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Visualisation studies and glomerular filtration in early diabetic rats ☆

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ABSTRACT

The purpose of this mini-review is to show that more modern multi-photon microscopy approaches allow quantitative glomerular filtration experiments. Modern science has now entered a transition period from light microscopy to multi-photon confocal microscopy. Since the late 20th century, multi-photon microscopy has been applied in the study of organ function. In keeping with observations made in renal physiology and other representative studies throughout this transition period, and in the context of advancing microscopy techniques, this review has been presented as a comment on the glomerular filtration barrier, with a focus on the early aetiopathogenesis of diabetes.

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1. Review

1.1. *In-vivo visualisation of glomerular circulation using light microscopy*

Visualisation is a simple but reliable approach to scientific investigation. It has been and still is a method for pattern recognition. It is also a method to investigate structures and functions. Renal microcirculation has previously been examined in juxtamedullary nephrons (Edwards, 1983; Ito et al., 1991; Yuan et al., 1990), in hamster cheek pouch allografts of renal tissue (Joyner et al., 1988), and in hydronephrotic kidney models (Dietrich et al., 1993; Loutzenhiser et al., 1991; Steinhausen et al., 1983). These studies were performed using light microscopy, and based on either isolated preparations or pathological animal models. Therefore, the results from these studies may differ from those of studies performed under physiological conditions. Only a few visualisation studies, however, have been performed in-vivo, including a study by our group, which used a charge-coupled device (CCD) intravital videomicroscope (Nakamoto et al., 2008). In addition, a number of studies have examined glomerular filtration function quantitatively using visualisation under in-vivo conditions (Russo et al., 2009; Tanner, 2009; Yu et al., 2007). Figs. 1 and 2 show in-vivo figures using the different modalities, MRI (Lee et al., 2012) and ultrasonography plus scintigraphy (Stock et al., 2016) respectively. The resolutions are not good as light microscopy or multi-photon microscopy.

Fig. 3 shows a representative image from an in-vivo video recording of glomerular circulation, which was acquired with a CCD intravital videomicroscope (Nakamoto et al., 2008). The spatial resolution of the system used to generate this image was 0.8 μm, comparatively high for a light microscope. Blood flow velocities can be computed from sequential analysis of video images (Ogasawara et al., 2000). Using intravital videomicroscopy, it has been demonstrated that afferent arteriolar diameters are larger in control rats and 2 week-diabetic rats. In diabetic rats, both afferent and efferent diameters were larger than those of control rats. Renal blood flow in diabetic rats has also been shown to be greater than blood flow in control rats (Yamamoto et al., 2001a, 2001b); therefore, it is suggested that diabetic rats are in a condition of hyperfiltration. The exact mechanism underlying the development of hyperfiltration in early diabetes remains unknown (Sällström et al., 2007). As previously shown, animal studies have indicated that afferent glomerular arterioles dilate to a greater degree than efferent arterioles, increasing not only the glomerular filtration rate, but also intraglomerular pressure and filtration fraction (Helal et al., 2012). The early augmentation of glomerular filtration may play a crucial role in the development of diabetic nephropathy, especially given evidence supporting the notion that inhibition of diabetes-induced hyperfiltration delays the progression of kidney damage (Nath et al., 1986; Nordquist et al., 2009).

Before video recording was available, observations were made by Steinhausen et al. (1983) using either incident light or transillumination. Fluorescent probes, now indispensable in multi-photon microscopy, were also a topic of considerable focus for

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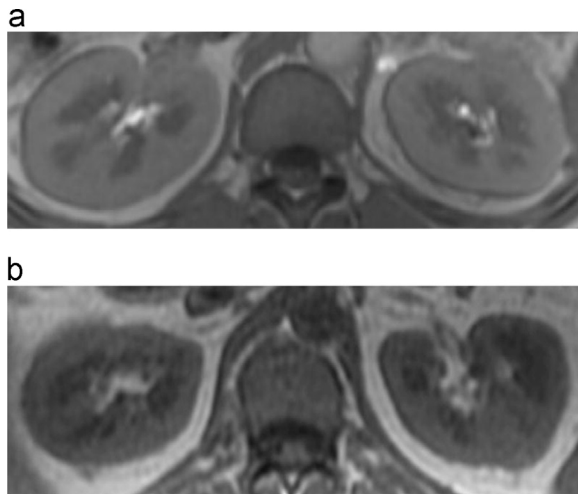

Fig. 1. Human kidney images by MRI. Axial T1-weighted in-phase gradient echo images in a (a) 56-year-old female with cirrhosis and a (b) 55-year-old male without liver disease demonstrate increased corticomedullary differentiation of both kidneys in the cirrhotic patient compared to the control subject (Lee et al., 2012).

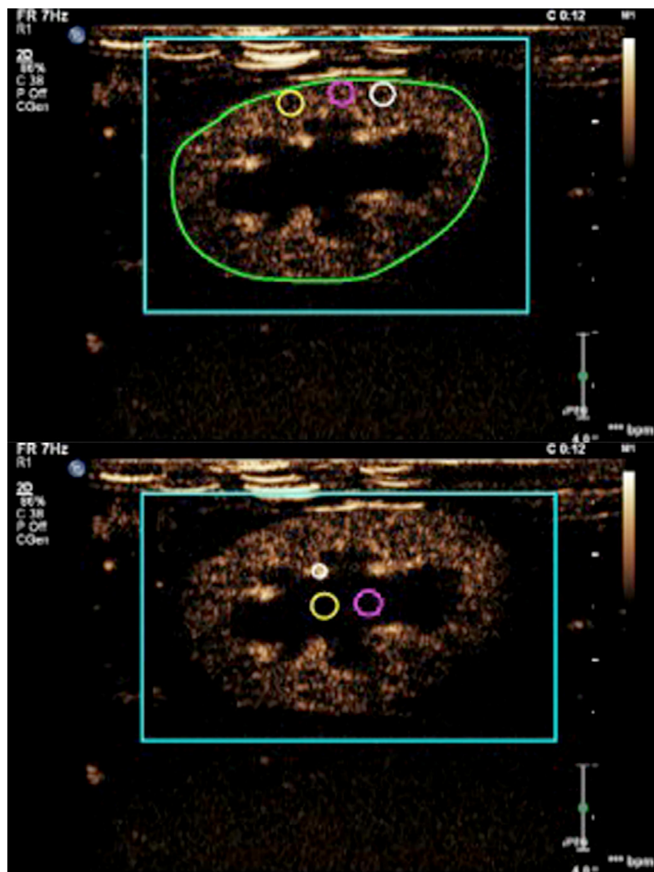

Fig. 2. Contrast-enhanced image of the left kidney of a cat. Note the ROIs drawn around the entire kidney, in the renal cortex (top image), renal medulla and centered on an interlobar artery (bottom image) (Stock et al., 2016).

Steinhausen when visualising renal physiology. Light microscopy enabled the observation and measurement of structures in 2 dimensions, and sequential analysis allowed the measurement of blood flow velocity; however, the demand for a method that facilitates quantitative analyses of renal functions required the development of more advanced imaging techniques. Therefore, we have previously presented a novel 2-photon confocal microscopy technique to visualise filtration, a primary function of the kidney, in-vivo (Molitoris et al. 2005, Nakamoto et al., 2007).

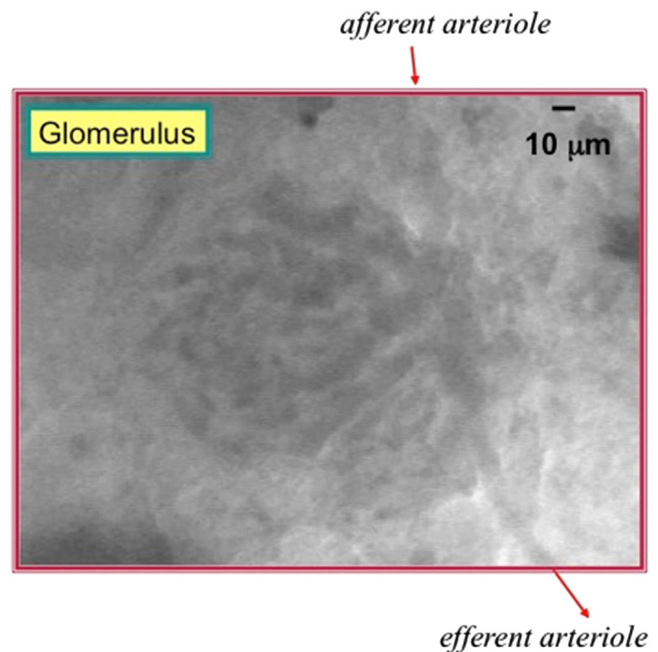

Fig. 3. Still image of glomerular circulation (Nakamoto et al., 2008). Blood flow into the glomerulus from the afferent arteriole, and out from the efferent arteriole, is evident from the visual acquisition. Scale bar indicates a length of 10 μm. Modality: a pencil-type CCD intravital videomicroscope (Nihon Kohden, Tokyo, Japan).

1.2. In-vivo visualisation of glomerular circulation using multi-photon microscopy

The advent of multi-photon microscopy has enabled the imaging of deep sections of living tissue using fluorescent labels, a technique that could be applied to the study of organ function (Sipos et al., 2007). Pioneering investigations by Peti-Peterdi (2006) revealed the existence of a calcium wave that facilitates tubuloglomerular feedback, in an isolated perfused nephron sample. This discovery was an extension on a previous in-vivo study using light microscopy, which demonstrated constriction of the glomerular afferent arteriole (Yamamoto et al., 2001a, 2001b). Similarly, Peti-Peterdi et al. (2004), have visualised renin release from the juxtaglomerular cells in an isolated perfused kidney model. Currently, only a small number of studies have examined glomerular filtration function quantitatively, using visualisation under in-vivo conditions (Russo et al., 2009; Tanner, 2009; Yu et al., 2007); however, it remains difficult to gain access to renal microcirculation. Novel 2-photon confocal laser microscopy technique has been used to visualise filtration, a primary function of the kidney (Fig. 4-a) (Molitoris and Sandoval, 2005; Nakamoto et al., 2007; Nakamoto and Kajiya, 2013). During such visualisation, the leakage of macromolecules (approximately the size of albumin) from the glomerulus has been observed, even in the early stages of diabetes (Nakamoto and Kajiya, 2013). Early in disease progression, albumins can be reabsorbed in the tubules. However, at a later stage, when the tubules become damaged as the duration of disease increases, chronic proteinuria becomes apparent. Such discoveries, facilitated by multi-photon microscopy, have added a new dimension to the study of renal physiology, both in-vitro and in-vivo.

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