The eye, the kidney and microcirculation

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When Hermann von Helmholtz invented the direct ophthalmoscope in 1850, he opened the door to a non-invasive visualization of human microcirculation in vivo at the retina (Figure 1). Only a few years later, on 4 September 1864, a young man presented a talk on ‘The blood vessels of the human eye’ at the Heidelberg Ophthalmology Congress—his name was Theodor Leber, and today, he is regarded as one of the founders of ophthalmic research. Only relatively minor changes have been made subsequently to Leber’s original anatomical drawings of the ocular vasculature [1].

In 1904, W. M. Bayliss was the first to describe the myogenic constriction of arterioles when transmural pressure is elevated [2]. This so-called ‘Bayliss effect’ is a central mechanism of the autoregulation to maintain blood flow in an organ despite variations in perfusion pressure. The kidney is the classical organ in which autoregulation of blood flow with changes in perfusion pressure has been demonstrated [3,4].

The retina provides an opportunity for the in vivo investigation of a part of human circulation. It has been shown that blood flow in the human retina is autoregulated [5], and with modern technology, the retina offers the unique chance to measure the ‘Bayliss effect’ on a non-invasive basis in human retinal arterioles [6]. As it is generally accepted that the retinal vessels have no functioning autonomic innervation beyond the lamina cribrosa, this autoregulation occurs in response to changes in perfusion pressure or in response to metabolic stimuli. The mammalian retina has been found to possess an unusually high rate of glycolysis [7] and oxygen consumption [8], with this activity fuelling the active transport processes that maintain the ionic gradients necessary for visual transduction and electrical activity. As it is widely accepted that cerebral blood flow is spatially and temporally coupled to brain function and metabolism [9], the same neurovascular coupling was postulated for the retina [10].

Different measuring methods have been developed to quantify ocular perfusion. They have profoundly changed our understanding of the regulation and dysregulation of perfusion of the eye, and given new insights into the pathogenesis of ocular diseases. These findings were brought to the attention of ophthalmologists, and in clinical practice and research, use of these technologies was limited to the ophthalmic community.

However, some devices have demonstrated their functionality in the hands of neurologists and diabetologists. The Dynamic Retinal Vessel Analyzer (DVA, Imedos, Jena, Germany) consists of a modified CCD camera fitted to a fundus camera (Carl Zeiss Meditec, Jena, Germany) (Figure 2) [11].

In ‘static vessel analysis’, a single fundus picture is used to measure arterial and venous vessel diameters around the optic nerve and calculate the central arterial equivalent, the central retinal venous equivalent and the arterial-to-venous diameter ratio (AVR) [12]. Large epidemiological studies showed evidence that these values are indicators for cardio- and cerebrovascular events [13].

In ‘dynamic vessel analysis’, the instrument measures vessel diameter in relation to time and local position along a vessel in real time continuously 25 times per second. The examination of function and individual capacities of vessel segments along the vessel is based on the fact that the vessel diameters are the essential adjusting elements of autoregulation. As an additional stimulation test for vessel function, the DVA interrupts the green measuring light and generates a flicker light with a frequency of 12.5 Hz with a bright-to-dark ratio of 25:1. The diameter responses can be recorded, and the dilation of vessel diameter is used as a functional diagnostic parameter for the endothelium-derived vasodilation. Since autoregulation is a generic term for different local feedback control systems, superimposed on each other vessel behaviour ranges from dynamic vessel changes within seconds (flicker response) to minutes (metabolic response).

Although a general outline of the circulation and its autoregulation is useful for haemodynamic purposes, special circulations exist to meet the functional needs of individual organs. In many diseases, the kidney and the eye are linked—only recently in this journal, an editorial comment reviewed the linkage between dense-deposit disease and retinal drusen [14]. In type 1 and type 2 diabetes, patients...
may develop nephropathy and retinopathy [15]. Hyperglycaemia is a modifiable risk factor of microvascular disease in the eye and the kidney, and microalbuminuria is associated with an increased risk of proliferative retinopathy and blindness. However, both of these complications may be asymptomatic initially. By the use of the DVA, different stages of impairment of autoregulation on the retina can be demonstrated [16], and the effect of an active intervention results in a significant change [17]. The functional damage to the retinal vessels by the disease can be measured before the morphological changes of diabetic retinopathy are visible [18].

Both in diabetic and in non-diabetic nephropathy, there is a well-established association between progressive renal failure and the risks of death and chronic vascular disease (CVD). Indeed, the risk for cardiovascular events can increase more than 3-fold in patients with an eGFR < 15 mL/min/1.73 m² [19]. In diabetic and non-diabetic patients with established CVD but normal renal function, urine albumin excretion predicts cardiovascular morbidity and mortality. This association begins below clinically defined thresholds [20].

The Framingham Risk Score and other models, which estimate individual risks of myocardial infarction or coronary death within 10 years, bear three important limitations. Firstly, current static models are based entirely on the accumulation of risk factors including age, gender, smoking, cholesterol and blood pressure, but data on the actual stage of early arteriosclerosis or vessel dysfunction are not included [21]. Secondly, CVD risk models have limited capabilities to evaluate the success of specific cardiovascular interventions in modifiable risk factors including blood pressure, cholesterol and lifestyle. Thirdly, 10-year risk estimations for CVD can be misleading. For example, the Framingham Risk Score classifies individuals <30–50 years and most women as at low 10-year risk for CVD despite substantial differences in the burden CVD risk factors that may exist [22]. Since the lifetime risk can be 4–7 times higher than the calculated 10-year risk for CVD, practice guidelines recommend both current and lifetime risk estimations [23].

A method that could separate patients with low short-term but high lifetime risk from individuals with low short-term and low lifetime risk for CVD might be of clinical value. Probably, information on current vessel dysfunction might be crucial in this context. There are a number of investigators who demonstrated the link between retinal vessels and kidney function in their studies [24]. Studies in patients with non-diabetic nephropathy are underway [25]. However, one should recognize that even in diabetes, microvascular disease of the eye and the kidney does not necessarily go hand in hand. We found in a cross-sectional study looking at 323 ambulatory patients with type I diabetes and 906 patients with type 2 diabetes that there was a good correlation between the presence of retinopathy and microalbuminuria in type 1 diabetes but a discordance of retinopathy and microalbuminuria in patients with type 2 diabetes. Even some dialysis-dependent patients, stage 5 type 2 patients, revealed no signs of retinopathy [25]. A considerable discordance between glomerulopathy and retinopathy in patients with type 2 diabetes has also been reported by other groups [26,27]. Schwartz and co-workers found that the majority of patients with type 2 diabetes without retinopathy had diffuse mesangial sclerosis, whereas typical Kimmelstiel–Wilson lesions correlated closely with proliferative retinopathy [28]. This suggests that, presumably, a different underlying pathophysiology may account for these findings [29].

In chronic kidney disease (CKD), renal function, BP status and renin–angiotensin blockade independently predicted AVR in the retina as a marker for microvascular damage. Moreover, retinal arteriolar diameter predicted renal function independently of the primary renal disease suggesting that renal disease per se may modulate retinal vessel function [30]. Myeloid-related protein 8/14—a marker for transendothelial migration—was positively associated with the degree of microvascular alterations in the glomerular and retinal bed [31].

Finally, this editorial can remind us that the eye, the kidney and the vessels are distinct organs which share common features in many systemic diseases. But it also provides a draft of new perspectives the eye may open for the non-invasive and in vivo measurement of autoregulatory responses in human microcirculation.
References


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