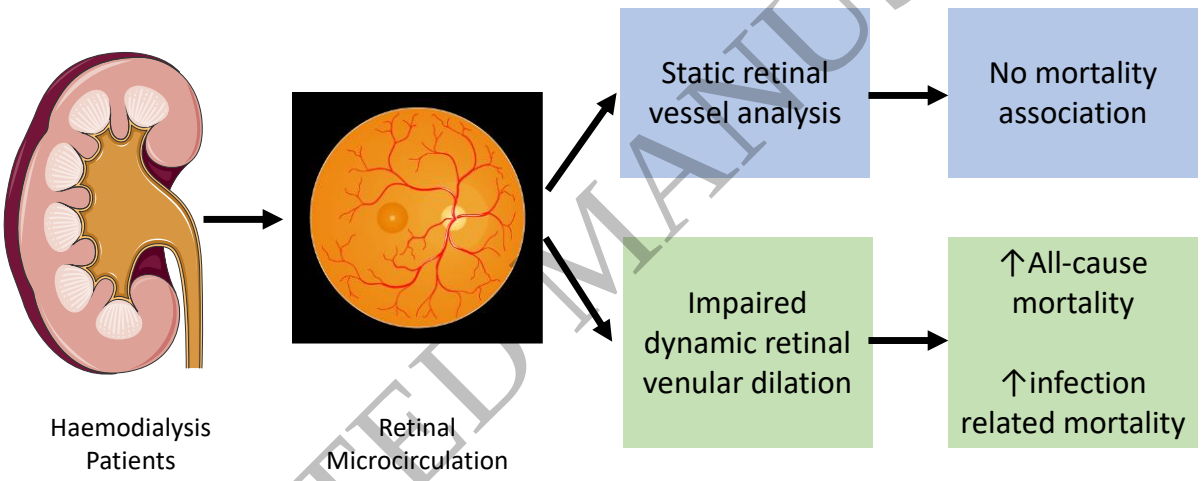
Consistent with their previously published work[10], the authors found that vMax was most strongly correlated with markers of inflammation (hsCRP and IL-6) and vascular co-morbidities. Thus, suggesting a possible mechanistic link between chronic systemic inflammation and microvascular dysfunction.

In summary, Günthner et al have demonstrated that retinal venular flicker light-induced dilatation is an independent predictor for all-cause and infection-related mortality in long-term follow-up of haemodialysis patients. Using this technique to screen for microvascular dysfunction may allow for more accurate phenotyping, risk stratification, and personalised stratified therapy. However, it will be important to consider how this will be translated to improve clinical outcomes and reduce mortality in this group. The DVA technique has potential to identify patients with an increased risk of death, who will require aggressive management of traditional cardiovascular risk factor, and it may also identify patient groups who may benefit from targeted disease modifying precision therapy. The aim of precision medicine is to tailor therapy to the individual patient. Allowing for more effective, individualised treatment, and avoiding unnecessary investigations and treatments. An example is the Precision Medicine with Zibotentan in Microvascular Angina (PRIZE) trial (NCT04097314). Zibotentan is a potent, oral, selective inhibitor of the endothelin A receptor. Dysregulation of the endothelin system is implicated in the development of microvascular dysfunction, and therefore zibotentan has potential as a disease-modifying therapy. Potentially, a similar approach using novel anti-inflammatory drugs or other drugs with potential disease-modifying effects, could be studied in patients identified by measuring retinal microvascular function.

Another important consideration is that ideally a biomarker should be transferable to the clinic and not limited by complexity or cost. An whilst the authors state that clinicians or researchers

do not require ophthalmic expertise to measure DVA, they do acknowledge that practice and experience is required to generate reliable data. In addition, the technique is currently only available at expert centres and relies on a single commercial device. We believe technology advances to increase automation to minimise user dependency will facilitate the path to the clinic.

Figure.



References

Bonetti PO, Lerman LO, Lerman A. Endothelial Dysfunction. *Arteriosclerosis, Thrombosis, and Vascular Biology* 2003;**23**:168–175.

Alexander Y, Osto E, Schmidt-Trucksäss A, Shechter M, Trifunovic D, Duncker DJ, Aboyans V, Bäck M, Badimon L, Cosentino F, Carlo M de, Dorobantu M, Harrison DG, Guzik TJ, Hoefer I, Morris PD, Norata GD, Suades R, Taddei S, Vilahur G, Waltenberger J, Weber C, Wilkinson F, Bochaton-Piallat M-L, Evans PC. Endothelial function in cardiovascular medicine: a consensus paper of the European Society of Cardiology Working Groups on Atherosclerosis and Vascular Biology, Aorta and Peripheral Vascular Diseases, Coronary Pathophysiology and Microcirculation, and Thrombosis. *Cardiovascular Research* 2021;**117**:29–42.

Newman EA. Functional Hyperemia and Mechanisms of Neurovascular Coupling in the Retinal Vasculature. *Journal of Cerebral Blood Flow & Metabolism* 2013;**33**:1685–1695.

Kondo M, Wang L, Bill A. The role of nitric oxide in hyperaemic response to flicker in the retina and optic nerve in cats. *Acta Ophthalmologica Scandinavica* 2009;**75**:232–235.

Heitmar R, Lip GYH, Ryder RE, Blann AD. Retinal vessel diameters and reactivity in diabetes mellitus and/or cardiovascular disease. *Cardiovascular Diabetology* 2017;**16**:56.

Kotliar KE, Lanzl IM, Schmidt-Trucksäss A, Sitnikova D, Ali M, Blume K, Halle M, Hanssen H. Dynamic retinal vessel response to flicker in obesity: A methodological approach. *Microvascular Research* 2011;**81**:123–128.

Ritt M, Harazny JM, Ott C, Raff U, Bauernschubert P, Lehmann M, Michelson G, Schmieder RE. Impaired Increase of Retinal Capillary Blood Flow to Flicker Light Exposure in Arterial Hypertension. *Hypertension* 2012;**60**:871–876.

Seidelmann SB, Claggett B, Bravo PE, Gupta A, Farhad H, Klein BE, Klein R, Carli M di, Solomon SD. Retinal Vessel Calibers in Predicting Long-Term Cardiovascular Outcomes. *Circulation* 2016;**134**:1328–1338.

Sarnak MJ, Foley RN. Cardiovascular Mortality in the General Population Versus Dialysis: A Glass Half Full or Empty? *American Journal of Kidney Diseases* 2011;**58**:4–6.

Günthner R, Hanssen H, Hauser C, Angermann S, Lorenz G, Kemmner S, Matschkal J, Braunisch MC, Küchle C, Renders L, Moog P, Wassertheurer S, Baumann M, Hammes H-P, Mayer CC, Haller B, Stryeck S, Madl T, Carbajo-Lozoya J, Heemann U, Kotliar K, Schmaderer C. Impaired Retinal Vessel Dilation Predicts Mortality in End-Stage Renal Disease. *Circulation Research* 2019;**124**:1796–1807.