Retinal microvascular diameters: normative data and their use in clinical hypertension

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Microvascular dysfunction has been recognized as a crucial pathway in the (early) development and progression of cardiovascular and metabolic disease \cite{1–6}. In addition, microvascular dysfunction has been shown to be associated with increased (cardiovascular) mortality \cite{7}. However, in-vivo assessment of microvascular structure and function is technically demanding which limits its broad applicability in observational studies and clinical trials. One exception in this respect is imaging of the retinal microcirculation. Since the early 1920s, fundus photography has played a prominent role in diagnosing eye diseases, and because of the widespread availability of this technique it has been applied in many mechanistic and epidemiological studies.

Retinal microvascular diameters appear to be relevant, valid, and consistent markers of microvascular function. Many studies in different cohorts have consistently shown that both current and past higher arterial blood pressure (BP) is associated with reduced arteriolar diameters \cite{8–12}. This BP-related arteriolar narrowing seems to be reversible. Antonio et al. \cite{13} measured retinal arteriolar and venular diameters in 189 hypertensive patients before and after 6 months of antihypertensive treatment. The average arteriolar-to-venular diameter ratio increased significantly following 6 months of treatment, which was because of an increase in arteriolar diameter. Hughes et al. \cite{14} compared the effects of 12 months BP lowering with amlodipine versus lisinopril on retinal arteriolar diameters in 25 untreated hypertensive study participants. Both treatments resulted in similar BP reduction and also in comparable reversal of arteriolar narrowing. Apart from antihypertensive treatment, also lifestyle factors may contribute to reduce unfavorable changes in retinal microvascular diameters. In an Australian cohort (n = 2683), the frequency of fish consumption, evaluated with a questionnaire, was associated with retinal arteriolar/venular diameters \cite{15}. It was shown that, particularly in hypertensive study participants, a higher frequency of fish consumption was associated with narrower arterioles and wider venules. Also exercise training can be used to improve retinal microvascular diameters, as was shown by Hanssen et al. \cite{16}. They showed that following a 10-week exercise training program, arteriolar narrowing improved in obese study participants. Finally, arteriolar narrowing may not only be an adaptive response to higher BP, but also predict and possibly contribute to the development of hypertension \cite{6}. As was shown in a recent meta-analysis by the Meta-Eye Study Group \cite{17}, both narrower arterioles and wider venules were independently associated with an increased risk of hypertension.

Based on the above, retinal microvascular diameters seem to be promising variables for individual risk prediction and/or an intermediate endpoint in the evaluation of antihypertensive treatment. An important requisite for this is normal reference values of retinal arteriolar and venular diameters. In the current issue of the Journal of Hypertension, Ponto et al. \cite{18} present age and sex-specific nomograms of retinal microvascular diameters based on cross-sectional data from 4309 individuals of the Gutenberg Health Study. They calculated normative data and reference values of retinal arteriolar diameters (Central Retinal Arteriolar Equivalent), venular diameters (Central Retinal Venular Equivalent), and arteriolar-to-venular diameter ratios in a subset of 890 individuals (20\%) who were defined as 'cardiovascular healthy', meaning absence of any of the following cardiovascular risk factor or condition: systemic hypertension, diabetes, smoking, dyslipidemia, obesity, peripheral arterial occlusive disease, heart failure, history or family history of stroke or myocardial infarction. Unfortunately, demographics and clinical characteristics were presented for the total cohort only, not for the 'cardiovascular healthy' subset. In the total cohort (n = 4309), 50.2\% were men and mean age was 54.8 ± 10.8 years. This is the first study to provide such normative data, applicable to this population. Additional studies are required to obtain more normative data for other populations and different disease groups. Some limitations of the present data are, as pointed out by the authors, the wide variability in retinal vessel parameters between individuals, a broad zone of overlap...
between different groups, and large reference ranges. Hence, the estimation of cut-off values for individuals at risk is difficult to assess. One aspect that may contribute importantly to this wide variation is that the authors have chosen to represent diameters as vessel equivalents instead of actual μm. The actual vessel dimension in micrometres at the retinal plane has to be calculated using a magnification factor based on axial length and refractive error [19]. Axial length and refractive errors differ greatly between study participants, and the change in magnification from myopia to hyperopia ranges from ~25 to 18% [20]. To determine vessel widths accurately in individual eyes, it is therefore essential to correct the magnification of the image captured by the fundus camera on an individual basis.

Data reported in the paper by Ponto et al. [18] have an immediate clinical impact. Indeed they provide reference values for retinal vascular parameters in healthy study participants, to which comparison of data obtained in different studies and population can be done. Static and dynamic imaging of the retinal microcirculation clearly has added valuable insight into (patho)physiological processes involved in microvascular (dys)function in cardiometabolic diseases. However, to use these techniques for individual risk stratification and evaluation of treatment efficiency, additional technical improvements and standardizations in both image acquisition and, preferably, fully automated analyses are required.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES